Poster: Applications- Anti-infectives

Chantal Csajka Population pharmacokinetics of voriconazole in patients with invasive mycoses

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Objectives: Therapeutic drug monitoring may improve the efficacy and safety of Voriconazole (VRC), a novel antifungal agent. However, the optimal VRC concentration range remains to be established. This investigation aimed to: 1) describe VRC population pharmacokinetics in patients with invasive mycoses, 2) assess inter- and intrapatient variability, influential covariates, and concentration-effect/toxicity relationships, 3) define a dosing regimen ensuring drug exposure within the therapeutic target.

Methods: A population pharmacokinetic analysis was performed using NONMEM VI based on VRC plasma samples collected from patients with invasive mycoses. Doses of 100 to 450 mg were administered twice daily (bid) either orally or by short i.v. infusion. One-compartment linear and non-linear disposition models were tested. The influence of demographics (sex, age, body weight), concomitant medications (rifampicine, omeprazole, metronidazole) and clinical characteristics (severe hepatopathy) on VRC clearance were assessed. Individual average, peak and trough concentrations correlated with efficacy and toxicity markers using logistic regression models. Simulations enabled to devise a dosing regimen ensuring a drug exposure within the therapeutic target.

Results: 505 VRC concentrations from 54 patients were analyzed. VRC CL was 5.2 L/h, distribution volume 192 L, absorption rate constant 1.1 h-1 and bioavailability F 0.63. Rifampicin induced CL by 300%; severe hepatopathy decreased CL by 55%. Large interpatient variability of CL (CV 40%) and F (84%) was observed, and interoccation variability of F (62%) was found. Drug concentrations correlated with antifungal response and toxicity, identifying a VRC therapeutic range of 1-5 mg/L Population-based simulations predicted 40% and 22% of patients with trough level 5 mg/L, respectively).

Conclusions: This study indicates a voriconazole therapeutic range of 1-5 mg/L. An oral dosing regimen of 300 mg bid improves the achievement of concentration targets, compared to the current recommended dosage of 200 mg bid. Variability makes individualization of VRC regimen based on concentration monitoring suitable for efficacy and safety optimization.

Oleg Demin Application of pharmacokinetic-pharmacodynamic model to optimize dosing regime of antimicrobial drug Grammidin containing gramicidin S

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Objectives: To predict the dependence of antimicrobial effect of the gramicidin S applied as oral melting tablets on dosage, time of resorption and minimal inhibitory concentration (MIC) of the drug characterizing its ability to kill different bacteria.

Methods: Mechanism based PK/PD modeling of antimicrobial effect of gramicidin S.

Results: The model has been employed to optimize dosing regime of the commercially available drug Grammidin. Efficacy of the drug has been studied for the diverse gram-positive and gram-negative bacteria with different MIC. The number of bacteria located in the oral cavity and killed by one-pass administration of the drug (resolution of one tablet) has been calculated under condition of various dosing regimes.

Conclusion: Based on the simulation results it has been found [1] that (1) two fold prolongation of prescribed resorption time (from 30 min to 60 min) of the Grammidin tablet comprising standard dosage of 3 mg of gramicidin S results in 1.5-fold increase in efficacy, (2) 1.5-fold decrease in gramicidin S dosage (from 3 mg to 2 mg per administration) under condition of holding prescribed resorption time (30 min) does not lead to any considerable decrease in the efficacy of the drug.

References:
[1] *Smirnov S., Belashov A., Demin O.* Optimization of antimicrobial drug gramicidin S dosing regime using biosimulations (2009) Europ J Pharmac Sciences. 36(1), 105-109.

Anne laure Flaugere Population pharmacokinetics of imipenem bone concentrations in pigs

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Objectives: Imipenem (IPM) is a broad-spectrum β-lactam antibiotic frequently used in intensive care units to treat nosocomial infections and BGN infections. It allows to treat severe infections of all body systems notably bone infections. The objective of the present study was to investigate the bone distribution of IPM by microdialysis in healthy pigs.

Methods: Eight healthy pigs (26-30kg) were included. They were anesthetized and an arterial catheter and a medullar bone microdialysis probe were inserted in the left posterior tibia. Then, pigs received an intravenous infusion of 15mg.kg^{-1} of IPM over a 30-min period. Blood samples and bone dialysates were collected at 5, 15, 30, 45, 60, 120, 180, 240 and 300 min following infusion. Determination of IPM concentrations in plasma and microdialysat were determined by a validated HPLC method with UV-VIS detection (Dionex detector UVD170U). The in vivo recovery of the microdialysis was evaluated by retrodialysis (63%). Data were analysed using the non linear mixed effect modeling software program nonmem (version VI.2). Plasma and bone concentrations were described using the nonmem subroutines ADVAN3 and ADVAN6.

Results: A 3-compartments model was used to describe the whole dataset, 2 compartments for the plasma concentrations and 1 compartment for bone concentrations. The PK parameters were the following : total clearance CL 7.08 L/h (se 13%), volume of distribution of the central compartment V1 2.56 L (se 8%), intercompartmental clearance Q 3.43 L/h (se 18%), volume of distribution of the peripheral compartment V2 2.59 L (se 9.9%), the first order intercompartment rate constant from central to bone compartment (K13) 0.21 L/h (se 45%) and the first order intercompartment rate constant from bone to the central compartment (K31) 2.46 L/h (se 23%). The InterIndividual Variability was evaluated only on CL (22%, se 44%) and K13 (61%, se 25%). Two residual errors were used, one for plasma (22%, se 33%) and one for bone data (37%, se 43%). The model was validated using a bootstrap analysis and goodness of fit plots with normalized predictive distribution error.

Conclusions: The estimation of total clearance (0.25 L/h/kg) and volume of distribution (0.17 L/kg) in pigs are in agreement with those obtained in human (0.2 L/h/kg and 0.2-0.3 L/kg). These results suggest that pig is a useful model for evaluation of IPM PK. Our 3-compartment model which includes bone allows extrapolating bone concentrations in human.

Monika Frank Population pharmacokinetic model development and evaluation after nevirapine administration to mothers and newborns

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Objectives: To reduce the risk of HIV transmission in resourced-limited areas a single oral dose of nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor, was administered to 62 HIV-1 positive pregnant women and their newborns. Due to the sparse data situation population pharmacokinetic (PK) analysis was performed to characterise the PK of three different matrices (mother and newborn plasma as well as breast milk).

Methods: Study medication were a 200 mg NVP tablet for pregnant women during labour and a 2 mg/kg NVP syrup for newborns within 3 d after birth, resulting in 113 mother plasma, 95 breast milk and 113 newborn plasma samples over 3 weeks. Population PK analysis for mother and newborn data were performed using the nonlinear-mixed-effect modelling approach implemented in NONMEM^{TM} (ADVAN6, TRANS1, TOL5; FOCE INTERACTION estimation method). The process of model refinement of previous models for mother and newborn data [1] was guided by standard diagnostic tools and by visual predictive checks (VPC) to investigate model performance.

Results: A 2 compartment PK model was developed for mother data and a 1 compartment model for newborn data. Due to sparse data, absorption rate constant was fixed to 1.66 h^{-1} [2]. Model simulated maximum concentrations for mother plasma, breast milk and newborn plasma were approximately 2300 ng/mL, 1800 ng/mL and 1500 ng/mL, respectively, indicating high drug transfer into milk and into foetus/newborn. Refined models comprised: i) different types of transfer for NVP from plasma to breast milk, e.g. uni- vs bidirectional, ii) time-dependence of switching on the NVP transfer into breast milk and iii) varied residual error structures. First VPC revealed an adequate central tendency although late time points (2 weeks after birth) were generally underestimated. However, the variability of the model was sufficiently reflected.

Conclusions: Population PK models for mother data and newborn data were developed and evaluated by different diagnostic tools. Preliminary results suggest adequate model performance for both patient groups. Final PK models could assist single dose NVP prevention strategies of HIV transmission from mother-to-child.

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[1] Frank M, Kunz A, Harms G, Kloft C, Nevirapine - Population pharmacokinetic model building and simulation for mothers and newborns, PAGE 17 (2008) Abstr 1249 [www.page-meeting.org/?abstract=1249].
[2] Kappelhoff BS, van Leth F, MacGregor TR, et al. Nevirapine and efavirenz pharmacokinetics and covariate analysis in the 2NN study. Antivir. Ther., 10: 145-155 (2005)

Maria Kjellsson Modeling the permeability of Fosfomycin into Abscess Fluid

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Background: Most drugs do not exert their effect in plasma, where concentrations generally are measured, but in a defined target tissue which the drug must reach in concentrations high enough to have the desired effect. Target site concentrations are seldom identical to plasma concentrations and may also vary greatly depending on where in the body the target tissue is located. For the treatment of abscesses using anti-infectious drugs the penetration of the drug into the abscess is crucial, although oftentimes unknown, and highly variable depending on location and size of the abscess. Understanding any differential penetration in diseases such as tuberculosis may help understand treatment failures and/or suggest alternate therapeutic strategies. In tuberculosis, it has been suggested that lesion diversity in size, location, structure and cellular/acellular content may contribute to the long treatment duration, treatment failure and the development of drug resistance.

Objective: To investigate the permeability of fosfomycin, a broad spectrum antibiotic, into abscess fluid and investigate how the size and location of abscess may affect the permeability. This is as a broader objective to study the penetration of drugs into tuberculosis lesions.

Methods and data: The data used for this analysis have previously been published using a non-mixed effect modeling approach (1). Patients (n=12) scheduled for abscess drainage were administered an intravenous dose of 8 g fosfomycin at different time points before their surgery. Repeated plasma concentration measurements were made and one concentration measurement in the drained pus was available. In the model-based analysis, the PK was described using a three compartment model with one of the peripheral compartments being the target site. All analyses were conducted using non-linear mixed effects modeling in NONMEM.

Results and conclusions: The previously reported high inter-individual variability (IIV) in the permeability of the drug into the abscess (1) was quantified. The impact of covariates such as abscess size and location to explain fosfomycin PK variability and drug penetration into abscess lesions was investigated and was shown to explain some of the IIV but will be reported in more detail in the poster.

Reference:

[1] Sauermann et al, Antimicro. Agents Chemother. 49(11), 2005

Chantal LE GUELLEC Population pharmacokinetics of Ceftriaxone in intensive care unit (ICU) adult patients

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Objectives: Pharmacokinetics may be altered in severely ill patients. We describe population pharmacokinetics of ceftriaxone in a large group of critically ill patients suffering from sepsis, severe sepsis or septic shock. The influence of several clinical and biological covariates was analyzed. The model was used for dose simulation in reference to MIC of common ICU pathogens.

Methods: The dose of ceftriaxone was 1 g or 2 g once a day. A full or semi-rich pharmacokinetic (PK) profile was obtained on two occasions for each patient. The first PK was drawn on the second day of ceftriaxone therapy; the second PK occurred following the resolution of sepsis. Population pharmacokinetic analysis was performed using NONMEM VI. Fourteen potential covariates were evaluated, including demographic, biological and clinical characteristics, and co-administered drugs. Between Occasion Variability (BOV) was analyzed from PK1 to PK2. Simulations were made at various doses for hypothetical patients having different covariates values.

Results: We included 54 patients: 19 suffered from sepsis, 9 from severe sepsis and 26 from septic shock. Eleven patients were hemofiltrated or haemodyalized. For the other patients creatinine clearance (CLcr) ranged 5.5 to 214 ml/min. Renal function improved from PK1 to PK2. A 2-compartments model best fitted the concentration data and the covariate selection analysis showed that V1 increased with more severe type of sepsis (V1 = 8.21 ± 3.55 L, 9.77 ± 3.83 L and 11.5 ± 4.16 L for sepsis, severe sepsis and septic shock, respectively) but its inclusion in the model was not significant. Ceftriaxone CL was independent of CLcr for values below 60 ml/min and then increased linearly with GFR [CL=THETA(1)+THETA(2)*(CLcr/4.26);THETA (1)=0.56; rse=19.6; THETA(2)= 0.32; rse=37.5]. The model did not supported BOV on any parameter. The other PK parameters were V2 (7.35 L; rse=10.2%; CV=65%) and intercompartment clearance (5.28 h^{-1}; fixed). The residual variability modelled as proportional was 24%. Simulations performed for 2 different ceftriaxone doses and 4 different renal functions indicated that most patients will achieve effective concentrations, even with a dose of 1 g.

Conclusions: We found a wide inter-patient but weak intrapatient variability of ceftriaxone PK. The only parameter that influenced ceftriaxone pharmacokinetics was CLcr, but only when CLcr was > 60 ml/min, suggesting participation of non-renal phenomenon. Simulations indicated that the risk of being under 4 MIC for the entire dosing interval is very low and exists only in patient with high glomerular filtration rate (CLcr > 120 ml/min).

Ana Martin Suarez Population pharmacokinetic model for Ritonavir (RTV) in HIV-infected patients treated with Lopinavir (LPV)/RTV (KaletraTM)

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Objectives: Having the population model previously obtained for LPV with the same data-set (Santos Buelga D. PAGE 2009), the aim of this study was to develop and validate a population pharmacokinetic (PK) model for RTV in HIV-infected patients treated with Kaletra^{TM}.

Methods: 201 ambulatory HIV-infected adult patients from two Spanish hospitals, treated with LPV/RTV (dose 400/100 twice daily) were included. 686 LPV and RTV plasma concentrations at a single time-point and 62 full PK profiles were available, resulting in a database of 1110 LPV and RTV steady-state plasma concentrations. The patients were divided randomly into two groups for model building (n=954 RTV plasma concentrations) and model validation (n=156). RTV and LPV plasma concentrations were determined by HPLC with UV detector. The population PK parameters of RTV were estimated using the NONMEM software package version V.1, and FOCE method with INTERACTION. The influence of different patient characteristics (age, gender, height, weight, body mass index, total bilirrubin, hepatitis C co-infection, PK behaviour of LPV and concomitant treatment with saquinavir (SQV), tenofovir and atazanavir) on the PK of RTV was explored.

Results: RTV plasma concentration-time data were modeled using a one-compartment PK model with first-order absorption and elimination including lag-time. The model was parameterized in terms of clearance (CL/F, for unknown true bioavailability) and volume of distribution (V/F). An additive statistical model was selected to describe the residual error and a proportional model for the interindividual variability. The inclusion of the CL/F of LPV in the basic model produced a decrease from -658.66 to -801.18 in the objective function value and a decrease from 45% to 29% (CV%) in the interindividual variability of clearance. RTV clearance was also influenced significantly by SQV concomitant treatment. No covariates were found to explain the high variability of other parameters estimated.

Final model (mean parameters (SE)):

CL/F (L/h) = 2.15 (2.46%) *CL_{LPV}*1.25 (7.50%)**SQV(0/1); CV_{CL} = 30.07% (14.16 %)

V/F (L) = 303.00 (12.01%); CV_{Vd} = 86.02% (19.02%)

Ka (h^{-1}) = 2.06 (14.66%); CV_{KA} = 65.12% (61.69%)

Lag-time (h) = 2.44 (4.96%); CV_{ALAG} = 52.1 %

Residual variability (SD) = 0.12 mg/L (5.68%)

Conclusions: The clearance of LPV and the concomitant use of SQV significantly influence the PK of RTV. Validations results obtained confirm the adequacy of the proposed model.

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France Mentré Parameter estimation of long-term HIV dynamic model in the COPHAR2 – ANRS 111 trial using MONOLIX

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Objectives: HIV dynamics studies, based on differential equations, have significantly improved the knowledge of HIV infection. While first studies use simplified short-term dynamic models, recent works consider more complex long-term models combined with a global analysis of whole patients data based on nonlinear mixed models. This approach increases the accuracy of the HIV dynamic analysis, however statistical issues remain given the complexity of the problem. We propose to use MONOLIX 2.4 (www.monolix.org) to simultaneously analyse the HIV viral load decrease and the CD4 increase in patients using a long-term HIV dynamic system.

Methods: In the prospective COPHAR2 – ANRS 111 trial, 115 naïve HIV patients started an HAART containing two nucleosides analogues and one protease inhibitor: nelfinavir, or indinavir (+ ritonavir), or lopinavir (+ ritonavir) [1]. Patients were followed one year with several measurements of HIV viral load and CD4 cells. We consider three previously proposed mechanistic models and implemented them using MLXTRAN [2, 3, 4]. Maximum likelihood estimation of the parameters of these models was performed using the SAEM algorithm implemented in MONOLIX 2.4 [5, 6]. which also takes into account the censoring issue due to detection limits of viral load [7]. We selected the best model using the BIC criteria and also tested the difference of efficacy of the 3 protease inhibitors.

Results: We showed that the model with latent CD4 cells was the best model. The goodness of fit of this model with 5 differential equations is very satisfactory. The 10 parameters, 7 with between patient variability, are well estimated. We showed that the efficacy of nelfinavir is reduced compared to indinavir and lopinavir.

Conclusions: We were able to use maximum likelihood estimation in order to analyze adequately, through a complex differential equation model, both viral load and CD4 count changes during treatment in HIV patients using the SAEM algorithm implemented in MONOLIX.

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Michael Neely Voriconazole Population Pharmacokinetics and Pharmacodynamics in Children

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Objectives: Published voriconazole pharmacokinetic (PK) and pharmacodynamic (PD) data are limited in children and adolescents and differ from adults. We reviewed our experience with voriconazole therapeutic drug management (TDM) in this population.

Methods: Records at the Childrens Hospital Los Angeles were reviewed for children with ≥1 serum voriconazole concentration measured (at a commercial laboratory) from May 1, 2006 to June 1, 2007. Demographics, dosing histories, serum concentrations, and toxicity/survival data were obtained. The non-parametric population modeling and simulation MM-USCPACK software was used to compare distributions of concentrations simulated from published PK parameters1 as well as to fit the observed data to additional candidate PK models, which were evaluated on the basis of log-likelihood and observed vs. predicted plots. Statistical analyses were done with R 2.8.0.

Results: There were 207 voriconazole levels obtained from 46 patients (0.8 – 20.5 years). The median (range) dose was 5.8 mg/kg (2.0 – 12.9); 90% were oral. There were 3 (1 – 21) levels per patient. In each patient, levels were measured after different doses 99% of the time. The max concentration was 21.3 mg/L; min was 12y, whose geometric mean concentration was 1.5 mg/L vs. 1.0 mg/L in those 1 mg/L in >50% of children, but that the EMEA-approved oral dose of 200 mg twice daily for all ages will achieve this trough in only 25-50% of children.

Conclusions: We found marked between-individual voriconazole PK variability, and additional within-individual variability after enteral dosing, likely due to random temporal changes in absorption. Nonetheless, we found a PD association between a voriconazole trough >1 mg/L and survival. Voriconazole TDM with a target trough of >1 mg/L appears to be indicated.

References:

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Saeed Rezaee Population Pharmacokinetics of Vancomycin in Iranian Paediatric Patients

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Objectives: The pharmacokinetic profile of vancomycin (VCM) differs between paediatrics and adult patients, therefore understanding VCM pharmacokinetics in paediatric patients is needed for planning of individualized optimal VCM dosage. The main goal of this study was to develop a pharmacokinetic model for vancomycin in a population of Iranian paediatric patients.

Methods: Sparse serum samples (n = 100) were collected prospectively from 62 paediatric patients aged one month to 14 years(3.8±4.2 years) in the weight range of 2.6 to 48 (13.7±11.6) kg . Serum samples were assayed for VCM concentration using fluorescence polarization immunoassay technique. A one-compartment PK model with zero order input was used. Population pharmacokinetic analysis was carried out using Monolix 2.4 software. For 49 patients (who had complete covariate data set), the influence of patients' characteristics on VCM PK parameters was assessed using both graphical approaches and Multivariate Adaptive Regression Splines method.

Results: The values of PK parameters (inter-individual variability %) obtained from the base model are: CL=0.13(380%) L/kg/hr and V=1.28(70%). Creatinine clearance (calculated by Schwartz method) seemed to be the only covariates that influence VCM clearance; however it could not decrease the variability in the vancomycin clearance significantly.

Conclusions: Large inter individual variability observed especially in vancomycin clearance could be due to heterogeneous nature of the study population especially with regard to the age range. Weight did not influence vancomycin clearance and volume of distribution as a significant covariate because its effect has been already taken into account by using the weight normalized doses in calculations. However, the parameters derived by the base model have the potential to be used as prior of Bayesian estimation for individualization of the vancomycin dosage regimen.

Mª Dolores Santos Buelga Population Pharmacokinetics of Lopinavir (Kaletra®) in HIV-Infected Patients

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Objectives: To develop and validate a population pharmacokinetic (PK) model of lopinavir (LPV) associated to ritonavir (RTV) (KaletraÒ) in HIV-infected patients.

Methods: The study was carried on ambulatory HIV-infected adult patients from two Spanish hospitals, treated with lopinvir/ritonavir (dose 400/100 twice daily). From 201 patients, 686 lopinavir plasma concentrations at a single time-point and 62 full pharmacokinetic profiles were available, resulting in a database of 1110 LPV steady-state plasma concentrations. Samples were analysed by HPLC, UV detector. Pharmacokinetic analysis was performed with NONMEM. The first-order conditional estimation (FOCE) with Laplace approximation was used throughout. Age, gender, height, total body weigth (TBW), body mass index (BMI), ritonavir through concentration (RTC), total bilirrubin, VHC, gender and concomitant administration of saquinavir (SQV), tenofovir (TFV) and atazanvir (ATV) , were explored using GAM implemented in Xpose.A total of 954 and 156 LPV concentrations were included in two datasets for model building and model validation, respectively.

Results: A one -compartment model with first-order absorption (with lag-time) and elimination, specified to NONMEM by the routines (ADVAN2, TRANS2) with proportional and additive error models for interinditivual and residual varaibilities, respectively, best described the pharmacokinetics of lopinavir.

LPV clearance was influenced by patient BMI, RTC and ATV concomitant administration. No covariates were found to influence the other PK parameters. Thus final regression model for LPV was as follows:

$CL\ (L/h) = 0.29*BMI*e^{-0.48*RTC}*e^{-0.34*ATV}$; V (L) = 170; Ka ($h^{-1}$) = 0.68; ALAG (h) = 0.69

CV_{CL} = 26.9 %; CV_V= 72.5 %; CV_{KA} = 44.7 %; CV_{ALAG} = 52.1 %

Residual variability = 3.2 mg/L

Validation results in another dataset confirm the adequacy of the proposed model, as MPE ± SD and SMPE ± SD were -0.20 ± 2.72 and -0.05 ± 0.91

Conclusions: The population model proposed, adequately describe the lopinavir pharmacokinetics. Concomitant use of ritonavir and atazanavir significantly influence its elimination. This model could be used to estimate LPV appropriate dosage guidelines. Moreover their simple structure will allow an easy implementation in clinical PK software and their application in dosage individualization by Bayesian approach.

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Wynand Smythe Mechanistic pharmacokinetic enzyme model for the characterisation of rifampicin pharmacokinetics in South African pulmonary TB infected adults

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Introduction: The treatment of TB requires the use of multiple drug containing regimens. As rifampicin (RMP) has the ability to eliminate persisting Mycobaterium organisms within TB lesions it forms the backbone of most first line regimens (1). Nonetheless RMP is known to have highly variable absorption (2, 3) and to induce its own metabolism (4). These characteristics, coupled with potential drug-drug interactions and low RMP concentrations (5), may increase the likelihood of treatment failure and the emergence of drug resistance.

Objectives: The primary objective of this pharmacokinetic analysis was to determine the population pharmacokinetics of rifampicin using nonlinear mixed-effects modelling amongst African patients with pulmonary tuberculosis. Subsequently, population PK models will be developed for the remaining drugs used within the study's multi-drug regimens and potential drug-drug interactions will be assessed.

Methods: Pulmonary tuberculosis infected adult patients were randomized to receive once daily doses of rifampicin, isoniazid, pyrazinamide and ethambutol with or without gatifloxacin for 6 days of the week. Blood samples were taken for pharmacokinetic determination after the first dose (pre-induction) and after approximately 28 days (steady state). In total, 1 142 rifampicin plasma concentration-time data points collected from 195 patients were included in the analysis. A mechanistic pharmacokinetic model incorporating an enzyme turn over model to address rifampicin's auto-inductive properties, together with a multiple dosing transit absorption compartment model to describe the drugs highly variable absorption was developed using the first order conditional method in NONMEM.

Results: A multiple dose transit absorption compartment model (3, 6) was used to describe the highly variable absorption characteristics of rifampicin. The transfer of drug through the transit compartments followed by first order absorption allowed for the model to mimic a delay in absorption observed occasionally in patients taking rifampicin. Rifampicin's propensity to induce its own metabolism was modelled by an enzyme compartment where the amount of drug within the central compartment was allowed to influence the production of enzyme. As more enzyme was produced within the enzyme compartment so the oral clearance (CL/F) of drug from the central compartment was increased. The CL/F was around one fold higher at the steady state compared to the pre-induced state. The predicted enzyme turn-over half-life was predicted to be approximately 62 hours.

Conclusions: The developed mechanistic model described the pharmacokinetics of rifampicin and will be extended to include potential drug-drug interactions seen between rifampicin and the other drug components of the anti-tuberculosis regimens.

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Ami Fazlin Syed Mohamed Pharmacokinetic/Pharmacodynamic Modeling of Adaptive Resistance of Gentamicin

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Objectives: Adaptive resistance is a pharmacodynamic process that is characterized by a reversible refractoriness to the bactericidal action of an antibacterial agent [1]. This phenomenon, specific to the aminoglycosides group, is not fully understood but it emerges already at the administration of the first dose, is enhanced by higher doses, and augmented by consecutive doses if administered before the bacteria return to their susceptibility stage [2]. The underlying mechanism is postulated to be a reversible down regulation of the active transport of gentamicin into gram negative bacteria [1]. The aim of this study is to develop a pharmacokinetic/pharmacodynamic model that describes the bactericidal activity of gentamicin and can predict the adaptive resistance.

Methods: In vitro time kill curve experiments were conducted for 24-48 hours on a strain of *Escherichia coli*. Gentamicin exposure was either at constant concentration ranging between 0.125-16 times the MIC or in a dynamic kinetic system with different dosing regimens; 1-8 times the MIC every 12 or 24 hours with simulated two-compartment kinetics. Bacterial counts were monitored with frequent sampling throughout the experiments. All data were fit simultaneously in NONMEM using a previously developed semi-mechanistic model for antibiotics as the basis [3]. The adaptive resistance was modeled either as an empirical function where Ec50 increased with dose and time [4], or, as a component in a hypothetical compartment that affected Ec50 and accumulated following drug administration and diminished with time.

Results: The data showed that gentamicin has a fast bactericidal effect with clear indication of adaptive resistance in static as well as dynamic experiments. The original semi-mechanistic model [3] could not describe the gentamicin data. The semi-mechanistic model with the added hypothetical component resulted in a better fit to the data (OFV>80 units) and improved goodness-of-fit compared with the model with the empirical component.

Conclusion: The semi-mechanistic model with the added hypothetical component, that allows adaptive resistance to be reversible, was superior to the model with the empirical function earlier described. After further refinement the developed model may be used for improved dosing strategies of gentamicin.

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Mita Thapar Population pharmacokinetics of artesunate and dihydroartesunate in adults and children following administration of a fixed dose combination formulation of chlorproguanil-dapsone-artesunate

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Objectives: To describe the population pharmacokinetics (PPK) for artesunate (ART) and its active metabolite dihydroartesunate (DHA) following the administration of a fixed-dose combination of chlorproguanil-dapsone-artesunate (CDA) in healthy adults and adult/pediatric patients with *P. falciparum* malaria.

Methods: Plasma concentration-time data from four Phase I-III clinical studies including 61 healthy adults (HV),115 adult malaria patients (AP) and 1101 pediatric malaria patients (PP) with median age of 3 years (range; 1-14), were included in the PPK analyses. Separate PPK analyses were performed on log-transformed data for ART and DHA using a non-linear mixed-effect modeling (NONMEM) approach The exponents for allometric scaling for both oral clearance (CL/F) and apparent volume of distribution (V/F) were estimated. Separate random residual variability terms were applied to the adult and pediatric populations and a common inter-individual variability (IIV) term on the residual variability (eta on epsilon) was also included for both populations. Effects of covariates (e.g., age, gender, subject status) were evaluated on ART and DHA pharmacokinetics (PK).

Results: The final PPK model for ART was a one-compartment model with two sequential first-order absorption components and with first-order elimination. The first and second absorption rate constants, Ka1 and Ka2 were estimated to be 0.58 hr^{-1} (IIV 51%) and 0.44 hr^{-1} (IIV 58%), respectively, with the change in absorption rate (MTIME) occurring at 2.4 hr post dose. Inter-occasion variability (IOV) in Ka was 41%. Allometric scaling exponents on CL/F and V/F were estimated to be 0.95 and 0.78, respectively. V/F was estimated to be 249 L (IIV 107%). Only subject status was found to significantly impact CL/F. The CL/F in HV was 1730 L/hr with the CL/F estimated to be 43% lower in AP and 2-fold higher in PP, with an associated IIV of 42%. All parameters for the structural and error models were estimated with a relative standard error (RSE) of less than 20% and 26%, respectively. Random residual variability estimates for pediatric and adult data were 111% and 59%, respectively, with an associated IIV of 11%.

The final PPK model for DHA was a one-compartment model with an absorption (metabolic conversion) lag time, simultaneous zero-order and first-order absorption with first-order elimination. The fractions absorbed from the first-order and zero-order absorption processes were estimated to be 0.71 and 0.29, respectively. The lag-time for absorption was estimated to be 0.20 hr with a Ka of 0.50 hr^{-1} (IIV 24%) and a duration for zero-order input of 3.3 hr. CL/F was estimated to be 104 L/hr (IIV 43%) and V/F was 85.3 L (IIV 99%). All parameters for the structural and error models were

estimated with RSE of less than 10% and 36%, respectively. Random residual variability estimates for pediatric and adult data were 150% and 59%, respectively, with an associated IIV of 25%. None of the covariate effects were found to have a clinically significant impact on DHA PK.

Conclusions: The final PPK models which incorporated the influence of weight on CL/F and V/F using allometry described ART and DHA PK data well following the administration of a fixed-dose combination formulation of CDA. Additionally, subject status (HV, AP vs. PP) was found to be a predictor of ART oral clearance.

Jan-Stefan van der Walt Effect of rifampicin-based antitubercular therapy and cotrimoxazole on the population pharmacokinetics of stavudine (d4T) in HIV-1 infected patients

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Objectives: The coadministration of antiretroviral and antitubercular therapy is known to result in drug-drug interactions due primarily to the induction of metabolising enzymes and drug transporters by rifampicin. Nucleoside analogue reverse transcriptase inhibitors, including stavudine (d4T), are predominantly eliminated by renal tubular secretion and not affected by this interaction. The aims of our analysis were to describe the population pharmacokinetics of stavudine during and after antitubercular treatment, to assess the effects of cotrimoxazole on stavudine pharmacokinetics and to quantify the interoccasional variability in this population.

Methods: Stavudine concentration-time data from 16 patients who received stavudine-containing antiretroviral therapy during and after rifampicin-based antituberculosis therapy were analysed using nonlinear mixed effects modelling (NONMEM version VI, FOCE). The effects of antitubercular therapy were assessed on both fixed effects (the relative bioavailability, i.e. during vs after antitubercular therapy, and the first order absorption rate constant) and random effects (interoccasional variability).

Results: A one-compartment disposition model with first order absorption and elimination, and absorption lag time best described the data. The pharmacokinetics of stavudine was highly variable and the base model included between-subject variability (BSV) on the apparent clearance (CL/F), absorption rate constant (K_a) and relative bioavailability. Antitubercular therapy did not have a significant effect the relative bioavailability or absorption of stavudine. During antitubercular treatment the bioavailability was 3% lower (proportional change: -0.03; 95% CI: -0.237, 0.174) and K_a was 30% higher (proportional change 0.3; 95% CI -0.71, 1.31).

Adding between-occasional variability (BOV) in the relative bioavailability significantly improved the model fit (BSV F = 15%CV, BOV F = 16%CV). In this population stavudine absorption was rapid (K_a = 10.6/h) and highly variable (BSV K_a = 142 %CV, BOV K_a = 27 %CV). The estimates of CL/F (15.2 L/h, 16 %CV) and V/F (32 L) were similar to those previously published.

Cotrimoxazole was used by 14 patients during antitubercular therapy and 10 patients continued cotrimoxazole prohylaxis after completion of antitubercular therapy.Concomitant use of cotrimoxazole increased the clearance of stavudine by 18% (95% CI 3% - 32%).

Conclusions: Rifampicin-based antitubercular therapy did not significantly affect the population pharmacokinetics of stavudine. The coadministration of cotrimoxazole and stavudine resulted in a

modest increase in the apparent clearance of stavudine by 18% (95% CI 3% - 32%) but is unlikely to justify dose adjustment of stavudine when coadministered with cotrimoxazole..

Jianping Zhang Use of Eltrombopag Exposure-Platelet Response Relationship for Dose Optimization in Patients with Chronic HCV-Infection with and without Interferon

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Objectives: Eltrombopag is the first oral small-molecule, non-peptide thrombopoietin receptor agonist. It is under development for the treatment of thrombocytopenia in patients with hepatitis C virus (HCV). A population pharmacokinetic/pharmacodynamic (PK/PD) model was developed to characterize the effect of eltrombopag on platelet counts in HCV patients with and without IFN (peginterferon alfa-2a and peginterferon alfa-2b) and ribavirin treatment and to identify covariates that influence eltrombopag PK and PD. The final PK/PD model was used to guide the dose selection for Phase III studies in HCV patients to achieve and maintain sufficient platelet counts to initiate and complete the full course of IFN therapy.

Methods: PK/PD data were constructed from 3 studies including 63 healthy subjects, 41 subjects with HCV, and 24 subjects with mild to severe hepatic impairment (HI). Dosing of eltrombopag in these studies ranged from 5 to 75 mg QD as a single dose or repeat doses for up to 16 weeks. Nonlinear mixed effects modeling was conducted using NONMEM V. Influential covariates were identified using step-wise forward addition and backward elimination technique. A sequential analysis approach was applied to characterize the PK/PD relationship between plasma eltrombopag concentrations and platelet counts in patients with HCV. Visual predictive check and non-parametric bootstrap were implemented for final model evaluation. Platelet response (>50, >75, >90, >200 Gi/L) at daily eltrombopag doses of 12.5, 25, 50, 75 and 100 mg with and without IFN were simulated for HCV patients using the final population PK/PD model.

Results: Eltrombopag PK was described by a two-compartment linear model with sequential zero-order and bolus input in absorption compartment and first-order absorption. The typical oral clearance (CL/F) and volume of distribution (Vc/F) of eltrombopag were 0.71 L/hr and 8.72 L, respectively, for a healthy subject. Vc/F correlated with body weight, consistent with the theoretical allometric scaling for volume of distribution. Age and aspartate aminotransferase (AST) correlated negatively with CL/F. Subjects with severe HI displayed a 46% reduction in rate of absorption (Ka). Overall, CL/F was 66% and 18% lower in subjects with HCV and HI, respectively, when compared to healthy subjects. Concomitant IFN had no effect on eltrombopag PK. The relationship between plasma eltrombopag concentrations and platelet response was well captured by a catenary cell production and loss model, with an estimated maximum stimulation (Smax) of 6.4 fold increase in platelet production and 50% of maximum stimulation achieved at 17.2 µg/mL (SC50). The model also characterized the inhibitory effect of IFN on platelet counts. PK/PD simulations supported 50 mg QD as an appropriate starting regimen for patients with HCV at which >75% of patients should achieve >75 Gi/L platelet counts after 2 weeks of eltrombopag alone treatment. Following initiation of IFN therapy, platelet counts were reduced by 40% from peak levels. At steady state, ³78% of patients who initiated IFN therapy were

predicted to maintain platelet counts above 50 Gi/L over the course of IFN therapy with concomitant eltrombopag. A 25mg dose increase in patients with insufficient platelet response was predicted to improve their platelet counts. Following the dose adjustment, >70% of patients who did not respond (platelet counts <75 Gi/L) initially were predicted to respond, and >25% of patients who would have stopped IFN therapy due to reduction of platelet counts (<50 Gi/L) were predicted to complete the full course of IFN therapy.

Conclusions: The relationship between eltrombopag exposure and platelet response in HCV patients with and without IFN was well characterized by the population PK/PD model. Simulations based on the model optimized dosing strategies for the Phase III studies. By minimizing thrombocytopenia these strategies should enable more HCV patients to achieve adequate platelet counts in order to initiate and maintain IFN therapy.

Leonid Gibiansky Population Pharmacokinetics of AMG 317, a Fully Human Anti-IL-4Rα IgG2 Monoclonal Antibody Evaluated in Healthy and Asthmatic Subjects

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Background: AMG 317 is a fully human IgG_2 monoclonal antibody that was tested as a treatment for asthma based on its potent ability to block both IL-4 and IL-13 activity in-vitro by binding to IL-4R**α**.

Objectives: To investigate the population PK of AMG 317 following subcutaneous and intra-venous administration of AMG 317 in healthy and asthmatic subjects.

Methods: The population PK analysis was conducted via nonlinear mixed-effects modeling with the Nonmem VI 2.0. The first-order conditional estimation method with interaction option (FOCEI) was employed for all model runs. The final model was evaluated using the diagnostic plots, bootstrap analysis, and predictive check simulations.

Results: The dataset included 2184 AMG 317 concentration values from 295 subjects. Among 291 subjects with available covariate information, there were 169 males and 122 females. The median (range) age and weight were 36 (12 - 64) years and 83 (44 - 256) kg. There were 9 patients with weight > 140 kg; 248 asthmatic patients (84.1%) and 47 healthy volunteers (15.9%). AMG 317 was administered as an IV bolus or infusion to 29 subjects (9.8%) and as a SC injection to 266 subjects (90.2%). The IV doses ranged from 10 to 1000 mg, while the SC doses ranged from 30 to 600 mg.
A two-compartment model with the target-mediated drug disposition (TMDD) described the PK of AMG 317 [1, 2]. The Michaelis-Menten (MM) approximation with parallel linear and nonlinear elimination routes was sufficient to describe the concentration-time data that were above the 300 ng/mL level. The quasi-steady-state (QSS) approximation of the TMDD model adequately described the entire range of the observed data.
AMG 317 central volume and clearance for a typical subject (WT=80 kg, AGE=40 years, SC administration) were estimated as V2 = 2100 mL (95%CI: 1760 - 2270 mL) and CL = 41.3 mL/hr (95%CI: 36 - 45 mL/hr), respectively. Inter-compartmental clearance Q and peripheral compartment volume were estimated at 30.2 L/hr (95%CI: 26.2 - 33.8 mL/hr) and 6150 mL (95%CI: 5300 - 6840 mL), respectively. The total receptor concentration (RMAX) was estimated at 296 ng/mL (95% CI: 249 - 331 ng/mL) that is close to the lower limit of the concentration range where the concentration-time data are well-described by the MM model. QSS constant KSS was estimated at 45 ng/mL (95% CI: 36 - 55 ng/mL), in agreement with the value of the AMG 317 dissociation constant (KD=1.8*10-10 M or about 27 ng/mL).
Bioavailability of the SC formulation was estimated at 28.2% (95% CI: 24.4 - 29.7%). Absorption was slow, with the absorption half-life of 3.4 days (95% CI: 3.3 - 4.4 days). Central volume following IV administration was estimated to be 70% (95%CI: 52 - 99%) higher than central volume following SC administration. The inter-subject variability of CL, Q, V2, and KA was moderate, ranging from 33 to 41%. An allometric model for linear clearance and central volume described the dependence of parameters on body size measures.

Absorption rate decreased with age. It was 36% higher (95%CI: 27 – 80%) for a 20-year old and 17% lower (95%CI: 13 - 29%) for a 60-year old, respectively, than for a 40-year old subject. AMG 317 concentrations were slightly lower in subjects with detected anti-AMG 317 antibodies, but results do not indicate any significant and unexplained decline in the observed AMG 317 concentrations for these subjects.

Conclusions: Population PK model was able to adequately describe AMG317 pharmacokinetics in the entire range of available doses, routes of administration, weight and age ranges.

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Nathalie Gobeau Target-Mediated Drug Disposition Model to Describe Non-linear Kinetics of a Monoclonal Antibody

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Introduction: CDP791 is a Monoclonal antibody (Mab) showing non-linear pharmacokinetics. It is a VEGFR-2 (Vascular Endothelial Growth Factor Receptor-2) antagonist developed for use in cancer therapy.

Objectives: To develop a target-mediated drug disposition (TMDD) model to:
i) explain the non-linear pharmacokinetic (PK) behavior observed with this Mab.
ii) identify and characterize the covariate effects on the PK behavior of CDP791.

Methods: Data were available from a phase II study in patients with Stage IIIb or Stage IV non-squamous non-small cell lung cancer requiring chemotherapy. A Target-Mediated Drug Disposition (TMDD) model was implemented in NONMEM. It included a central and a peripheral compartment as well as a third compartment (binding compartment) linked to the central, to model drug/target binding. A linear clearance was defined from the central compartment as well as distribution parameters with the peripheral compartment. Elimination from the binding compartment was nonlinear and dependent on the prevalence of both the drug and the receptor.
Biological and physiological parameters were tested as covariates on the BASE model based on their implication in the VEGF/VEGFR-2 loop and their potential impact on the drug/target binding.

Results: This TMDD model with two compartments (central and peripheral) and a third one for the drug/target binding described the PK adequately. The volume for the central compartment was around 3 L, which is closely similar to plasma volume. Linear clearance was 0.0101 $L.h^{-1}$. Those values are consistent with pharmacokinetic parameters reported for other macromolecules presenting TMDD behavior[1]. The target/drug binding was faster than both degradation and synthesis of the target, as is generally expected for the kinetics of such processes.
The binding of drug to free target decreased in inverse proportion to plasma s-VEGFR-2 (up to a factor 10 between extreme values) or platelet count at baseline (up to a factor 2.5 between extreme values). Linear clearance appeared to increase with increasing tumor size although in a moderate proportion (± 25%, compared to a typical subject)

Conclusions: We have developed a specific TMDD model that describes adequately the PK of CDP791.
Some biological parameters such as the s-VEGFR-2 and platelet count at baseline might be key parameters to consider if one wants to identify sub-populations of patients exhibiting differing CDP791 PK behaviors.
This TMDD model could be adapted to other Mabs that also present non-linear PK. Appropriate covariate analysis could also be adapted based on the characteristics of the Mab in question.

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Helene Karcher Harnessing clinical knowledge on ligand-targeting drug to develop a new compound targeting the associated receptor : an example of model-based biologics design in pre-clinical development

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Objectives: The modeling work aims at supporting the design of a new biologics compound (B) against a new cellular-receptor target (R). The model predicts the affinity (Kd), half-life (t1/2) and mechanism of action (non-competitive vs. competitive) that B should have to achieve similar or better human efficacy than the known, marketed drug (D) that binds the ligand (L) associated to the new target R. The efficacious dose, half-life and affinity of the ligand-binding drug (D) are known.

Methods: A 2-compartment PK/PD model was developed to predict the amounts of compound B (or drug D), ligand L, receptors R, and bound species as a function of time following an injection in a human. We assumed bi-directional distribution of B between plasma and interstitium via passive exchange across the vascular endothelium. In addition, we included convective transport of B (or D), and L from the interstitium to the plasma via lymph flow. Clearance from the plasma compartment was varied to yield a half-life for B between 3 and 14 days. We also included molecular binding as follows: B + R -> complex (or D + L -> complex for the marketed drug) and L + R -> complex2, as well as receptor turnover in the 2 compartments. B was considered efficacious when it achieved at steady-state the same receptor occupancy as D acting at its known clinical efficacy. The model was formulated as a system of ordinary differential equations and solved with MATLAB (v.7.4, The Mathworks, Natick, MA).

Results: The mechanism of action that led to the best efficacy was the non-competitive binding mechanism given the desired dose, affinity, half-life and disease conditions. A half-life > 7 days and affinity Kd < 2.5nM for B were predicted to yield greater receptor occupancy than D acting at its clinical efficacy.

Conclusions: Knowledge of dose yielding to clinical efficacy for a marketed ligand-targeting drug was used to deduce associated receptor occupancy using a PKPD model that included ligand and receptor binding, and receptor turnover. The information was used to deduce necessary characteristics (half-life, affinity, mechanism of action) to achieve human efficacy for a new compound targeting the receptor associated to the ligand.

Wojciech Krzyzanski Receptor Mediated Disposition PK/PD Model of Filgrastim in Healthy Adults following Intravenous and Subcutaneous Administrations.

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Objectives: To develop a mechanism based pharmacokinetic (PK) and pharmacodynamic (PD) model of human granulocyte-colony stimulating factor (G-CSF), that would account for the change in the filgrastim clearance upon multiple dosing due to an increase of the G-CSF receptor mediated endocytosis.

Methods: The data consisted of filgrastim (Neupogen®) plasma concentrations and absolute neutrophil counts (ANC) which were obtained from clinical studies in healthy volunteers. Three subcutaneous (SC) doses of 2.5 μg/kg (n = 14), 5 μg/kg (n = 14) and 10 μg/kg (n = 19) μg/kg and one intravenous (IV) infusion (n = 12) of 5 μg/kg over 0.5 h were studied. The PK model included first-order elimination from plasma, receptor binding, and internalization of drug receptors complexes. The PD model consisted of a series of transit compartments that represented the aging populations of neutrophil precursors in the bone marrow pool, a neutrophil blood compartment, and a marginal pool. The serum filgrastim concentration stimulated the differentiation and maturation of the precursor cells as well as the neutrophil mobilization from the bone marrow, and the marginalization. All effects were described by the stimulatory Hill functions with a common SC_{50} and process specific S_{max} parameters. A feedback process from ANC controlling the total G-CSF receptor pool was included. Population nonlinear mixed-effect modeling was done using NONMEM VI. The first-order conditional estimation with interaction (FOCE) method was used. The confidence intervals of population parameter estimates were determine by a non-parametric bootstrap procedure.

Results: The estimate of the filgrastim volume of distribution (V_D) was 3.4 L. The typical value of the linear elimination rate constant (k_{el}) was 0.3 1/h whereas the internalization rate constant was 0.8 1/h. The equilibrium dissociation constant (K_D) was estimated as 1.7 ng/mL (94.4 pM), and the filgrastim bioavailability was 78 %. The typical value of the SC_{50} was 13.3 ng/mL, and the estimates of the S_{max} values corresponding to the filgrastim mobilizing effect was 30.0. The PD model also predicted a strong effect of filgrastim on the acceleration of the differentiation and maturation of the neutrophil precursors in the bone marrow. The inter-individual variability was determined for the neutrophil baseline counts, k_{el}, and V_D.

Conclusions: The presented model expanded previously published TMDD PK model for filgrastim. The increase in filgrastim clearance upon multiple dosing was attributed to the increased in ANC paralleled by an increase in the total G-CSF receptor density. Simultaneous modeling of filgrastim plasma concentrations and ANC was necessary to adequately describe PK data.

Brigitte Lacroix Comparison between the Exposure-Response Modeling of the ACR20 and ACR50 Scores in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol.

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Objectives: To describe the effect of exposure to certolizumab pegol (CZP) on the ACR20 [1] and ACR50 (American College of Rheumatology 20% and 50% improvement criteria) in rheumatoid arthritis (RA), by developing pharmacodynamic Markov mixed-effects models, and to compare the outcomes from the two models.

Methods: Exposure response analysis of ACR20 and ACR50 data was undertaken as representative measures of response and remission respectively. Data from 1747 patients treated with CZP and 633 patients treated with placebo were used for non-linear mixed effects modeling using NONMEM VI. Placebo or CZP at doses ranging from 50 to 800 mg was administered subcutaneously every 2 or 4 weeks (Q2W/Q4W), with or without concomitant administration of methotrexate, for 8 to 48 weeks. At each visit, the ACR (20 or 50) outcomes (responder/non-responder) and drop out events were coded in 3 categories. The probabilities of the transitions between these 3 different states were modeled using logit functions and described as function of CZP exposure, disease- and patient-related factors. The models were used to predict the clinical outcome following various treatment regimens in a variety of patient sub-populations.

Results: For both the ACR20 and ACR50 outcomes, the Markov model accurately described the response and dropout events. The best models combined E_{max} functions on the logit scale to describe the increase in the probability of becoming a responder and the decrease in the probability of becoming a non-responder as a function of the average plasma concentration between successive doses (C_{avg}). The population value of EC_{50} was similar for both outcomes (17 and 12 µg/mL, respectively). Simulations from the final models predicted similar response probabilities for the 200 mg Q2W and 400 mg Q4W dosing schedules (response rates of 0.71 vs. 0.69 for ACR20 and 0.40 vs 0.39 for ACR50, at week 22). Loading doses of 400 mg at weeks 0, 2 and 4 were predicted to result in a faster onset of response, with a maximum effect observed at week 8 (median response rate increased by about 10%).

Conclusions: Significant exposure-response relationships for CZP were demonstrated for both the ACR20 and ACR50 outcomes. The exposure-response model supports the proposed dosing regimen of 400 mg at weeks 0, 2 and 4 followed by 200 mg Q2W for CZP in RA. The model also supports 400 mg Q4W as an alternative dosing regimen. A future approach would be to model the two outcomes simultaneously as this would allow simulating consistent ACR20 and ACR50 response at a given visit for a given subject.

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[1] Lacroix. Exposure-Response Modeling of the ACR20 Score in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol. PAGE 17 (2008) Abstr 1318 [www.page-meeting.org/?abstract=1318]

Philip Lowe On the ability to predict free ligand suppression when free ligand assays are not available or impossible

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Objectives: Monoclonal antibodies are often used to capture soluble target ligands when excess expression causes disease symptoms. Ideally, as in the case of free IgE with omalizumab, one should measure the free ligand and correlate the suppression of this with clinical endpoints. However, in many instances, the free ligand is present at concentrations too low to be assayed directly. The objective of this analysis was to assess whether it is possible to predict the suppression of a free target soluble ligand using the drug and total (captured) ligand concentrations using a binding model.

Methods: Omalizumab pharmacokinetic, free and total IgE biomarker data were used in a one compartment binding model. The first clinical trial, the original purpose for which was bioquivalence was richly sampled and used data from 152 atopic but otherwise healthy volunteers. The second clinical trial used data from 440 severe atopic asthmatics, both omalizumab treated and placebo controls. The model parameters were estimated on either i) the PK, free and total IgE, or ii) just the PK and total IgE. In the latter case, the model was used to predict the suppressed concentrations of free IgE, then the predictions compared with the observed data.

Results: Both estimations converged successfully, with FO also completing the covariance step. The residual errors for the control model were 18% for omalizumab, 22% for total IgE and 21% for free IgE. For the test model, the residual errors were 17% for omalizumab and 20% for total IgE. The diagnostic plots were well centred with few outliers. There were only slight differences in the PK parameter values between the two models. For example, the estimate of clearance of omalizumab was 0.259 ± 0.00878 L/d per 70 kg for the control model, 0.259 ± 0.00798 L/d for the test. The volume of distribution was also comparable at 10.8 ± 0.341 L with the free IgE data, 10.5 ± 0.348 L without. For the PD, IgE production was estimated to be greater when using only the total IgE data, 1680 ± 121 µg/d versus 1180 ± 63.6, and the binding constant, 0.857 ± 0.0359 nM when using the free IgE data, was somewhat higher, 3.12 ± 0.754 nM, when the free IgE was ignored. Plots of the individuals' predictions for the test model compared with that including the free IgE data showed that there appeared to be a slight bias to overprediction of free IgE levels at the later timepoints during the washout phase, but peak suppression was very well predicted.

Conclusions: A mathematical model describing omalizumab binding to and thereby reducing levels of free IgE described the pharmacokinetics and the observed increase in total IgE. Through the use of the binding reaction and LeChatelier's Principle cast into a PKPD setting, it was demonstrated that it was possible to predict the suppression of free unbound IgE from omalizumab PK and total IgE.

Philip Lowe Omalizumab (Xolair) may normalise IgE production rate in patients with moderate-to-severe atopic asthma

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Objectives: Long-term anti-IgE therapy may attenuate the excess IgE expression observed in atopic individuals.

Methods: We investigated and quantified the timescale over which IgE production could be normalised using a direct binding model incorporating both dissociation constants and kinetic parameters for omalizumab, IgE and omalizumab-IgE complexes. This was written into a nonlinear mixed effect PK/PD model accounting for inter- and intra-patient variability. Input data were total serum omalizumab (sum of free and complex), free and total IgE from 1682 individuals with allergic asthma or rhinitis in four clinical studies of omalizumab. Two versions of the model were fitted: one with constant parameters; the other where IgE production rate could change over time. Normal IgE production was defined as 264 µg/day[1].

Results: Each model allowed relatively precise parameter estimation (maximum residual error, 25% coefficient of variation [CV]). The time-changing IgE production model gave a highly significant 2067-point decrease in log-likelihood objective function versus the constant IgE expression version. The estimated mean initial IgE production rate was 1840 µg/day (inter-patient CV, 29%). In control patients, IgE production appeared to increase slowly at an average rate of 2.4 ± 2.5% per year. IgE production rate decreased in omalizumab-treated patients and was projected to stabilise, ultimately, at 132 µg/day (168% CV). The apparent half-life of this change was approximately 1.5 years, providing a testable hypothesis that atopic patients may achieve normal IgE expression after 3-4 half-lives.

Conclusions: PK/PD models based on total and free IgE data suggest that, over the long term, omalizumab may be able to reduce IgE production towards normal (non-atopic) rates.

References:
[1] Waldmann TA, Lio A, Ogawa, M, et al J Immunol 1976; 117: 1139-44.

Philip Lowe Relationship between omalizumab pharmacokinetics and IgE pharmacodynamics in adult and pediatric patients with moderate to severe persistent allergic (IgE-mediated) asthma

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Objectives: To use a population-based PK-binding model that describes the binding and turnover of omalizumab and IgE to compare the kinetics of omalizumab and IgE in pediatric patients with adults.

Methods: Omalizumab, free IgE, and total IgE plasma concentrations were measured in patients from six clinical studies. Single dose data from a bioequivalence study were also included to confirm that the model captured the rapid suppression of free IgE and the return to baseline following treatment cessation.

These data were fitted to a dynamic drug-ligand binding and turnover model based on the omalizumab-IgE binding reaction; the model integrated drug and IgE inputs and elimination together with binding affinity. The model was written as differential equations in NONMEM. Typical values of the parameters and intersubject variability terms were estimated. Bodyweight and baseline IgE were included as covariates based upon prior work; other potential covariates such as age were explored graphically.

Results: The model fitted well both single-dose data from healthy but atopic volunteers and longer-term multiple-dose data from patients with severe persistent allergic asthma. All parameters were scaled to body weight; once weight was accounted for, the relationships between age and the posthoc estimated ETA values for the parameters did not show a notable trend.

For a typical subject weighing 70 kg and with a baseline IgE of 365 ng/mL, CL/F and V/F for omalizumab were 0.196±0.003 L/d and 8.07±0.192 L. The clearance of free IgE was 2.68±0.387 L/d and the clearance and volume of the omalizumab-IgE complex were 0.613 ± 0.0857 L/d and 2.13±0.42 L, respectively. The model estimated the production rate of IgE to be 857±122 µg/d and the binding affinity of omalizumab to IgE to be 1.84±0.071 nM.

A predictive check demonstrated that the model had the ability to predict both the central tendency and the distribution of exposure to omalizumab, the increase in total IgE, and the suppression of free IgE across the omalizumab bodyweight and baseline IgE based dosing table.

Conclusions: A population-based PK-binding model was fitted to free IgE, omalizumab and total IgE concentrations from six clinical studies. Both adult and pediatric data fitted well, and it was determined that once differences in bodyweight and baseline IgE are taken into account, pediatric allergic

asthmatic patients were not different from adults in terms of parameters of monoclonal antibody disposition and target binding.

Philip Lowe Pharmacokinetics of canakinumab and pharmacodynamics of IL-1β binding in patients with cryopyrin associated periodic fever syndromes

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Objectives: To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of a fully human anti-IL1β monoclonal antibody (canakinumab, ACZ885) in pediatric patients <18 years and to compare the PK and PD parameters with those of adults to determine the need for dosing adjustments.

Methods: A clinical efficacy study in patients with cryopyrin associated periodic fever syndrome (CAPS) in which canakinumab was administered intravenously or subcutaneously included 12 pediatric patients. PK and PD data from these studies were pooled with adult PK and PD data from canakinumab trials in other indications for a total of 233 subjects. Extensive characterization of the pharmacokinetics of canakinumab and pharmacodynamics of total IL-1β in serum was performed using PKPD modeling. A dynamic drug-ligand binding and target turnover model based on the relationship:

canakinumab + IL-1β ⇔ canakinumab-IL-1β complex

which integrates both monoclonal and IL-1β inputs and elimination (turnover) and binding affinity, was developed and parameter values estimated for both PK and PD using the NONMEM software.

Results: Estimates of drug clearance and volume of distribution were closely correlated with body weight; pediatric subjects, being smaller, had slower overall clearances and reduced volumes compared with adults, such that the half-lives were similar. The equilibrium dissociation constant for binding of canakinumab to IL-1β (Kd), was similar in adult and pediatric patients.

Conclusions: The linear dependence of canakinumab clearance with body weight justified weight normalized dosing in pediatric patients weighing less than or equal to 40 kg. The pharmacodynamics of canakinumab were comparable between adult and pediatric patients indicating no change in sensitivity with age or in factors that might compete for IL-1β binding.

Scott Marshall Population Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis of the Effect of Tanezumab on Overall Daily Pain Score Data in Adults with Moderate-to-Severe Pain due to Osteoarthritis of the Knee

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Objectives: The primary aim of this work was to characterize the exposure response (overall daily pain score, DPS) relationship across time for tanezumab a MAb for treatment of pain**.**

Methods: Four hundred and forty-four osteoarthritis patients were randomized to one of the following dose groups: 0, 10, 25, 50,100 and 200 mg/kg. Two doses of tanezumab or placebo were administered as a 10-min intravenous infusion 56 days apart. PK and DPS (VAS scale 0-100) data was collected for ~200 days. The PK/PD model was built according to the following steps: i) population PK model was developed, ii) individual PK parameter estimates were fixed during the PK/PD model development. The final PK/PD model was then used for simulations conducted to explore dose strategy and dose regimen.

Results: The PK of tanezumab was well described by a two-compartmental model. Body weight was found to be a significant covariate on clearance and volume but this only explained 4% of the in total 47% unexplained inter-subject variability [1].
In the PK/PD model it was assumed that the placebo and drug effects were proportional to the baseline. Placebo effect was well described by an exponential time-dependent model. The onset of placebo effect was relatively fast with an equilibrium half-life of 7.7 days (RSE 23%) after the first dose. The maximum placebo effect was estimated to be 25.2% (RSE 16%) of the baseline value.
An indirect response model was found to best characterize the delay between the response and the tanezumab concentrations. It was assumed that tanezumab inhibits the production of a pain stimulus (i.e. Nerve Growth Factor) measured by the DPS. The drug effect was characterized by an inhibitory E_{max} model, which was expressed as a maximal inhibiting effect (I_{max}) and the tanezumab concentration (IC_{50}) to achieve half of I_{max}. The I_{max} and IC_{50} were estimated to be 0.538 (RSE 9.4%) and 69.3 (RSE 48%) ng/ml, respectively.
The apparent transitory dose related attenuation of DPS approximately 14 days following the first dose was well captured by an empirical model expressed by a modified Gamma distribution function. It was assumed that the reduction of I_{max} is related to dose described by an E_{max} model.

Conclusions: The DPS data was adequately described by the proposed semi-mechanistic PK/PD model. Subsequent simulations using the PK/PD model supported moving forward in tanezumab Phase 3 in osteoarthritis patients with 8 week dosage regimen at fixed doses of 2.5, 5 and 10 mg.

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Etienne Pigeolet Artefactual inflation of pharmacokinetic difference between two Granulocyte Colony Stimulating Factor (G-CSF) drug products by non compartmental analysis.

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Objectives: Conventional bioequivalence analysis between Zarzio(r) and Neupogen(r) (two formulations of G-CSF) showed that their Cmax and AUC ratios were decreasing between single and repeated administration at 2.5 and 5 but not 10 ug/kg daily dose. The aim of the modeling analysis was to assess whether the drift in these ratios when doses are decreased or repeated could be explained by the mechanisms underlying the well known pharmacokinetic non-linearity for this drug.

Methods: Rich sampling pharmacokinetic and pharmacodynamic (blood neutrophil count) profiles of 112 healthy male and female volunteers were evaluated. G-CSF was administered as repeated s.c. daily administration for one week of 2.5, 5 and 10 ug/kg doses and single i.v. dose (5 ug/kg) in a cross-over design. A semi-mechanistic population PK/PD model was built from these data. From the parameter estimates and assuming a rapid equilibrium, the ratio of unbound drugs (what is measured by the assay) was computed for 10, 2.5 and a low dose of 1 ug/kg doses.

Results: The pharmacokinetic part was a one compartment binding model. The pharmacodynamic part of the model was described by bone marrow, blood and tissue compartments for neutrophils. The serum G-CSF concentration was stimulating the proliferation of neutrophils. The total number of neutrophils was driving the amount of receptors capturing the unbound drug in the binding model. The pharmacokinetic part only was fitted on the single administration data with very good diagnostic plots. The PK/PD model was fitted on the full dataset with reasonably good diagnostics although some bias could still be detected. The unbound amount of G-CSF was computed from the parameters of the PK only model except the receptor amount whose relative increase after repeated dose was simulated from the full PK/PD model. If there was between the 2 drug products a true 4% difference in the drug amount systemically available at all doses, the model based computed ratio of unbound drug amount was 0.961, 0,958 and 0,952 after a single dose and 0.955, 0.937 and 0.892 after 7 daily administrations of 10, 2.5 and 1 ug/kg respectively, indeed indicating a drift away from unity, when dose is decreased, especially after repeated administration.

Conclusions: The inflation of a small pharmacokinetic difference when doses are decreased or repeated is a plausible hypothesis for a drift of Cmax and AUC ratio away from unity when measured through the unbound G-CSF concentrations. As suggested by the model, this inflation is due to the non-linear receptor mediated drug disposition.

Maurice Ahsman Population Pharmacokinetics of Midazolam and Metabolites during Venoarterial Extracorporeal Membrane Oxygenation in Neonates

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Objectives: Midazolam is used to sedate neonates during extracorporeal membrane oxygenation (ECMO). During the procedure, midazolam pharmacokinetics are expected to change due to extracorporeal circulation and maturation. We present a population pharmacokinetic model for midazolam and major metabolites in neonates during venoarterial ECMO.

Methods: We included 20 patients on venoarterial ECMO, with a median postnatal age (range) of 0.79 (0.17-5.8) days and a body weight of 3.0 (2.7-3.9) kg at onset of ECMO. Median ECMO duration was 124 (70-275) h. Plasma concentrations (293 in total) were measured at introduction and discontinuation of midazolam infusion (100 - 300 mg/kg/h). Nonlinear mixed-effects modeling (NONMEM) was used to describe the pharmacokinetics of midazolam (MDZ), 1-hydroxymidazolam (OHM) and its glucuronide (HMG). A 2-compartment model for MDZ and 1-compartment for OHM and HMG were used to describe the data. PK parameters were allometrically scaled.

Results: Median MDZ volume of distribution in a median patient increased from 1.4 to 4.9 L/kg (98-343 L/70kg) within the first 8h. Median MDZ and OHM clearance increased 3-fold in the first 5 days, from 2.6 to 7.6 mL/kg/min and 9.3 to 29 mL/kg/min (4.9-15 and 18-56 L/h/70kg, respectively), whereas HMG clearance remained constant (1.0 mL/kg/min or 1.9 L/h/70kg). Postnatal age was positively correlated with clearance of OHM, but not MDZ or HMG. Interpatient variability estimates on clearances and volumes of distribution ranged from 87% to 129%. Concomitant catecholamines increased HMG clearance by 23%. HMG accumulated during ECMO whereas MDZ and OHM were effectively cleared; median HMG concentration after 7 days was 4500 ng/mL. Simulations in 1000 individuals show that a dose regimen of 0.50 mg/kg of midazolam followed by continuous infusion of 0.30 mg/kg/h for 6 h, and 0.15 mg/kg/h thereafter, provides adequate plasma concentrations (400 ng/mL MDZ) for sedation of ECMO-patients. The dose will have to be increased after approximately 5 days to compensate for increased clearance.

Conclusions: During ECMO, MDZ and OHM clearance increase. Collinearity complicates differentiation between changes caused by maturation, the extracorporeal circuit, or disease progression. A dose of 0.50 mg/kg followed by 0.30 mg/kg/h for 6 h, and 0.15 mg/kg/h thereafter, will lead to adequate sedation of ECMO-patients. Large unexplained interpatient variability warrants careful titration on sedation and side effects.

Roberto Bizzotto Multinomial logistic functions in Markov-chain models for modelling sleep architecture after placebo administration

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Objectives: The aim of this work was to generalize the previously proposed [1] mixed-effect Markov-chain model based on piecewise linear binary logistic functions through the implementation of multinomial logistic functions, in order to characterize the time course of transition probabilities between sleep stages in insomniac patients.

Methods: Polysomnography data were obtained from the first night of a placebo-controlled treatment of insomniac patients. Assuming that the time course of sleep stages (awake stage, stage 1, stage 2, slow-wave sleep and REM sleep) obeys to a Markov-chain model, a population approach was implemented with NONMEM VI. In particular, the relationship between time and individual transition probabilities between sleep stages was modeled through piecewise linear multinomial logistic functions. For example, assuming that ST1, ST2 and ST3 are three sleep stages, two multinomial logit functions can be defined as:

$g_{1T} = \log (Pr(ST2_T|ST3_{T-1}) / Pr(ST1_T|ST3_{T-1}))$,

$g_{2T} = \log (Pr(ST3_T|ST3_{T-1}) / Pr(ST1_T|ST3_{T-1}))$.

Using these equations and recalling that the sum of the three probabilities conditional on $ST3_{T-1}$ must be equal to one, the transition probabilities $Pr(ST1_T|ST3_{T-1})$, $Pr(ST2_T|ST3_{T-1})$, $Pr(ST3_T|ST3_{T-1})$ can be easily derived from the logits. The choice of the multinomial model was motivated by the following reasons: (1) to assure that the sum of all probabilities of transitions starting from a certain stage is equal to one; (2) to reduce the number of sub-models to be identified: from 20 sub-models using the binary-logit approach to 5 sub-models in the new approach (one for each sleep stage); (3) to estimate probabilities of all transitions at any time avoiding the need for a preliminary analysis aimed to identify zero-probability transitions. Performance was evaluated through visual inspection of model fitting on post-hocs and through posterior predictive check as suggested by Gelman et al. [2].

Results: The identification of the five sub-models produced a good adherence of mean post-hocs to the observed transition frequencies. Parameters were generally well estimated in terms of CV, shrinkage and distribution of empirical Bayes estimates around the typical values. The posterior predictive check showed good adherence of most of the simulated distributions of sleep macro parameters to the observed parameter values. A slight overestimation of the transition probabilities from the slow-wave sleep stage to other stages was found. This outcome may be explained by the small number of

occurrences of these transitions, although further work is needed to investigate the reason for this finding.

Conclusions: This work confirms the adequacy of mixed-effect Markov-chain models for describing sleep architecture of insomniac patients treated with placebo. Moreover, the use of multinomial logit functions in place of binary ones yields physiologically constrained parameters, reduces the influence of exploratory data analysis, and requires the identification of fewer sub-models.

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Marcus Björnsson A two-compartment effect site model describes the Bispectral Index Score (BIS) after administration of propofol

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Objectives: Different estimates of the rate constant for the effect-site distribution (k_{e0}) of propofol have been reported, depending on the rate and duration of administration [1,2]. This analysis aimed at finding a more general pharmacodynamic model that could be used when the rate of administration is changed during the treatment.

Methods: Twenty healthy volunteers were randomized to receive a 1-minute infusion of 2 mg/kg of propofol at one occasion, and a 1-minute infusion of 2 mg/kg of propofol (bolus) immediately followed by a 29-minute infusion of 12 mg/kg/hour of propofol (primed constant infusion) at another occasion, in a cross-over fashion. Arterial plasma concentrations of propofol were collected up to 4 hours after dosing, and Bispectral Index Score (BIS) was collected before start of infusion and until the subjects were regarded as no longer sedated after the anaesthesia. The population pharmacokinetic/pharmacodynamic (PK/PD) analysis was performed using NONMEM VI. Goodness of fit was assessed using objective function values, standard errors, graphics and visual predictive checks.

Results: A three-compartment model under-estimated the propofol concentrations during the constant infusion. An empirical model with time-dependent clearance parameters described the PK better for both regimens, and was used as an input to the PD model. An effect-compartment model could not accurately describe the delay in the effects of propofol for both treatments. When a two-compartment effect site model was used to describe the PD the predictions were significantly improved. The model included a central and a peripheral effect site compartment. The decrease in BIS was linked to the central effect site compartment concentrations through a sigmoidal E_{max} model. The rate constants from plasma compartment to effect site, and from central to peripheral effect site and back were approximately 0.2, 0.1 and 0.02 min^{-1}, respectively. Inter-individual variability in PD parameters was moderate.

Conclusions: The time-courses of BIS after both treatments were well described by a two-compartment effect-site model, possibly representing a distribution within the brain.

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Kristina Bondareva External Validation of the Population Models for Carbamazepine Pharmacokinetics and the Individualizing Carbamazepine Dosage Regimen Procedure

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Objectives: The objective of external validation is to examine whether the model can equally describe a new data set, which has not been used for model parameter estimation. The study is aimed at evaluating the predictability of the patient-specific Bayesian posterior PK models for carbamazepine (CBZ) monotherapy in the post-induction period.

Methods: The PK analysis was performed using the USC*PACK software based on the earlier developed linear one-compartment population PK models for CBZ and routine TDM data (peak – trough strategy). This study included epileptic patients for whom at least two pairs of measured serum levels related to different CBZ dosages were available. These data were not included in the population CBZ PK models. The first pair of each patient's serum levels on a specific dosage regimen was used to estimate the individual PK parameter values and to predict future serum levels according to the planned changes in CBZ regimen. Then the observed serum levels on the new CBZ regimen were compared with those predicted initially by the patient-specific Bayesian posterior PK model. The percentage prediction error was estimated as the difference between observed and predicted levels compared to observed level.

Results: TDM data of adult epileptic patients on chronic CBZ and CBZ-retard monotherapy were used to estimate predictability of the CBZ PK models separately (98 and 42 predictions, respectively). The Kolmogorov-Smirnov test demonstrated that the residuals had approximately normal distribution ($p=0.7$ and 0.5), the mean errors were not statistically significantly different from zero ($p=0.25$ and 0.18) (random errors). Bias of the predictions was not observed. The mean absolute errors (MAE) were 14.7±11.4% and 17.0±10.1%. A statistically significant bias and higher MAE were observed in predictions when patients were switched from CBZ to CBZ-retard (n= 42, p

Conclusions: The study demonstrated that predictions of future CBZ concentrations (for each dosage form) based on the population PK models, TDM data and a patient-specific Bayesian posterior parameter values provided clinically acceptable estimates.

Irina Bondareva Population Pharmacokinetics of Carbamazepine and Estimation of Influencing Factors

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Objectives: Carbamazepine (CBZ) is an effective anticonvulsant for partial and generalized seizures in both adults and children. Because of a considerable interindividual variability of CBZ PK and PD, many investigators have recommended individualizing CBZ dosage regimens based on TDM for better seizure control. This study aimed at developing PK models for post-induction CBZ behaviour in children, adults and elderly patients as well as at estimating the influence of dosage form on CBZ PK and drug – drug interactions for combined therapy with CBZ plus another "old" AEDs.

Methods: The population PK analysis was performed using the USC*PACK software (the NPEM program) based on a linear one-compartment model and routinely collected CBZ TDM data (peak – trough strategy). The influence of age and dosage form (CBZ versus CBZ-retard) on CBZ PK parameters was examined. After internal and external validation, the estimated population PK models for age subgroups, dosage forms and CBZ duotherapy were used for Bayesian adaptive control in clinical practice.

Results: TDM data of 237 epileptic patients on chronic CBZ monotherapy were used to develop CBZ PK models for adults (n=99), children (n=90) and elderly (n=48) separately. The PK models for CBZ controlled – release dosage form were based on data of 176 epileptic patients on chronic CBZ-retard monotherapy (adults, n=94; children, n=82). Two subpopulations of slow and fast CBZ metabolizers were discovered by the NPEM in adults. CBZ PK drug – drug interactions were estimated from data of 235 patients on chronic CBZ duotherapy (CBZ+VPA, n=75; CBZ+PHN, n=43; CBZ+PHB, n=117). A statistically significant difference in the mean Kel values for the age subgroups (p

Conclusions: The study demonstrated the need for TDM and individualizing of CBZ dosage regimens. A PK model based only on the population mean values even when adjusted for the known covariates cannot correct well for interindividual variability, but these models can be used to develop an initial dosage regimen as well as to make an individualized patient-specific model from sparse TDM data for Bayesian adaptive control in optimal epilepsy management.

Chao Chen Concentration-Response Modelling of Adjunctive Lamotrigine Extended-Release for Primary Generalised Tonic-Clonic Seizures

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Background: Lamotrigine (LTG) immediate-release (IR) is indicated for several seizure types, including partial seizures and PGTC seizures, in adult and paediatric patients. Efficacy and safety of an extended-release (XR) formulation as an adjunctive therapy for Primary Generalised Tonic-Clonic (PGTC) seizures was investigated in a placebo-controlled Phase III trial. Daily doses were escalated to the recommended maintenance levels for the IR, depending on the known nature of PK interaction with the background drugs. Sparse PK samples were collected throughout the trial; and seizure frequency was calculated for baseline and treatment periods.

Objectives: This was a retrospective analysis to explore PGTC seizure frequency as a function of LTG concentration following XR administration as an adjunctive therapy.

Methods: A previously developed population PK model, along with covariates body weight and PK interaction, was fitted to the trial data. Model parameters and steady-state average concentration for individual patients were estimated. Seizure frequency data were modelled as an Emax or linear function of the concentration, with an exponential error term. The model included baseline and placebo terms. Between-subject variability was explored for structure parameters. NONMEM version 5 was used for the analyses.

Results: The PK dataset included up to six samples per patient from 66 patients. Although absorption and distribution parameters could not be estimated with good precision, likely due to the flatness of the curve and sparseness of the data, individual concentrations were well estimated. Consistent with the dosing strategy, the spread of the estimated steady-state concentration was limited: 90% of the values were within a five-fold range. The data could not support an Emax model, which would be mechanistically and clinically meaningful. A small bias was observed, in the pattern that was expected when a linear function was forced through the data. Nonetheless, within the observed concentration range, the linear model described the data reasonably well for both placebo and active treatments.

Conclusion: These results suggest a potential for further therapeutic benefits at higher exposure in some patients. The analysis revealed certain limitations associated with retrospective analysis, thus raising the issue of cost-effective application of modelling approach and highlighting the importance of design-by-simulation.

Chantaratsamon Dansirikul Population pharmacokinetic analysis of pramipexole extended-release formulation in Parkinson's Disease (PD) patients

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Background and Objectives: A pramipexole extended release (ER) formulation administered once daily was developed to facilitate improved compliance compared to the immediate release (IR) formulation administered three times daily. A recently performed phase III study investigating the efficacy and safety of pramipexole ER in early PD patients included sparse pharmacokinetic (PK) sampling. Objectives of this analysis were to describe the PK and to investigate possible covariates for their influence on the PK of pramipexole in early PD patients, as well as to provide dosing recommendation for the use of pramipexole ER in renally impaired PD patients.

Methods: Concentration-time data from 146 early PD patients (699 plasma concentrations) who received pramipexole IR or ER formulation were available. Model development was based on Phase I data (1058 plasma concentrations, from 39 healthy volunteers). The developed base model was fitted to the phase III data and refined. Stepwise covariate analysis was performed. A dosage regimen for early PD patients with mild (creatinine clearance (CRCL) 50 to 80 mL/min) and moderate (CRCL 30 to 50 mL/min) renal impairment was defined using a simulation approach.

Results: Pramipexole plasma concentrations were best described by a two-compartment model with first order elimination. For the IR formulation, absorption was described by a first-order rate constant and a lag time. For the ER formulation, a sequential zero and first order absorption process was applied. The effect of CRCL on pramipexole apparent clearance (CL/F) and of body weight on apparent volume distribution of peripheral compartment (V3/F) for pramipexole ER were identified. The typical CL/F was 29.2 L/h when CRCL is greater than or equal to 121 mL/min. It was reduced by 0.74% for one unit smaller in CRCL. The typical V3/F for a 75 kg patient was 313 L, which changed by 2.26% for 1 kg change in body weight. Patients with mild renal impairment do not need any dose adaptation. Patients with moderate renal impairment should receive an initial dose of 0.375 mg (lowest dose) every second day for the first 7 days. In patients with moderate renal impairment, administration every second day provided a similar exposure to patients with mild to no renal impairment who received a once daily dose.

Conclusions: The PK model was successfully developed to describe the sparse data in early PD patients. CRCL was the clinically relevant covariate that leads to a dosing schedule adjustment for patients with moderate renal impairment.

Jeroen Diepstraten Population pharmacokinetics and pharmacodynamics of Propofol in morbidly obese patients

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Objectives: The number of morbidly obese patients (Body Mass Index (BMI) > 40 $kg.m^{-2}$) undergoing (weight-reducing) surgery increases. However, the dose of anesthetics is unknown because of the lack of evidence of the exact pharmacokinetics and -dynamics. We therefore developed a population PK-PD model of propofol used for anaesthesia in morbidly obese patients, thereby studying the influence of covariates.

Methods: In morbidly obese patients induction and maintenance of anesthesia was performed using propofol with use of the Bispectral index (BIS). Population PK-PD modelling was performed using NONMEM VI. A step-wise covariate analysis was performed for TBW, LBW, IBW, BMI, age, sex, creatinine, bilirubin, PEEP and remifentanil. The analysis was repeated with inclusion of non-obese patients [1, 2].

Results: In twenty morbidly obese patients (TBW 98-167 kg, BMI 38-60 kg.m-2) 517 propofol samples were collected. In the three-compartment model, TBW was the only significant covariate ($p< 0.001$). Its influence was best characterised using an allometric equation with an estimated exponential scaling factor of 0.72. In the final model, Cl was (2.29*(TBW/70)** 0.75)) and no other covariates proved to be significant for any of the parameters. When the non-obese data sets were added, similar pharmacokinetic parameters were obtained, including the estimated allometric function for clearance. Depth of sedation using the BIS could be described by an indirect sigmoid E_{max} model. Based on preliminary results, we anticipate that EC50 is higher compared to non obese patients (analysis still in progress).

Conclusions: In morbidly obese patients, propofol clearance is significantly affected by TBW in a 0.75 allometric function. The model can be used for extrapolation to patients outside the study population.

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Pinky Dua ADAS-Cog Placebo Modelling in Alzheimer's Disease

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Background: The cognitive portion of the Alzheimer Disease Assessment Scale (ADAS-Cog) is the standard cognitive endpoint for clinical trials of Alzheimer's disease (AD). It is scored by number of errors, ranging from 0 to 70 [1]. An increase in ADAS-Cog score implies worsening cognition. Several recent 6 month clinical trials of investigative medications for AD have failed to detect cognitive decline in the placebo groups by ADAS-Cog, potentially obscuring true treatment effects. The lack of cognitive decline in the placebo groups has renewed interest in a better understanding of the time course of placebo response.

Objective: The aim of this work is to investigate the ADAS-cog placebo model in AD to aid the design of future clinical trials by taking into account the information about which patients are more likely to be placebo responders.

Methods: Data from the placebo arms of 3 recent internal clinical trials including 307 subjects were pooled to investigate the placebo response as a function of time and disease severity given by Mini-Mental Status Exam (MMSE). Nonlinear Mixed Effects Modelling Approach was applied to this data using NONMEM V6. The following models were explored:

Model A: $ADAS_{ij} = ADAS0_j + K_j\, t_{ij} - A_j\, [\exp(-koff_j\, t_{ij}) - \exp(-k_j\, t_{ij})] + e_{ij}$ [2]

Model B: $ADAS_{ij} = ADAS0_j \times \exp(-k_j\, t_{ij}) + K_j\, t_{ij} + e_{ij}$ [3]

where *ADAS0* = baseline, K_j is the disease progression slope, A_j is the magnitude of placebo contribution, *koff* is the offset rate of placebo response and k_j is the rate of placebo response. For each parameter, between-subject variability was tested and covariate analysis was investigated. Results were assessed in terms of goodness of fit plots, Akaike Information Criterion and posterior predictive check. External validation was carried out using data from internal GSK studies.

Results: Numerical convergence problems were encountered with Model A, which failed to adequately describe the data with FOCE interaction. A theoretical analysis was carried out to explore the reasons of this failure. Structural Identifiability Analysis based upon Taylor's Series approach [4] showed that in presence of no or positive placebo response Model A parameters were not uniquely identifiable. To alleviate this problem, Model B was used. The covariate analysis was carried out using Model B. The addition of MMSE at baseline and on each parameter further improved the data fitting. The placebo response model was finally described as a function of time and of the disease severity at inclusion.

Conclusions: Model B adequately describes the data when a flat placebo response is observed. The advantage of model B is that ADAS-cog response based on the MMSE at baseline can be predicted and

thus maximize the possibility of detecting a clinical response by selecting the subjects who can deliver greater signs of drug activity.

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Bart Laurijssens Integrated analysis of Human PET data across multiple brain regions and receptors to make inferences from limited data.

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Objectives: To estimate the concentration - receptor occupancy relationship for the main target brain receptor (R1) for centrally acting drugs using human PET data. The data was limited in that for R1 maximal displacement was observed for all dose levels studied, and the extent displacement differed between two relevant brain regions.

Methods: Data consisted of 1 baseline scan + 2 scans at steady state for each subject 5 hrs after dosing. There were 8 subjects divided over 3 dose levels (10 fold range). For each scan, data was available for 3 brain regions and 2 target receptors (R1 and R2): frontal cortex (FCTX, R2), caudate (CDT,R1) and putamen (PTM, R1), as well at the average plasma concentration during the scan. A model integrating data in all brain regions and both receptors was fitted to the measured Volume of distribution (Vd) ratio (Vdt/Vdr, which is equal to the Binding Potential + 1). Several hypotheses for the difference in displacement between caudate and putamen were tested. Although the IC50 for R1 could not be estimated accurately (no data below maximal displacement), a likely upper limit could be determined using log-likelihood profiling.

Results: The plasma IC50s were estimated to be: R2 (FCTX) 69 ng/ml (95% CI: 55, 90), and R1 (CDT and PTM) < 2.6 ng/ml. The analysis also suggested about 29% unexplained non-specific binding in PTM.

Conclusions: The final integrated model allowed estimation of the concentration -receptor occupancy relationship for R2 (FCTX) (not the main objective), as well as the likely upper limit of the IC50 for our main receptor of interest. From this the minimal R1 occupancy for a given dose could be estimated. The results were consistent with previous results and predictions. The modelling also allowed identification of the most likely explanation of those tested, additional unexplained non-specific binding in PTM, for the discrepancy between CDT and PTM data.

Amelie Marsot External validation of pharmacokinetic population model of alfentanil in obese patients.

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Objectives: Alfentanil is a short-acting opioid commonly used in anesthesia with a target-controlled infusion (TCI). This method uses a model previously described in a population with a normal BMI [1]. An external validation was performed to check if this model was accurate in a population of obese patients.

Methods: Ten obese patients (weight: 99-145kg) undergoing laparoscopic gastroplasty and five normal weight patients undergoing surgery, aged 18 to 68 years were studied. Anesthesia was induced with propofol (2.5mg/kg) and TCI of alfentanil calculated with Stanpump software. The effect-site alfentanil target concentration was initially 100ng/l but was modified during surgery as a function of blood pressure and cardiac frequency. Blood samples were collected at 1 and 5 minutes after the start of infusion and at 0, 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 180, 220 and 300 minutes after the definitive stop of infusion. Blood alfentanil concentrations were determined with a gas chromatography method. Pharmacokinetic analysis was made by using a non linear mixed-effect population model. Data analysing included calculation of performance error (PE), median performance error (MDPE) and median absolute performance error (MDAPE).

Results: A three compartment model with two covariates [1]: age (clearance and K31) and sex (volume of distribution of the central compartment), gave the following results. MDPE (range) was 29.94% (-47.70 to 225.67%) during infusion and 39.84% (-98.68 to 350.4%) after infusion. MDAPE (range) was 34.88% (0.60 to 225.67%) during infusion and 25.09% (0.60 to 350.4%) after infusion. This pharmacokinetic model underestimated the predicted concentrations. Another model including two covariates with three compartments was proposed: age (K12) and weight (K13). MDPE (range) was -5.33% (-58.39 to 74.59%) during infusion and -10.75% (-81.53 to 263.20%) after infusion. And MDAPE (range) was 8.99% (0.65 to 74.59%) during infusion and 31.77% (0.02 to 263.20%) after infusion. This model significantly improved the prediction of the high concentrations (during infusion).

Conclusions: For alfentanil infusion in morbidly obese individuals, a pharmacokinetic model deriving from normal weight patients underestimated the predicted concentrations. The proposed model gave interesting results which could be used to predict more efficiently concentrations for obese patients.

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amir hooshang mohammadpour Population pharmacokinetics of carbamazepine in Iranian epileptic and manic patients

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Objectives: The aim of the present study was to develop a population pharmacokinetic model of carbamazepine from routine therapeutic drug monitoring data

Methods: Steady-state carbamazepine plasma concentrations in 126 epileptic and manic patients determined by HPLC method. Non-linear mixed effect method was used to construct population pharmacokinetic model of carbamazepine using WinNonMix software. After deriving the base model, influence of various covariates upon pharmacokinetic parameters of carbamazepine were assessed. Age, total body weight, sex, creatinine clearance, carbamazepine dosage, disease and concurrent medication were the fixed effects (covariates) tested simultaneously for their influence on the carbamazepine clearance in the regression model

Results:A one-compartment model was fitted to the data using nonlinear mixed effects modeling.In initial screening of covariate model, we found that carbamazepine clearance were significantly more in manic patients than in epileptic subjects (0.128 ± 0.016 L/kg/hr vs 0.112 ± 0.0147 L/kg/hr, P<0.001l). The only covariate which had significant influence on pharmacokinetics of carbamazepine in this population was the type of disorder; finally, this covariate entered in final model according to the following equation. CI = 0.099 [1+ (0.149 ± Disease)].The corresponding interindividual variability in clearance was described by using an exponential' .model and the residual error (including intraindividual variability, model misspecification and assay error) was described by using a simple model. The w2 and s2 values in final model were 0.0147 and 0.02 respectively. The carbamazepine clearance value was 0.104 ± 0.001 L/kg/hr.

Conclusions: The model can be used for estimation of carbamazepine CL/F in individual patients in the postautoinduction phase and for selection of optimum dosing regimen in routine patient care.

MYM Peeters The pharmacodynamics of isoflurane in children using Bispectral index and composite auditory evoked potentials

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Objectives: Bispectral index (BIS), derived from the electroencephalography (EEG), and the composite A-line autoregressive index (cAAI), derived from both the EEG and auditory evoked potentials, have been promoted as monitors of depth of anaesthesia. The aim of the study was to characterize the relationship between isoflurane end-tidal concentrations and its effect measured by BIS and cAAI in children.

Methods: Twenty children, aged 3-16 years, undergoing standardized isoflurane anaesthesia for cardiac catherization, were enrolled. Population pharmacodynamic modelling and covariate analysis was performed using NONMEM VI.

Results: The relationship between end-tidal isoflurane concentration and its effect was best described by an indirect sigmoid E_{max} model for the BIS and a direct sigmoid E_{max} model for the cAAI. For BIS, the EC_{50} was higher (1.19% *versus* 0.34%) and the Hill coefficient lower (2.56 *versus* 12.2). The EC_{50} using the BIS as endpoint decreased linearly with age (-2LL decrease of 7.767). No covariates were found for the cAAI.

Conclusions: Compared to the BIS, the cAAI is more sensitive to isoflurane and is associated with an on-off response with lower time delay in response calculation, which is reflected by the lower EC_{50}, the steeper Hill coefficient and the direct model. Higher end-tidals isoflurane concentrations are needed in younger children, as age is a covariate using the BIS as an endpoint. At this stage there is little evidence to suggest superiority for cAAI over BIS.

Klas Petersson Could prolactin levels be a more informative predictor for clinical effect of D2-receptor antagonists than drug concentrations in the treatment of schizophrenia?

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Objectives: In a setting with many simultaneously ongoing processes and high variability like in schizophrenia a clear drug concentration-effect relationship can be hard to establish. Disease progression, placebo response, compliance and dropouts are issues important to consider but difficult to characterize. The clinical effects of antipsychotics are due to their antagonistic effects at the D_2-receptor, which also gives rise to side effects such as elevated prolactin levels. The objective of the present study was to use a model-based approach to investigate if increases in prolactin concentrations are better predictors of clinical response, measured using PANSS, than drug concentrations.

Methods: Data were from 1187 patients with acute schizophrenia, pooled across 3 phase III trials, who were treated with placebo or paliperidone for 6 weeks. The prolactin data was previously modeled with an agonist-antagonist interaction model in which a potency parameter for individual prolactin release after treatment was estimated [1]. PANSS data from the same patients were subjected to modeling in NONMEM VI using a bilinear placebo model where the shift between the two slopes was estimated by a sigmoid Emax function:
$shift=t^{\gamma}/(t^{\gamma}+break^{\gamma})$,
Panss=(1-shift)*(base1+slope1*t) + shift*(base2+slope2*t)
Individual potency parameters, predicted change in prolactin concentrations from baseline, and predicted drug concentrations were tested as predictors for clinical effect of paliperidone.

Results: In the placebo group, the typical early decrease in PANSS was 0.7 units/day and in the later phase PANSS increased by 0.17 units/day. The shift between the first and second phase occurred around day 10. γ was estimated to 1.8 which gives a smooth transition between the slopes. For paliperidone treated patients slope1 was correlated to the relative prolactin increase from the baseline model. For slope2, drug concentrations, treatment-no treatment effect, and the prolactin potency parameter gave similar fits to the data. The best predictors were prolactin elevation at the time of PANSS measurement or AUC of elevated prolactin during the preceding 24 hours.

Conclusions: The prolactin elevation of antipsychotic treatment was here shown to be a better predictor of clinical efficacy than drug concentration. This could be expected since prolactin elevations contain information both about the individual sensitivity to D2-antagonists and compliance.

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Monica Simeoni Prediction of remifentanil metabolic ratio using sparse data collected during non-steady-state infusion with rapidly changing rate

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Objectives: Remifentanil (R), an analgesic, is metabolised by non-organ dependent blood and tissue non specific esterases, and has a short plasma half-life of less than 10 minutes [1] [2]. It is metabolised to remifentanil acid (RA) which is eliminated via the kidney with a half-life of about 17 h [3]. Our objective was to estimate metabolic ratio (MR) from sparse data in a 10-day study with rapidly changing IV infusion rates which greatly varied among subjects.

Methods: The work was conducted in three steps:
1) The absence of the steady state condition implied that MR could not be calculated directly as RA/R but a modelling solution was necessary. Using historical data from a 3-day study, a previously presented model [3] was modified and extended into a mixed effect model to fit R and RA data simultaneously. Three and two compartment models were used for subjects with normal/mildly impaired renal function and subjects with moderate/severe renal impairment respectively, with creatinine clearance (CrCL) as a covariate. The new model was tested on the original dataset.
2) Given the between subject variability of the infusion profile, a novel VPC technique was introduced for the model validation: 300 simulations were performed for each subject, with its own infusion profile and CrCL, but typical parameter values.
3) Individual MR in the combined dataset was then estimated using the priors from the original dataset.

Results:
1) A model was successfully identified with good parameter precision and fitting of the data, assuming an exponential relationship between MR and CrCL.
2) The VPC showed that the model described the data well. Only 2 of the 40 estimated MR values fell outside the 5th to 95th percentile interval.
3) Results from the fitting of the spare and fully sampled datasets can be summarized as below. In subjects with normal or mildly impaired renal function the geometric mean of MR was 12, the 5th percentile was 1.9 and the 95th percentile was 71.9, while in subjects with moderate or severe renal impairment the geometric mean was 71, the 5th percentile was 19.7 and the 95th was 251.4.

Conclusion: A population parent/metabolite model was developed and validated with a new VPC technique, taking into account CrCL and input function. The model-based analysis indicated that the MR varied with the degree of renal impairment but not with the Remifentanil IV infusion rates.

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Nicolas Simon Population Kinetic Pharmacodynamic and Logistic Regression Analysis of Intravenous Morphine Titration in Immediate Postoperative Period

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Objectives: Intravenous morphine titration has currently become the gold standard for pain management. However, concerns over accurate morphine titration adapted to the patient's need persist. The goal of this study was to develop a population kinetic pharmacodynamic (K-PD) model describing the morphine-induced analgesia during i.v. morphine titration in the immediate postoperative period and to evaluate sedation occurrence according to morphine dose in this setting.

Methods: Data was collected from patients undergoing major orthopedic surgery, who received titrated i.v. morphine during the immediate postoperative period as boluses of 2 or 3 mg, every 5 min until analgesia was established. Pain was assessed using visual analogue scale (VAS) scores. Morphine analgesia – time data were analyzed using a non-linear mixed-effect model NONMEM (version VI). Sedation was assessed by the Ramsay score with scores > 2 representing clinically significant sedation. The relationship between sedation occurrence and morphine dose was modeled using logistic regression.

Results: 1289 pain assessments from 228 patients were available for population modeling. The time course of the morphine-induced analgesia was best described by an indirect response model with an inhibitory function affecting pain onset (Kin) (1). Since model development depended solely on the assessed PD data where no PK data are available, a (K-PD) approach was employed (2), and the elimination half-life for morphine ($t_{½}$) was fixed at 180 min (3). Mean PD parameters estimations were as follow: pain baseline (BASE) = 67 mm, morphine dose that produces 50% of the maximum analgesia (ED50) = 10.2 mg, first-order rate constant for the dissipation of pain (Kout) = 0.26 min-1 and sigmoidicity parameter (γ) = 1.9. The effects of (i) the delay between extubation and titration DEL, (ii) the intra-operative NSAIDs, and (iii) the initial VASi were significant on ED50. Logistic regression showed that a morphine dose of 20 mg was associated with a high likelihood of sedation occurrence.

Conclusions: The (K-PD) model developed supported the possibility of accurately modeling the time course of a complex response in the absence of PK data. The current data should lead to a more rational management of the immediate postoperative pain.

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Pyry Välitalo CSF and Plasma Pharmacokinetics of Flurbiprofen in Children

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Objectives: There has recently been interest in mechanism of action of NSAIDs in CNS. We have evaluated the CNS penetration of flurbiprofen in children undergoing lower body surgery in spinal anaesthesia. We also estimated the pharmacokinetics of flurbiprofen in children aged 3 months to 13 years, and estimated the absolute bioavailability of flurbiprofen in children. Previously, there has been only one study of flurbiprofen pharmacokinetics in children aged 6-12 years and no absolute bioavailability was estimated in that study [1].

Methods: 64 children aged 3 months to 13 years were enrolled in the study. 27 of the children received intravenous dose of flurbiprofen axetil corresponding to circa 0.65 mg/kg of flurbiprofen. 37 of the children received 1 mg/kg of oral flurbiprofen syrup. 304 total plasma concentrations, 62 unbound plasma concentrations and 60 total CSF concentrations were analyzed and included in the data. Modeling was performed with NONMEM VI 2.0. For flurbiprofen distribution into CSF, an intercompartmental clearance QCSF was estimated. The volume of CSF reported in literature was used as Vd(CSF). The rate constant of flurbiprofen transfer from central compartment V(central) to CSF was calculated as QCSF/V(central), multiplied by fraction unbound in plasma and multiplied by "uptake factor".

Results: In raw data, flurbiprofen concentrations in CSF were about sevenfold compared to unbound flurbiprofen in plasma. Hence, the "uptake factor" estimated for CSF kinetics was 6.8 (+-0.070 RSE). The fraction unbound of flurbiprofen in plasma was 0.0314% (+- 0.043 RSE). The oral bioavailability of flurbiprofen was 0.8 and CYP maturation did not seem to affect elimination rate of flurbiprofen in infants. Weight alone was an adequate covariate for clearance.

Conclusions: Flurbiprofen enters CSF readily. The reason for flurbiprofen concentrations in CSF being higher than free lurbiprofen in plasma is likely a result of protein binding or active uptake. Typically, lipophilic drugs with extensive protein binding have CSF concentrations higher than unbound plasma concentrations [2].

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Katarina Vucicevic Effect of Valproic Acid Daily Dose on its Clearance in Adult Patients with Epilepsy – Population analysis of TDM data

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Objectives: The aim of the study was to investigate the influence of valproic acid (VPA) daily dose on its oral clearance (CL/F) using therapeutic drug monitoring (TDM) data in adult patients with epilepsy.

Methods: A total of 200 measured total (bound + free) VPA concentrations were obtained from 129 adult patients. VPA was administered 1-3 times per day in the form of film tablets containing 333 mg of sodium VPA and 145 mg of VPA (Eftil® retard 500, Hemofarm, Serbia) either as monotherapy or in combination with other antiepileptic drugs. Nonlinear mixed effects modeling was applied for the pharmacokinetic (PK) analysis using NONMEM software (Version 6 level 2, GloboMax LLC, Ellicott City, MD, USA) and Perl speaks NONMEM (Version 2.3.0, http://psn.sourceforge.net). A one-compartment model with first-order absorption and first-order elimination as implemented in ADVAN2/TRANS2 PREDPP subroutine was used to fit the concentration-time data. Based on literature data volume of distribution and absorption rate constants were fixed at 0.14 L/kg and 0.67 h-1, respectively. Validation of the final model was performed.

Results: An average daily dose of VPA in the model building set was 1107.75 ± 412.05 mg/day, while in model validation set 1031.25 ± 306.74 mg/day. Interindividual variability of VPA CL/F was best described by the exponential error model, while a combination error model most adequately characterized residual variability in VPA concentrations. In the first step inclusion of VPA daily dose (DVPA) greater than 1000 mg/day into the base model, resulted in the highest decrease in objective function value (OFV) of 16.809 ($p < 0.0001$) and reduced interindividual variability. Estimates generated by NONMEM indicated that if VPA daily dose is greater than 1000mg/day, VPA CL/F increase by 43%. Interindividual variability of VPA CL/F (95% CI) was 31.9% (22.4 – 37.9%), while residual variability was 23.8% (15.4 – 32.4%) for the proportional and 13.2 mg/l (3.17 – 18.8 mg/L) for the additive component. Model validation indicated little bias, good precision and acceptable predictive performance.

Conclusions: In the present study, CL/F was found to increase significantly with DVPA greater than 1000 mg/day in a step-like manner. The relationship between DVPA and CL/F may be associated with the so-called TDM-effect. This implies the use of higher doses of VPA in patients with higher elimination rates, or in patients who are insensitive to lower VPA doses.

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Jonathan Wagg Estimation of cortical amyloid beta turnover rates

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Objectives: To estimate the turnover rate of cortical amyloid beta (Aβ) in a non-transgenic preclinical mouse model and to compare this rate with literature derived estimates for both other preclinical animal models and human subjects.

Methods: Preclinical data from a non-transgenic mouse model of efficacy was used to develop a pharmacokinetic-pharmacodynamic model to describe the relationship between plasma and brain concentrations of a new chemical entity (NCE) and cortical Aβ levels. The linked PD model consisted of a semi-physiological Aβ turnover model which was used to provide an indirect estimate of Aβ turnover rates. The animal level data consisted of plasma and brain NCE levels and cortical Aβ levels. Each animal received a single oral NCE dose and administered doses spanned a 30-fold range of dose distributed across 5 distinct dosing groups. Animals were sacrificed at 0.25, 1, 3, 6, 10, 14 and 24 hours post dose with 5 animals per time point per dose group. A limited review of the scientific literature was completed and comparable Aβ turnover rates estimated for other preclinical animal species and human subjects. Data analysis and graphical displays were performed with S-PLUS, while model building was performed with NONMEM.

Results: Robust NCE plasma and brain exposures were observed across all dose groups, leading to significant reduction of cortical Aß. Plasma and brain concentrations of the NCE were well described by a three-compartment PK model with plasma levels represented by the central compartment and the blood-brain barrier represented by the first peripheral compartment in series with the brain levels represented by a second peripheral compartment. The PD model consisted of a semi-physiological Aβ turnover model. Saturating NCE doses were used to estimate the Aβ turnover rate in the FB mouse at 1.27 hr-1 ($t_{½}$ = 33 minutes). This estimated rate was consistent with the literature derived value of 38 minutes (Barten et al, 2005). When allometrically scaled to humans, the estimated Aß turnover rate (0.17 hr-1) was reasonably close to the recently estimated CSF Aβ turnover rate in healthy volunteers of 0.085 hr-1 (Bateman et al, 2006).

Conclusions: Aβ turnover rates in the FB mouse model were estimated at 1.27 hr-1. This rate is consistent with that reported in another mouse model. When allometrically scaled to humans, this rate was approximately twice the rate recently estimated for cerebrospinal fluid Aβ turnover in healthy human subjects.

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Ekaterina Gibiansky Population Pharmacokinetics of Eltrombopag in Healthy Subjects and Patients with Chronic Idiopathic Thrombocytopenic Purpura

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Objectives: Eltrombopag is an orally bioavailable small molecule agonist of thrombopoietin receptor (TPO-R) that has been recently approved for treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP). The aim of this analysis was to develop a population pharmacokinetic (PK) model of eltrombopag, predict steady-state exposure at therapeutic doses, and identify and quantify main demographic/covariate factors influencing eltrombopag exposure.

Methods: 111 subjects from 3 Phase 1 studies (dense data) and 88 patients from a Phase 2/3 study (sparse data) contributed 4093 plasma eltrombopag concentrations. Dosing in the studies ranged from 5 to 200 mg QD as a single dose, or as multiple doses administered for 5 days to 6 weeks duration. The analysis was performed using a mixed-effects modeling approach with the first-order conditional method (FOCEI) of NONMEM. The full model approach was implemented for covariate modeling, followed by elimination of insignificant or poorly estimated covariates. Visual predictive check and non-parametric bootstrap stratified by major covariates were implemented for model evaluation. Estimates of individual eltrombopag steady-state exposure were obtained by simulations and summarized for subpopulations identified by the model.

Results: PK of eltrombopag was described by a 2-compartment linear model with dual sequential first-order absorption, absorption lag-time, and inter-occasion variability in absorption. Mean (95% CI) parameters of a typical 70 kg Caucasian male ITP patient not taking corticosteroids were estimated as CL/F=0.668 (0.561, 0.775) L/hr, Vc/F=8.76 (8.14, 9.38) L, Vp/F=11.3 (10.1, 12.5) L, and Q/F=0.399 (0.361, 0.437) L/hr. Inter-individual variability was 40.6%, and 37.4% in CL/F and V/F, respectively, with correlation of R=0.743. Inter-occasion variability in Ka (CV=127%) was much higher than inter-individual variability, which was therefore dropped from the model. In the ITP patients that received 50 mg QD dosing, mean (95% CI for the mean) steady-state exposure was estimated as AUC_{τ}=108 µg*hr/mL (88, 134) and C_{max}=8.01 (6.73-9.53) µg/mL. Weight increased CL/F, Vc/F, Q/F, and Vp/F equally with a power coefficient of 0.62 ((0.45-0.78) for CL/F and Q/F, and (0.25-0.98) for Vc/F, and Vp/F). For the range of weights in the analysis (43 to 122 kg), CL/F, Vc/F, Q/F, and Vp/F increased with body weight from 26% lower to 41% higher values than for 70-kg individual. The mean (95%CI) CL/F was 33% (26%, 41%) lower in Asians compared to other races, 26% (7%, 45%) lower in patients taking corticosteroids concomitantly, 19% (7%, 31%) lower in females compared to males; and 17% (0, 34%) higher in healthy subjects compared to ITP patients. Age and mild renal impairment did not influence the eltrombopag PK.

Conclusions: The developed population pharmacokinetic model identified and quantified patient characteristics predictive of eltrombopag exposure, and enabled further analysis to characterize pharmacokinetic-pharmacodynamic relationships.

Anna-Karin Hamberg A longitudinal model describing the relationship between warfarin dose and INR response taking CYP2C9, VKORC1 and age into account

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Objectives: To reformulate and update a previous NONMEM model [1] for the relationship between warfarin dose and INR response.

Methods: The analysis was performed in two steps. In the first step, the effect of *CYP2C9* genotype and age on S-warfarin clearance was estimated from high quality single dose PK data from 57 patients included in a previous study [1]. In the second step, a K-PD model was developed based on warfarin dose, INR response, age, *CYP2C9* and *VKORC1* genotypes from the 57 patients and a subset of 139 patients from the Swedish WARG study enriched for rare genotypes [2]. The contribution of each *CYP2C9* *1, *2 and *3 allele and *VKORC1* rs9923231 (-1639 G>A) allele was estimated separately and combined to yield genotype effects. The variability in clearance due to *CYP2C9* genotype and age was included as a covariate in the K-PD model as described by Jacqmin *et al* [3]. The remaining 1287 WARG patients were used for internal model validation.

Results: The final K-PD model accounted for the delay between exposure and INR response through two parallel transit compartment chains with 3 and 2 compartments each. The model described the data well, and passed internal validation tests. The EC_{50} parameter was related to the *VKORC1* genotype. The effect of variant *CYP2C9* genotypes on warfarin dose requirements was in good agreement with published data from a meta-analysis of thirty-nine studies with a total of 7907 patients [4].

Conclusions: The reformulated K-PD model reduces the need for PK data and enables robust assessment of INR response and dose predictions even in individuals with rare genotype combinations.

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Siobhan Hayes Population PK/PD Modeling of Eltrombopag in ITP Patients and Optimization of Response-Guided Dosing

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Background: Eltrombopag is the first oral, small molecule, non-peptide thrombopoietin receptor (TPO-R) agonist. It has been shown to induce differentiation of normal marrow progenitors and to increase platelet counts in pre-clinical and clinical studies[1, 2]. Eltrombopag is being developed for medical disorders associated with thrombocytopenia, and has been recently approved in the United States for treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP). The population pharmacokinetics of eltrombopag in ITP patients has been described previously (PAGE 18 (2009) Abstr 1502 [www.page-meeting.org/?abstract=1502]). The model identified weight, Asian race, concomitant use of corticosteroids, and gender as predictors of eltrombopag exposure.

Objectives: The population pharmacokinetic/pharmacodynamic (PK/PD) analysis was performed to 1) characterize the relationship between plasma eltrombopag concentrations and platelet counts (PLTC) in patients with ITP, and 2) estimate PLTC response for different dosing regimens, subpopulations, and dose adjustment schemes guided by PLTC response (target PLTC >50 and <200 Gi/L).

Methods: Eighty eight patients who received 30, 50 or 75 mg of eltrombopag once-daily (QD) for 6 weeks and 67 patients who received placebo contributed 627 and 590 platelet measurements, respectively. A life-span[3] PK/PD model composed of a precursor production compartment, maturation compartments, and a blood platelet compartment was implemented in NONMEM. Individual plasma eltrombopag concentrations, computed from the population PK model, increased the production rate of platelet precursors. A mixture model was introduced to account for non-responders. Demographics, use of corticosteroids, prior use of ITP medications, splenectomy, and thrombopoietin concentration were explored as potential covariates. A posterior predictive check was used to evaluate the model. Extensive simulations were performed to understand the impact of age, gender, race, baseline PLTC, corticosteroid use, and responder vs. non-responder following 10 weeks of QD dosing of 50 mg eltrombopag. Additional simulations were carried out to determine the impact of dose reductions to 25 mg QD/25 mg QOD/12.5 mg QD if PLTC >200 Gi/L or dose increases to 75 mg QD if PLTC <50 Gi/L following at least 2 weeks of dosing.

Results: The final model consisted of 7 compartments (3 PK, 1 precursor, 2 maturation, and 1 circulation). The zero-order production rate (KIN) and the first-order maturation rate of platelet precursors (KT) were fixed to the values previously estimated in healthy subjects (KIN=1.43 Gi/L/hr, KT=0.0253 hr^{-1}, CV_{KT}=75.7%). The first-order platelet degradation rate (KDEG) was inversely proportional to baseline PLTC. In responders (estimated as 81% of patients), KIN increased linearly with eltrombopag concentration (SLOP=0.579 mL/mg, CV=89.7%). Eltrombopag did not increase platelet production (SLOP=0) in non-responders. Females and older patients were more sensitive to

eltrombopag, with higher SLOP estimates compared to males (2.42-fold, 95%CI=1.15-3.69) and younger patients (power coefficient 1.27, 95%CI=0.525-2.01 for AGE/50).

Simulations of PLTC over time following different dosing regimens predicted higher PLTC for the following subpopulations (in descending order): Asian race, age ³65 years, baseline PLTC >15 Gi/L, female, and concurrent corticosteroid use due to either higher eltrombopag exposure or greater PD response. Simulations supported 50 mg QD as an appropriate starting regimen, with biweekly individual dose adjustment to titrate each patient's dose until a target platelet response is achieved. Following dose decrease (to 25 mg QD), PLTC of 60% of patients who exceeded the upper target level (PLTC > 200 Gi/L) were predicted to decrease to below that level. Following dose increase (to 75 mg QD), 29% of patients who did not respond initially (PLTC < 50 Gi/L) were predicted to respond.

Conclusions: The developed PK/PD model was prospectively predictive of platelet response in different subpopulations and of the impact of dose adjustment on PLTC. Simulations based on the model identified dose adjustment regimens that minimized the risk of high PLTC and maximized the patient's chance to respond to treatment.

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Toshihiro Wajima A comprehensive model for the coagulation network in humans

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Introduction: Coagulation is an important process in haemostasis. Experimental tests of clotting are difficult to conduct and interpret, because (a) haemostasis is a complex series of interactions including positive feedforward, negative feedforward, positive feedback and negative feedback processes and (b) the reaction rates range are a wide time frame of seconds to days. A mathematical representation of the system therefore serves as a direct source from which cause-effect relationships can be assessed as well as providing quantitative information.

Objectives: To develop a mechanistic quantitative model for the comprehensive humoral coagulation network.

Methods: A full mathematical derivation of a multi-compartmental model for the coagulation network was developed based on individual mechanistic components described in the literature. The model consists of a series of 51 ordinary differential equations. The model includes components for describing the time-courses of coagulation factors by extrinsic and intrinsic pathway activation, as well as the *in vitro* coagulation tests of prothrombin time (PT, often reported as international normalized ratio [INR]) and activated partial thromboplastin time (aPTT). The model also includes the components related to vitamin K cycle and antithrombin-III:heparin complex for simulating the profiles for drug therapies of warfarin, heparins and vitamin K. The model was applied for simulation of INR (PT) and aPTT tests for the data from the literature [1] and for simulating time-courses of coagulation factors after envenomation by the taipan snake bite. [2]

Results: The model accurately describes the time courses of coagulation factors following *in vivo* activation (snake bite data) as well as of *in vitro* blood coagulation tests of PT and aPTT. The model predicts the concentration-time and time-effect profiles for warfarin, heparins and vitamin K in humans as well as the effects of various haemophilias.

Conclusions: The model developed in this study is the first comprehensive description of the *in vivo* coagulation network and the time course of changes in the clotting factors. The model was effective at describing the time courses of effects of anticoagulants (warfarin and heparins). The model would be useful for clinical situations and for drug development.

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Anne Chain Not-In-Trial Simulation: Predicting cardiovascular risk from clinical trial data

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Objectives: The objective of this study is to better translate clinical findings to real life situations and resolve the discrepancies in pre- vs. post-market estimates of cardiovascular risk associated with QTc interval prolongation. Based on clinical trial simulation scenarios we demonstrate how to assess risk of not-in-trial patients, i.e., those ineligible due to inclusion/exclusion criteria.

Methods: In contrast to the long-established assumptions for the assessment of QTc interval prolongation (i.e., QTc = baseline + circadian rhythm + drug effect), a new mechanism-based tool is developed using the approach QTc (real life population) = current clinical model + effects of concomitant medications + effects of co-morbidity conditions. d,l-sotalol is used as a paradigm compound to assess the effects of co-medications and co-morbidities in the Rotterdam Study cohort as reference population. The additional effects are evaluated by calculating the absolute differences in QTc prolongation between taking d,l-sotalol alone and in conjunction with co-medications and comorbidities. Then the final distribution of QTc values associated with all causal factors is simulated and compared non-parametrically with the observed QTc distribution.

Results: Using the well established clinical model, simulations of the drug effect on the reference cohort showed that it is insufficient to describe the high observed QTc values. However, calculations of the absolute differences in QTc prolongation between taking d,l-sotalol alone and in conjunction with co-medications and comorbidities revealed that the additional causal factors provide additive effects. Final risk assessment is achieved by combining all the causal factors in a single simulation where the distribution of the observed QTc values is confirmed to fall within the simulated distribution.

Conclusions: QT-prolongation has become the second most common cause for post-market drug withdrawal. This situation strongly suggests that the current approach to clinical evaluation of cardiovascular risk continues to lack the predictive power required to translate findings in a clinical setting to real life situations. Our work combines all relevant causal factors that affect QTc prolongation in an integrated PKPD model, thereby enabling better estimation of the true risk-benefit ratio and possibly mitigating future drug-withdrawal due to cardiovascular safety.

Stefanie Hennig Characterizing time to conversion to sinus rhythm under digoxin and placebo in acute atrial fibrillation

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Objectives: The underlying trial was a randomized, double-blind comparison of intravenously administered digoxin and placebo in patients with acute atrial fibrillation. The primary end point was conversion to sinus rhythm within 16 h after randomization, while effect on heart rate (HR) was a secondary end point. Sparse plasma samples and 5 HR measurements were taken. The primary publication [1] concluded: "There was no clear correlation between serum concentration of digoxin and changes in ECG or HR". A later analysis [2] reported on the population PK of digoxin and a HR model. The aim now was to evaluate if any predictor of conversion to sinus rhythm can be found using a Time-to-event (TTE) analysis.

Methods: Data from the studies were analyzed using the Laplace method in NONMEM VI. The F_Flag functionality was used to simultaneously predict the continuous data (PK and HR observations) and estimate probabilities for the categorical data. Since the PK and HR analyses were performed previously, PPP&D[3] was used for the combined PKPD and TTE analysis. The final model was also rerun fitting the HR and the conversion data simultaneously. The assessment of statistical significance of additional parameters was based on the difference between the OFV at 5% significance. The predicted performance of the TTE analysis was assessed using Kaplan-Meier VPC graphics.

Results: The main influence on having conversion was ‘time' followed by ‘age' and ‘sex'. Time was included as exponential, step or spline functions. The final model included time as a step function with an estimated break point at 4.2h. The chance of having a conversion declined exponentially with age. The hazard of having conversion was estimated to be $5.2\%.h^{-1}$ for the typical male (62 year) and $8.7\%.h^{-1}$ for the typical female (71 year). After 4.2 h the chance of having a conversion to sinus rhythm was reduced by 52% for males and 60% for females.
Even though HR decreases with time, including HR or the change of HR from baseline had no explanatory value in the presence of a time effect. Similarly, models including digoxin concentrations were not significant. The simultaneous fit of HR and TTE data provided very similar estimates to the PPP&D method.

Conclusions: The chance of having a conversion was higher for the first 4.2h. Overall, the model estimated a 30-40% higher chance for females to convert compared to males. No difference could be found between the digoxin and the placebo group.

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Carlos Hoyo-Vadillo Pharmacokinetic Model for Losartan Administered to Young Mexican Healthy Volunteers.

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Objectives: To evaluate the pharmacokinetics of Losartan (100 mg) in a Young Healthy Volunteers Mexican Population.

Methods: Eighty two healthy volunteers of both genders were enroled at Guadalajara City (Western of Mexico). Dose was 100 mg given at the morning after overnight fast. NONMEM VI was used on a laptop running Vista. Basic for Nonmem (presented last year at Page at Marseille) was used as an auxiliary tool. 296 runs were evalauted to look for combinations of exp(eta) and different initial values. ADVAN4 TRANS 3 was employed. F1=EXP(ETA(1)) was incluided. Summary tables were examined at Microsoft excel. xpose4 was employed to evaluate the models.

Results: Minimal objective function was 8412. Lag time was not included. Clearance was 89.9 +- 4.5 L/h, Volume of distribution was 103 +-10.0 L, absoption constant was 2.23+_0.24 h-1, intercompartmental clearance was 11.4 +- 1.2 L/h. This clearance was greater then the reported for Caucasian populions, which can be due to the low rate of CYP2C9 mutations on Mexican population. But enviromental factors can also play a role.

Conclusions: This Mexican Population of West Mexico had a high clearance probably due to genetic (CYP2C9 low frequency mutations [1,2]) and enviromental factors.

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Fredrik Jonsson A pharmacokinetic-pharmacodynamic model for ECG pattern changes in dog and monkey

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Objectives: Drug-induced prolongation of cardiac repolarization is a significant reason for early-phase failure of drug candidates. Changes in PR interval and QRS complex that raised safety concerns were observed following administration of potential CNS compound R1551 to dog and monkey. The aim of the study was to investigate the use of non-linear mixed-effects PK-PD modeling to relate R1551 exposure to the changes of the ECG pattern.

Methods: Using a crossover design, eight beagle dogs received single oral doses of R1551 (ranging 0-100 mg/kg) and seven cynomolgus monkeys received oral doses of 0-30 mg/kg once daily for 5 days. Telemetry was used to measure ECG parameters (PR interval and QRS complex) and heart rate up to ≥24 h after the final dose. Pharmacokinetic parameters were estimated by fitting a two-compartment model to the data. This estimation included data from 32 additional dogs and 9 additional monkeys given peroral or intravenous doses. The model-predicted individual concentration-time profiles of R1551 were then linked to the PR interval and QRS complex via an effect compartment.

Results: A linear concentration-effect model provided a good fit to the observed data for both ECG parameters in dogs and QRS data in monkeys. In monkeys, there was no effect delay and the effect compartment was removed. For the PR interval in monkeys, fit was improved by the addition of a placebo effect compartment to the linear model, to account for a suspected vehicle effect. The estimated slope factors for the PR interval were 0.0093 and 0.0934 ms mg^{-1} kg^{-1} l^{-1} in dog and monkey, respectively. For the QRS prolongation, the corresponding slope factors were 0.00274 and 0.00200 ms mg^{-1} kg^{-1} l^{-1}.

Conclusions: The modeling approach used in our study shows the value of characterizing the complete time-course of a drug when assessing its safety profile. The use of a separate effect compartment accounts for the possible presence of active metabolites and for the distribution to the active site. The similarity of the slope factors between dog and monkey indicates that the effect on the ECG pattern is similar in magnitude between species, even if its timing is different. This is an indication that a similar magnitude of ECG change would be expected in humans.

Etienne Pigeolet Introducing the renin-angiotensin-aldosterone (RAAS) hypertension platform: an in-silico approach to evaluating efficacy of RAAS modulating drugs on blood-pressure control and end-organ protection

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Objective: We present a systems-biology approach to modeling blood-pressure (BP) regulation and end-organ protection offered by RAAS modulation therapy.

Background: Data from the National Health and Nutrition Examination Survey (NHANES) indicate that more than 50 million Americans suffer from elevated BP; worldwide, these figures are close to one billion. Suboptimal BP control is recognized as the leading risk factor for morbidity and mortality throughout the world, and in particular in the elderly population (JNC7). Data from observational and outcomes studies have confirmed a clear and consistent relationship between BP elevation and increases in cardiovascular and renal events from end-organ damage.

Methods: The focus of the present work is to capture the pathophysiological mechanisms of hypertension and its impact on end-organ status using a deterministic modeling approach. The resulting RAAS hypertension model features a modular design with four key modules, namely, systemic, renal, cardiovascular and nervous systems. The first two modules are explicitly represented in the first generation RAAS platform. The systemic module captures a systems-level representation of the RAAS pathway and its interactions with sodium and water regulation to achieve long-term BP control. The renal module includes a representation of the kidney as an assembly of single nephrons and associated fluid dynamics processes that influence glomerular filtration rate.

Results: Here, we present the key features of the first generation RAAS hypertension platform and the model parameterization using literature data. Model based simulations of systemic and renal biomarkers in select patient phenotypes following treatment with angiotensin-converting-enzyme inhibitors, angiotensin-receptor-blockers and direct renin-inhibitors and their comparison to observed data is reported.

Conclusion: These results demonstrate the RAAS hypertension platform as a valuable tool in elucidating multi-faceted disease progression patterns in various hypertensive patient phenotypes, and the benefits and limitations of different treatment options.

Key words: Renin-angiotensin-aldosterone-system (RAAS), Mechanistic modeling, Hypertension, Biomarkers, Renal disease progression

Patanjali Ravva Population Pharmacokinetic-Pharmacodynamic Analysis of Weight Loss Efficacy of CP-945,598 in Adult Obese Subjects

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Objectives: To characterize the time course of weight loss efficacy of CP-945,598 (CP) in obese subjects following multiple oral doses for up to 6 months

Methods: This was a double-blind, placebo- and positive-controlled dose-ranging study designed to assess the efficacy and safety of CP in obese subjects (BMI³27 and <40 kg/m^2) with co-morbid conditions. A total of 282 subjects were randomized to receive 5, 15, or 25 mg QD of CP, or 15 mg QD of sibutramine (S) or placebo (P). All subjects followed the same disease management program for obesity. Outpatient visits were scheduled for weight measurements on study Days 14, 28, 56, 84, 112, 140, and 168. Serum samples were collected for concentration analysis on 5 clinic visits.

A nonlinear mixed effects modeling approach was utilized to describe the disease progression and the effects of CP on weight loss. The model was structured as an exponential decrease of body weight (WT) over time (first order rate constant a) from the baseline weight (*A*) resulting in a maximum fractional weight loss (*B*). This maximum fractional weight loss was described as the sum of placebo (B_{Pbo}) and drug effects, with the latter described as a hyperbolic E_{max} function of estimated individual steady-state average CP concentration (parameters E_{max} and $EC_{ss,50}$). In addition, model was comprised of additive inter-individual variance (IIV) on *B*, exponential IIV on *A* and a, and an additive residual variance.

$$WT_{ij} = A*\exp(\eta_1)*(1-(B+\eta_2)*(1-e^{(-\alpha*\exp(\eta 3)*tij)})) + \varepsilon_{ij}$$

Results: A total of 211 subjects (86.7% Females), equally balanced across treatments; P (51), 5 mg QD (51), 15 mg QD (52) and 25 mg QD (57) contributed data for the longitudinal analysis. An exponential decay function captured the time course of weight loss. A monotonic relationship was characterized between steady-state average concentration of CP and weight loss efficacy across the dose range studied. Key final model parameter estimates (95% bootstrap CI) were: 0.0275 **(**0.0125-0.0397) for B_{pbo}, 0.0824 (0.048-0.260) for Emax, 17.6 (3.54-101) for EC_{50} (ng/mL) and 0.0825 **(**0.0345-0.1248) for a ($week^{-1}$). IIV on B and a was 0.00359, 67% CV, respectively. The residual variance was estimated as 0.923. A visual predictive check indicated adequate model performance.

Conclusions: The model adequately captured the time course of weight change from baseline. Doses of 20-25 mg are predicted to produce a clinically meaningful extent of weight loss (4-5% at 6 months).

Paolo Denti A NonLinear Mixed-Effects Approach to the Estimation of the Glucose Disposition Index

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Objectives: The glucose Disposition Index (DI) was first introduced Bergman et al. [1] with the purpose of assessing the efficiency of glucose-insulin metabolism by calculating the product of insulin sensitivity and secretion indices. This paradigm is called Hyperbolic Law. A more complex model, proposed by Kahn et al. [2], suggests the use of an additional exponent α. This work proposes a NLMEM to analyse the DI in a population and assess the statistical significance of the parameter α.

Methods: As explained in Cobelli et al. [3], the classic method to apply and investigate the validity of the DI laws consists in studying a population of subjects with similar glucose disposal efficiency and supposedly sharing the same DI level. For each individual, insulin sensitivity and secretion indices are estimated (e.g. with an IVGTT) together with their precision, then a geometrical fit is used to find the best curve. Since many simplifications have been proposed to deal with the difficulties of a 2-variable fit [4, 5], we first suggest an exact Total Least Square (TLS) fit approach. However, all geometrical fits account only for the variability caused by the estimation uncertainty of insulin sensitivity and secretion, but the statistical analysis of a real dataset [6] and common sense suggest that, even in a relatively homogenous population, a certain degree of biological variability is inevitably present in the DI values. Therefore, a NLME approach is proposed, which estimates the DI information from population features such as the typical values and covariance matrix. Simulated data, with and without variability in the DI, were used to compare the methodologies. Matlab [7], NONMEM [8] and SPK [9] were used for the fits.

Results: On our simulated data, TLS proves superior to the approximated approaches, but, as all geometric fits, it fails when in presence of population variability. In this context, the NLMEM is much more reliable and works well also with no or small population variability in the DI. Current work on real IVGTT data suggests a value of α significantly smaller than 1, supporting Kahn's model.

Conclusions: When analysing the DI in a population, it is important to account for both estimation uncertainty and population variability. These results also suggest that, if a population model were used to jointly assess both insulin sensitivity and secretion, the population features could be used directly to provide prior information on the DI.

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Paolo Denti Covariate Selection for the IVGTT Minimal Model of Glucose Disappearance

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Objectives: Nonlinear mixed-effects modelling and its advantages have recently been discussed in the context of glucose-insulin metabolism [1,2,3] The research presented here aims at extending the use of these techniques, by proposing the introduction of covariates in the analysis of the IVGTT minimal model of glucose disappearance [4].

Methods: The dataset consists of IM-IVGTT on 204 healthy subjects (mean age 56 yrs, range 18-87; mean BMI 27 kg/m^2, range 20-35) [5]. Besides blood samples, additional information about the patients was collected including age, gender, height, weight, body fat amount and distribution, basal glycemia and insulinemia. Given the high number of potential covariates, a standard step-wise procedure would have been unduly time-consuming, so a hybrid selection method was used. In a first step, the individual parameters provided by the base model (without covariates) were regressed on the covariates with a traditional linear regression to narrow down the pool of candidate models. In a further step, the most promising models were implemented in SPK [6] and ranked analysing the value of the objective function.

Results: Our method selects age, visceral abdominal fat and basal insulinemia as predictors for Insulin Sensitivity (SI), and age, total abdominal fat and basal insulinemia for the insulin kinetics parameter (P2). The predictors for the volume of distribution are age, gender, percentage of total body fat and basal glycemia. For glucose effectiveness (SG) our method selects height, weight and body surface area; however the actual physiologic significance of these covariates is not obvious. An alternative model for SG uses age and basal glycemia as predictors. For SI and P2 in particular, the incorporation of covariates results in a significant shrinking of the BSV. (from 70% to 44% and 51% to 39% respectively).

Conclusions: Our results support the hypothesis that the overall predictive power of the minimal model can be increased by the incorporation of easily, inexpensively and non-invasively collectible physiological information. We offer a starting point for further investigation about the significance of the relationships detected; issues that remain to be investigated include the role of collinearity in the predictors, especially for SG. Ultimately, this approach would provide a tool to allow the design of less invasive and less expensive protocols for epidemiological studies of the glucose disposal metabolic system.

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Srividya Neelakantan Exposure-Response Analysis of a DPP-IV Inhibitor, PF-00734200 on HbA1c in Type 2 Diabetic Subjects on Stable Metformin Treatment

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Objectives: PF-00734200 is a dipeptidyl peptidase-IV (DPP-IV) inhibitor intended for use in the treatment of type 2 diabetes mellitus. The purpose of this analysis was to investigate the relationship between PF-00734200 exposure and change in glycosylated hemoglobin (HbA1c) at Week 12 in type 2 diabetic subjects.

Methods: Two randomized, placebo-controlled, parallel group, multiple-dose studies were conducted for 12 weeks in diabetic subjects on stable treatment with metformin in combination with once daily PF-00734200 doses ranging from 2 to 30 mg. A population PK analysis was performed using a nonlinear mixture model. The predicted PF-00734200 exposures (average steady-state concentrations) were subsequently incorporated into an inhibitory E_{max} model to characterize the effect of PK on the change from baseline in HbA1c at Week 12. Covariates of interest were identified to help explain the inter-individual variability in the model parameters. The predicted median change from baseline in HbA1c response at Week 12 for the various doses and the 95% confidence intervals (CIs) was derived from the parameters estimated from 1000 replicate bootstrap parameter vectors. The probabilities of having greater reduction in the HbA1c compared to other treatment arms, particularly 20 vs 10 and 30 vs 20 mg doses were also calculated from the bootstrap parameter vectors and the observed median exposures.

Results: Data from a total of 482 subjects who had both baseline and Week 12 HbA1c data were analyzed. The E_{max}, EC_{50} and E_0 (placebo response) parameters were estimated to be -1.01%, 20.7 ng/mL and 0.133% respectively. Baseline HbA1c and age were identified as influential covariates describing the maximal HbA1c response (E_{max}). The potential clinically relevant doses of 10, 20 and 30 mg resulted in mean (95% CI) percentage change from baseline in HbA1c of -0.632 (-0.759, -0.501), -0.758(-0.925, -0.585) and -0.801 (-1.02, -0.604) respectively. The probability of observing a greater than 0.1% decrease in the HbA1c at Week 12 for the 20 mg over 10 mg and for 30 mg over 20 mg doses are 0.614 and 0.064 respectively.

Conclusions: The inhibitory Emax model adequately described the exposure-change from baseline HbA1c response. In conclusion, the 20 mg dose is superior to the 10 mg dose in reducing the HbA1c response over 12 weeks whereas the 30 mg and 20 mg doses produced clinically similar HbA1c reductions.

Sergej Ramusovic A physiologically based pharmacodynamic model of the Renin-Angiotensin-Aldosterone-System

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Objectives: Hypertension and blood pressure control are major cardiovascular targets to decrease morbidity and mortality in adult and paediatric patients. The Renin-Angiotensin-Aldosterone- (RAA-) System is an endocrinological cascade involved in blood pressure (BP) regulation. We aim at getting a better understanding of this system and of the drugs that interfere at the different levels of the RAAS. Therefore, we developed a physiologically based model describing central parts of the system at steady-state conditions and the dynamic disturbances of the system caused by its pharmacological blockade by enalapril.

Methods: A description of the RAA-System was obtained by literature review as were concentrations of the by-products of the cascade, Angiotensin I (Ang1) and Angiotensin II (Ang2), their half lives and the effects of enalapril application on them respectively [1]. The production of Ang 2 was modelled in terms of a subsequent proteolytic cascade including a negative feedback of Ang2 on renin production as indirect response model. So was the effect of enalapril application on Ang 2 levels. The model was built in MoBi 2.0 ® (Bayer Technology Services GmBH).

Results: The final model consisted of ten reaction steps with twenty two molecular species. Simulations for steady-state concentrations were comparable with literature data (simulation: 14.06 pM Ang1, 4.32 pM Ang2; literature: 14.93 pM Ang1, 4.73 pM Ang2 [1]). During ACE-Inhibition a maximum concentration of Ang1 and a minimum concentration of Ang2 (74.61 pM after 960 min and 0.8 pM after 240 min) comparable to literature data (86.4 pM after 960 min Ang1 and 1 pM after 240 min for Ang2 respectively [1]) were simulated. The concentration-time profiles of both by-products were described adequately by visual inspection.

Conclusions: A pharmacodynamic model including a relevant feedback mechanism to describe the time course of the RAAS components during ACE-Inhibition was developed. Due to its physiological nature, this model can be expanded to encompass further aspects of the RAA-System as well as it has the potential to become a part of a physiological model for blood pressure regulation.

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Elba Romero Impact of pharmacokinetic information reported as being below limit of quantification on the prediction of important response endpoints.

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Objectives: Pharmacokinetic (PK) and pharmacodynamic (PD) information are in occasions reported as being below limit of quantification (BQL). Most of the modelling experience with BQL information come from PK analysis where the potential impact on the model parameters estimation has been discussed.
In the current analysis we provide an example in the context of hormone-related tumours, where BQL values in pharmacokinetics, without major effect on PK model estimates, have a clear impact on important pharmacodynamic endpoints.

Methods: Fifteen male healthy subjects and eleven male cancer patients received a single subcutaneous injection of an GnRH agonist at three different dose levels and two type of formulations. Blood samples were taken over a period of six months and plasma concentrations of the GnRH agonist and the hormone testosterone (TST) were measured at the same sampling time. PKPD modelling was done sequentially using NONMEM VI.

Results: The percentage of BQL observations for the current analysis were 12.5% and 1.4% from the total of GnRH agonist (515) and TST (561) data, respectively. All of them were located after 20 days after drug injection.
PK and PKPD models were developed excluding BQLs from the analysis or treating BQLs as censored observations according to method 3 in Beal 2001[1].
PK of GnRH agonist was best described using a one compartment disposition model and an absorption model characterized by a simultaneous zero- and first-order absorption which included a delay absorption compartment.
The time profiles of TST were described using a variant of the pool-precursor model[2], where the GnRH agonist elicited a dual effect: (i) increasing the release of TST from the precursor compartment and (ii) blocking the synthesis of new precursors.
Regarding the most critical treatment endpoint, time of TST below 0.5 ng/mL ($T_{<0.5}$), the models excluding BQLs of GnRH predicted a median $T_{<0.5}$ of 120, 180, and 190 days for the low, middle, and high dose levels. When BQLs were treated as censored observations the corresponding values of $T_{<0.5}$ were 65, 110, and 130 days, respectively.

Conclusions: The current analysis shows the importance of considering BQL samples in pharmacokinetics, even in cases where the impact on populations PK parameters is marginal. This methodology is especially indicated in those cases where there is a strong correlation between plasma drug concentrations and pharmacodynamic endpoints.

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Hanna Silber An integrated model for glucose-insulin regulation to describe oral glucose tolerance test data in healthy volunteers

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Introduction: Oral glucose tolerance tests (OGTT) are commonly used in drug development. The study design is less invasive than the intravenous provocations and often sparse in sampling which makes it attractive both for patients and researchers. An integrated model for glucose and insulin regulation has previously been developed based on different intravenous glucose provocations in healthy volunteers and type 2 diabetes mellitus (T2DM) patients and extended to also include the OGTT in T2DM patients (1, 2). With the extension to also include healthy volunteer OGTT valuable information can be gained regarding differences between healthy and diabetic individuals during oral provocations.

Methods: Data from 23 healthy volunteers receiving an OGTT was included for the analysis. The subjects were given 75 g of glucose solution to drink and blood samples were drawn every 15 minutes during 4 hours following the glucose dose and analyzed for glucose and insulin. Non-linear mixed effects analysis was performed with NONMEM VI (FOCE) and was based on the previous models. The disposition parameters were initially fixed to the final parameters of the intravenous model (1). The validity of this assumption was later tested by estimation of separate disposition parameters for the OGTT. The validity of the included control mechanisms and the need for incorporation of additional control mechanisms were also evaluated. Model extensions for glucose absorption and for the incretin effect on insulin secretion were added and the starting point was the final model for OGTT in patients (2). Complex glucose and insulin profiles, with multiple glucose and insulin concentration peaks, were observed in most individuals. Both semi-mechanistic and empirical models were evaluated for the description of this behavior. The incretin effect was included as a direct effect on insulin secretion, which was previously done also in the patient population (2). The predictive properties of the final model were evaluated by simulation through the visual predictive check (VPC) and the uncertainty in parameter estimates was quantified by a bootstrap.

Results: The OGTT data was successfully described by the basic intravenous model with extensions for the absorption, the incretin effect on insulin secretion and an additional control effect on glucose production. The final model could successfully capture the multiple peaks in glucose and insulin plasma concentrations seen in most individuals. An empirical flexible input model (3) with 12 steps was used to describe the absorption phase and revealed a complex absorption pattern in line with previous literature indicating inhibition of gut emptying of glucose. Most patients displayed at least a biphasic absorption pattern. The bioavailability was estimated to 72% which is in line with previous results in patients where it was estimated to be 81%. The incretin effect was described using a linear function of glucose absorption rate and was incorporated as a direct effect on insulin secretion. An additional control mechanism of insulin on glucose production was included and was found to be

important for the description of the hypoglycemic episode seen in most individuals during the second half of the experiment. The inhibitory effect of insulin on glucose production is a well known effect of insulin. In previously publications with this model it has, however, not been possible to separate it from the effect of glucose on its own production. The effect of insulin on glucose production was found to be stronger than the previously included effect of glucose and to affect the glucose production mainly during the first half of the experiment. Insulin dependent clearance in patients has previously been found to be higher during oral provocations compared to intravenous (2). In this study it was however found to be similar. A possible explanation for the difference could be that in the patient population it was not possible to identify an inhibitory effect on glucose production and that the higher insulin dependent clearance was needed to compensate for the constant glucose production. In contrast to the previously analyzed intravenous data in healthy volunteers it was not possible to identify the first-phase secretion of insulin during the oral provocation experiment. As the first phase insulin response has been shown to be important for glucose regulation it is likely that it is present also in this population but that it is described by the incretin effect on insulin secretion which sets in quickly after the administration of the glucose dose. The VPC showed that the model was able to predict real-life like data although the variability in the simulated data of glucose was somewhat higher compared to the observed data. The bootstrap showed that most parameters were estimated with good precision. Population parameters were in general estimated with a standard error of less than 35 %.

Conclusions: In conclusion, a previously developed model has been extended to also include the OGTT in healthy volunteers. New structures include description of the biphasic absorption profiles and identification of the inhibitory insulin effect on glucose production. As the previously developed model in T2DM patients this model could become important in drug development.

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Lorea Bueno Semi-Mechanistic Modelling of the Tumour Growth Inhibitory Effects of a New Anti-angiogenic Drug.

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Objectives: To develop a mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model for a new antiangiogenic drug using human xenografts.

Methods: *Experimental*. Human xenografts (NCIH460) were implanted subcutaneously onto nude mice. Experiments started 7 to 10 days after tumour implantation. Two types of investigation were carried out: (i) An experiment providing information about the plasma levels of the antiangiogenic drug and the percentage change (inhibition of a biomarker) with respect to baseline of phospho-pKDR in tumour, and (ii) A tumour growth experiment where the kinetics of tumour growth was monitored during 20 to 41 days after the first day of drug administration. In both experiments, either saline or drug (dose range 1.5 to 40 mg/kg) was administered orally as a single dose or in a multiple dosing design.

Data modeling. Plasma levels of the compound, percentage of pKDR in tumour, and tumour size were used to establish a semi-mechanistic, population PK/PD model that was used to predict tumour stabilisation using NONMEM[1].

Results: ***Pharmacokinetics.*** Drug disposition was best described using a two compartment model with first order absorption. Plasma clearance was dose-dependent and was described as a function of plasma concentration using the Michaelis-Menten expression.

Biomarker model. An indirect response model was used to relate the predicted plasma concentrations to the observed inhibition of pKDR. The model assumes the existence of factors within the tumour cell responsible for the synthesis and degradation of pKDR. This process is inhibited by the compound under investigation. The model predicted a complete inhibition of pKDR, and a very rapid turnover rate.

Tumour growth model. The mean signal propagation time was estimated at over 20 days. The effect originated by the decrease in pKDR levels demonstrated a non-linear (amplified) inhibition of tumour proliferation. The results show that 75% tumour growth inhibition is associated with a corresponding decrease in pKDR of 50%.

Conclusion: The integrated model provided a useful tool to investigate different experimental scenarios, and provided valuable insights into the mechanisms of signal transduction and tumour growth. From a developmental perspective, these types of models provide a simulation platform to explore the relationship between drug exposure, efficacy, and toxicity *in silico*.

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Damien Cronier A fully integrated PK/IVTI/IVE model in mouse to help design the FHD trial for a cell cycle inhibitor X

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Objectives: The primary objective of this modelling study was to describe the effect of compound X on the cell cycle of cancer cells by means of a multi-biomarker approach allowing full monitoring of the cell cycle kinetics. The secondary objective of this study was to estimate a pharmacologically effective dose range for compound X in human, in preparation of the First Human Dose (FHD) study.

Methods: An integrated PK/IVTI/IVE model was developed in mouse using a seauential approach. The PK of X were connected to the level of in vivo target inhibition (IVTI) in Colo-205 xenograft tumours by means of a PK/IVTI moel describing the kintics of the different phases of the cell cycle using a series of transit compartments. Cell cycle progression was assumed to be inhibited by means of an indirect resposne mechanism. In vivo efficacy (IVE) of compound X in Colo-205 was then described by means of a fully integrated PK/IVTI/IVE model consisting of a modified Gompertz model connected to the PK/IVTI model using both a cytostatic and a cytotoxix component. Finally, a humanised PK/IVTI/IVE model was obtained by connecting the mosue IVTI/IVE model to a projected human PK model obtained by allometric scaling. This humanised PK/IVTI/IVE model was used to predict an efficacious dose range in human.

Results: the fully integrated PK/IVTI/IVE model could account for the dose-dependency of IVE accross a dose range of 25 to 100 mpk and over a dosing period of 21 days. The 3 biomarkers collected along the cell cycle of colo-205 cancer cells wre connected in a mechanistic manner and the time shift for the peak of inhibition observed in the 3 compartments as well as the rebound effect were wel accounted for, suggesting a block of the cell cycle associated with cell synchronisation. The model also made it possible to correalte IVE with a minimum of 30-50% maintained thoughout the whole treament period. This IVTI threshold was subsequently used to derive an efficacious dose range in human.

Conclusions: The PK/PD relationship of compound X in Colo-205 tumours was modelled by means of a fully integrated PK/IVTI/IVE model. This model made it possible to understand the determinants of IVE and to correlate the latter to the maintaining of a minimum of 30-50% IVTI throughout the whole treatment period. This model was successfully applied to project an efficaicous dose range in human to support the design of the FHD trial.

Maxime FONTANILLES Modelization of bevacizumab effect on tumour perfusion assessed by Dynamic Contrast Enhanced Ultrasonography

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Objectives: Bevacizumab (Avastin®) is an angiogenesis inhibitor. Its clinical efficiency in the treatment of solid tumour in association with classical chemotherapy has been demonstrated by several authors [2]. The clinical use of bevacizumab would be improved if a predictive factor of its efficacy was established. The aim of this work is to assess the role of Dynamic Contrast Enhanced Ultrasonography (DCEUS) as an early predictor of response to chemotherapy with bevacizumab. DCEUS is a medical imagery by ultrasonography which uses a contrast agent containing microbubbles (Sonovue®). This agent is strictly intravascular and its kinetics (intensity function of time) allows an assessment of tumour vascularisation.

Methods: 13 patients with metastatic colorectal cancer, treated by 5FU, irinotecan, leucovorin and bevacizumab entered this study. The imagery analysis performed on the hepatic metastases resulted in three curves of intensity at day 0, 21 and 49 plus 3 measures of tumour diameters (scanner) at month 0, 2 and 4 were obtained. The work is divided into two parts (1) estimation of hemodynamic parameters in tumour and (2) building of a predictive model of response. (1) The hemodynamic parameters were estimated from the curve of intensity using a multivessel model adapted from the model published by Krix and al[1]. The model was fitted using Adapt II. The estimated parameters were: the slope of increase m (~velocity: ν), the maximum intensity N0 (~ blood volume) and the elimination rate constant Ke. The secondary parameters were: blood flow f (~ N0*ν) and perfusion P (~ f / Tumour volume). (2) The predictive model of tumour volume variation at month 4(M4) was built by multivariate linear regression. The explicative variables are the estimated and secondary parameters, plus their relative variation between day 0 and day 21 or 49

Results: The modified Krix model fitted very well the sonographic data. The median tumoral perfusion at D0, D21 and D49 was 3.87E-02, 3.74E-02 and 4.38E-02 mL/s/tumour volume respectively. The best predictive model incorporated N0, P, the variation of both blood flow and perfusion between D0 and D49 as variables to explain the relative variation of tumour size at M4: Δtumour size at M4 = -0.0063*N0 + 0.19* P + 0.132*Δ f - 0.0978*Δ P Each parameter contributes significantly ($p < 0.05$) to the model with a standard error acceptable. The overall p value is < 10-6 and the R-squared is 0.96. No significant relation has been found between parameters at D21 and tumour size at M2 or M4.

Conclusions: A model able to predict early the treatment response by using a non invasive medical imagery was established. The analysis provided relevant information for understanding the pharmacological action of bevacizumab on metastatic vascularisation. The inhibitor of VEGF seems to reduce blood flow but to improve the action of associated chemotherapy by increasing the perfusion of the tumour. The study is ongoing in order to validate the model.

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Ludivine FRONTON Population model of Human Chorionic Gonadotropin to predict resistance in low risk gestational trophoblastic neoplasia patients

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Objectives: Conventional methotrexate regimen (MTX) is recommended for treatment of patients with FIGO (International Federation of Gynecology and Obstetrics) low risk Gestational trophoblastic neoplasia (GTN). The treatment efficiency is assessed by Human Chorionic Gonadotropin (hCG) concentrations follow up. In case of MTX resistance or intolerable toxicity, no clear guidelines are available about the method used to analyse hCG kinetic curve [1]. The aim of this study was to evaluate the influence of hCG pharmacokinetic parameters, as prognostic factors able to inform early MTX resistance after the treatment start. Present work presents the population model building of hCG.

Methods: All data derived from a French retrospective study involving 154 patients treated with MTX (IM 1 mg/kg on days 1,3,5,7 q2w) for a low risk GTN between 2000 and 2008. A kinetic population approach using NONMEM VI was performed to model hCG decrease between day 0 (D0) and day 40 (D40) during the first 3 MTX cycles. Since no information on endogenous hCG production was available, its volume of distribution was set to a literature value 3.4L [2]. One, two and three compartments were tested, and extensive testing of model covariates was performed using FOCE INTER method.

Results: The present modelling analysis was performed on a total of 845 hCG concentrations sampled between D0 and D40, representing an average of 5.5 per patient. As data included concentrations below the limit of quantification (BLOQ), the first concentration in a series of BLOQ observations was replaced by LOQ/2 and later observations were censored [3]. hCG decrease was optimally described by a mono-exponential model: $hCG(t) = 3900 * e^{-0.149 * t}$. Baseline hCG measurement before methotrexate administration showed large inter-individual variability (273.5%) and moderate one for elimination rate constant (53%). On average, apparent individual clearance was estimated to be equal to 0.57 L/day. None of the available covariates was able to explain variability in baseline hCG or K.

Conclusion: The population "PK" model is a useful tool to estimate individual Bayesian posthoc CL. This work is ongoing and those CL will be used in a next step to better predict MTX resistance in hCG patients, database which is under construction.

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Maria Garrido Pharmacokinetics and antitumor efficacy characterization of cisplatin-loaded PLGA nanoparticles in tumor-bearing mice.

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Background: Cisplatin (CDDP) shows a significant dose-limiting due to its side effects. Polymeric nano-sized carriers seem to be able to improve the therapeutic index of the encapsulated drug, although that characterization has been in general very empirical.

Objective: The characterization of the antitumor efficacy of CDDP nanoparticles by a semi-mechanistic pharmacokinetic/pharmacodynamic model in tumor-bearing mice.

Methods: CDDP-encapsulated PLGA nanoparticles (NP) [1] were developed to characterize their efficacy in SCID mice xenografted with colorectal adenocarcinoma DHDK12-ProB cells. Animals were divided in five groups to receive: G-I, saline; G-II, unloaded-NP; G-III, 5mg/kg of CDDP i.v.; G-IV, 5mg/kg of CDDP i.p. and G-V, 5mg/kg of CDDP-NP i.p., once a week for three weeks. Blood samples were used to measure Pt plasma concentrations, blood urea nitrogen (BUN) and vascular endothelial growth factor (VEGF). Tumour growth and body weight were recorded daily.

All analysis were performed using the population approach with NONMEM version VI using the FOCE interaction method.

Results: CDDP disposition administered in saline solution was described by a three-compartments model associated with a first order absorption process, however for NP was described by one compartment model with a zero order absorption process. The estimate of the apparent volume of distribution was higher after NP administration than after free-drug. The inter-animal variability could be associated with total plasma clearance.

The tumour growth in saline and unloaded-NP groups, was described by an exponential growth followed by a linear growth, as has been previously reported by Simeoni et al.[2]. In groups treated with CDDP, the inhibition of the tumour growth was related to a factor dependent on CDDP plasma concentrations, which represents the potency of the drug. In addition, a transit compartmental system was also used to model the delay in the process of the cell death, estimated in approximately 5 days.

Finally, the similarity between time profiles of VEGF and tumour growth suggests that this biomarker could be used to model the efficacy of a specific treatment.

Conclusions: The selected model provides a tool to explore *in silico,* alternative *in vitro* and *in vivo* scenarios to optimize the controlled delivery systems of CDDP, new dosing schedule or drug combinations.

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marianne guery Data mining analysis of survival data in cancer of pancreas : first exploratory step for identification and validation of explicative variables

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Objectives: Pancreatic cancer is a relative sparse pathology with few Evidence Base Medecine. Given the rapid progression of the disease, metastatic stage treatment is based on non standardized chemotherapies. This study aimed to explore explanatory variables (therapeutic strategies and physiopathological covariates) which may influence individual global survivals. These variables may therefore be included in time to event modelisation.

Methods: We explore datas from a cohort of unselected patients with metastatic pancreatic cancer. Analysis of explanatory variables with respect to the time dependant variable was performed by a two stage bootstrap method (Abdelaziz Faraj,Michel Constant, personal communication). A multivariate analysis was made on the selection of possibly discriminant variables with Datapilot software (1) (Philippe Bastien, personal communication).

Results: 42 patients contributed to the time-dependant variable values. After first one stage bootstrap analysis with Datapilot, 16 categorical variables were selected for their clinical significance: Age (more or less 65), gender, stage at diagnosis (local or metastatic), number of treatment lines (more/less than 2), first protocol schedule, prior surgery, dose reduction, platinium salt introduction, presence of Gemcitabine alone, of GEMOX protocol (Gemcitabine-Oxaliplatin), of GEMOX-Gemcitabine sequence, of outlier protocols, of erlotinib. Probability of each first category > the other range from 0,202 to 0,987 (significant difference for 3 variables). Covariance matrix estimation leads to no intragroup correlations. We explore a two stage approach that is : stage one bootstrap of observed datas (500 replications for each value to insure good estimation of CI (confidence interval), and stage two Datapilot analysis on the population of stage one. This two stage approach improve the results of single stage approach in terms of significance on the 16 variables.

Conclusions: Selection of statistical and clinical pertinent variables seems to be an interesting prerequisite to time to event modelisation under Weibull or Cox approaches. This exploratory method could also be used further during clinical trial simulation, to avoid clinical studies having a high risk of failure, and to properly design future clinical studies, specially in case of poor regulatory therapeutic references.

References:
[1] http://www.colorpilot.com/datapilot.html

Emma Hansson Pharmacokinetic-Pharmacodynamic Modeling of the Angiogenic Factors VEGF, sVEGFR-2, sVEGFR-3 and sKIT following Sunitinib Treatment in GIST

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Objectives: An identified relationship between suitable biomarkers and tumor response could potentially improve measures of treatment activity and facilitate treatment individualization for anti-angiogenic drugs both during drug development and in clinical practice. The aim of the present study was to investigate dose-exposure-biomarker relationships following Sutent® (sunitinib) treatment with focus on the potential biomarkers VEGF, sVEGFR-2, sVEGFR-3 and sKIT.

Methods: Data on the four angiogenic factors following up to 85 weeks of treatment with the oral tyrosine kinase inhibitor sunitinib and/or placebo in 303 patients with gastro-intestinal stromal tumors (GIST) were available. The sunitinib PK was described using individual PK parameters [1] and indirect response models [2] were fitted to the log transformed biomarker data using the FOCE method with INTERACTION in NONMEM VI. Symptomatic and protective disease progression models were evaluated to describe biomarker modulations due to natural history of the disease.

Results: The dose-exposure-biomarkers relationships were adequately described using indirect response models where sunitinib treatment decreased the production of sVEGFR-2, sVEGFR-3 and sKIT and inhibited the degradation of VEGF. A linear symptomatic disease progression model with a common slope described the increase of VEGF and sKIT over time in the absence of drug. The estimated mean residence time for the different biomarkers were 4 (VEGF), 23 (sVEGFR-2), 17 (sVEGFR-3) and 98 (sKIT) days. A common typical IC_{50} parameter for the four biomarkers could be estimated and the individual parameters for VEGF, sVEGFR-2 and sVEGFR-3 were highly correlated.

Conclusions: : The time-courses of the angiogenic factors VEGF, sVEGFR-2, sVEGFR-3 and sKIT following placebo and sunitinib treatment were well characterized. The high within-patient correlations in IC_{50} indicate that it may be sufficient to measure a limited set of the angiogenic factors for exploring correlations of treatment outcome.

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Georg Hempel Physiologically-Based Pharmacokinetic (PBPK) Model for High- and Low Dose Etoposide: From Adults to Children

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Objectives: Etoposide is a widely-used anticancer drug in both paediatric and adult oncology. The pharmacokinetics is well- characterized with high interpatient variability in individual exposure partly due to drug interactions during polychemotherapy regimens. The aim of the current project was to evaluate a generic physiology-based pharmacokinetic (PBPK) model to predict the systemic drug exposure of high- and low dose etoposide in children from a model developed with adult data..

Methods: The simulations of etoposide were performed with the software PK-SIM® (Bayer Technology Services). The model was developed and evaluated using concentration-time profiles from adult patients receiving intravenous etoposide in a conventional and high dose polychemotherapy regimen before stem cell transplantation (Busse et al. 2002). To describe the main metabolism and excretion processes by P450 enzymes and drug transporters, Michaelis-Menten kinetics using parameters from in-vitro experiments reported in the literature were applied. The validated model was scaled down to children and finally compared to observed etoposide plasma concentrations in this age group (Würthwein et al. 1999; Würthwein et al. 2002). In addition, drug interactions triggered by eg. P-glycoprotein inhibitors or nephrotoxic drugs such as cyclosporine A and carboplatin were elucidated.

Results: Simulated plasma concentration-time courses of protein-bound and free etoposide in adults for high- and low dose schedules agreed with the observed data. Mean simulated total clearance of high – and low dose etoposide were 0.74 ml/min/kg (CLpred: 0.7 ml/min/kg) vs. 0.52 ml/min/kg (CLpred: 0.6 ml/min/kg), respectively. Integrated Michaelis-Menten kinetics was adequately transformed to age-related pharmacokinetics in children. The predictions of the pharmacokinetics in different age groups by the PBPK model were also in good agreement with observed data. .

Conclusions: The PBPK-model simulations matched the etoposide pharmacokinetics in different dosing regimens in adults. Furthermore, the scaling procedure from the adult model to children by adjusting model parameters for metabolism and excretion procedures to the physiological processes in children provides useful predictions of the pharmacokinetics in paediatric patients. This approach can be useful for planning pharmacokinetic studies in children. However, comedication with drugs influencing the metabolism and excretion has to be taken into account.

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Åsa Johansson Pharmacokinetics of high-dose methotrexate in adults and children

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Objectives: Adults and children with osteosarcoma receive high dose (12 gm^{-2}) intravenous chemotherapy with the dihydrofolate reductase inhibitor methotrexate; daily TDM is performed until concentrations fall below 0.2 $\mu molL^{-1}$. The aim of this study was to develop a population pharmacokinetic methotrexate model, and investigate important covariates for use in TDM.

Methods: Patients undergoing treatment following the EURAMOS 1 osteosarcoma protocol were prospectively recruited, and records made of methotrexate dosing, TDM sampling times, and clinical and demographic details. A population pharmacokinetic model was built in NONMEM VI (FOCE INTER), with 1-, 2- and 3-compartment structural models tested. Inter-occasion variability was tested on CL, V1 and F, and allometric weight scaling added to CL and V a priori. Further covariates tested were body mass index (BMI), creatinine clearance (CrCL), serum creatinine, and age. Evaluation tools used were basic goodness of fit plots, stochastic simulations and estimations (SSE), visual predictive check, and an exposure comparison with a previously published model [1].

Results: In total 943 plasma concentrations from 46 patients (4-51 yr) on up to 12 occasions were collected. Following most doses (89%), 3 samples were taken, but in patients with concentrations persisting above 0.2 $\mu molL^{-1}$, more samples (up to 8) were collected. The 3-compartment model gave a significantly lower OFV than the 2-compartment, but this seemed to be caused by patients with higher concentrations providing more samples; an SSE was performed to investigate the impact of censoring on model selection, and the 2-compartment model was chosen.

Between occasion variability was added to CL, and CrCL was a significant covariate on CL. Despite a range of 13-36 kgm^{-2}, no further improvement in fit over allometric body weight was found when including BMI as a covariate. Parameters for a typical 70 kg individual with CrCL of 120 $mLmin^{-1}$ were: CL 12.9 Lh^{-1}, V1 69.7 L, Q 0.11 Lh^{-1}, V2 3.59 L, proportional residual variability was 29.6%.

Conclusions: A 2-compartment model with allometric weight and CrCL scaling adequately described the data, elevated BMI did not appear to affect methotrexate pharmacokinetics. Methods for handling the type of censoring in pharmacometric data seen in this study warrant further investigation.

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Andreas Lindauer Pharmacokinetic/Pharmacodynamic Modeling of Sunitinib in Healthy Volunteers

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Objectives: Sunitinib is a novel tyrosine kinase inhibitor approved for the treatment of advanced renal cell carcinoma and gastrointestinal stroma tumor [1]. It has been shown that sunitinib influences blood pressure as well as plasma concentrations of various proteins (VEGF-A, VEGF-C, soluble VEGFR-2 and VEGFR-3) linked to its antiangiogenic properties [2]. It has been proposed that these biomarkers might be useful for biomarker-guided dose individualization in clinical practice [3].
We are currently conducting an explorative study in healthy subjects to investigate the influence of sunitinib on the time course of these biomarkers. PK/PD models will be developed to evaluate the concentration-effect relationship for this drug.

Subjects and Methods: In a pilot phase 50 mg sunitinib were orally administered to 4 healthy subjects on 3 consecutive days. In the (ongoing) main phase the same dose was given to 8 subjects on 5 days. Blood samples were drawn frequently. Plasma concentrations of sunitinib and its major equipotent metabolite (SU12662) were determined by LC-MS/MS. Concentrations of circulating biomarkers were measured by immunoassays. PK/PD analysis was performed using NONMEM 6.2.

Results: A multi-compartment model that accounts for systemic and pre-systemic formation of the metabolite was simultaneously fitted to concentrations of sunitinib and SU12662. The model also included a series of transit compartments mimicking delayed absorption. PK parameter estimates for the first 4 patients were in excellent agreement with published data [4]. The biomarkers changed in the same direction as it was previously observed in cancer patients [2]; VEGF-A levels and blood pressure increased whereas levels of VEGF-C, sVEGFR-2 decreased after sunitinib administration.

Conclusions: These preliminary results indicate that biomarker response to sunitinib exposure also occurs tumor-independently in healthy volunteers.
Since the main part of the study is currently ongoing (last study day 3rd of April) final results and PD models for the biomarkers will be included in this abstract as soon as they are available.

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Laurent Nguyen Validation of a neutropenia PK/PD model built from intravenous vinflunine and its application to design phase I trials with oral vinflunine

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Objectives: Vinflunine (VFL) is a fluorinated microtubule inhibitor and its dose limiting toxicity is neutropenia [1]. A semi-physiological population PK/PD model of chemotherapy-induced myelosuppression had been previously developed from early phase I data with intravenous (IV) VFL [2]. The first objective of the study was to qualify this PK/PD model based on larger datasets from VFL IV studies with and without PK information. The second objective was to use this model for designing phase I studies with oral VFL and exploring new dosing schedules.

Methods: The model was developed from single agent studies (n=210 patients and 423 administrations) with different schedules (D1q1W, D1q3W, D1/D8q3W). A linear four-compartment model was used to fit the PK data. The time course of neutrophils was fitted using the established PD model [2] consisting in 1 proliferative, 3 transit and 1 circulating compartments plus a feed-back loop. Data were analysed with the NONMEM program (version VI.0) using the FOCE interaction method. An internal validation was performed using VPC for both PK and PD data. An external validation was performed on clinical data not including PK: frequencies of toxicity grades were compared between simulations and observed IV data.
Simulations of fractioned oral doses were performed by mimicking oral PK profiles (information obtained from a pilot bioavailability study) and by comparing haematological toxicity among different schedules with the same dose intensity.

Results: Both the VFL concentrations and the neutrophil data were well described by the PK/PD model. VFL PK showed moderate inter-patient (CV ~ 25%) and little inter-occasion (CV < 10%) variabilities whereas PD variabilities were higher (CV > 20%). External validation demonstrated that mild or severe grades of neutropenia were well predicted following IV administration of VFL. Concerning oral VFL simulations, lower doses and more continuous administrations (shorter wash out interval) were associated with better tolerability (*e.g.*: D1-5, D8-12 q3W *vs* D1-D5q3W). Constant exposure (daily regimen) showed also good tolerability.

Conclusions: The validation confirmed the consistency of the model with IV VFL and enabled to implement and use new clinical designs for oral VFL. The current preliminary results in phase I trials are in line with the simulations.

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Celine Pitou Modelling of PK/Efficacy/Toxicity in rats to help design a First Human Dose for a cell cycle inhibitor X

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Objective: The primary objective of PK/PD modelling in preparation of the FHD study was to estimate a pharmacologically effective and safe dose range in humans, based on preclinical data. In addition, doses and administration schedules for this compound were optimized in order to minimise the duration of neutropenia.

Methods: Two mechanistic rat models were built sequentially: the first one describing the efficacy, the second one describing the toxicity. These rat models were generated as follows:
- PK/efficacy model describing the tumour growth rate proportional to both the drug concentration and the number of proliferating tumour cells in both the placebo and the treated groups,
- PK/Tox model describing the neutrophil count over time as a function of the drug concentration. An allometric scaling approach was also applied to predict the human PK parameters. The fully integrated model was then connected to the projected human PK model.

Results: The two fully mechanistic models adequately described the tumour growth and neutrophil data in the rat. A linear relationship between tumour regression and myelosuppression was characterized, allowing to select a targeted efficacious exposure while maintaining myelosuppression to an acceptable level. A similar linear relationship between efficacy and toxicity was assumed in human and the same approach was adopted using an humanised neutrophil model connected to the projected human PK model. The result of the simulations in humans suggested that a dose range of A-E administrated once every 21 days in human was expected to provide efficacy while maintaining neutropenia to a manageable level.

Conclusions: This modelling study combined both efficacy and toxicity rat data within one fully integrated mechanistic model. This integrated model described the rat data adequately and helped connect efficacy and toxicity outcomes. The model was translated to human to derive an efficacious and safe dose range for the FHD study.

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Christian Pobel Time to event models of survival in cancer of pancreas : confirmation of explanatory variables pre-selected by bootstrap analysis.

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Objectives: Treatment of pancreas cancer often involves protocols out of references. These are argued by phase 2 studies, small cohorts studies or case reports. Important goal is to rank these protocols according to efficacy and safety.This ranking and associated statistical models are of potential interest for patient, help to proritize phase 3 studies to undertake, help to design phase 3 studies. Multivariate statistical analysis lead to select appropriate explanatory variables, with events of interest like progression free survival, tumor size kinetics, score of toxicity, and for this study time to death. Here modelisation involve logistic regression, Weibull model, in order to confirm explanatory variables pre-selected by 2-stage bootstrap analysis.

Methods: The population multivariate analysis was performed using NONMEM based on datas from a cohort of 42 unselected patients. Logistic regression and Weibull models were implemented in NONMEM with prediction of probability of death (at 12 months)(1)(2) , and probability of non observed event, respectively. Confirmation of explanatory variables pre-selected was test on individuals predictions.

Results: 42 patients were analysed, with combinations of 12 different protocols of chemotherapy. 16 pre-selected variables were : age (more or less 65), stage at diagnosis (local or metastatic) , number of treatment lines (more/less 2), first protocol schedule, prior surgery, dose reduction, platinium salt introduction, gemcitabin-oxaliplatin protocol exposure, erlotinib exposure. Check of individual probabilities predictions against the variables showed agreements with 2-stage bootstrap selection.

Conclusions: Such models as part of more global analysis strategy can take into account separation of sources of variability (by use of mixed effects models), and interactions between explanatory variables. This techniques are efficient for sparse and heterogenous datas like outliers of references in cancer treatment. This methodology will improve the determination of the prognostic indicators. Such approach could also be part of methods be used for clinical trial simulation, a technique allowing to avoid clinical studies having a high risk of failure, and to properly design future clinical trials.

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Angelica Quartino A semi-mechanistic myelosuppression model of docetaxel treatment in liver impaired patients

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Objectives: Docetaxel is a commonly used anti-cancer drug. Due to higher incidence of severe neutropenia in patients with impaired liver function it is rarely given to these patients. A PK model including covariates have been developed for docetaxel in normal and liver impaired patients [1]. However, it is not yet established if a patient with liver impairment has the same concentration-toxicity relationship as a patient with normal liver function. The aim of the study is to develop a PKPD model describing the docetaxel induced neutropenia in patients with normal and impaired liver function and to explore patient factors that may explain differences in toxicity.

Methods: In the study, 77 cancer patients were treated with docetaxel (75, 50 or 40 mg/m^2 depending on liver function). Neutrophils were recorded on day 0, 7, 14 and 21 during one cycle of treatment. Individual concentration-time profiles were generated using the published population pharmacokinetic model for unbound docetaxel [1].

A semi-mechanistic model of myelosuppression [2], with some modification [3], was used to describe the neutrophil time-course, e.g. the drug-related effect was described by a sigmoid Emax model.A step-wise covariate analysis was performed. The covariates evaluated were patient demographics, α1-acid glycoprotein (AAG), haemoglobin and liver function variables: liver function group (LFG) and ERMBT (erythromycin breath test). The patients were divided in to LFG according to their AST, ALT, AP and bilirubin levels, where group 1 has normal liver function and group 2, 3A and 3B has increasing severity of liver impairment [1].

Results: In the first step liver function group was evaluated. Patients with impaired LF (2, 3A, 3B) were found to have a higher baseline ($p<0.05$) and EC50 ($p<0.01$) compared to patients with normal liver function. In the second step the remaining covariates were investigated. Patients with high levels of AAG were found to have a lower Emax and a higher Baseline than patients with low AAG levels, which supports earlier findings [4]. The addition of a linear increase in baseline with age further improved the model.

Conclusions: The integrated PKPD model describing the time-course of neutropenia showed that when the difference in PK has been considered, patients with impaired liver function are less sensitive to docetaxel than patients with normal liver function. The model described the data well and showed good simulation properties. Also other factors significantly improved the predictability of the model and decreased the unexplained variability between patients.

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Alexandre SOSTELLY Simultaneous modelling of PSA production in Prostatic Benign Hyperplasia (PBH) and prostatic adenocarcinoma patients treated by prostate surgery

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Objectives: Prostate Specific Antigen (PSA) is mainly produces by prostate and is used as a biomarker of prostatic diseases. Prostatic Benign Hyperplasia (PBH) is a benign adenoma developed within transitional zone and treated by its removal [1]. Prostatic adenocarcinoma initially develops in peripheral zone and is treated by radical prostatectomy [2]. The aim of this work is to characterise PSA production from each part of the prostate (transition zone, peripheral zone, cancer zone) using a semi-mechanistic model in order to better characterize patient relapse.

Methods:
Patients: Postoperative PSA concentrations for 149 patients with prostatic diseases: 81 PBH patients treated by Millin´s adenomectomy and 68 cancer patients treated by radical prostatectomy were assessed [3]. Patients' characteristics were similar in both cohorts and a mean of 2.5 assays per PBH patient and 9 per cancer patient were available. No preoperative PSA concentration was available. Prostate volume, prostate residual volume and tumor weight were assessed after surgery but information was missing in 20% of patients.
Model: Non linear mixed effects model including IIV was fitted to the PSA plasmatic concentration. Different rates of PSA production for peripheral zone, central zone and cancer zone and PSA elimination from plasma were described by first order constant. Prostate volume was treated as observations in order to handle missing data. Model was built firstly on PBH and cancer data separately and then simultaneously on both subpopulations using NONMEM VI with FOCE.

Results: PSA concentrations were best described by a two-compartment model with elimination from the plasma compartment. Parameter estimation was supported by both datasets. PSA elimination was "directly" observed in cancer patients after radical prostatectomy (no more PSA production) and PSA production from transition zone was observed in PBH patients after Millin's adenomectomy (residual PSA production). Rates of PSA production were in accordance to their description in the literature: higher rate in cancer zone than in peripheral zone than in central zone. Model evaluation was performed using classical goodness of fit and visual predictive check.

Conclusions: A model for PSA production, distribution and elimination was built in PBH and cancer patients after surgery. In the future, this model may be used to assess the quality of prostate surgery and to help the prediction of relapse risk after prostate surgery.

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Mirjam Trame Population Pharmacokinetics of Dimethylacetamide in Children During Once-daily and Standard IV Busulfan Administration

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Objectives: *N,N*-dimethylacetamide (DMA) is applied to children during high-dose chemotherapy as a solubilizer with the intravenous (IV) formulation of busulfan (Busilvex®). DMA has shown liver toxicity in rats, but relatively little is known of the behaviour of DMA in humans. This investigation was conducted because of concerns of altered pharmacokinetics after high doses of DMA in children. In a previous investigation (J Clin Oncol 25:1772-1778, 2007), we analysed the pharmacokinetic of DMA in 18 children. To confirm the results, we applied the model to a new dataset from children receiving a once-daily schedule of IV busulfan before combining the datasets from both schedules.

Methods: Out of fourty-three children receiving busulfan before bone marrow transplantation aged 0.1 to 18.9 years (median age 2.7), 18 children received IV busulfan as a 2 h infusion every 6 h in 15 doses of 0.7 to 1.0 mg/kg. Each dose contained between 5 mmol (437 mg) and 70.5 mmol (6142 mg) of DMA. The other 24 children received IV busulfan as 3 h infusion once daily for 4 consecutive days with a targeted AUC of busulfan of 4263 µM x min. The DMA concentration during this regimen devoted to be between 11 mmol (988 mg) and 105 mmol (9464 mg) per dose. All samples were analysed by LC-MS with a limit of quantification of 0.25 mg/L. By means of population pharmacokinetic modelling using nonlinear mixed-effects modelling (NONMEM) plasma concentration-time data were analysed. Several covariates such as age, body weight and body surface area were tested on their effects on the pharmacokinetic parameters.

Results: Peak plasma concentrations of DMA up to 3.09 mmol/L for the standard dosing and up to 8.77 mmol/L for the once-daily dosing were observed, respectively. Using a one-compartment model with clearance (Cl) increasing by 0.17% per hour the DMA kinetics was best described. By using body weight as a covariate for Cl and volume of distribution (V) the best results were obtained. The final population estimates for both dosing regimens of busulfan resulted in a $Cl_{initial}$ of DMA of 77.2 ml h^{-1} kg^{-1} ± 57.6% and a V of DMA of 493 ml kg^{-1} ± 26.5% (population mean ± interindividual variability). Interoccasion variability (IOV) for $Cl_{initial}$ (31.5%) was lower than interindividual variability.

Conclusion: Including the new dataset we were able to confirm the population pharmacokinetic model from our previous study without observing significant differences in $Cl_{initial}$ and V between the two cohorts.

Johan Wallin Model Based Neutrophil Guided Dose Adaptation in Chemotherapy

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Objectives: Severe neutropenia is one of the most important dose limiting events in many anticancer regimens. One of the most employed approaches to this problem has been to reduce the consecutive dose in fixed steps, commonly by 25%. Another approach has been to use pharmacokinetic (PK) sampling to tailor dosing, but only rarely have model-guided computer-based approaches utilizing PK and/or pharmacodynamic (PD) data been used. A previously described semi-mechanistic model for myelosuppression has been used to characterize a wide range of anticancer drugs(1), and both interindividual and interoccasion variability (IIV/IOV) has been described for a number of agents(2). This knowledge could be used in a clinical setting to make model-based dose individualization, which compared to current stepwise procedures, may tailor doses in a more precise manner, and allow increased overall dose intensity in the population without increasing the risk for severe toxicity. In this study we investigated by simulations the outcome of model-based dose adaptation, and the influence of type and amount of data provided to the model. We also investigated the influence of IIV and IOV magnitudes for adaptation outcome.

Methods: PK and PD data were simulated for one thousand patients in five treatment courses. Different portions of data were used to obtain empirical Bayes estimates that were subsequently used to adjust the dose to a level predicted to result in a target neutrophil nadir. Performance was evaluated with different levels of IIV and IOV.

Results: In the presence of PD measurements, PK data provided little additional information. By a limited PD sampling the number of patients on target could be increased with the model-based approach compared to standard dose-adjustment methods. Thereby the model-based dose-adjustment method could facilitate increased overall dose intensity in the population, without a corresponding increase in patients experiencing severe neutropenia. The number of patients achieving target range neutropenia was increased by 27% compared to the standard method. Successful dose adaptation seemed to be more sensitive to IOV magnitude in the drug efficacy parameter than in other PK or PD parameters, whereas IIV magnitude was of little importance.

Conclusions: A model-based dose adaptation procedure with a limited neutrophil measurement schedule may increase the chance of success in treatment as it allows for increased dose intensity. When neutrophil counts are available PK data provide little additional information on the expected myelosuppression time-course.

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xiaofeng wang Population PK modeling and simulation to select a dosing schedule in Phase II trials for a novel TKI agent with time-dependent and nonlinear PK

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Objectives: Compared to other TKI agents, TKI258 additionally targets FGFR. Over 2 fold of induction of plasma VEGF was observed at 500mg/day, FGF23 induction was observed at 400 mg/day. Significant reduction in Ktrans (DCE-MRI) also occurred at dose 400mg above. However, prolonged and over-proportional exposure was observed at dose 500mg and above following continuous daily dose. The objective of the analysis was to applying modeling and simulation to selecting a dosing schedule that can achieve higher but under controlled exposure for Phase II clinical trials.

Methods: TKI258 plasma concentrations from 93 patients following continuous daily dose were used for model development. Time-dependent PK resulted from enzyme induction was characterized by an indirect-response model; the over-proportional increases in exposure was described by inhibitory metabolism. Different dosing schedules were simulated with the model. A "5 days on/2 days off" intermittent dosing schedule that can achieve higher but under-controlled exposure was proposed and tested in a new dose escalation study (mRCC trial). Model predictions were compared with observed concentrations from mRCC trial. The final dosing schedule for phase II trials was then determined based on the exposure and tolerability from clinical trials following different dosing schedules. .

Results: The population PK model well described the TKI258 time ~ concentration across 25 to 600 mg daily. Volume of distribution was 2440 L, suggesting extensive extravascular distribution of drug. The EC50 for enzyme induction (0.3 ng/mL) agrees with the observed time-dependent decreasing in exposure at the lowest dose of 25mg/day. The baseline clearance of TKI258 was 56 L/h, whereas the maximum induced clearance could reach 3 times baseline value. The IC50 for inhibitory metabolism of TKI258 (170ng/mL) also explains that over-proportional increase in exposure occurs only at dose 400mg above (at 400mg daily dose, the median Cmax is < 200ng/mL). The observed plasma concentration of TKI258 from the mRCC trial agreed well with the model predictions. At both 500mg and 600mg dose levels, no prolonged accumulation of TKI258 was observed. Steady state was achieved in the 2nd week. Higher exposure during TKI258 administration following the intermittent dosing schedule was achieved, while the tolerability was improved..

Conclusions: The intermittent dosing schedule suggested from model simulation and confirmed by the mRCC trial was selected as the dosing schedule for Phase II pivotal trial.

Claire Ambery Population PK-PD Modelling of Wheal and Flare Area in a First-Time-in-Human Study

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Objectives: To characterise the pharmacokinetic wheal and flare area relationship of a novel anti-histamine in healthy male subjects in a single ascending dose first-time-in-human study. The pharmacodynamic wheal and flare inhibition was estimated by assessment of the histamine induced cutaneous reaction (wheal and flare response). The purpose of the modelling work was to establish the concentration-effect relationship to inform dose selection in subsequent clinical studies.

Methods: A randomised, double-blind, placebo-controlled, cross-over single oral dose study was conducted in healthy male subjects over the dose-range 10-100 mg. The population pharmacokinetic-pharmacodynamic (PK-PD) analysis was performed using NONMEM VI utilising all data obtained in the study. A two-step sequential PK-PD methodology was employed. In the first step various compartmental pharmacokinetic models were fitted to the population data. In the second step an inhibitory pharmacodynamic model was fitted to the wheal and flare area population data accounting for the relationship between drug concentration and effect.

Results: A one-compartment pharmacokinetic model with first-order absorption which was allowed to change rate over time was selected and adequately described the pharmacokinetic time course. The inhibitory pharmacodynamic model adequately described the pharmacodynamic time course and accounted for baseline and placebo effect. Diagnostic methods and posterior predictive checks showed the goodness of fit of these models to the data.

Conclusions: A population PK-PD model of wheal and flare area response of a novel anti-histamine was developed from data obtained from healthy male subjects in a single ascending dose first-time-in-human study. The pharmacokinetic-pharmacodynamic model developed has been used to simulate repeat dose scenarios and to inform dose selection in subsequent clinical studies.

Kyle Baron Evaluation of Assumptions in the Clinical Use of the Cockcroft-Gault Equation

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Objectives: The Cockcroft-Gault (CG) equation is the most widely used method in US clinical settings for estimating creatinine clearance (CLCR)[1]. Clinicians commonly make adjustments to CG to improve estimation, such as using an alternate body size metric (e.g. ideal body weight) and rounding serum creatinine (Scr) up to 1 mg% in elderly subjects. A 15% reduction in CLCR is also assumed for female subjects. This study aims to evaluate the appropriateness of these adjustments.

Methods: A database of measured 24-hour CLCRs was assembled consisting of 748 measurements in 319 ambulatory subjects. The CG model was re-estimated on the current data using WinBUGS. Predictive performance measures[2] for the original CG equation were calculated after plugging in actual (WGT), ideal (IBW), lean (LW), or dosing (DW=IBW+0.4*(WGT-IBW)) weight into the equation. The distribution of percent prediction error (%pe) conditioned on different covariates was summarized. Confidence intervals (alpha=0.05) for %pe were constructed using non-parametric bootstrap methods. Models were constructed to estimate a data-driven body size metric for the original CG equation.

Results: WGT-normalized 24-hour excretion rate (EXCR) was regressed on AGE with a proportional reduction for female subjects. The estimates revealed a slower decline in EXCR with AGE (-0.13 [-0.16,-0.11] mg/kg/24hour/year in males) compared with the CG estimate (-0.2 [-0.22,-0.17]). On average, females had 11% [7-15%] lower CLCR compared with males, conditional on the other published CG parameters. Overall, using WGT in CG gave the least biased estimates of CLCR (median %pe: -5.8 [-8.8,-3.3]). Using IBW, LW, or DW in CG resulted in persistent under-prediction that increased with WGT. For subjects greater than 100 kg, median %pe was +2% when using WGT in CG, but -19.4% with DW, and -35% when using IBW. Models estimating a modified dosing weight for use with CG always reduced to WGT as the body size metric. Plots of %pe versus AGE and Scr indicate that rounding Scr to 1 mg% in the elderly gives estimates that are more negatively biased than those obtained with actual Scr values.

Conclusions: A 15% reduction in CLCR for females is a reasonable assumption. Using WGT in CG resulted in the least-biased estimates of CLCR. Using IBW, LW, or DW in CG resulted in poorer rather than improved estimates. Rounding Scr up to 1 mg% in elderly subjects also diminished the predictive performance of the CG equation.

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Martin Bergstrand Semi-mechanistic PK/PD modeling of Paracetamol and Sulfapyridine to characterize effects on gastric emptying and small intestinal transit

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Objectives: Drug-induced changes in gastric emptying (GE) and small intestinal transit time (SITT) can cause altered absorption of other drugs as well as constipation and diarrhoea. As a consequence, it is desirable to identify if drug substances alter these processes in an early stage of drug development. The paracetamol (PCM) and sulfapyridine (SP) double marker technique (1) is based on combined gastric administration of PCM and sulfasalazine followed by plasma concentration measurements for PCM and SP. Paracetamol is rapidly absorbed from duodenum and can be regarded as marker for GE. Sulfasalazine is poorly absorbed in the small intestine and is in colon extensively metabolized by bacteria into SP. As SP is absorbed from colon only it serves as a marker for SITT. Present explorative modeling of studies with the double marker technique aims to increase mechanistic understanding and develop a new standard study design and modelling approach.

Methods: Two similar double marker studies, one under fed and one under fasting conditions, each included 6 dogs each receiving, atropine (0.06 mg/kg), erythromycin (1 mg/kg), and vehicle treatment in a cross-over design. In addition, a study with two dogs receiving intragastric and intravenous infusions of PCM was included in the analysis. A semi-mechanistic compartmental population model was applied for simultaneous analysis of PCM and SP plasma concentrations. The influence of drug treatment and concomitant food intake was investigated for GE and SITT.

Results: Gastric emptying was described by a combination of an active and a passive process, both governed by first order rate constants. The active part of the GE was stimulated by erythromycin and potently inhibited by atropine treatment. For atropine, a concentration-effect relationship was identified based on *a priori* information on $t_{½}$ for atropine (~2 hr). The estimated IC_{50} corresponds to atropine concentrations four $t_{½}$ post dose. A chain of five transit compartments was found to best describe small intestinal transit. Erythromycin treatment significantly prolonged SITT whereas no effect of atropine was seen for this parameter. Food intake was identified to influence both GE and SITT in a complex manner, possibly corresponding to an initial transient increase in motility followed by a decreased motility for a longer duration.

Conclusion: Simultaneous modelling of PCM and SP is feasible and can increase mechanistic understanding of effects on GE and SITT.

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method using salicylazosulfapyridine and acetaminophen as the marker compounds for determination of the gastrointestinal transit time in the dog. Chem Pharm Bull (Tokyo). 1990 Oct;38(10):2810-3.

Dmitry Bordin Relating Pharmacokinetics and Pharmacodynamics of Proton Pomp Inhibitors (PPIs) to Clinical Performance in Patients with Gastroesophageal Reflux Disease (GERD)

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Objectives: The aim of the study was to estimate pharmacokinetic (PK) parameters of PPIs after a single oral dose and repeated dosing and to evaluate the relationship between PK, pharmacodynamic (PD) and clinical efficacy parameters in GERD patients.

Methods: PK, PD and clinical efficacy data were prospectively collected in 66 GERD patients (median age 38.9 years, male 79%). At baseline, in all patients, GERS symptoms (heartburn and acid regurgitation) were scored, upper gastrointestinal endoscopy and 24-h intraesophageal pH monitoring were performed. Then the patients were randomized into 3 treatment groups: omeprazole 20 mg twice a day, lansoprazole 30 mg once a day and pantoprazole 40 mg once a day. The patients underwent pH- and PK- monitoring at day 1 and at day 7 of PPI therapy. Sampling schedule for PK study was the following: baseline (predose), then every half an hour up to 4 h postdose, 5, 6 and 12 h postdose. The PK parameters – AUC, Tmax, Cmax, kel have been estimated from measured plasma concentration profiles via non-compartment approach. Every day, the patients assessed intensity of GERD symptoms according to the Likert scale in their diaries.

Results: 25 patients were enrolled in omeprazole group, 22 received pantoprazole and 19 – lansoprazole. The PK analysis showed that, in average, at day 1 compared to day 7, patients in the omeprazole group had a significant increase in AUC and Cmaxvalues, on the contrary, patients in other groups had similar mean AUC and Cmax values on single and repeated dosing. Pantoprazole group showed the biggest mean AUC value. Initially, individual values of DeMeester score and of percent of time with pH in esophagus

Conclusions: A wide interindividual variability in PK parameter values was observed in all groups. AUC after oral dosing was the PK parameter that is the best predictor of antisecretory effect. The bioavailability of omeprazole increased during the first 7 days of oral dosing. The biggest pantoprazole average AUC value can probably explain the superior efficacy at its usual use.

Adriaan Cleton Enhanced quantitative drug development (EQDD) of a selective PDE5 inhibitor for the treatment of benign prostatic hyperplasia (BPH)

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Objectives: Enhanced quantitative drug development (EQDD) is a global initiative at Pfizer to promote the development of integrated analysis (models) of available data (internal and external sources) and their application to inform strategy, trial design and decision-making in drug development[1]. This quantitative approach was used in the development of UK-369,003, a selective PDE5 inhibitor. The Phase 2 program (2 studies) was complex with multiple endpoints to meet the objective of delivering proof of concept for male lower urinary tract symptoms. These endpoints included traditional assessment for overactive bladder (OAB), erectile dysfunction (ED) and benign prostatic hyperplasia (BPH). Traditionally, the joint analyses of the two Phase 2 studies would be used to inform the Phase 3 ‘go/no go' decision. However, this was not the first time Pfizer had investigated a NCE for the treatment of OAB, ED or BPH nor was it the first indication investigated for UK-369,003. In addition, there was much published literature giving study summaries of other such investigations. It was therefore logical to use these additional sources of information to help support any UK-369,003 Phase 3 decision. The aim of this presentation is to discuss how EQDD was successfully implemented and delivered on time for a more informed ‘go/no go' Phase 3 decision for UK-369,003. For brevity details will focus on the EQDD activities related to the treatment of BPH.

Methods: EQDD building blocks:

- **EQDD sub-team:** Core to implementation and timely delivery of EQDD at Pfizer is the early formation of an EQDD sub-team. Consisting of at least one Clinician, Statistician, Pharmacometrian and Clinical Pharmacologist from the UK-369,003 study team (see Pfizer author list), the team met on a weekly basis to discuss and manage the EQDD strategy, responsibilities and timelines.
- **EQDD plan:** Outlined the key individual EQDD components, responsibilities and timelines.
- **Unblinding strategy:** Early start to modeling and simulation activities were achieved by unblinding key individuals to the data.
- **Knowledge management:** Data sources were reviewed to include prior internal information on UK-369,003, data from previous internal BPH studies and selected external literature information on placebo, current competitor (tamsulosin) and potential competitors (other PDE's).
- **Decision criteria:** Based on both regulatory and commercial profiles, quantitative decision metrics were developed for the UK-369,003 ‘go/no go' criteria.
- **Dataset creation:** Patient-level internal datasets were produced by our internal programming group and specified external literature data was extracted by an outside vendor.

- **Restricted access repositories:** Unblinded UK-369,003 datasets were developed and stored in restricted access folders (CDARS). All modeling and simulation activities were undertaken in our ePharmacology grid repository or by restricted access folders set-up by external consultants.
- **Modeling & simulation:** A non-linear PK model and exposure/AE models were developed using internal data collected from 21 UK-369,003 Phase 1 and 2 studies[2]. Internal and external efficacy datasets were merged into a LIKE dataset and integrated using a model based meta-analysis. The efficacy response (IPSS) was described by a non-linear hierarchical random effects model and probability of technical success was predicted using simulation[3,4].

Results: No clear decision could be made using just the data from the two Phase 2 studies. However, combining additional internal and external data with timely delivery of EQDD enabled a more informed 'go/no go' decision. Although UK-369,003 would meet the regulatory guidelines for the treatment of BPH it was unlikely to meet the target commercial profile. As a result, further development of UK-369,003 was stopped.

Conclusion: Successful application of EQDD involved:

- Collaboration between Clinical, Statistics, Programming, Pharmacometrics, Clinical Pharmacology, Project Management & Clinical Study Management.
- Endorsement from TA Senior Management to the EQDD strategy and 'go/no go' decision criteria.
- Early start to the EQDD process, ideally at the design stage.
- Early formation of an EQDD sub-team that met regularly.
- Early buy-in from commercial to develop quantitative metrics by which a meaningful 'go/no go' decision could be achieved.
- Timely delivery of EQDD components.

Although the development of UK-369,003 was terminated, this was considered to be a successful application of EQDD by enabling a quantitative and clear decision.

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Jonathan French Safety monitoring of a kidney transplant study using a Bayesian time-to-event model

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Background: Studies to investigate new treatments to prevent kidney rejection are typically active controlled studies with a primary endpoint of Month 6 biopsy proven acute rejection (BPAR). When designing these studies, there is a strong desire to monitor the study in an on-going fashion and use formal stopping rules to stop the study quickly if the experimental treatment is clearly inferior to the active control. However, because the endpoint can be 6 months from randomization, stopping rules based on the primary endpoint can be inefficient. We desired a model and stopping rule that allowed for formal incorporation of historical control data and that does not require waiting until subjects reach the Month 6 endpoint. To this end we examined stopping criteria based on estimates from a Bayesian time to event model for BPAR.

Methods: Based on a review of the literature for the active control, we developed a Bayesian piecewise exponential time-to-event model for BPAR. We assumed that the hazard function was constant over pre-specified intervals of 0-1 week, 1-4 weeks and 4-26 weeks post-transplant and not necessarily monotonic. Through moderately informative prior distributions, we formally incorporated information about historical BPAR rates for the active control. For the experimental treatment we used weakly informative priors. This model was used to estimate risk of rejection within 6 months.

We investigated stopping rules that were based on both a comparison to active control and absolute BPAR rates. Through simulation we evaluated the operating characteristics of the proposed stopping rules and compared them to classical stopping rules based on comparing hazard rates through a log-rank test.

Results: With this approach we developed stopping rules that yielded a high probability of stopping the study very quickly if the risk of rejection is much higher than the control rate and a moderately high probability of stopping before 25% of the patients are enrolled if the BPAR rate is double the control rate. The false stopping rate was controlled at a pre-specified level. The Bayesian approach was substantially better than the classical stopping rules.

Conclusions: Bayesian time-to-event modeling of acute rejection can enable efficient early monitoring of transplant studies. By formally incorporating prior belief into the analysis, we can stop earlier than with traditional stopping methods when the risk of BPAR is high.

Iztok Grabnar Population Pharmacokinetics of the Active Metabolite of Leflunomide in Patients with Rheumatoid Arthritis

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Objectives: Leflunomide is a disease-modifying antirheumatic drug. It is converted to the active metabolite A77 1726 with immunosuppressive effects. In the first year of treatment 40 - 70% of patients are withdrawn from therapy due to adverse drug reactions (ADRs) or lack of efficacy [1]. A study on microsomes suggested that CYP1A2, CYP2C19 and CYP3A4 may be involved in the metabolism of leflunomide to A77 1726 [2] and CYP1A2 was associated with leflunomide toxicity [3]. The aim of this study was to assess pharmacokinetics of A77 1726 to evaluate the influence of genetic polymorphisms of CYPs on interpatient variability in A77 1726 concentration and to explore the relationship between drug exposure, efficacy and toxicity.

Methods: Pharmacokinetic analysis was performed using NONMEM 6.2 and PSN 2.3 based on steady-state plasma samples. A one-compartment model and FOCEI were used. The influence of demographic, biochemical and genetic parameters on pharmacokinetics of A77 1726 was investigated. To explore the relationship with clinical effects, Bayesian estimates of CL/F were used to calculate average steady-state concentration (Css) in individual patient. Patients were divided at the median values of the clinical assessments into low and high group and differences in Css were tested by Mann-Whitney U test.

Results: The study enrolled 71 patients who provided 213 concentrations. CL/F was estimated at 0.0302 L/h and an inter-individual CV of 78%, while V/F was estimated at 8.55 L. Residual variability was 7.48% (proportional) and 0.250 mg/L (additive). Absorption rate was fixed at 1 h-1. Inter-individual variability in V/F could not be estimated. Patient's renal function and CYP2C19 polymorphism had an influence on CL/F. In carriers of CYP2C19*2 allele CL/F was 71% higher compared to non-carriers. V/F was affected with patient's gender. Css was associated with the response. Patients with high decrease in C-reactive protein (CRP) had higher Css compared to patients with low decrease in CRP. No association of Css with ADRs was observed.

Conclusions: Our results suggest that genetic variability in CYP2C19 and variability in renal function influence plasma concentration of the active metabolite of leflunomide which is associated with the treatment response.

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Thaddeus Grasela Improving the Efficiency and Ensuring the Quality of Data Assembly for Pharmacometric Analysis

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Introduction: The creation of an analysis-ready dataset consists of preparing a time-ordered sequence of events for each subject, based on a statement of clear and concise specifications for the analyses. Once data programming begins, the programmer is likely to face a host of issues that arise from deficiencies in the specifications or inconsistencies between the specifications and raw data. These issues typically spawn a series of e-mails and discussions between the project team members. In the process of answering these questions, more specific questions are formulated as the team members clarify issues and resolve uncertainties. The cycle of questioning and discussion is a valuable source of information on how to improve specifications and reduce the time and effort required for data assembly.

Objectives:

1. Analyze e-mail communications between team members to identify common issues
2. Incorporating findings into formalized programming specifications

Methods: A systematic analysis of communications between programmers and pharmacometricians generated during the course of data assembly for numerous independent projects was performed. Information extraction and discovery techniques were utilized to uncover the most frequently discussed topics, issues and problems. These issues and the attendant queries and answers were used to develop formal programming specification forms.

Results: Inadequate or incomplete information regarding analysis population selection and dosing were common issues. Of these, issues pertaining to dose were most important. For example, proper dosing specification requires instructions on handling first dose versus multiple dose, criteria for ascertaining steady-state, and instructions for managing multiple doses prior to achieving steady-state.

The specification forms were deployed in conjunction with a secure, website (wiki) to capture communications between scientists and programmers in a structured format. System-generated and user-provided metadata serve to facilitate the discussion and resolution of residual issues. Subsequent review will enable future refinement of the specification forms.

Conclusions: The development of these specification forms is anticipated to improve the performance characteristics of data assembly in terms of consistency, reliability, timeliness and quality. Future work will involve quantifying the benefits of these improved programming specification forms.

Roger Jelliffe Optimal Stochastic Control Of Drug Dosage Regimens

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Objectives: Maximally precise dosage regimens.

Methods and Results:

1. Nonparametric (NP) population PK/PD modeling. NP models estimate the entire most likely joint parameter distribution [1]. The distribution is supported at multiple discrete points, up to one for each subject, each with an estimated probability [1-3].

2. Determining assay noise as Fisher information, not CV%. CV% provides no method for weighting data. Fisher information [4] does, and avoids censoring low data.

3. Estimating environmental noise. This can then be estimated, as a separate term, quantifying the contribution of both noise sources.

4. Evaluating Changing Renal Function in Clinical Settings. Most methods for estimating creatinine clearance (CCr) assume stable renal function and use only a single serum creatinine (SCr). We use pairs of SCr's and calculate the CCr that would make SCr change from the first to the second value over a stated time in a acutely ill patient of stated age, gender, height, and weight [5].

5. Multiple Model (MM) dosage design. The many NP model support points provide multiple predictions of future responses to a dosage regimen. Each prediction is weighted by the probability of its support point. One can calculate the weighted squared error of the failure of any regimen to hit the target, and find the regimen specifically minimizing this error [6,7].

6. MM Bayesian Analysis. This computes the posterior probability of each support point given the population model and an individual patient's data. Usually a few or one point remain. Most become negligible. That distribution is used to develop the next MM dosage regimen.

7. Hybrid Bayesian (HB) Analysis. As an unusual patient may be outside the population parameter range, a MAP Bayesian estimate is first made. Extra support points are added in that area. This "hybrid" population model is then used for MM Bayesian analysis.

8. Interacting MM Bayesian (IMM) Analysis. An unstable patient's parameter values may change. Current Bayesian methods assume fixed values. We implemented a sequential interacting MM (IMM) Bayesian method which permits a patient's posterior support points to change to others with each new

dose or serum concentration if more likely [8]. In over 130 post cardiac surgery patients on gentamicin and over 130 on vancomycin, IMM tracked drugs better than other methods [9].

Conclusions: Maximally precise therapy with toxic drugs requires specific methods. The above methods now provide this [10].

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Helene Karcher Interpreting QT in a Patient Population After Surgical Intervention

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Objectives: A drug D was tested patients after a surgical intervention in two Phase II trials. The standard of care includes drugs such as M that can have deleterious side effects. The goal of clinical program is to assess the minimization or replacement of M with the potential new agent D. To that purpose the two trials included treatment arms with M as a comedication or alone as control. A cardiac safety concern arose in one study as a higher proportion patients with at least one ECG (electrocardiogram) sample for which deltaQTcF>30ms in the D + M treatment arm in comparison to the control arm. The aim of this analysis was to assess the robustness of this finding by looking at the raw QTcF data and furthermore determine whether any apparent change in QTcF is correlated with D concentration.

Methods: Pharmacokinetic data and ECG (electrocardiogram) samples were collected in two phase II trials with drug D and comedication/standard of care M. Clinical data exploration and analysis were carried out with the software R. Assessment of cardiac safety was based on QTcF data, the time between the start of the Q wave and the end of the T wave in an ECG signal, Fridericia-corrected by the heart rate [1].

Results: (i) Neither study has a constant QTcF signal over time. Instead, large (~40ms), systematic change in QTcF over time are seen in control arms in both studies after the surgical intervention. Hence, evaluating cardiac safety with ΔQTcF does not make sense in these studies. In all 5 arms of the 2 studies, the whole distribution of QTcF values changes systematically with time, independent of drug treatment. The magnitude of systematic changes in QTcF across trial periods is much larger than any apparent between-treatment differences. (ii) Observed maximum QTcF values in a patient depend on the number of ECG samples taken. The number of ECG samples per patient, per treatment and per treatment period is not constant in both studies. In particular, more samples were taken in the 0-12 week period in all treatment arms. This is consistent with a higher maximum QTcF in this period. In contrast, the median QTcF decreases consistently with time in all treatment arms. As a consequence, the higher incidence of elevated QTcF values in this period is most likely an artifact of sampling frequency. (iii) No apparent correlation between QTcF and drug concentration was observed for any treatment (D or M).

Conclusions: Text The analysis shows that random & systematic variability in QTcF confounds assessment of any potential drug-induced effect in both studies. A large, systematic treatment-independent change in QTcF of approximately 40 ms in the 12 weeks following the surgical intervention impedes the cardiac safety evaluation using deltaQTcF.

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Andreas Kuttler A 3D mechanical model of the gastric esophageal junction: model-based assessment of muscle stretch tension in the gastric smooth muscle with emphasis to reflux disease

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Objectives: Gastroesophageal reflux disease (GERD) is a complex disease that is influenced by a number of biomechanical variables. It occurs following transient relaxation of the lower esophageal sphincter (LES). These relaxations (TLESRs) allow acidic stomach contents to reflux into the esophageal lumen, where exposure of the esophageal lining to the acidic refluxate causes gradual erosive damage. The objective of this modeling exercise was to develop a computer-based model that describes the biomechanical processes involved in the onset of TLESRs. In particular, the model, in combination with experimental measures, can be used to obtain a quantitative measure of the stretch-tension relationship at the stomach wall.

Methods: The 3D mechanical model of the stomach includes an approximation of the orientation of muscle structure and support conditions, both estimated from the literature [1,2]. Starting from an initial geometry [1], features such as stomach filling, the accommodation process, as well as adaptations to environmental conditions (e.g., abdominal pressure, breathing) can be reconstructed from first principles. Quantitative information and relationships, important from a biomechanical perspective, such as Lower Esophageal Sphincter (LES) properties or the stretch-tension state in the smooth muscle may be derived from these conditions.

Results: The model shows a significant influence of material properties (e.g., fiber orientation or smooth muscle tone) and the surrounding organs (e.g., local elasticity) on LES competence and stretch-tension conditions in the stomach wall. With appropriate experimental inputs such as shape and volume information for different stomach fillings and their corresponding intragastric pressure states, a comparison of stretch-tension relationships in subjects with different conditions in clinical research has become feasible. The model has been qualified to represent the actions of agents such as erythromycin and glucagon, which have opposite effects on the compliance of the stomach [3].

Conclusions: In this work, we present a methodology whereby the measurement of a key variable in the pharmacology of a complex disease is enabled through a model-based analysis of experimental results. This variable, the stretch-tension condition and its effect on the LES, is believed to be one critical part of the difference between healthy and disease physiology. There is no direct way to measure this quantity, so an indirect use of a computer model provides a valuable option to clinical research.

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Lia Liefaard Modelling non-linear dose-dependent absorption profiles after oral prolonged release formulations

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Objectives: After oral administration of prolonged release tablets of a new candidate drug compound, complex absorption profiles were found that showed high inter-individual variability and multiple peaks. In addition, dose dependencies in C_{max} but not in AUC were observed after initial exploratory analysis. The objective of the study was to develop a population PK model that was able to describe the complex absorption adequately.

Methods: Data from five phase 1 studies were included in this population PK analysis. 140 patients were dosed (SD) with 50-250 mg of a prolonged release formulation of a new candidate drug compound. 26 subjects took the study drug after a high-fat, high-calorie breakfast (non-fasted conditions), 84 subjects took the study drug under fasted conditions, and 30 subjects took the study drug under fasting and non-fasting conditions in a crossover design. Data for all dose strengths are available under fasted conditions, and for the 250 mg dose only under non-fasted conditions.

The absorption process was explored using deconvolution of the raw data, in which the rate of absorption was estimated for arbitrarily chosen small time frames. For deconvolution, all disposition parameters were fixed to the values obtained from data analysis after administration of an immediate release formulation of the compound and bioavailability was set to 1. Nonmem 6.2 was used for model building.

Results: Deconvolution displayed two peaks in the absorption profiles of which one showed dose dependency. Two absorption routes were used to describe the absorption process. A buffer compartment with first order absorption (ka_1) was used to describe the immediate dose-independent absorption peak. A time-dependent first order rate constant (ka_2) with saturation was required to describe the slower, dose-dependent absorption peak. Furthermore, ka_2 appeared to be doubled for non-fasted subjects. Drug disposition was described by a 1-compartment model with linear elimination from the central compartment.

Conclusions: Deconvolution of the initial raw data is a valuable tool in assessing the components of the absorption process including detection of the dose-dependent process. The data were well described after including a mathematical description of these processes in the proposed PK model.

Igor Locatelli Population Pharmacokinetic Analysis of Silymarin Bioavailability in Rats

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Objectives: Silymarin, an extract of the seeds of Silybum marianum L. (milk thistle), is used for treatment of liver diseases. It contains several active flavonolignans; the major are silybin, which is a mixture of diastereomers A and B, and silychristin [1]. Low bioavailability of silybin and silychristin is related to low solubility of dry extracts. In order to enhance the solubility, S. marianum dry extract was coground with two polymers: crospovidone (PVP-CL) and carboxymethylcellulose (Ac-Di-Sol) [2]. In this study population PK analysis was used to investigate the relative bioavailability of silybin A, silybin B, and silychristin for the coground systems.

Methods: A new HPLC-UV method was developed for quantification of the three components of interest [2]. The amount of silybin A, silybin B, and silychristin in S. marianum dry extract was 17, 16, and 21%, respectively. Two dose levels of the dry extract (50 and 100 mg/kg), one dose level for Ac-Di-Sol coground system (50 mg/kg) and three dose levels for PVP-CL coground system (50, 100, and 200 mg/kg) were administered to rats. Single blood samples per animal were drawn at 0.5, 1, 2, and 4 h post dose. The plasma concentrations were modeled separately for each of the compounds measured. BLQ levels were replaced with LLOQ/2 values. The base model was a one compartment model with first order absorption and interanimal variability on CL/F and V/F. Residual error was fixed to the highest variability of the assay for the quantified concentrations and to 25% for the BLQ levels [3]. FOCE with interaction was used for parameter estimation in NONMEM.

Results: Bioavalability for Ac-Di-Sol coground system compared to the dry extract was 20, 6.2, and 7.1 times higher for silybin A, silybin B and silychristin, respectively. Comparing PVC-CL coground system to the dry extract, 5.9 and 3.2 times higher bioavailability was noted for silybin A and silybin B, respectively, while for the silychristin it was lower (0.76). Additionally, for silybin A and silybin B bioavailability decreased with dose.

Conclusions: The bioavalilability of silymarin components was substantionally improved in Ac-Di-Sol coground system. However, lower bioavailability can be expected with higher doses.

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Guangli Ma Quantifying Lung Function Progression in Asthma

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Objectives: Lung function is an important indicator of asthma [1]. Although the relationship between aging and lung function in healthy people has been previously studied [2], lung function progression in asthma has not been similary explored [1]. This study aimed to quantify lung function, expressed as FEV1, progression of asthma and to evaluate short-term and long-term effects after formoterol and terbutaline treatments.

Methods: The FEV1 data set was collected from two randomized, double-blind, multi-centre, parallel designed clinical trials [3] in patients with intermittent asthma and mild persistent asthma. These two trials contained 1130 patients with formoterol or terbutaline treatments with an age range between 6 to 88 years [3].

The equation for healthy subjects [4] was re-estimated to quantify lung function progression in asthma. Drug effects, aging effects, and the difference between intermittent asthma and mild persistent asthma were analyzed in NONMEM. Visual predictive checks (VPCs) were employed for model evaluation.

Results: : The difference in lung function progression between intermittent asthma and mild persistent asthma was not significant. FEV1 in asthma could be quantified by age (AGE), body weight (WT), and height (HT): FEV1 = EXP(0.174*LOG(AGE) + 0.122*LOG(WT) + 0.0168*HT – 0.00141*WT – 0.011*AGE – 2.33. VPCs stratified on age, weight and height revealed that the predictions were in accordance with observations.

Based on the above FEV1 progression function, the drug effects of formoterol and terbutaline, regardless of asthma status (intermittent or mild persistent), were determined to be similar. The acute improvement of lung function after treatments was about 6%. Neither of these two drugs appeared to change long-term lung function progression of asthma.

Conclusions: Lung function progression of asthma was quantified. Formoterol and terbutaline equally improved lung function, but no influence was determined on lung function progression. This study also proposed a population approach to model chronic disease progression from normal clinical trial designs.

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Sven Mensing Markov Modeling of Side Effect Related Dropout Rates by Introduction of Previous State Memory

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Objectives: Describe the relationship between drug-induced level of a common side effect and dropout using a mixed effects markovian exposure-response model. The model assessment was done by predictive checks and external validation.

Methods: A cumulative logistic exposure-response model with markovian elements was developed to describe the observed side effect severity recorded daily for patients in two clinical studies (4 weeks, N= 241 and 6 weeks, N=252). Side effect severity was classified as none (0), mild (1), moderate (2) and severe (3). Dropout was included as a separate state. Drug concentration was assumed to increase transition probabilities to states of more severe side effect. This drug effect was assumed to be reduced by co-medication and tolerance development. A side effect memory boosting the drug effect with a non-linear integration of previous side effect intensities was found to improve the model.
Parameter estimation was performed using NONMEN and predictive checks were performed using simulations with Pharsight Trial Simulator.

Results: The distributions of the state transfer rates from 1000 simulated trial replicates are in good agreement with the observed transfer rates. The 95% confidence interval of the simulations included all observed transition rates, demonstrating the appropriateness of the model.
The dropout observed in a 16 weeks, N=384 study were simulated for external validation using the developed model. Daily recordings of the side effect intensity were not included in this study. The observed dropout rates were enclosed by the 95% confidence interval of the simulation

Conclusions: The Markov model including a side effect memory predicts the observed transition rates and time courses adequately. A Markov model without information of previous side effect intensities was at considerable disparity with the data.
The model was able to predict the drop out rates of a 16 week study based on the data from a 4 week and a 6 week study. The clinical perspective of the modeling is to minimize the dropout as response to side effect intensity by designing/selecting an appropriate run-in period of administered drug and co-medication.

FLORA MUSUAMBA-TSHINANU Multivariate and Population Pharmacokinetic Analyses for Tacrolimus Area Under The Concentration-Time Curve Prediction in De Novo Renal Transplant Recipients

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Objectives: Tacrolimus pharmacokinetics are characterised by a very high variability in the early period after transplantation. The aim of the study was to identify pathophysiological and biochemical determinants of AUC_{12} (tacrolimus area under the concentration-time curve during one dosing interval) in the early period after renal transplantation and to predict this parameter based on a minimum number of blood samples.

Methods: Data from 63 renal transplant recipients were analyzed. They were immunosuppressed with tacrolimus, mycophenolic acid and methylprednisolone. From day 1 to day 15 post-transplantation, a total of 2184 samples, including daily C_{min} levels and a full kinetic profile on day 15, were analyzed for tacrolimus by immunoassay. A stepwise multiple linear regression analysis was performed to predict AUC_{12} based on a limited number (two) of early (0 to 3 hours) blood concentrations. In addition to timed blood concentrations (C_0-C_3), the following parameters were checked as covariates in the modelling process: weight, age, sex, weight normalised doses, serum bilirubin, liver enzymes (ASAT, ALAT, GGT, PAL), serum creatinine, and creatinine clearance (CLcr). ABCB1 phenotypes (Rhodamine test) and CYP3A5 genotypes obtained from the graft donors and recipients were also analysed as possible covariates. Linear regression analysis and an agreement test (Bland and Altman, Lancet 1, 307-310, 1981) were used to assess the reliability of the tested models, comparing predicted AUC_{12} with AUC_{12} computed by the trapezoidal rule.

Results: The following expression $AUC_{12} = 25 + 8*C_3 + 2*C_{1.5} + 17 *CYP3A5*1 - 10*Cr - 0.6*CLcr$ was selected. In addition, data were described by a two compartment model with a weibull-type absorption model and a first order elimination model. A Bayesian estimator was developed after population pharmacokinetic analysis. Here are the predictive performance of both models :

Multivariate model: $r^2 = 0.78$, mean relative prediction error = -9.4 and root mean squared error = 14.7.

Bayesian estimator: $r^2 = 0.85$, mean relative prediction error = 8.9 and root mean squared error = 19.9.

Conclusions: Both models were judged reliable to accurately predict AUC_{12} from only 2 blood samples and therefore can be used for tacrolimus therapeutic drug monitoring.

FLORA MUSUAMBA-TSHINANU Time of Drug Administration, Genetic Polymorphism and Analytical Method Influence Tacrolimus Pharmacokinetics: A Population Pharmacokinetic Approach

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Objecives: Tacrolimus (TAC) pharmacokinetics (PK) are characterised by a very high unexplained variability that complicates its therapeutic use. The aim of the study was to identify pathophysiological and biochemical determinants of TAC exposure in the absence of drug-drug interactions and yo investigate the impact of the analytical method on TAC variability.

Methods: Data from 19 renal transplant candidates were analyzed. They were given 2 doses of TAC: one at 8.00 am and the other at 8.00 pm. A total of 266 samples (38 pharmacokinetic profiles) were analyzed for tacrolimus by immunoassay and by LC-MS/MS successively. A population pharmacokinetic analysis was performed using NONMEM version VI software. IMx and LC-MS/MS concentrations were modelled in a unique dataset. The following parameters were checked as covariates in the modelling process: weight, age, sex, total plasma protein concentration, analytical method (IMx OR LC-MS/MS) ABCB1 and CYP3A5 genetic polymorphisms and time of drug administration(daytime or nighttime). Bootstrapping, cross-validations, case deletion diagnostics and simulations were used to validate the final model.

Results: A two compartment model with first order absorption and elimination rates best fitted TAC IMx and LC-MS/MS concentrations but parameter values were significantly different and the residual variabilitywas higher with IMx concentrations. The following covariates were retained in the final model: time of drug administration on the absorption constant and CYP3A5 genotype on TAC clearance. ABCB1 genotype was retained in the final model on LC-MS/MS but not on IMx concentrations. All parameters were well estimated in the final model. The model validation by bootstrapping (2000 bootstraps), case deletion diagnostic, cross-validation and visual predictive check (1000 simulated samples) gave satisfactory results.

Conclusion: The final model was found to be stable and generated parameters with good precision. This is the first POP-PK study confirming the chronopharmacokinetics of TAC and showing an effect of ABCB1 genotype and analytical method on TAC PK parameters. These results may be a helpful for TAC dose individualisation.

DAVINIA OLTRA-NOGUERA Population pharmacokinetics of Ropivacaine and Bupivacaine after loco-regional administration as anesthetic in hip or knee replacement surgery.

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Objectives: Ropivacaine and Bupivacaine are two local anesthetics commonly used for epidural and regional anesthesia. The joint and simultaneous administration can be beneficial with respect to their separate administration. The aim of this study was to establish the population pharmacokinetics of Ropivacaine (RO) and Bupivacaine (BU) after joint loco-regional administration as anesthetic in hip or knee replacement surgery, and to study the influence of patient covariates on drug disposition.

Methods: A population pharmacokinetic (PK) analysis was performed in NONMEM V using a dataset comprising 32 patients (164 plasmatic concentrations dataset). Demographic and biochemical data were recorded. Ropivacaine (168.75mg) and Bupivacaine (112,5mg) were administered. Venous blood samples were collected to determine Ropivacaine and Bupivacaine concentrations at 1, 4 and 24 hours after administration. The final population model was validated through bootstrapping (n=200).

Results: The PK of Ropivacaine after local administration was described by one compartment model with first order absorption and the PK of Bupivacaine after local administration was described by two compartment model with first order absorption. Interindividual variability (IIV) was included in Ropivacaine clearance CLRO (53%), Bupivacaine clearance CLBU (113%), distribution volume of Ropivacaine VdRO (62%), central distribution volume of Bupivacaine VcBU (4%) Ropivacaine absorption rate constant KARO (0%) and Bupivacaine absorption rate constant KABU (545%). Bioavailability F was fixed to 100%. Residual error was a proportional: 25.8% error model. The FO estimation method was used.

The final population PK parameters were: CLRO=3.51 L/h; CLBU=5.44 L/h; VdRO=65.3 L; VcBU=3.14+0.027*(body weight-70) L; KARO=3.85 h^{-1}; KABU=1.41+0.013*(age-75) h^{-1}; K_{12}BU=46.1 h^{-1}; K_{21}BU=0.353 h^{-1}.

Mean values from the bootstrap analysis were close to the parameter estimate from the original dataset.

Conclusions: A population PK model for Ropivacaine and Bupivacaine, after local administration, has been developed. This model incorporates measure of body weigt to predict Bupivacaine total drug clearance and age to predict Bupivacaine absorption rate constant. Validation of this model with external patients should be performed in order to assess the suitability of further RO-BU therapy.

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Ines Paule Population Pharmacokinetics and Pharmacodynamics of Hydroxyurea in Sickle Cell Anemia Patients, In Silico Comparison of Two Dosing Regimens

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Objectives: The antineoplastic agent hydroxyurea (HU) is the first approved pharmacological treatment of sickle cell anemia (SCA). It stimulates the production of fetal hemoglobin (HbF) in place of the hemoglobin S that causes SCA and thus reduces the rate and severity of painful attacks and was shown to possibly increase survival time. This study aimed to develop population PK and PD models for HU and to compare two dosing regimens via a simulation of a clinical trial.

Methods: The population PK and PD models were built using NONMEM VI (FOCEI method) based on two datasets of SCA adult patients receiving 500-2000 mg of HU once daily (sparsely sampled PK and PD data of 36 patients and densely sampled PK data of 16 patients). PK and PD models were built sequentially. The datasets included 10 demographic and biological covariates. The PD data included HbF%, Hb, reticulocytes, PMN and platelets. Models were evaluated by VPC, NPC, NPDE. In the clinical trial simulation, the two dosing regimens were 1000 mg daily 7 days a week and 1000 mg daily 5 days a week; the duration was 6 months. The results were compared graphically by representing the HbF% kinetics and its variability.

Results: The PK profiles were described by a bicompartmental model (with first-order absorption and elimination). The typical value (and interindividual CV %) of apparent Cl was 0.95 L/h (46%), the apparent Vcentral was 3.5 L (62%), the apparent Vperif. was fixed to 50 L, and the Ka was 2 h^{-1} (180%). None of covariates was significant in the PK model. The relationship between mean weekly concentrations of HU and HbF% was described by an indirect effect (inhibition of elimination) model (without significant covariates). The typical value (and interindividual CV %) of Kin was 0.13 %/day (0%), Kout - 0.04 day^{-1} (134%), the mean concentration needed for 50% of Emax (CM50) - 11 mg/L (155%). PMN and platelet profiles were normal and therefore were not modelled. The simulated HbF% profiles in both arms were comparable.

Conclusions: The PK of HU and its effect on HbF% show high variability. The results suggested that 1000 mg daily doses may reach drug effect saturation. Dosage of HU should be adjusted individually by HbF monitoring.

Gregory Pinault Quality, Efficiency and Industrialisation Initiatives during the evolution of a dedicated SAS Programming Group

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Objectives: We previously described the role, advantages and experiences of a dedicated SAS Programming Group working in a pharmaceutical Modeling & Simulation organization [1]. Since its creation, the demand for the skills and services of the Novartis M&S Programming group has increased and grown in tandem with the increase in size of the core modeling group. The authors would like to highlight the opportunities and challenges that this fast development entailed, and to collect feedback on strategies for role expansion and career development for associates working in such a group.

Methods: The programming group has had a net doubling in size in 2 years. The M&S organizational structure evolved into a matrix arrangement comprising the 4 core discipline functions (Biology, Pharmacology, Statistics and Programming) and 8 therapeutic area clusters, loosely matching the global organization of major partner and client groups of the M&S department. Each programmer is assigned to one of these groups. Several quality, efficiency and industrialization projects were initiated and will be described in this presentation.

Results: Analogous to an M&S project, success in increasing the group size entailed analysis of historical demand for the group's services (modeling) as well as prediction of the future influence and impact of the programmers within the whole M&S group (simulation). This served to convince management of the needs (headcount and infrastructure) as well as defined the hiring and on-boarding strategy for new hires. The core competencies of the programming group requires: proficiency in ≥ 1 programming language, skills in working with databases, an appreciation of pharmacology and study design, an eye for potential data quality issues, an in-depth understanding of the regulatory requirements, and how the data will ultimately be modeled. Infrastructure to support activities being currently developed: Guide to M&S Programmers, on-line form for dataset specification, SAS tool kit, and Literature database.

Conclusions: We remain convinced of the critical role for a dedicated programming group that is integrated within an M&S department. Attracting, developing and retaining associates in such a group requires special efforts to distinguish the group from the traditional roles played by SAS programmers in a Pharma company.

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[1] Buchheit et al. 2007. A dedicated SAS Programming Group working in a pharmaceutical Modeling & Simulation organization - Current role, experience and prospects . PAGE 16 (2007) Abstr 1122 [www.page-meeting.org/?abstract=1122].

Rogier Press Is Calcineurin Activity Useful as a Biomarker to Optimize Cyclosporine A Therapy in Renal Transplant Recipients?

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Objectives: The occurrence of acute rejection episodes and clinical nephrotoxicity relates to cyclosporine A (CsA) exposure in renal transplant recipients[1]. Due to the large inter-individual variability in CsA exposure therapeutic drug monitoring (TDM) is mandatory. However, still patients suffer from acute rejection episodes and acute and chronic nephrotoxicity. To further reduce these clinical events, insight into the individual susceptibility for CsA therapy is warranted. A biomarker other than drug concentration could be a useful addition to explain differences in clinical response between patients[2]. Specifically, the measurement of the phosphatase-activity of calcineurin, the target enzyme of CsA, has potential to serve as a basis to further individualize CsA therapy. Therefore, in the present study the pharmacokinetic-pharmacodynamic (PK-PD) relationship between CsA exposure and the activity of the calcineurin enzyme was evaluated. The aim of the study was to determine whether this biomarker complies with the conditions to be useful in clinical practice. First, the biomarker should describe the between patient variability in clinical response to CsA better compared to exposure measurements. Second, variability in PD parameters such as potency (EC50) or efficacy (Emax) should relate to clinical outcome, such as rejection episodes or nephrotoxicity.

Methods: Renal transplant recipients (n=95) were followed for 6 months after transplantation. These patients received quadruple immunosuppressive therapy with basiliximab, mycophenolate-sodium, prednisolone and CsA. The initial CsA dose of 4 mg/kg b.i.d was adjusted to a target AUC[0-12h] of 5400 μg*h/L in the first 6 weeks after transplantation and 3250 μg*h/L thereafter as part of a strict TDM strategy. In this context CsA concentrations were measured together with calcineurin activity in the mornings of weeks 1, 4, 8, 16 and 26. During weeks 1 and 26, a 6-hour profile of both CsA concentrations and calcineurin phosphatase activity after dose intake was obtained. On the other occasions a limited sampling strategy was applied, routinely measuring on t = 0, 2 and 3 h to estimate the AUC of CsA as described by Cremers et al[3]. Furthermore, baseline calcineurin activity was determined prior to the transplantation. Calcineurin phosphatase activity was determined in the white blood cell fraction with a spectrophotometric-assay based on phosphate quantification as described by Sellar et al[4]. Calcineurin activity was expressed in two ways, as enzyme activity per million white blood cells and per mg protein. CsA concentrations were determined in whole blood with a fluorescence polarization immunoassay (Axsym-Abbott). Non-linear-mixed-effects-modelling was used for data analysis (NONMEM VI)[5]. A PK-PD analysis was performed after obtaining accurate PK parameter estimates from the combination of this dataset with that of a densely sampled population of 33 renal transplant recipients (Press et al., submitted TDM 2009). Moreover, a series of covariates

were collected to evaluate their effect on the PK and PD. These covariates include demographics (age, bodyweight, sex), prednisolone dose, white blood cell fraction differentiation (monocytes, lymphocytes, granulocytes (basophil, neutrophil, eosinophil)), amount of intracellular protein, and creatinin values. Finally, the occurrence of acute rejection episodes in the first 6 months after transplantation was obtained, while at 6 months a protocol biopsy was performed to identify subclinical rejection.

Results: CsA displayed variable and delayed absorption which could be described with a transit compartment, using a first-order rate constant describing the transfer from the dose compartment into the transit compartment and subsequently into the central compartment. Disposition and elimination was described by a two compartment model with first-order elimination. The PK parameters were allometrically scaled to bodyweight to the power of 0.75 and 1 for clearance and volume of distribution respectively. Furthermore, CsA disposition was affected by concomitant prednisolone administration, with a prednisolone dose over 20 mg resulting in a 15% higher apparent clearance and a 50% lower absorption rate constant. The PD relationship clearly was a direct-effect and could best be described with an Emax-model in the form: $E = E0 * [1 - (Emax * CsA\ conc.) / (IC50 + CsA\ conc.)]$, with E0 defined as the baseline activity, Emax as the maximum effect, IC50 as the concentration at the half-maximal effect and finally CsA concentration as the concentration of cyclosporine A. The baseline activity (E0) with a median of 210 pmol/min/106 white blood cells or 12 pmol/min/mg protein showed considerable within subject variability of 28% for both activities, which was much greater than the between subject variability. A maximum inhibition (Emax) of 65% of the baseline activity and an IC50 of 150 μg/L were estimated, using both the activity expressed per million cells and per mg protein. The considerable within subject variability (inter-occasion variability) in the baseline hampered the identification of between subject variability in Emax and IC50. The cause of the inter-occasion variability could result from the biological system itself, from the calcineurin assay or it could be related to variability in the composition of the white blood cell sample. The biomarker was measured in white blood cell samples consisting of lymphocytes, granulocytes and monocytes. Each of these subsets could have a different activity of calcineurin. Moreover, they each have different protein contents in the cell. The amount of intracellular protein ranged from 93 mg to 407 mg with a median of 193 mg. Therefore, the covariate intracellular protein was used to explain part of the within subject variability and was structurally related to baseline activity (E0). The relationship was linear with an increase of 2.4% upon a 10 mg increase in amount of protein for activities expressed per million white blood cells. Finally, only 13 acute rejection episodes were observed in this AUC-controlled population, while 11 biopsies demonstrated subclinical acute rejection at 6 months after transplantation. The fact that clinical events still occur, despite exposure monitoring, indicates differences in susceptibility for CsA which provides a basis for biomarker use. However, the lack of observed inter-individual variability in the efficacy and potency parameters hindered the correlation with clinical outcome.

Conclusion and discussion: A clear concentration versus effect relationship between CsA and calcineurin activity was observed. However, the variability in the biomarker between occasions was too large to identify interindividual variability in efficacy and potency of CsA to inhibit calcineurin. Therefore, differences in susceptibility for CsA could not be related to this biomarker. Still, this biomarker seems relevant from a mechanistic point of view. Therefore, further optimization of this biomarker resulting in a reduction in the within subject variability might result in a clinically relevant biomarker. Indeed, such a biomarker can be used to identify which patients are more or less susceptible to CsA therapy compared to other. This could be achieved by improving the sample preparation procedure or by measuring calcineurin activity at the target site, i.e. calcineurin activity in T-cells.

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Klaas Prins Use of model based meta-analysis combining patient-level with summary-level data using multilevel random effects to provide a quantitative assessment of the clinical efficacy (IPSS) profile and competitive positioning of a PDE5 inhibitor (UK369,003) for the treatment of benign prostatic hyperplasia (BPH).

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Objectives: International Prostate Symptom Score (IPSS) is a questionnaire-based scale for patients suffering from benign prostatic hyperplasia (BPH) to rate their symptom burden ranging from 0 (no symptoms) to 35 (worst symptoms). In two trials, the phosphodiesterase type 5 (PDE5) inhibitor UK-369,003 was tested versus the alpha blocker tamsulosin (in one trial) and placebo (in both trials) in patients who met the criteria for BPH. Substantial variability between trial results for all treatments impeded attempts to build a robust model using only patient-level data. However, with the addition of supporting data from published trial results a robust model was developed that enabled a valid comparison of UK-369,003 to that of placebo and tamsulosin 0.4 mg.

Methods: Patient IPSS time course data from internal studies on UK-369,003, placebo and tamsulosin efficacy in BPH patients were concatenated to a comprehensive literature database containing mean trial outcome on a range of BPH treatments. The literature data included placebo, tolterodine, alfusozin, tamsulosin and PDE5 inhibitors (sildenafil, vardefanil and tadalafil). Using nlme package in SPLUS v8.0, a mixed effects model described IPSS as a function of drug, dose, time, and IPSS at baseline. While the structural components of the model were universal for both trial mean and patient-level data, the multi-level random effects model explicitly separated inter-trial and inter-subject variability [1], while the residual variance was weighted by sample size.

Results: The model fitted the data well and quantified a significant placebo and treatment response. For some treatments the response was best characterized using an Emax model and/or a separate time course. The simultaneous estimation of inter-trial and interindividual random effects provided a significant improvement of model fit. The UK-369,003 dose response predicted that doses greater than 50 mg were expected to be superior to tamsulosin 0.4 mg. At UK-369,003 100 mg the probability of superiority and a 0.5 IPSS point improvement was 83 and 42 % respectively.

Conclusion: Using a multilevel random effects maximum likelihood model based on summary-level and patient-level data enabled a more valid comparison of UK-369,003 to that of placebo and current and potential competitors in the treatment of BPH. To our knowledge, this is the first example of a maximum likelihood multicovariate nonlinear dose/PD model where multilevel random effects have successfully been applied.

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Nelleke Snelder Safety pharmacology screening using a standardized population pharmacokinetic pharmacodynamic modelling approach

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Objectives: Translational PKPD modelling has been recognized as an efficient tool for bringing forward early insights in drug efficacy and safety into the clinical development stage [1]. In respect to safety, detailed understanding of the safety pharmacology of NCE's early in development is essential to better predict potential safety issues in the clinic. At Pfizer, the safety pharmacology of lead compounds is routinely investigated in rats using a standardized study design, resulting in a high volume (up to several studies per week) of studies that require rapid PKPD analysis. In order to make efficient use of this information in making timely go-no go decisions, we propose a standardized PKPD modelling approach for estimating the PKPD relationship of possible effects on cardiovascular side effects, such as changes in heart rate and blood pressure. This approach also allows less experienced modellers to report the PKPD relationship, including a simulation of the concentration resulting in a pre-defined effect level, within 2 days after receiving the data.

Methods: Using data from six studies, a standardized population PKPD modelling approach was developed, providing guidance on how to estimate the PKPD relationship for a specific compound in a practical and efficient manner. The data were obtained from experiments in which heart rate and blood were measured in telemetry implemented rats. This approach was validated using data from three other compounds.

Results: The standardized PKPD modelling approach provided detailed guidance on the modelling process, i.e. which models should be evaluated and how to interpret the modelling results, to identify the best PKPD relationship considering available data and timelines. Following this approach, three modellers with different modelling experience reported the same PK-PD relationship for all compounds within two days after receiving the data.

Conclusion: The developed standardized PKPD modelling approach for safety pharmacology screening allows quick and easy identification of the concentration- (side) effect relationships of discovery compounds in a routine based setting. We are currently in the process of implementing this approach into a desktop tool which will perform most of the analysis in a semi-automated manner. Currently, this approach has been validated to describe data from one type of rat study. However, it is foreseen that this standardized approach can be applied to other study designs also. Such a standardised approach towards PKPD analysis may also have applications outside safety testing.

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based pharmacokinetic-pharmacodynamic (PK-PD) modeling in translational drug research. *Trends Pharmacol Sci*, 29: 186-91. Epub 2008 Mar 18. (2008)

Joe Standing Population Pharmacokinetic Modelling of Esomeprazole Nonlinearity

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Objectives: Esomeprazole is a proton pump inhibitor that binds covalently to H+,K+,ATPase. The pharmacokinetics of esomeprazole are non-linear, with decreased CL occurring with increasing time and dose [1]. The first stage of a population pharmacokinetic description of this nonlinearity is presented, whereby the effect of repeated dosing on clearance was investigated.

Methods: Data from a previously published non-compartmental analysis were used [1]. Healthy volunteers (n=25) received 40mg esomeprazole by 30min intravenous infusion. After a washout, subjects then received 5 days of once-daily oral esomeprazole 40mg, followed by a second intravenous dose on day 6. Rich blood sampling for esomeprazole and two metabolites (sulphone and hydroxy) were collected until 24hr post-dose for both intravenous doses and the first and last oral dose.

Population pharmacokinetic modelling was undertaken in NONMEM VI (FOCE INTER), initially using the intravenous esomeprazole data only. One and two compartment disposition models were tested, along with autoinhibition models derived from Michaelis-Menten and saturable turnover behaviour to describe CL.

Results: The final model consisted of a single disposition compartment with a linear component of CL, along with a second saturable elimination pathway. This pathway was best represented by a saturable turnover model, the parameters being a zero-order synthesis rate (Ksyn), second order binding constant (Kon) and pathway degradation (Kdeg).

Basic goodness-of-fit and model derived versus non-compartmental AUC at first and steady-state doses showed the model described the time-dependent AUC well. For a typical 70kg individual the linear component of CL was 6.4 L/hr and VD 14.3 L. Kdeg was estimated to be 0.0198/hr (i.e. t1/2 of 35hrs), which would explain the steady-state decrease in CL taking around 5 days [2].

Conclusions: The nonlinearity in esomeprazole clearance with time has been described. Future work will include metabolite concentrations and different doses to further investigate non-linearity.

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Charlotte van Kesteren Prediction of drug effects using a longitudinal turnover model for FEV1 in patients with chronic obstructive pulmonary disease (COPD).

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Objectives: Currently, FEV1 (forced expiratory volume in one second) is widely used for assessment of disease severity and evaluation of treatment response. As part of a model-based analysis, the objective of this investigation was to explore putative drug effects on different model parameters under varying clinical trial conditions, accounting for dropout and other relevant implementation factors.

Methods: Simulation scenarios were evaluated using a turnover model based on data from placebo-treated patients in phase III clinical studies. In addition to the putative drug effect on disease progression, the influence of relevant disease and demographic covariates was explored by varying inclusion and exclusion criteria (i.e., Baseline FEV1, gender, smoking status, age and BMI). A putative symptomatic and a combination of symptomatic and disease modifying effect were tested.

Results: Following placebo treatment and symptomatic treatment, FEV1 decreases with time and age. A gender difference was observed with a faster decline in FEV1 for female patients. Non-smokers do not seem to differ significantly from smokers. In contrast, ex-smokers experienced a faster decline of FEV1 than smokers. The effect of disease-modifying treatment is currently being analysed.

Conclusions: Simulation scenarios with a longitudinal turnover model can be used to predict the decline of FEV1 in COPD patients during the course of treatment in a clinical trial. The approach will serve as a basis to further optimise patient stratification (inclusion/exclusion criteria) and overall clinical trial design for the assessment of efficacy in COPD.

Jason Williams Bayesian Network Approach to Modeling Spinal Muscular Atrophy Populations

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Background & Objectives: Proximal recessive Spinal Muscular Atrophy (SMA) is the most frequent heritable lethal disease in infants and a debilitating disease afflicting both pediatric and adult populations. Wide ranging severities are associated with a variety of distinct symptoms thus complicating enrollment and conducting of clinical trials. Furthermore, factors such as the presence of genetic modifier genes, intercurrent complications and surgical interventions result in markedly different disease course trajectories among patients and are not included in general prognostic indicators such as age-of-onset and highest motor-milestone achieved. Currently, available observation data is sparse and not optimal for modeling this complex disease. Standardization of clinical care [1] and progressing observational studies [2] aimed at describing the natural history of disease progression will likely result in richer clinical data available for future modeling efforts. The overall objective of this project was to develop a model for quantifying disease progression in populations with SMA which can be further refined once longitudinal studies have been completed.

Methods: A Bayesian Network was constructed based on expert knowledge and data from observational studies described in the SMA literature and consisted of a hierarchical nodal structure with directional links to define key dependencies between model parameters. Case-learning of parameter conditional probability tables was performed using the expectation-maximization algorithm implemented in Netica [3]. We explored several models using clinical questionnaire data (N=1700) from the SMA patient registry, extracted from medical records database and patient charts (N=55) within The Children's Hospital of Philadelphia network. Sensitivity analysis was performed across all model parameters and model performance was determined using receiver operating characteristic curves.

Results & Conclusions: Bayesian Networks allowed for calculation of posterior probability densities simultaneously across all model parameters and to combine empirical data from various sources with expert knowledge into the same modeling structure. Overall, the Bayesian Network approach seemed to be appropriate for the type of sparse longitudinal data that may arise from clinical observational studies and can be easily implemented in Netica for visual interpretation by clinicians involved in disease progression modeling efforts.

Emmanuelle Comets A bibliographic review of non-parametric methods and their application

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Objectives: Nonparametric (NP) methodology within non-linear mixed effects framework has been increasingly discussed and evaluated in recent years. Even though it has proven to be precise, accurate and to have several advantages over the parametric methodology, its use has still been limited for various reasons. In order to identify these limiting factors, and to increase the understanding of utilisation of nonparametric methods, we perform a systematic review of all pharmacokinetic (PK) / pharmacodynamic (PD) analyses concerned with nonparametric methods. We also investigate in which instances modellers would utilise the nonparametric methodology as well as different approaches to performing nonparametric model building.

Methods: We selected the articles which matched the keywords "NPEM or NPAG or NPML or ((non-parametric or nonparametric) and mixed and effects and model))" in the PubMed (for biomedical and life sciences articles) or MathScinet (for maths articles) databases. These articles were analysed using a comprehensive data abstraction form (DAF). The DAF, a check list of items, was built to extract all relevant information from the articles. The items focused on the study, the data, the models, the NP estimation methods and software, the model development and evaluation, and the report of NP results.

Results: The PubMed search returned 153 articles. The MathScinet returned 36 articles with 2 already found in the PubMed search. 69 papers were excluded from the analysis: in 21 papers, an abbreviation used in the search was used in a different meaning and the paper did not in fact concern NP methods; in 17 papers, the regression function was non-parametric; in 15 papers, a non-parametric test was used; in 7 papers, a non-parametric bootstrap procedure was used; 5 papers were reviews; 4 papers were written in foreign languages. The final database contained 118 papers.

The number of papers concerning non-parametric methods has increased over the last decade, with 79 papers published since 2000 compared to 36 papers published between 1990 and 1999. Most of the papers were published by academia; about half were classified as primarily methodological, the other half being more concerned with applications of non-parametric methods. There was no significant difference in this trend before or after 2000.

These findings may reflect a lack of diffusion of non-parametric methods; possible reasons include a perceived higher conceptual difficulty, a lack of easily usable software, as well as unsolved issues such as estimation of some parameters, model comparison, or model evaluation. For instance, the estimation of fixed effects such as parameters of the residual error models is generally a challenge for non-parametric methods and these parameters were often fixed in the papers found in this review, although some papers proposed methods to deal with this problem. Another issue found is the lack of estimates of uncertainty.

Conclusions: In this paper, we provide an overview of the development and use of non-parametric methods in the literature. We highlight key issues with these methods and point at unresolved problems which need to be tackled for these methods to become more widespread.

Vivek Dua Initial Estimates for Parameter Estimation

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Objectives: Parameter estimation for models involving differential equations corresponds to a dynamic optimization problem, which in general has multiple locally optimal solutions. The solution techniques for global optimization can be broadly classified as deterministic and non-deterministic methods. Deterministic methods can guarantee that solution obtained is globally optimal within a certain pre-specified tolerance whereas the non-determinstic methods do not provide any such guarantee. However these methods are computationally demanding and most of the commercially available softwares for parameter estimation are based upon local optimization techniques. The main objective of this work is to develop algorithms for obtaining good quality initial estimates, which can speed-up the solution times, reduce solver failures, and increase possibility of obtaining the globally optimal solution.

Methods: The parameter estimation problem is decomposed into two sub-problems. The first sub-problem corresponds to developing an Artificial Neural Network (ANN) model for the given data. The ANN model represents a reduced data set [1]. The second subproblem is formulated as a parameter estimation problem where the differential terms in the model are obtained by analytically differentiating the ANN model. The second subproblem corresponds to a Linear Program (LP) or a Nonlinear Program (NLP), for which reliable solvers are available. The solution of the second subproblem provides initial estimates for parameters. These estimates are then used to solve the original parameter estimation problem.

Results: This methodology was tested on several parameter estimation problems and the solution was obtained reliably and in a few iterations only.

Conclusions: The main advantage of using the proposed decomposition approach is that the error between the data and model predictions is carried out in the first step and the parameter estimation for a reduced data set is carried out in the second step. ANN is well known for their ability to handle large data sets and characterize highly nonlinear functions very effectively. This ability together with the differentiability properties of ANN makes the proposed approach a very useful tool for parameter estimation of problems involving differential equations and large data sets.

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ANNE DUBOIS Extension of the SAEM algorithm and evaluation of Wald and likelihood ratio tests for interaction or bioequivalence studies

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Objectives: The context of our work is the analysis of pharmacokinetic (PK) crossover trials using nonlinear mixed effects model (NLMEM) in similar way as the recommendations for results based on non compartmental approach [1]. In that context, our objectives are to adapt the SAEM algorithm and the MONOLIX software for the analysis of crossover trials, to develop the likelihood ratio test (LRT) for bioequivalence and to evaluate the type I error of global comparison and bioequivalence tests in crossover trials using those developments.

Methods: We extend the SAEM algorithm to any number of periods and to any structure of the matrix of random effects, based on the work done by Panhard and Samson [2]. This extended SAEM has been implemented in the version 2.4 of MONOLIX. For bioequivalence trials, Wald test based on NLMEM has been developed [3, 4] and we propose an extension of the LRT. The extension of SAEM and the type I error of these tests are evaluated by simulation using 1000 replicates. We use the theophylline example with a one-compartment PK model. Two-period two-sequence crossover trials are simulated under the null hypothesis with 40 subjects and two different numbers of samples. We call rich design the designs with 10 samples per subject and sparse design the designs with 3 samples per subject. We simulate with treatment effect on clearance and volume of distribution. We use two levels of between-subject (BSV) and within-subject variability (WSV): BSV=20%, WSV=10% and BSV=50%, WSV=15%.

Results: Estimations of all parameters by SAEM are satisfactory for both variability settings and both evaluated designs. The type I error of comparison and bioequivalence tests are rather similar, as the results of Wald tests and LRT. We present here results on bioequivalence Wald tests for the clearance. The type I errors are respectively 5.3% (6.6%) and 5.6% (8.6%) for the low (high) variability, respectively for the rich and sparse design.

Conclusion: The extension of SAEM is accurate for crossover trials that can be analyzed with NLMEM. The simulation study does not show advantage to use the LRT instead of the Wald test since the results for the type I error are similar and the LRT is time consuming. Further work is needed for the use of these tests for design with little information as a slight increase of the type I error was found for the sparse design with high variability.

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Charles Ernest Improved parameter estimation and design optimization for In Vitro ligand binding experiments

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Objectives: Previous analyses have demonstrated that simultaneous non-linear regression (SNLR) versus sequential non-linear regression (NLR) provided better approximation to the true values of ligand binding parameter estimates with focus on resolution of two binding sites, relative binding densities, receptor occupancy and number of data points[1]. The aim of this study was to extend this previous work and compare SNLR and NLR with commonly encountered experimental error, specifically residual variability (RUV) of binding measurements, experiment to experiment variability (BEV) and non-specific binding (NSB). Additionally, optimal design of these ligand binding experiments was examined.

Methods: Monte Carlo simulation and estimation were used to evaluate the performance of various NLR and SNLR methods for estimating ligand binding parameters. Data simulation and estimation were performed using FOCE(I) in NONMEM VI. Simulation followed by parameter estimation of ligand binding data was performed for equilibrium, dissociation, association and non-specific binding experiments. Subsequently, these four experimental types were implemented in the optimal design software PopED 2.08 [2] to optimize ligand concentrations and sampling times for SNLR analysis.

Results: Parameter estimation was significantly improved using SNLR compared to NLR when RUV and BEV were varied up to 25%. Evaluation of NSB demonstrated that subtraction of non-specific from total ligand binding data led to highly biased and variable parameter estimates using both NLR and SNLR. However, simultaneous analysis of total binding and NSB data resulted in <5% bias of parameter estimation. In contrast, NLR analysis of NSB and total binding data still lead to highly biased parameter estimates. Optimization of these highly standardized experiments show that the ligand binding experiments can be substantially improved by the use of an optimized design compared to the standard design when using SNLR. These designs resulted in low predicted uncertainty of parameter estimates in most tested cases with a dramatically decreased sampling schedule.

Conclusion: Overall, SNLR provided superior resolution of parameter estimation in both precision and accuracy compared to NLR. In addition, substantial improvement can be made to the design of these experiments enabling a large reduction (>50%) in the samples/ligand concentrations needed to estimate parameters with high certainty.

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Bo-Hyung Kim Hierarchical-likelihood approach for nonlinear mixed-effect models

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Objectives: Nonlinear mixed effect models have been widely used for the analysis of pharmacokinetic data. These models frequently lead to an analytically intractable and computationally intensive likelihood that involves multi-dimensional integration. The popular application such as NONMEM® uses analytical approximation to avoid such numerical difficulties. However, it gives biased estimators. In this study, we used the hierarchical likelihood method [1,2] to obtain unbiased estimators.

Methods: The one compartment pharmacokinetic model was developed to obtain simulated drug concentrations. This model included inter- and intra-individual variability. The simulated drug concentrations were used to estimate pharmacokinetic parameters, which were calculated using NONMEM® and new applications based on hierarchical likelihood method.

Results: A total of 270 observations were obtained in 30 subjects, and then PK parameters for these simulated data were estimated using NONMEM® and H-likelihood method (Table)

Conclusions: This study suggested that the H-likelihood method showed less unbiased estimators than NONMEM®.

$y_{ij} = (\text{Dose}/\eta_{1i})\exp(-\eta_{2i}t_{ij}) + \varepsilon_{ij}$ $1 \le j \le 9$, $1 \le i \le 30$

$\eta_{1i} = \beta_1 + b_{1i}$, $\eta_{2i} = \beta_2 + b_{2i}$

True Value	$\beta_1 = 1.5$	$\beta_2 = 2.5$	$\sigma = 0.001$	$\omega_{11} = 0.7$	$\omega_{22} = 0.3$
H-likelihood (1st-order)	1.469	2.355	0.00073	0.672	0.222
H-likelihood (2nd-order)	1.468	2.353	0.00074	0.677	0.223
PQL (NONMEM®)	1.458	2.344	0.00073	0.665	0.222

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Elodie Plan New models for handling correlated underdispersed Likert pain scores

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Objectives: Pain intensity is principally assessed using rating scales comprising eleven categories, like the Likert scale. Population models available to analyse such data don't usually treat scores as ordinal but as continuous [1].
Frequent observations of pain are generally dependent within each other and present low variability. The inclusion of features handling correlation and underdispersion into non-linear mixed-effects scores models remains to be done.
The aim of this study was to develop a model adapted to fit 11-point data.

Methods: Likert pain records were collected on a daily basis over 18 weeks from 231 individuals. These patients suffering from painful distal diabetic neuropathy were under placebo treatment. An exponential placebo model was used to describe the mean score time course.
A truncated generalized Poisson model [2], with four levels of probabilities inflated by Markov elements, was implemented in NONMEM VI. It was compared to a continuous model including a logistic transformation of the individual predictions and data, and an auto-correlation factor for the residual error model.
Capacities for handling underdispersion were assessed by computing the variability of the observations within individuals. Evaluation of the ability of the models to handle serial correlation was done through the number of transitions between scores.

Results: The placebo effect was estimated to be of 22 % of the baseline with a half-life of 30 days with the count model. Very similar estimates were obtained with the continuous model. The correlation half-life was 0.75 days in the continuous model. In the count model the probability of an observation to be identical to the previous one was a function over the scores with a maximum of 76 %.
Diagnostics plots, with respect to time course, distribution of the scores and transitions, displayed concordance between observed and simulated data for both the continuous and the count models.

Conclusions: Two models have been developed that adequately describe observed Likert pain scores. Novel features to handle underdispersion and serial correlation were proposed.

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Klaas Prins Comparison of a maximum likelihood versus a full bayesian method to jointly model individual with summary level data

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Objectives: In a different presentation at this meeting we have described a model based meta-analysis combining individual and summary-level International Prostate Symptom Score (IPSS) data from benign prostatic hyperplasia (BPH) patients [1]. To jointly model these different data sources, a multi-level random effects approach was performed using the maximum likelihood estimation (MLE) nonlinear mixed effects regression package 'nlme' in SPLUS. In order to investigate the validity and usefulness of the MLE approach, the data were re-analyzed employing Full Bayesian Estimation (FBE) using WinBUGS. The distributions of the parameters and the model predictions were compared.

Methods : The structure and inferences from the IPSS model is detailed in [1]. The probability density function of the exact same structural components, the multi-level random effects as well as the residual error model from the MLE model was transferred to WinBUGS and posterior distributions were then obtained using FBE. The quasi-posterior parameter distribution of the MLE regression were obtained by sampling from the variance-covariance matrix of fixed and random effects. The corresponding parameter distributions as well as the predicted IPSS dose response curve of a selected compound (UK-369,003) relative to tamsulosin 0.4 mg of the MLE and FBE approaches were compared.

Results: The FBE approach required a full day of computation, whereas the MLE model took ~2 min to converge. The shape of the posterior parameter distributions (FBE) were reminiscent of normal in most cases, with only occasional tailing. By default, the MLE parameter distributions are normal. The location of most parameter distributions was very similar across methods. When FBE was compared to MLE, the derived relative IPSS dose response curve was marginally shifted to the right without loss in maximum effect. This was due to slightly higher efficacy being estimated for tamsulosin using FBE, while the UK-369,003 parameters were superimposable using the 2 methods.

Conclusion: The MLE approach provides a pragmatic, useful and statistically sound method to jointly model individual and trial statistic data. As the computation time is substantially longer with the FBE method, it may be less suitable for pragmatic modeling work. But as FBE is statistically superior to MLE, we propose that the MLE method can be used as model-building tool, where the final model run(s) could be evaluated using FBE.

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Vladimir Vainstein Comprehensive Virtual Patient Platform Implemented For Anti-Angiogentic Drugs Development

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Background: Over the past decades biomathematical model have evolved and their usage in actual clinical research is growing. Together with this growth there are also a growing number of computerized tools whose aim is to support a specific research area. There is a variety of tools with various user-levels controls and flexibility that exist today, including NONMEM Pharmacokinetics with extension for population analysis, MATLAB bioSIM for model building and analysis and more. For a comprehensive research in the field of drug development there is frequently a need to combine few tools. Moreover there is no standard computational tools to find an optimum between conflicting requirements, e.g. high efficacy and low toxicity of a drug.

Objectives: Our objective is to provide the researcher with a tool that will be able to suggest best treatment considering computed efficacy and toxicity. Using the concept of Virtual Patient we establish a unified platform that covers different aspects of drug development during clinical trial phases.

Methods: We have developed a unified platform with integrated features that covers all the aspects for virtual drug development. The platform integrates a simulation engine, a database engine, a parameter estimation tool and a treatment optimization tool. The simulation engine includes several Biological-SubSystems (BSS), representing pharmacokinetics as well as pathological and physiological processes affected by a drug (e.g., hematopoesis, tumor growth etc.). In this engine pharmacodynamics is realized as interaction between the PK module and the relevant BSS's. The database module contains the relevant parameters for different individuals, or for groups of individuals. The parameter estimation module performs the task of best fitting the BSS parameters to a given experimental data set. The treatment optimization module automatically searches in the space of all feasible treatment schedules for the best option - given a specified goal function. All the modules can operate in a modular way with GUI. The user can have high degree of flexibility to choose the model to be run, the optimization algorithms, the goal function etc. The output contains graphical representations for relevant dynamics and internal model parameters.

Results: We will describe our technology as well as demonstrate several applications of it in drug development, e.g. for deciphering unknown drug action mechanisms, for predicting Phase I results (eg., DLT, Dose escalation process for establishing therapeutic window) and Phase II optimal treatment regimens. The system can operate on a regular PC and can also be configured to take advantage of a heterogeneous array of computing nodes locally or over the network. Using this platform we have been able to analyze the results of unsuccessful clinical drug development case and suggest a different less toxic highly efficacious treatment schedule, which currently is in a clinical trial. Some results from the clinical trial are expected in few months.

Conclusions: A Virtual Patient system that encompasses a large spectrum of activities in drug development was built and is being used by skilled biologists. The system can significantly improve the drug development process.

Caroline BAZZOLI Prediction of power of test of discrete covariates in population analyses and influence of design: application to gender effect in joint pharmacokinetic models of nucleoside analogs and their active metabolites

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Objectives: To predict power of test of gender effect and to study the influence of design in population pharmacokinetic (PK) analyses of nucleoside reverse transcriptase inhibitors (NRTI) and their active metabolite using joint pharmacokinetic models.

Methods: Methodology for design evaluation and optimization in nonlinear mixed effects models has been extended for models with parameters quantifying influence of discrete covariates [1, 2]. The predicted standard error (SE) from the computation of the Fisher information matrix (MF) is used to predict the power of the Wald test of a discrete covariate as well as the number of subjects needed to achieve a given power. We apply this development on multiple response PK models: the joint population model of zidovudine (ZDV) and its active metabolite ZDV-TP and the joint population model of lamivudine (3TC) and its active metabolite 3TC-TP [3]. Results from clinical trials suggest that there may be clinically important gender differences in antiretroviral PK, especially on intracellular concentrations of NRTI [4, 5]. Data are obtained from the COPHAR2-ANRS 111 trial in 75 naïve HIV patients receiving oral combination of ZDV and 3TC, as part of their HAART treatment. Four blood samples per patient were taken after two weeks of treatment to measure the concentrations at steady state at 1, 3, 6 and 12 hours. Intracellular concentrations were measured in 62 patients, 11 patients had 4 samples the remaining had 1 or 2 samples at 3h and/or 12h. Using the SAEM algorithm implemented in the MONOLIX software [6], we estimate the PK parameters of ZDV and 3TC and their active metabolites including in each model a gender effect on the apparent clearance of the metabolite. Using PFIM 3.2, a new extension of PFIM [7, 8], we then compute the expected power to detect the gender effect with the initial design and thus, we predict the number of subjects needed to achieve a power of 80% for the test. Influence of optimized design on the power and the number of subjects needed from the whole matrix of population parameters from both responses is studied.

Results: The apparent metabolite clearance of ZDV-TP increases by 30 % for male compare to female, although not significant (p=0.162). With the initial design and a type I error of 5%, an expected power of 28% is computed to detect this gender effect. To achieve a power of 80%, 300 subjects would be needed to detect such an increase with the same sampling design. An optimized design using PFIM 3.2 yields a greater power. Regarding 3TC and 3TC-TP, because a very small decrease of 3% of the clearance of the metabolite in male is found we do not investigate further the power of this test.

Conclusions: We illustrate the consequence of the choice of the design and the number of patients needed to achieve a given power of the Wald test of discrete covariate for complex PK models, i.e. accommodating several responses. This approach can also be applied to compute power of test of absence of effect of covariates, i.e. using an equivalence test, given "equivalence" limits.

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Massimo Cella Scaling of fixed dose combinations in children

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Objectives: Drug combinations with fixed dose ratio are standard therapy for various infectious diseases. In these circumstances, dose adjustment in children has been dealt with in the same way as single agent therapy, under the assumption that a comparable risk : benefit ratio is maintained across populations. The objective of this investigation was to evaluate the implications of linear scaling of dosing regimens by body weight (mg/kg) using the combination of antimalarial drugs atovaquone (ATV) and proguanil HCl (PGN) as example. This combination is prescribed in the ratio (2.5:1) in adults and children. We hypothesise that different dose ratios may be required for some drugs to ensure that exposure to either moiety is equivalent to that observed in adults.

Methods: Atovaquone and proguanil plasma concentrations of 861 subjects (379 adults and 482 children) were obtained from 9 different clinical studies. Both drugs were administered orally at different dose levels. A population pharmacokinetic model was developed using NONMEM 6.2. A one compartment model with 1st order absorption and elimination best described the pharmacokinetic profiles of ATV and PGN. Model parameter distributions and total exposure (AUC) in the paediatric population were compared to findings in adults. Subsequently, clinical trial simulation scenarios were evaluated assuming different clearance distributions across weight groups for each agent in the combination. With the aim of warranting children with the same exposure that was assessed as efficacious in adults, new dosing recommendations and new ratios were proposed.

Results & Conclusions: Preliminary results show that the assumption a priori of a fixed ratio between two active compounds when scaling the dose from adults to children may lead to inappropriate exposures in the paediatric population. Adjustment of the dose ratio according to the distribution of covariates affecting the pharmacokinetics of either moiety is critical to achieving effective and safe exposure across a wide weight /age range. A model-based approach seems critical to prevent failure in paediatric trials with fixed dose combinations.

Thaddeus Grasela Modeling and Simulation Approach to Pediatric Drug Development

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Objectives: Administration of a fixed daily dose of Drug X in children five to ten years of age resulted in lower exposure relative to adults given the recommended dose. Clinical trial simulations were designed to support selection of an optimal pediatric dosing regimen expected to attain sufficient exposure for drug effectiveness.

Methods: Data were obtained from two pediatric Phase III studies. A total of nine different scenarios based on three alternative dosage regimens (weight-based or 2 fixed dose regimens based on weight), varying regional distribution of study sites in Europe (EU) and US (100%/0%, 80%/20%, and 50%/50%, respectively), and three levels of baseline response were simulated. Each of the trials was replicated 100 times. A previously developed population PK model was used to generate an estimate of $AUC_{0\text{-}24}$ for each simulated patient for each of the 3 dosage regimens. Patients were then randomized to placebo or drug treatment. A linear pharmacodynamic model was used to predict response at 12 weeks for each simulated patient. A statistically significant difference ($\alpha = 0.05$) in the change in efficacy response from baseline between placebo and drug-treated patients was considered a successful trial.

Results: When comparing the trial success rates using the three simulated dosing regimens, minimal differences are observed which is in accordance with the similar exposure estimates for these regimens. These results suggest that the most convenient regimen from a commercial perspective can be used without adversely affecting patient outcome. As expected, increasing the baseline response level results in an increase in the clinical trial success rate regardless of the dosing regimen or study site distribution. When comparing the various region-of-origin distributions, enrollment based on 50% US and 50% EU patients tends to predict slightly higher trial success rates. This finding may be due to region-specific differences in patient factors.

Conclusion: Overall, these simulations suggest improvements in design of future pediatric clinical trials would facilitate selection of appropriate dosing regimens in children. Furthermore, the application of this approach may support the objectives of the EU Pediatric Regulation.

Ivelina Gueorguieva Desipramine Population Pharmacokinetic Model and Designing CYP2D6 Drug-Drug Interaction Studies

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Objectives: The objectives of this analysis were to develop a population pharmacokinetic (PK) model to describe the pharmacokinetics of desipramine in healthy subjects, after oral administration of a 50mg dose and to examine the influence of demographic characteristics and other covariates on the PK parameters of desipramine. Secondary objectives were to propose a mechanistic population PK model for desipramine, which allowed simulation of CYP2D6-mediated inhibition when using desipramine as a probe substrate, and to identify optimal sample size and pharmacokinetic sampling schedules for extensive (EM), intermediate (IM) and ultrarapid (UM) metabolisers of substrates of CYP2D6.

Methods: Desipramine concentration-time data were available from seven studies comprising 108 healthy subjects who received a 50 mg desipramine oral dose. Different standard and semi-mechanistic pharmacokinetic models were fitted to the dataset using nonlinear mixed-effects modeling software (NONMEM, version V). Several potential covariates were tested to quantify their effect on desipramine population pharmacokinetic parameters. D-optimal sampling times (PopDes) and appropriate study designs to account for the differences in EM, IM and UM subgroups for CYP2D6 were suggested.

Results: A two-compartment model with first order absorption best described desipramine concentration-time data following oral administration. Body mass index was found to influence the apparent central distribution volume. Further, using the proposed semi-mechanistic hepatic intrinsic clearance model with Bayesian inference, mean population desipramine hepatic intrinsic clearance was estimated to be 289 L/h with between-subject variability of 86%. D-optimal sampling times for EMs were calculated to be 0.25, 20, 58, 90 and 200 hours and for the IMs subgroup similar optimal sampling times were found except now a sample at 105h instead of 90h was needed.

Conclusions: The population PK model developed is suitable to describe the behaviour of desipramine for the dose routinely used in drug-drug interaction (DDI) studies. Desipramine concentration levels can be simulated to guide clinical trial design for healthy subjects in DDI studies, which aim to assess CYP2D6 interaction potential of novel compounds incorporating sample size and optimal sampling schedules for the three CYP2D6 metabolizer subgroups.

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Stefanie Hennig Optimal design for models with semi-parametric distributions

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Objectives: To investigate the influence of semi-parametric parameter distributions on optimal study designs.

Methods: A PK model for monoxide[1] was originally presented with a normal η-distribution on the absorption rate parameter (ka). However, recently, the same model was found to be improved using a box-cox transformation of the η_{ka}. [2]
We used this example to investigate the feasibility of including such a shape parameter in models implemented in PopED v.2.0 (http://poped.sourceforge.net/) for optimal study design. The model was implemented in PopED using both a normal (model 1) and a semi-parametric box-cox-transformation distribution with a shape parameter of 0.769 (model 2). The design setup was adapted from the original study; 7 observations/patient were sampled on one occasion in a parallel design with 3 different doses (n=60 patients). D-optimal designs (OD) were found using the FO and FOCE method in PopED. Furthermore, a combined OD was found for both models. Stochastic simulations and estimation (SSE) were performed using NONMEM VI for all three designs to assess the performance of the optimal designs.

Results: The optimal sampling times for the models were different under the FO and the FOCE method. The choice of approximation method gave different designs for both models.
The ODs found under the FOCE method were quite different for the two models. The sampling times for model 1 were: 0.24, 0.32, 1.44, 3.68, 3.84, 8, 8 and for model 2: 0.24, 0.32, 0.32, 1.6, 1.6, 8, 8. The expected CVs obtained from PopED under FOCE for ka and ω_{ka} were smaller under the design for model 1.
The optimization under FOCE for the combination of both models found the following optimal sampling times: 0.24, 0.32, 0.32, 1.6, 3.68, 8, 8. This design is more similar to the OD for model 2, which is likely due to influential individuals with fast absorption rates. Under this design the expected CVs for all parameters in model 1 and 2 are very similar in comparison, however again with a trend to estimate more precise ka and ω_{ka} with model 1.
The SSEs confirmed that the most precise estimates for model 1 were obtained under the OD for model 1, followed closely by the combined OD and then under the OD found for model 2. Similarly, the precision of the estimates for model 2 was highest when simulated and estimated under the OD found for model 2, then the combined OD and last under the OD for model 1.

Conclusions: The choice of the parameter distribution and the approximation method used influences the outcome of the OD and will also influence the possibility of estimating semi-parametric distributions. This could be confirmed with SSEs in NONMEM.

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Andrew Hooker Autocorrelation reduces sample time clustering in optimal design

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Background: Optimal experimental design has been shown to be a useful way to improve the information content of experiments. Often these designs are optimized over sample times and result in the occurrence of samples clustered at the same time point. Such designs are both non-intuitive and likely to be less informative in reality, as they don't appropriately take into account error generation mechanisms. Further, the designs are clinically less appealing as multiple samples at the same time are often practically impossible and counter-intuitive to experimentalists. The clustering in optimal design occurs because the design is trying to minimize the signal-to-noise ratio between the measurement variable and the residual variability and is compounded by the assumption that the measurements between observations at the same time are independent from one another. Previous work (Federov et al.) has investigated the use of stochastic differential equations in models for optimal design to incorporate information about autocorrelation (AC). However this implementation was limited to a few simple PK models and would not be amenable for extension to more complex models.

Objectives: To develop a general method for optimal design implementation of the AR1 autocorrelation model and to compare optimal designs with varying degrees of autocorrelation between measurements within an individual.

Methods: The optimal designs were computed using PopED (http://poped.sf.net/), into which an AR1 model was implemented, allowing for correlation between measurements of an individual. Numerous models and were used to compute optimal designs with a range of correlation strengths. The designs were optimized for sampling times and compared to one another.

Results: Clusters of sample times in designs without autocorrelation are spread apart in models with AC present and the spread increases with increasing AC. The AR1 model is simple to implement and possible to use in any desired model. Optimal designs ignoring an existing AC are inferior to designs that take such patterns into account.

Conclusions: AC is a principled way to reduce or eliminate clustering from optimal designs. Recent work has also shown that incorporating AC can be important in hypothesis testing when model building and ignoring AC may result in biased parameter estimates (Silber et al. 2009). The present results demonstrate that incorporating AC will lead to more intuitive, practical and informative designs.

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Frank Kloprogge A model-based approach for dose selection of fixed dose combinations in paediatric indications.

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Objectives: Metabolism in children may differ significantly from adults. Differences in absorption, first pass, and ontogeny of enzymes are among the factors explaining such dissimilarities. Dose adjustment of drug combinations can therefore be challenging if fixed dose ratios are used. In the current investigation, we compare three different methodologies for scaling of the dosing regimen for drug combinations. The antimalarial drugs atovaquone and proguanil are used as example for this analysis.

Methods: Data from nine clinical trials were analysed. The study population consisted of 301 adult subjects, 168 adolescents (aged from 11 to 17 years) and 314 subjects aged from 0 to 10 years. A model-based approach was used to bridge drug exposure across the paediatric population. All analyses and simulations were performed with NONMEM VI. A one-compartment model with first-order absorption and first-order elimination accurately describe the pharmacokinetics of both compounds. Covariates for atovaquone were race, sex, co-medication and weight on clearance and weight on volume of distribution, whilst race and weight were identified on clearance and age and weight on volume of distribution for proguanil. Dose recommendations for fixed dose ratios were investigated by 1) performing a meta-analysis of adult and paediatric population under the assumption of common parameter distributions across the population; 2) estimating model parameter distributions for each sub-group separately, i.e., adults, adolescents, children, toddlers and infants (aged from 0 to 10 years); 3) allometric scaling of clearance and volume. Parameter estimates obtained by each of the aforementioned approaches were subsequently used to simulate exposure to atovaquone and proguanil across the paediatric population from 0 to 17 years of age. Selection of the dosing regimen and of the fixed dose ratio was based on exposure ranges and parameter distributions in the adult population.

Results: In contrast to single agent therapies allometric scaling does not perform well if fixed dose ratio must be warranted. The use of allometry also showed limitations with varying ratios of either agent. Pharmacokinetic bridging seems to best characterised by adaptive protocol design, including data from relevant population.

Conclusions: A model-based approach is required to accurately dose adjust drug combinations with a fixed dose ratio. Simulation scenarios also revealed that the dose ratio may be different across the wide range of body weight /age as compared to the adult dosing.

Sergei Leonov Estimation of Population Pharmacokinetic Measures and Selection of Sampling Times

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Objectives: In many pharmaceutical studies multiple blood samples are taken for each enrolled patient, and various population pharmacokinetic (PK) measures, such as area under the curve (AUC), maximal concentration (Cmax) and time to maximal concentration (Tmax) are of interest. The objectives of this presentation are:

(1) Comparison of a model-based approach, when a compartmental model is fitted and the explicit formulae for PK measures are used, and a nonparametric approach, when numerical integration is used for estimating AUC and sample values - for Cmax and Tmax. Since regulatory agencies usually require the model-independent estimation of PK measures, we focus on the nonparametric approach while using the model-based approach as a benchmark.

(2) Recommendation of how to "split" a single sampling grid into two (or more) subsets which substantially reduces the number of samples taken for each patient but often has little effect on the precision of estimation in terms of mean squared error (MSE).

(3) Introduction of costs, in particular costs of patient's enrollment and costs of analyzing samples, and comparison of sampling grids under cost constraints.

Methods: We exploit ideas from the earlier work on the selection of sampling schemes for parametric compartmental models which was based on optimal model-design methods; see [1-3]. Three types of population PK measures and methods of their estimation are introduced. The discussed methods involve calculating PK measures and averaging over the population yet differ in the order of the two operations; for details, see [4]. Special attention is given to a specific nonparametric method when one starts with averaging responses at each time point over all patients and then gets population estimates of PK measures for the "averaged" curve. This method is applicable in the case of sparse sampling which is often encountered in population PK studies.

Results/Conclusions: We present simulation results for nonlinear regression model generated by a one-compartment PK model, and closed-form solutions for the MSE of the empirical estimator of AUC for a simple quadratic regression model with random intercept.

(1) When the model is correctly specified, the model-based approach outperforms the nonparametric one in terms of precision of PK measures' estimation, but often not by much.

(2) Using split grids has little effect on the precision of estimation and has negligible effect on the bias term and terms associated with population variability for AUC estimation.

(3) If costs of analyzing samples and costs of patient's enrollment are taken into account, then sampling schemes with split grids may become optimal.

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Rocio Lledo Seeking ethically attractive dose-finding designs for narrow therapeutic index drugs

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Objectives: Recently, a simulation-based comparison study on the relative merits of dose control-trials (DCT) with exposure-response analysis vs. concentration control-trials (CCT) for drugs with expected narrow therapeutic index was performed[1]. Contrary to what had been suggested[2, 3], it shown that when learning about the exposure-response relationship, a DCT design is more informative than a CCT.

Herein, we revisit the question employing optimal design methodology, and propose strategies for designing ethically attractive trials for these drugs, which are balancing between individual-collective risk and informativeness.

Methods: A D-optimal study was performed using PopED 2.0, considering a hypothetical immunosuppressant agent with two clinical endpoints (rejections and infections). The drug exposure was described by a one-compartment model at steady state with clearances sampled from a normal distribution and the PD-relationship with two independent regression logistic models. Different scenarios were optimized applying cost-based designs (unwanted events vs. number of subjects/trial or maximal individual risk) both for DCT and CCT. For each design, two target doses (DCT) or exposures (CCT) were considered. The variables in the design which were simultaneously optimized were dose/exposure targets and number of subjects to include in the trial or in each arm. In order to decrease the costs of gaining new knowledge, the inclusion of prior information on baseline risks was also evaluated. .

Results: DCTs are more informative, needing smaller studies to provide the same information compare to CCTs. Using number of unwanted events, rather than subjects, as cost resulted in ethically more attractive designs. The inclusion of prior baseline risk information allowed substantial reduction in number of subject/events as well as utilization of targets closer to the optimal therapy.

Conclusions: Designing dose finding trials for narrow therapeutic index drugs can be substantially improved by using DCT with exposure response analysis, cost-based designs, use of prior information and optimal design analysis providing information on the ethical trade-off between individual risk and information gain..

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Kayode Ogungbenro Sample Size/Power Calculations for Population Pharmacodynamic Experiments Involving Repeated Count Measurements

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Objectives: To describe an approach for calculating sample size/power for population pharmacodynamic experiments involving repeated count measurements modelled as a Poisson process based on mixed-effects modelling technique. This work aims to extend the work of Rochon [1] on sample size/power calculations to repeated count measurements based on analysis by a mixed-effects modelling approach using hierarchical models and non-central Wald test.

Methods: The method proposed by Rochon (1) for hypothesis testing between groups under GLM based on analysis by GEE was extended to repeated count measurements under mixed effects modelling using a log link transformation. Expression for the information matrix based on the hypothesis to be tested were derived and used in the procedure for sample size/power calculations. The approach can be used to calculate power/sample size based on a model, parameter estimates and sampling design required to detect the difference in parameter estimates between groups, say placebo and treatment groups. Extensions to account for unequal allocation of subjects and sampling times between and within groups were also described. The approach was applied to a published example [2] based on the quantitative characterisation of the dose-efficacy and dose-side effect relationship of oxybutynin using mixed effects modelling approach. A model that defines the dose-efficacy relationship was developed for placebo and two other formulations: controlled release (XL) and immediate release (IR). Using the experimental design and parameter estimates described, the minimum sample size required to detect the difference between XL and IR dose groups were calculated at power=0.8,0.9 and significance level=0.05,0.01. The sample sizes obtained were also used for simulations in NONMEM and the empirical power of the designs were calculated and compared with the nominal power.

Results: The results obtained showed good agreement between the nominal power and the power of the design obtained from simulations. The results also showed that design factors especially number of sampling times and their placement can affect sample size. Designs obtained by optimising the information matrix required reduced total number of samples compared to the empirical design.

Conclusions: A fast and efficient approach has been described for calculating sample size/power for repeated count measurements in population PD experiments based on analysis by mixed-effects modelling. The method can account for unequal allocation of subjects and sampling times between and within groups. Carefully designed trial will produce efficient study and can help to reduce cost and other resources.

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Patanjali Ravva Enhanced Clinical Trial Design of a Proof-of-Concept Study via Bayesian simulation analyses

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Background: A proof-of-concept (POC) study was proposed to assess the efficacy and tolerability of 3 doses of a MR tablet versus placebo (P). Each MR dose (2 higher, 1 equivalent to IR) was also to be compared to the commercial IR tablet included as a reference. Based on the observed response rates from historical IR clinical trials the study was powered on an odds ratio (OR) of 3.77 (15% P, 40% IR) for standard pairwise comparisons. An estimated equal allocation of 72 subjects per arm would allow comparing each MR dose to P with 90% power and 5% type I error. However, the power to detect a difference between MR and IR was 19%. Thus a clinical trial simulation study was undertaken to compare how well different designs of approximately equal cost could meet the POC objectives.

Methods: A Bayesian logistic regression model was used with priors on the IR and log OR responses. A mild dose-response relationship was assumed over the MR dose range. A beta prior distribution was used for IR; the shape parameters were derived from historical P-controlled clinical trials and informativeness of the priors. A normal prior distribution was used for the log OR and MR response rates. Simulation was used to assess the impact of reallocating subjects from the IR and P groups to MR treatments by borrowing information from historical data. Prior information was varied across scenarios. 10,000 trials were simulated for each design scenario and analyzed using WinBUGS 1.4.1.

$$\text{logit}[P(y_i = 1 | TRT_i)] = \alpha + \beta_1*(TRT_i = IR) + \beta_2*(TRT_i = MR1) + \beta_3*(TRT_i = MR2) + \beta_4*(TRT_i = MR3)$$

$y_i = 1$ if the i^{th} patient is a responder, otherwise $y_i = 0$; TRT_i = treatment group

Results: Use of prior information resulted in an increased power for the pairwise comparison of MR to IR while maintaining the power for the comparison to P. The power of a sample size of 40 subjects for IR and P with 75 subjects for each MR dose was 63% versus 19% for equal allocation. The weight of the prior can be viewed as 35 additional subjects worth of information in the IR and P treatment arms. Trial performance metrics for the selected design was also explored using model-based analysis and the understanding of the IR exposure-response relationship.

Conclusions: An efficient POC design was achieved through simulation analysis. Formally using historical information in a Bayesian analysis allowed additional patients to be allocated to MR groups and increased the power to establish POC.

Marcus Scholz Optimal Design for the improvement of sampling schedules of microdialysis studies.

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Objectives: The methods of Optimal Design have been explored for various applications, but not for the design of sampling schedules in microdialysis (µD) studies. In contrast to plasma sampling, µD allows to determine the concentration of drugs or PD markers at the site of action. Microdialysate is continuously sampled over a longer time period which is divided in usually identical collection time intervals. Optimal Design usually focusses on sampling time *points* rather than time *intervals*, thus for µD studies a new approach has to be taken. In a first step the experimental basis for optimisation was laid by obtaining data from a clinical trial. From the developed population PK model, optimal sampling time points were determined. Finally methodological investigations due to the special settings in µD studies were performed.

Methods: 34 individuals were included in a clinical trial with linezolid, 600 mg bid [1]. Samples were taken after single dose and at steady state over a period of 8 h. 1176 unbound plasma and 2325 µD concentrations were determined. Population PK analysis was carried out using NONMEM. POPT and PopED were used to retrospectively optimise the sampling design as optimal time *points* for plasma and µD samples. Based on simulated concentration-time profiles in µD the impact of placement of time points as in the traditional sampling approach on bias is assessed.

Results: Unbound linezolid PK in plasma was described by a two-compartment model including a time-dependent nonlinear influence on clearance implemented by an additional inhibition compartment [1]. Microdialysate concentrations were incorporated into the model using two additional compartments. The optimised design reduced the number of plasma samples from 40 to 6 and of µD from 20 to 4 per indvidual [2]. Investigations of the impact on bias for different scenarios of placement of sampling time intervals around the optimised time points are performed. One scenario includes the analysis of differently long, fixed intervals where the measured concentration is placed at the midinterval as used in the conducted trial and as typically used in µD studies.

Conclusions: Prerequisites for methodological investigations of Optimal Design for µD studies were generated and the special characteristics of this sampling technique explored. These analyses give useful information about the utilisation of µD as an attractive tool to monitor target-site exposure in patients.

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Mike Smith MSToolkit – An R library for simulating and evaluating clinical trial designs and scenarios

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Objectives: The ability to quickly and easily simulate clinical trial scenarios is a vital tool in the modern statisticians' inventory. Advances in clinical trial design mean that sample sizing and evaluation of trial performance metrics and operating characteristics often require simulation.

Methods: MSToolkit is an R package that allows the user to quickly simulate clinical trial data and then apply analytical methods to this simulated data to evaluate trial performance. MSToolkit can simulate endpoint and longitudinal data, crossover trials, run-in periods, interim analyses including designs allowing stopping for futility or dropping doses. Model parameters and covariate values can be generated from distributions or sampled from external files. Data is output in CSV files which are easily read and used by a number of different analytical programs. Analysis is performed on each dataset and can be performed in R, SAS or any other program which can be called in batch mode e.g. WinBUGS. MSToolkit is GRID aware – analysis can be split across multiple GRID nodes allowing parallelisation of the analysis. Results are automatically collated and summarised.

Results: MSToolkit provides flexibility in specifying trial design components coupled with the ability to analyse data using a variety of analytical engines using the power of parallel processing in a GRID environment. It also provides a common framework for simulations allowing statisticians to share code and quickly understand the mechanisms and analytical techniques used by others in simulations. Separating data generation and analysis steps means that different analytical techniques can be applied to the same underlying data in order to compare results and operating characteristics of decision criteria. Users can quickly compare designs with and without interim analysis decision rules. Users specify their own functions for generating response variables, analysing the data, interim criteria for dropping doses or stopping the study. The only limitation is the ability to specify these in R code.

Conclusion: MSToolkit allows the statistician to concentrate on the design itself, the processes that will generate data, the analytical techniques to be used, the decision criteria for attributing success or failure to a particular trial, rather than spending time coding.

Shuying Yang Bayesian Adaptive Designs for Phase IIb Dose-ranging Study in Rheumatoid Arthritis (RA)

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GSK

Objectives: A Bayesian adaptive design was proposed for the phase IIb dose ranging study to effectively and efficiently find the minimum efficacious dose (MED) of an anti-inflammatory drug for the treatment of Rheumatoid Arthritis (RA). The purpose of this work was to assess the possibility and validity of this method using clinical trial simulations.

Methods: With this design, the study started from a pre-defined initial dose (e.g. the most likely dose), the dose for the next cohort was determined by the posterior probability of the response based on the accrued data. An up-and-down allocation rule was proposed to allow progression towards the MED in either dose escalation or reduction. For the simulation, a logistic regression model of ACR20 response (American College of Rheumatology definition of response using a composite clinical improvement of 20%) on log transformed dose was used to illustrate the method.

The simulations were conducted based on three scenarios on dose response curve: slope=1, slope=0.5 and slope=0 (no difference from placebo). For illustration, 100 simulations per scenario were generated. R[1] and WinBUGS1.4[2] with R2WinBUGS library [3] was used to perform the simulations.

Results: The simulation results indicated that with scenarios where target dose was in the dose range, the design was able to identify the MED for all simulations. For the scenario with no difference from active to placebo, the design was able to stop the trail as early as possible. However the number of cohorts may depend on the initial dose selected and the allocation rules.

Conclusions: Bayesian adaptive design was appropriate in finding MED in the dose ranging studies. It minimised the number of patients assigned to least efficacious doses or administered with high doses. The sample size for each cohort and the randomisation ratio could be calculated by simulations as described. Finally it was flexible enough to incorporate different allocation and stopping criteria within the framework

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Martin Bergstrand Visual Predictive Checks for Censored and Categorical data

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Background: Non random censoring of data as in the presence of observations below the quantification limit (BQL) can harm not only parameter estimates but also diagnostic plots such as Visual Predictive checks (VPCs). Treating this type of data as a combination of censored continuous data and categorical data (e.g. BQL) can facilitate unbiased interpretation. VPCs can be adopted for any type of categorical data by plotting the observed and the simulated fraction of observations of each category versus an independent variable. The visual interpretation of a VPC is its strength, however it can be difficult to distinguish if lack of agreement is due to random chance or model misspecification. Calculating non-parametric confidence intervals based on simulated data for different percentiles of continuous data or for the fraction of observations in a certain category for categorical data is likely to improve the interpretability. This work aims to illustrate a new approach for VPCs in the presence of categorised data.

Methods: VPCs were created based on different models for ordered categorical data, count data and continuous data with censored low and/or high observations. Each VPC was based on 1000 datasets simulated with obtained parameter estimates. For continuous data the median and 95 % prediction interval for the observed data are plotted together with non-parametric 95 % confidence intervals for the corresponding percentiles calculated from the simulated datasets. To ensure correctly calculated percentiles all censored observations was retained in the original dataset. Percentiles for observed data can only be adequately calculated and presented for percentiles where the censored observations constitute a smaller fraction than the percentile in question. For all categorical data the fraction of observations in each category was compared to a simulation based 95 % confidence interval. In all created VPCs time was chosen as the independent variable. Individual strategies for stratification and binning across the independent variable were adopted for each data-set.

Results: The combination of VPCs for both censored data and continuous data was found to more clearly indicate the presence of important model misspecifications than VPCs focusing on only the continuous observations. The inclusion of confidence intervals for the diagnostic variable (i.e. percentiles or fraction of observations) acts as an effective support to identify actual model misspecifications.

Anton Korobeynikov Comparison of Parameter Estimates for One Special Model of Survival Curves for Sample with Interval Censoring

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Introduction: In practice time to event data can rarely be observed directly. Usually, one can only know some time interval where observation lies in, thus data became censored. The mixed case interval censoring is one of the most important models of censoring seen in the practical applications. It is well-known that significant loss of information about underlying distribution due to censoring can lead to almost arbitrary large-sample behaviour of parameter estimates including inconsistency, etc.

Parameter Estimates: We consider the problem of parameter estimation for one special survival curve model [1] with incomplete data due to censoring. In particular, we propose new parameter estimator based on the non-parametric estimate of distribution function (which itself turns out to be Hellinger-consistent [2]). The computation procedure is described as well. Large sample properties of this new estimator such as consistency, efficiency, robustness in presence of outliers are studied by the means of Monte-Carlo simulations. All these properties are compared with the same properties of the ordinary maximum likelihood estimates.

Conclusions: It was found that compared to the maximum likelihood estimates proposed estimates have slightly bigger variance. However, they possess better robustness properties when sample contains significant amount of outliers.

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Elke Krekels Evaluation of morphine pharmacokinetic models in neonates and infants.

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Objectives: There is an ongoing debate on how to incorporate the influence of developmental growth in paediatric pharmacokinetic (PK) models. Bodyweight can be included *a priori* as a covariate by the use of a bodyweight-based allometric equation with a fixed exponent of 0.75 for clearance and 1 for distribution volume, or a more systematic approach in which bodyweight is regarded a covariate as any other can be applied. The performance of two population PK models for morphine in (pre)term neonates and children up to 3 years, developed using these two approaches, is evaluated in this study.

Methods: Using the same datasets [1,2], two population PK models were developed for morphine in this young population. Models were either based on a systematic data-analysis as described in Knibbe *et al.* [3], or on allometric principles based on bodyweight with fixed exponential scaling factors as described in Bouwmeester *et al.*[4] and Anand *et al.*[5]. The models were validated internally and externally using up to 4 datasets [6-9].

Results: In the analysis prediction-based diagnostics (basic goodness-of-fit plots), simulation-based diagnostics (NPDE), numerical diagnostics (bootstrap) and residual-type diagnostics (MDAWR, MAWR etc.) were evaluated, as were number of parameters needed to describe the data, ε- and η-shrinkage and the ease with which dosing recommendations can be derived. Neither of the models proved to be superior on all performed diagnostics.
To compare individual and population predictions from each model, individual *POSTHOC* parameters and population parameter predictions were plotted against each other. These plots show that both models predict comparable clearance values and distribution volumes, except for individuals at the boundaries of the weight-range.

Conclusions: Both methodologies for population PK model development in the paediatric population yield models that describe morphine PK in children younger than 3 years adequately. The choice of methodology depends on the aim and objective of the study. The model with the fixed exponential scaling factors is possibly more useful for extrapolations to older age-groups, whereas the model that was developed using a systematic analysis has fewer parameters. Moreover dosing regimens can be more easily derived from the latter model.

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Sergei Kulikov New parametric model for survival fitting

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Objectives: To introduce new class of function for survival function fitting and to increase the power of related parametric comparison testing.

Methods: It is common in oncology study publications that survival curves do not tend to the zero and reach a "plateau". For some types of events like remissions, expectation of the time to event can be infinity. That means a finite subset of subjects in whom the investigated event will not occur. In usual parametric survival analysis, only functions with $S(\infty)=0$ are taken into account because of the second Kolmogorov's axiom. The idea of the proposed approach is to reject the demand for "$S(\infty)=0$" . This implies new parametric functions for distribution fitting. Two simple approximation two-parametric functions which have non-zero asymptotic value are introduced. The first evaluated parameter is the "plateau" level. This also is known as cure rate. In practical usage, this value is often of interest as common endpoints of clinical trials, for example, remission rate or long-term survival rate.

Results: Two survival models were proposed:

$S(t)=a + (1- a)\exp(-t/t)$ (1) $S(t)=a^{(1-\exp(-t/t))}$ (2)

The first term is a typical exponential function. It describes binary heterogeneous population: with constant and zero hazard rate. The second term is easier to use in the maximum likelihood estimation procedures. It describes the object with time-dependent exponentially dropping hazard function. Geometrically, these two functions are very close but they capture two different failure processes. SAS macros which use NLIN procedure for model parameter estimation were developed to assess their performance. Two model functions were investigated and compared for fitting of simulations data, data of multicentre acute lymphoblast leukemia trials and data of multiple donation frequency.

Conclusion: A new re-parameterization of the survival function was proposed, which a specific algorithm for parameter estimation and tests for comparison. Their relevance in survival data analysis was demonstrated using empirical and simulated datasets.

Bojan Lalovic Impact of Dosing Regimens on Dropout Across Pregabalin Trials in the Treatment of Generalized Anxiety Disorder: Model Refinements and External Validation

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Background: We have previously analyzed the relationship of dizziness and somnolence as major determinants of study dropout in the treatment of generalized anxiety disorder (GAD) with pregabalin[1]. The relationship of dose to adverse-event was independently modeled using the two-part (incidence and severity) AE model[2]. The examination of dose-adverse-event-dropout relationship afforded a model-based strategy to mitigate incidence and severity of adverse events and reduce dropout, which was previously based only on subjective and empirical clinical judgment.

Objectives: To examine potential improvements to the initial modeling analysis by introducing several refinements to the adverse event and dropout sub-models and examine their predictive performance and impact of external validation.

Methods: Adverse-event incidence was modeled as a time-to event process, allowing incorporation of daily dosing (titrations) as a time-varying covariate. Conditional severity of adverse events was described as an ordered categorical variable with proportional odds accounting for both the time-course of effect and correlation between adjacent observations[3]. Parametric discrete-time, hazard models were fitted using dizziness severity as a time-varying covariate. The model-based predictions of dropout were evaluated against the nonparametric (Kaplan Meier) estimates (predictive check) and against data from an independent trial.

Results: Consideration of initial adverse event incidence within an individual as a time to event data represented a principled method in handling time-varying information across the both adverse event and dropout sub-models. Model predictions illustrate the benefit of a gradual titration on dropout as a result of lower initial dizziness incidence and severity. Predictive performance of the adverse-event dropout model was evaluated and the approach considered adequate, with the assessment based in part on an independent GAD trial providing an external validation.

Conclusions: Dropout represents an important clinical trial endpoint, which can be analyzed using time to event models that readily incorporate daily dosing, or other time varying information (covariates). Prospective simulations with the current model highlight the utility of this modeling approach in examining the impact of untested titrations schemes on dropout for future GAD trials.

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Marta Neve Assessment of NONMEM and WinBUGS performances when estimating power and sigmoid Emax models

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Objectives: Modeling of dose-response and dose-exposure relationship during Phase I studies is considered. In particular, the present work focuses on a couple of frequently used models: the sigmoid Emax model applied to efficacy (e.g. PET studies) or safety (e.g. vital signs) endpoints and the power model applied to dose escalation trials. Performances of NONMEM and WinBUGS have been assessed resorting to a number of simulated datasets exploring a variety of parameter conditions.

Methods: R software package was used to simulate 50 dose-response and 50 dose-exposure datasets for each set of fixed and random effects. The sigmoidicity factor for the Emax model was assumed to be 0.5, 1 or 2, whereas for the dose-exposure model the power coefficient was set to 0.8, 1 or 1.2. Low, intermediate and high variability around parameters was used when producing simulated data-sets. Moreover, the impact of weakly and more informative experimental designs (expressed in terms of sample size and number of doses) was evaluated. In both the simulation and estimation process, inter-subject variability was assumed to be log normally distributed and an additive residual error was used. Results obtained with NONMEM (ver. VI, FOCE interaction method) and WinBUGS (ver. 1.4.3) were then compared in terms of accuracy and precision of parameter estimates.

Results: Both NONMEM and WinBUGS showed a generally comparable accuracy in estimating fixed effects with either highly or less informative datasets. However, when considering random effects (inter-subject and residual error variability) NONMEM seemed to provide slightly more accurate estimates with a lower precision.

Conclusions: In the range of the explored experimental designs, neither NONMEM nor WinBUGS offered a significant added value when estimating fixed and random effects of power and sigmoid Emax models. Similar conclusions were drawn when evaluating both real and simulated datasets [1, 2]. Nevertheless, WinBUGS has the undoubted merit of providing posterior distribution of population parameters. This work does not aim to represent an exhaustive analysis of the performances that can be obtained resorting to these two different methodologies. As such, different experimental designs or more critical conditions may be considered for future evaluations.

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Richard Nixon Using short-term evidence to predict six-month outcomes in clinical trials of signs and symptoms in rheumatoid arthritis

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Objectives: A model is presented to generate a distribution for the probability of an ACR response at six months for a new treatment for rheumatoid arthritis given evidence from a one or three month clinical trial.

Methods: A model is presented to generate a distribution for the probability of an ACR response at six months for a new treatment for rheumatoid arthritis given evidence from a one or three month clinical trial. We denote j as the treatment arm within each clinical trial, and k the type of treatment used (k=1 for MTX, k=2 for biologic, k=3 for biologic plus MTX); t_0 as the earlier time point (either one month or three months depending on the model); and t_1 the six-month time point. We then denote n_j as the number of patients in treatment arm j for which there is data available at both time points, and r_{jt} as the number of patients achieving the ACR response criteria at time point t. We assume that r_{jt0} and r_{jt1} are binomially distributed with parameters φ_{jt0} and φ_{jt1} representing the probabilities of response, respectively. φ_{jt1} is assumed to be dependent upon φ_{jt0}, in a logistic regression. To estimate the ACR response rate at time point t_1 from the ACR response rate at time point t_0, we fit the following statistical model:

$r_{jt0} \sim \text{Binomial}(n_j, \varphi_{jt0})$
$r_{jt1} \sim \text{Binomial}(n_j, \varphi_{jt1})$
$\text{logit}(\varphi_{jt1}) = \alpha_j + \beta\text{logit}(\varphi_{jt0})$
$\alpha_j \sim N(\mu_k, \sigma^2)$

Results: The model is assessed by Bayesian predictive P-values that demonstrate that the model fits the data well.

Conclusions: The model can be used to predict the number of patients with an ACR response for proposed six-month clinical trials given data from clinical trials of one or three months duration

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Elodie Plan Eleven ordered categories data: which modelling options?

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Objectives: Ordered categorical responses are common pharmacodynamic outcomes; models dealing with these data using the non-linear mixed-effects approach have been successfully developed. However when the number of categories reaches 11, like in the case of the visual analogue scale (VAS), the number of needed parameters become high; therefore there might be other types of models to consider. Treating such data as continuous seems to be done frequently and needs to be evaluated, but treating them as counts is an option considering the flexibility of the probability distribution models.
The aim of this study was to explore different modelling approaches candidates for fitting simulated discrete VAS data.

Methods: This methodological study consisted of stochastic simulations followed by re-estimations performed in NONMEM VI FOCE or Laplace. A first set of 100 simulations was performed with an ordinal model including a baseline; parameters values were derived from a real case study on 231 patients recording 100 observations each on average [1]. A second set of 100 ordinal simulations included 3 dose levels in parallel with the placebo arm; the drug effect was linear with a slope of 0.045 (30% interindividual variability).
Estimations of the simulated data sets were performed with an ordinal, a continuous (with logit transformation of predictions and data), a truncated Poisson and a truncated generalized Poisson model [2]. Performances were evaluated by comparison of re-simulated score distributions with the true distributions at different doses.

Results: The ordinal model was composed of 11 parameters for the baseline profile, whereas all the other models had 2 or 3. The continuous model required a discretization of the simulated values.
In simulations from the four models the truncated Poisson model was clearly worst. The continuous model showed some discrepancy compared to the true values at the highest dose whereas the generalized Poisson model showed good agreement at all doses. The ordered categorical model showed good estimation properties and simulations mimicked closely the true score distribution at different dose levels.

Conclusions: VAS data can accurately be analysed with an ordinal model, at least with rich data sets and, as here, a lack of Markovian patterns. A logit-transformed model for continuous data performed reasonably and a generalized truncated Poisson model well. These latter models may be alternatives for sparser data sets and in the presence of serial correlations.

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Alberto Russu Dose escalation studies: a comparison among Bayesian models

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Objectives: To apply alternative Bayesian models for the population analysis of the dose-exposure relationship in dose escalation Phase I studies. In these studies, subjects receive increasing dose levels and, at each dose escalation, a decision is made on the next dose level to be administered, based on safety/tolerability constraints. In recent years there has been a growing interest in Bayesian methods applied to such experiments [1,2,3]. In the present work, the performance of four alternative Bayesian models was evaluated on real and simulated datasets and a model comparison procedure was developed for the identification of the most appropriate model.

Methods: The dose-exposure relationship was explored using a log-linear model (i.e. a linear model in log-log scale), a power model, an Emax model, and a nonparametric model based on population smoothing splines [4]. In all cases, a Bayesian population approach was adopted. The parametric models were estimated using WinBUGS 1.4.3. Sum of squared residuals, predictive root mean square error, AIC and BIC were used as model comparison criteria.

Results: Ten phase I dose escalation studies and 60 simulated datasets (generated with the three parametric models) were analyzed. In the experimental datasets, the power and log-linear models provided comparable results in terms of point estimates and credibility intervals, whereas the Emax model proved inadequate when data showed upward curvature. The population spline approach provided good results for both experimental and simulated datasets. In the former case, the goodness of fit was comparable to parametric models. In the simulated benchmark, population splines performed comparably to the true models used to generate the data. The proposed comparison approach correctly identified the true parametric model in most cases.

Conclusions: A thorough model comparison procedure was developed, based on model complexity criteria and crossvalidatory techniques. Applying several criteria represents a useful cross-check when one is faced with the problem of finding the most adequate model. It has been shown that the parallel estimation of four models (three parametric, one nonparametric), complemented with model comparison criteria, can robustly handle a variety of dose-exposure relationships overcoming possible misspecification problems. Moreover, population splines may represent an appealing first-try, especially in early escalation stages, when there is not enough information to support a specific parametric model.

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Paul Baverel Comparison of two PsN Bootstrapping Routines for Obtaining Uncertainty Measurement around the Nonparametric Distribution Obtained in NONMEM VI

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Objectives: To assess the performance of two different resampling-based methods aiming at quantifying uncertainty around nonparametric distribution (NPD).

Methods: An IV-bolus PK model was used to simulate three data sets of 200 individuals following a rich sampling design and for which the random effects conformed to a (i) normal, (ii) bimodal and (iii) heavy-tailed underlying distributional shapes. After subsequent estimation with FOCE-NONP in NONMEM VI, uncertainty measurement was derived for each parameter marginal density by means of two different bootstrapping procedures. The first, full, method described in a previous work [1] relies on N bootstrap samples of the original data and a reanalysis of both the preceding parametric as well as the nonparametric step. The second, simplified, method relies on bootstrap sampling of the vectors of individual probabilities associated with each unique support point of the NPD. From the bootstrap samples, confidence intervals (CIs) around the original NPD are calculated. This simplified method is far less computer intensive than the first one (ca 2 min vs. 4 hr for this example). In order to compare the outcomes of the full and simplified methods, the 95% CI of the true marginal density was derived by standard bootstrapping procedure [2] from the true individual parameters and this was used as reference to compute mean errors (MEs) of the 95% CI width for each method.

Results: Overall, both versions performed similarly with respect to the trend of the true uncertainty around the NPD for each distributional case. MEs of the distance across 95% CI boundaries for CL were equal to: (i) -0.024 and -0.012, (ii) -0.021 and -0.006, (iii) -0.009 and 0 for the full and simplified, respectively.

Conclusions: Two bootstrapping methods suitable for estimating uncertainty around NPD are currently available. Little bias was induced by these techniques when comparing the 95% CI width regardless of the distributional shape in case of rich sampling design.

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Aliénor Bergès An Efficiency Comparison between Concentration-Response Analysis and Dose-Response Analysis through Simulation

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Background: Identifying the dose of optimal benefit-risk ratio is crucial in drug development, therefore confident and efficient characterisation of efficacy or toxicity as a function of dose is important. Using concentration-response relationship as a potentially more powerful tool for dose finding is increasingly appreciated. However, PK sampling is inconvenient; drug assays are costly; and PKPD analysis is labour intensive and time consuming. In this investigation, we attempted to quantify the incremental value of concentration-response analysis (CR) over dose-response analysis (DR).

Objectives: The objective of the current work is to compare the accuracy and precision of ED_{50} estimation directly through DR and indirectly through CR analyses in common dose-finding scenarios.

Methods: Response of a hypothetical drug as a function of steady-state concentration was described by a direct Emax model with a fixed Emax. Three hundred replicate parallel dose-ranging trials were simulated using R software to investigate the impact of the following drug and design properties on bias and imprecision of ED_{50} estimation as a function of sample size: inter-individual variability in CL/F, inter-individual variability in EC_{50}, response measurement error, top dose and the number of dose groups. For each replicate, CR and DR models were fitted in R. Mean bias and imprecision for ED_{50} in each scenario were calculated for CR and DR. To allow comparison between the two analyses, the typical value of ED_{50} from the CR approach was calculated using CL/F and EC_{50} estimates.

Results: Under the scenarios investigated, higher variability in EC_{50} and less dose groups were the most important causes for greater bias and imprecision in ED_{50} estimation for both CR and DR. CR consistently out-performed DR, although the difference was not large under all circumstances. As expected, higher variability in CL/F differentially increased bias and imprecision for DR analysis over CR analysis. The difference in these metrics between CR and DR was not sensitive to response measurement error, top dose or variability in EC_{50}.

Conclusions: The work reported here forms a simulation frame work for assessing the value added by PK sampling and PKPD analysis in dose finding. In practice, simulation parameters can be modified based on drug prior and potential design options to suit specific project needs. These preliminary results are limited to a parallel design with fixed Emax. Ongoing further investigation includes situations of cross-over design and the needs to estimate Emax.

Massoud Boroujerdi A turnover longitudinal model for the analysis of FEV1 changes in COPD

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Objectives: The forced exhaled volume in one second (FEV1) is the most reproducible test in spirometry and it is commonly used for the assessment of disease severity in chronic obstructive pulmonary disease (COPD). The objective of this investigation was to characterise the changes in FEV1 up to a year from start of treatment using a second order turnover model. Model parameters are estimated for a population of COPD patients following placebo treatment and the effect of drugs simulated on different parameters.

Methods: Data from 3065 COPD patients treated with placebo were evaluated. The lungs are represented as compartment with a FEV1 "turnover". The model assumes that the turnover of lungs is inherently controlled by a turnover or feedback mechanism. The rate constant (k) charactering the turnover was estimated using the second order model. The mechanism of the lungs turnover was further postulated to be nonlinear with saturating turnover with increasing FEV1. The basal value of FEV1 was used as the capacity for the nonlinear model. The controls for the nonlinear model are on the turnover for lungs and the rate constant charactering the flow.

Results: The rate constant charactering the flow is estimated as k=2.446 $\pm$ 1.268 per/week (Mean $\pm$ SD). The k estimates were regressed with the subject specific variables and the results are shown in the following table.

	Estimate	CV%	P
intercept	2.864	7.44	<0.001
Gender (female)	-0.278	18.34	<0.001
Ex-smoker*	-0.441	10.88	<0.001
Non-smoker*	0.994	12.77	<0.001
age	-0.005	63.82	0.067
BMI	0.006	66.66	0.171

*The smoking status is compared to the current smokers.

Conclusions: .The FEV1 changes with time are described with a non-linear model based on the turnover and flow rate constant. This model provides the basis for a mechanism based simulation of FEV1 in clinical trials.

Phylinda Chan Population Pharmacokinetic-Pharmacodynamic-Viral Dynamics Modelling of Maraviroc Monotherapy Data Using MONOLIX

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Objectives: A 4-differential equation viral dynamics (VD) model was used to describe the kinetics and interaction of target cells, actively infected cells, latently infected cells and viruses in human immunodeficiency virus (HIV) infected patients[1]. NONMEM has been previously used for fitting pharmacokinetic-pharmacodynamic (PKPD)-VD model to the maraviroc (MVC) monotherapy data[2]. Not only are computation times very long but there are often convergence problems resulting from numerical difficulties in optimizing the linearized likelihood. Only a few of the parameters can be estimated and it is not feasible to perform simultaneous PKPD-VD modelling. MONOLIX implements a stochastic approximation of the standard expectation maximization (SAEM) algorithm for nonlinear mixed effects models without approximations. The SAEM algorithm replaces the usual estimation step of EM by a stochastic procedure which has been shown to be very efficient with improved convergence toward the maximum likelihood estimates[3].
This analysis compares population PKPD-VD modelling of monotherapy MVC data using MONOLIX with NONMEM.

Methods: Plasma concentration (1250 samples) and viral load (1169 observations) arising from 63 asymptomatic HIV infected patients were available. Patients received 10 days MVC monotherapy with doses ranging from 25-300mg QD and 50-300mg BID.
A 2-compartment disposition model with first-order absorption was used to describe the MVC concentrations. An inhibitory Emax model was used to describe the viral inhibition. The need of an effect compartment and/or a lag time was examined to describe the delay in onset of viral inhibition. Parameter estimation was performed using a 2-stage approach in MONOLIX version 2.4 and NONMEM VI. The predicted PK profile based on the Empirical Bayes Estimates (EBE) obtained from separate PK analysis was used to drive the viral inhibition. A simultaneous approach was also tested with MONOLIX.

Results: With a 2-stage approach, the time taken in MONOLIX to generate population and individual estimates including diagnostics (conditional means and standard errors, log likelihood profile, visual predictive checks and normalized prediction distribution errors) was over 50% less than in NONMEM without diagnostics. Parameter estimates were comparable between MONOLIX and NONMEM.

Conclusions: The SAEM algorithm allows simultaneous estimation of PKPD and viral dynamics parameters. MONOLIX provides an alternative option to NONMEM when facing lengthy computation times or convergence problems.

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Jeroen Elassaiss-Schaap Variability as constant coefficient of variation: Can we right two decades in error?

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Objectives: Derive mathematically correct equations that express variability components of PK-PD models as constant coefficients of variation

Introduction: The variability estimates that are reported by analysis software such as NONMEM are difficult to interpret for general audiences. Students of population PK-PD modeling are therefore routinely taught to calculate constant coefficients of variation by taking the square root of such estimates. Application of this method is widespread and can for example be found in contributions to the nmusers mailing list, in peer-reviewed papers on NONMEM analyses and in software packages. The square-root method is an approximation of the exponential variability transformation, which in practice is used as the default way to specify inter-individual variability in PK-PD models.

Methods: In this presentation it is shown how the mathematically correct equations for variability components as constant coefficients of variation (CCV) are derived. Expressions for the standard error and confidence intervals thereof are also provided.

Results: Differences between the approximation and the correct method are negligible when variability is small, e.g. for 10% CCV the difference is smaller than 0.5%. Unfortunately, biased results are obtained when variability becomes large. Calculation of CCV as square root of variability values results in a 10% downward bias at values of 64% and higher. This result is also valid for additive residual error in the logarithmic transform-both-sides (TBS) approach.

Conclusion: It is advised to consider correct equations instead of the usual approximation in calculating CCV of exponentially defined variability components as estimated by NONMEM or other software tools. This is especially important when reporting on data with high intrinsic variability such as encountered in population PK-PD analyses.

Leonid Gibiansky Pharmacodynamic Modeling of Biologics with Target-Mediated Drug Disposition: TMDD Approximations, Relation to Indirect-Response Models, and Application to Population PK-PD Analyses

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Objectives: To investigate the rapid binding (RB), quasi-steady-state (QSS) and Michaelis-Menten (MM) approximations [2,3] of the TMDD model [1] as applied to the pharmacodynamic (PD) data; to derive relationships between the parameters of the TMDD and indirect response models; to investigate and compare applicability of the TMDD approximations in cases when the drug-target complex is eliminated faster or slower than the free target; to test the identifiability analysis algorithm [3] on the example of the simulated population PK-PD data.

Methods: a) TMDD equations and its approximations were reviewed and compared with the indirect-response model equations. b) For several combinations of model parameters, concentrations of the drug, target, and drug-target complex were simulated from the TMDD model and the corresponding RB, QSS, and MM approximations. Simulated concentration-time profiles were compared to investigate the ability of the approximations to describe the TMMD model predictions. c) The population PK-PD dataset that included the data from two studies was simulated. The first study imitated the fist-in-man, dose-escalation, rich sampling study with 4 cohorts of six subjects administered single dose of 100, 300, 1000, or 3000 nmol. The second study imitated a phase 2 study with 2 arms of 100 subjects administered three doses of 1000 or 3000 nmol with 4 week intervals. Free drug concentrations and total target concentrations were measured. Identifiability of the TMDD model parameters and ability of the approximations to describe the simulated data, to estimate the TMDD model parameters, and to predict unobservable free target concentrations were investigated.

Results: a) When the free target is eliminated faster (or slower) than the drug-target complex, the equation for the total target concentration was shown to coincide (for RB, QSS, or MM approximations) with the indirect response models with stimulation (or, respectively, inhibition) of elimination. Correspondence between the TMDD and indirect-response models allows estimating unobservable free target concentrations using the indirect-response model parameters. b) For the investigated range of parameters, the RB and QSS approximations behaved similarly: they provided an adequate description of the data simulated from the TMDD model. The MM approximation was applicable when the degradation rate of the drug-target complex exceeded the degradation rate of the free target, and was not appropriate otherwise. c) In the population PK-PD simulation, the TMDD model, as expected, was able to estimate all model parameters except the binding constants. For the binding constants, the ratio was estimated with a good precision while the values themselves remained close to the initial estimates and far from the true values. The RB and QSS approximations were able to recover the true model parameters and estimate the drug, target, and complex concentrations correctly. As the MM approximation was not applicable (the drug-target complex concentration was comparable

to the free drug concentration), the combination of the PK model with MM elimination (to describe free drug concentrations) and the indirect response model with inhibition of elimination (to describe total target concentrations) was tested. The PK model provided unbiased individual predictions of the free drug concentration. However, random effects on the MM parameters strongly depended on dose, and population predictions for low-dose groups were biased. The indirect-response PK-PD model (using individual predictions of drug concentrations) precisely estimated the relevant TMDD model parameters, providing unbiased population and individual predictions of the total and free target concentrations.

Conclusions: In the variety of tested examples, the rapid binding and quasi-steady-state approximations provided excellent description of the PK and PD data simulated from the TMDD model. Equation for the total target concentration derived based on these approximations coincides with the indirect-response model with inhibition or stimulation of elimination. The simulated population PK-PD study demonstrated that for drugs with TMDD, parameters of the indirect response models can be used to estimate unobservable free target concentrations that are important for pharmacodynamic modeling.

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Varun Goel A Bayesian Multivariate Model for Repeated Measures of Correlated Data

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Objectives: Most often in proof-of-concept trials repeated measures of efficacy and safety outcomes are collected, for example a crossover trial with varying doses. These outcomes are often correlated. The objective of this analysis was to develop an exposure response analysis for a vector of correlated observations, each arising from a member of the exponential family of distributions. PD 0200390 is a ligand of the a_2d subunit of the voltage-gated calcium channel, being investigated for the treatment of primary insomnia and non-restorative sleep. Wake after sleep onset (WASO) and number of awakenings (NAASO-2) are the measures of efficacy while ease of awakening (AFS) and behavior following wakefulness (BFW) are measures of residual effects. The distribution of WASO, NAASO-2, are assumed to be Lognormal and Poisson; AFS and BFW are assumed Bernoulli.

Methods: Six dose levels (5mg-75mg), and placebo data were available for 126 patients with primary insomnia from two phase II double blind, randomized, placebo controlled, crossover studies. Hierarchical non-linear dose response models were developed for observation vector of WASO, NAASO-2, AFS and BFW in WinBUGS. The observation vector components were assumed independent conditional on the latent-subject-specific vector of random effects drawn from a multivariate normal distribution[1]. Comparison between multivariate and individual models was assessed by posterior predictive checks, deviance information criteria (DIC), conditional predictive ordinate,[2,3] and values of log pseudo marginal likelihood[2,3] (LPML).

Results: Dose response relationships for WASO, NAASO-2 were described by inhibitory Emax and for the logistic models for AFS, BFW as linear. Significant correlations were observed between baselines and ED50s for WASO and NAASO-2, and additive random effects for AFS and BFW. DIC and LPML values indicated multivariate model as significantly better at fitting and prediction of correlated outcomes.

Conclusions: Simultaneous PK PD modeling is often encountered in the Pharmacometrics literature, however simultaneous modeling of correlated safety and efficacy endpoints is rare. In this work we model correlations by introducing multivariate distributions for random effects. Knowledge of this correlation helps in understanding of drug's action and reduces uncertainty in future simulations for dose and sample size selection.[4]

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Sylvain Goutelle Performing Monte Carlo Simulation Based on Nonparametric Pharmacokinetic Parameter Distributions: Evaluation of Various Methods Applied to a Paediatric Population Study on Busulfan

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Objectives: Monte Carlo (MC) simulation techniques are increasingly used in population pharmacokinetic (PK) studies. Nonparametric (NP) population methods often result in singular distribution shapes. Little information exists about the way to perform MC simulation compatible with such results. The main objective of this study was to evaluate the ability of various MC simulation methods to reproduce the characteristics of a NP parameter distribution observed in real patients.

Methods: A population PK study was performed using the NPAG algorithm in 42 children who received busulfan (Bu) intravenously before bone marrow transplantation. Bu concentrations (N=166) were determined by a validated HPLC-UV method [1]. Various compartmental models were fitted to concentration data. Goodness of fit was assessed using standard criteria.

Then, seven methods were evaluated in a 1,000 subject MC simulation using Matlab software. Various options regarding parameter distributions, covariance, and other settings were tested. Methods 1 to 4 were fully parametric (FP) methods. Methods 5 to 7 were iterative, semi-parametric, two-step (TS) methods: first, one point is selected in the NPAG grid according to its probability, and then, it is used as a mean vector of an assumed multivariate distribution. Simulated distributions were compared with the actual NPAG parameter distributions using basic statistics and graphical analysis.

Results: A linear two-compartment model fitted the data very well. NPAG provided a 27 point grid as population parameter distribution of the four parameters. For Bu volume of distribution (VD), the probability distribution was typically multimodal. Mean, 25, 50, and 75 percentile values (all in liters) were 5.66, 0.649, 1.52, and 2.53, respectively. Overall, FP methods failed to reproduce all characteristics of the original NP distribution. Best results were observed with TS methods using a reduced covariance matrix derived from the NPAG one. For example, 25, 50 and 75 percentile values for the VD distribution were 3.39, 6.83, 11.2 with method 4, and 0.927, 1.84, and 3.29 with method 7, respectively. On scatter plots, parameter values provided by TS methods with a reduced covariance matrix were much more clustered around NPAG support points than those from FP methods.

Conclusions: Performing MC simulation based on NP parameter distribution requires specific methods. A new approach of MC simulation designed for such application has been presented.

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Emilie HENIN Tablet position in gastrointestinal tract derived from drug release measurements and plasma concentrations

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Objectives: To investigate the possibility of deriving the position of a tablet in the gastrointestinal tract (GI) from drug plasma concentrations and drug release measurements.

Data: Six healthy volunteers were administered magnetically labeled extended release tablets containing felodipine, under fasting and fed conditions (1). Three types of observations were collected: tablet GI positions and drug release were monitored using Magnetic Marker Monitoring (MMM) technique, and plasma concentrations of felodipine were measured. Tablet GI position was categorized into five regions: fundus, antrum, proximal small intestine, distal small intestine and colon.

Models: Two separate models were developed to describe on one hand GI tablet transit and on the other hand GI distribution of released drug, absorption and disposition for an extended release formulation of felodipine. In the second model tablet GI position was included as an important covariate affecting both drug release, GI distribution of released drug substance and absorption rate. This model development was presented in details elsewhere (2). In this work, both models were coupled and estimated simultaneously, using prior population parameter estimates for tablet GI transit, but not the position data measured by MMM.
Beside downstream transit, GI tablet transit model enables return from antrum to fundus. This movement has been taken into account by a mixture modeling defining 3 subpopulations: no return, 1 return or 2 returns to fundus.
Prior information based on the separate modeling of the GI tablet transit data (2) was included to govern the typical value and interindividual and variability for tablet residence time in each GI region. A series of step-functions was used to describe the tablet movement from one region to the following one.

Results: Empirical Bayes Estimates for each parameter were obtained using NONMEM VI and individual tablet movement profiles were compared to observed ones. At 7 occasions, subjects were affected to the first subpopulation (no return to fundus) whereas 5 were estimated as having 1 or 2 returns to fundus, which is in agreement with observed profiles. Tablet GI positions were adequately predicted in 10 out of 12 occasions, based on the model for drug release and pharmacokinetic data, as compared to positions measured by MMM. Similar results were obtained when only plasma concentration data was used.

Conclusion: This work represents a first step in the use of prior information on GI tablet movement in absorption modeling for extended release formulations.

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Ibrahim Ince Population PK modeling of Midazolam in Infants, the effect of age and other covariates

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Objectives: In order to develop rational dosing schemes for drugs in children, we investigate the influence of age-related changes on the PK and PD of drugs. For the ontogeny of the CYP3A subfamily, we use midazolam as an in vivo CYP3A probe to describe the biological system specific pathway for the clearance of CYP3A substrates. In this study, among other covariates the influence of age-related changes on the PK of midazolam is studied using population pharmacokinetic modeling.

Methods: Midazolam data from two different studies were used; 15 critically ill pediatric patients (2 days - 10 years) received midazolam for sedation [1] and 24, previously healthy children (3 months - 25 months) received midazolam postoperatively after elective craniofacial surgery [2]. The two datasets were merged in R and population PK modeling was performed using NONMEM VI. During the covariate analysis step, the influence of postnatal age, bodyweight, mechanical ventilation, gender and severity of illness were investigated.

Results: Population pharmacokinetic analysis showed remarkable differences in clearance and volume of distribution between the critically ill and postoperative children. A severity of illness factor added to both the clearance and the volume of distribution, together with bodyweight as a covariate for volume of distribution of midazolam, significantly improved the model.

Conclusions: While both age-related changes and severity of illness proved to be important covariates for the pharmacokinetics of midazolam, in this analysis a distinction between the influence of both these covariates could be made. More datasets will be added to the analysis, after which specific dosing guidelines taking into account these two covariates will be developed.

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hester kramer Phase II dose selection for a hypothetical novel Direct Thrombin Inhibitor (DTI): an integrated approach using experimental and literature data.

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Background: Phase II dose selection includes in general many uncertainties after first healthy volunteers trials, e.g efficacy, safety, dose regimen, number of doses. However, integrating available knowledge with new experimental data, improves dose selection and decision making. DTI's inhibit thrombin from clotting in the bloodstream and reduce the risk of venous-thrombo-embolism (VTE). The DTI's Dabigatran (DAB) and Ximelagatran (XIM) have been developed (ref 1-6) for this indication. Clinically efficacious and sub-efficacious dose were described and publicly available. Also pharmacokinetics (PK) and biomarker concentration relationships have been described, especially for the Ecarin Clotting Time (ECT) which specifically reflects the mechanism of action of DTI's**.**

Objectives: By integrating the available competitor literature data with experimental data of a hypothetical novel DTI, selecting an active and safe dose range for a Proof of Concept (POC) trial,

Methods: For a hypothetical new DTI, PK and ECT-concentration data were generated. The assumed typical values for a 2 compartment model for the hypothetical DTI were CL/F=600 L/h, V1=200 L, V2=600 L, Q12=60 L/h, Ka=0.75 h and the in vitro ECT potency at 60 s*L/mg. To link the available PK and ECT data of the new DTI to the competitor data an integrated target value was needed. To define such a target value it was assumed that Exposure (AUC) to a DTI with a certain ECT response relates to efficacy. Under this assumption the ECT data were used to calculate the Area-under-ECT-time curve (AUE), being the integrated target value. This was calculated as AUC_x*$potency_{xr}$=AUE_x. The target AUE range was based on sub-efficacious (SEff) and efficacious (Eff) doses of DAB and XIM from phase II clinical trials (**ref 1-6**).

AUCs for DAB and XIM were determined based on published pop-PK data. For DAB and XIM ECT curves were determined in vitro. The linear relationships were described with the difference in slope as a relative potency measure. The target AUE's at the SEff and Eff were calculated by multiplying the AUC with the relative potency value.

The PK of a hypothetical novel DTI was simulated by a pop-PK model, using NONMEM, and PD (AUE) was scaled by the in vitro relative potency relationship. This implies that the PK was multiplied with the relative potency resulting in an AUE at a certain dose resulting in a linear AUE-Dose relationship. This relationship was then used to identify SEff and Eff for the novel DTI.

Results: Integrating experimental and literature data for DAB and XIm resulted in the following parameters:

DTI	SEff (mg)	Eff (mg)	ECT potency (s*L/mg)	CL/F (L/h)	AUC SEff (mg h/L)	AUC Eff (mg h/L)	AUE (s*h) SEff	AUE (s*h) Eff
DAB	100	150	84	103	0.98	1.45	82	122
XIM	24	48	56	27.3	0.88	1.76	49	99

The integrated target value AUE to meet for the hypothetical DTI ranged between 49 and 122 s*h to achieve sub-efficacy or efficacy in a phase II PoC trial

As the slope of the linear relationship (AUE-Dose) was 0.1 it was estimated that for this DTI the dose-range for the POC trial would be 175-293 mg for SEff and 353 to 435 mg for Eff.

Conclusions: Experimental and literature data from a novel hypothetical Direct Thrombin Inhibitor and two existing competitors were successfully pooled in an integrated analysis. This approach allowed the selection of a dose range of 200-400 mg, which is anticipated effective in a POC trial patient population.

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Brigitte Lacroix Implementation of a NONMEM cluster and add-ons within UCB

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Objectives: The goal of this project was to provide modelers with an efficient IT infrastructure to run the NONMEM software, together with better tools to improve models' diagnostics and validation. Another goal was to better fulfill regulatory requirements.

Methods: The NONMEM application has been installed on a Linux cluster gathering one head node and 4 compute nodes (2 dual cores processors each). The LSF [2] cluster program has been deployed. The Perl-speaks-NONMEM (PsN) [3] package has also been installed on the cluster. The NONMEM source code has been modified to include the user identification and the description of the cluster configuration in the modeling result file. Besides the cluster implementation, the R [4] using Xpose4 library [5] and Census [6] applications were installed on users laptops.

Results: The LSF cluster program allows the modelers to start several NONMEM runs in batch mode. PsN is used to automate some modeling tasks (bootstrap, model diagnostics...) and to start parallel execution of NONMEM jobs. The R/Xpose and Census packages are used for model diagnostics and results visualization. The source code versions are managed through Subversion [7].

Conclusions: The implemented system is now used by around 15 users located on 3 sites. Most of the computer intensive model validation procedures would not have been possible without the cluster implementation due to the time they require. Using this system, the modelers are able to answer questions from regulatory agencies reviewers in a more timely manner. The compliance to computerized systems regulations is greatly improved due to a central NONMEM installation and a version control system.

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[4] R: R project - http://www.r-project.org/
[5] Xpose 4: A. Hooker, J. Wilkins, M. Karlsson and N. Jonsson http://xpose.sourceforge.net/
[6] Census: J. Wilkins - http://census.sourceforge.net/
[7]Subversion: source code management tool: http://subversion.tigris.org/

Hugh McDevitt Infrastructure development for building, maintaining and modeling indication- specific summary-level literature databases to support model based drug development.

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Background: Several Pharma Modeling and Simulation (M&S) departments and M&S Consulting companies have demonstrated the value of using models developed from summary level literature data to improve the efficiency of drug development [Corrigan, Mandema]. Health authorities and Payors (such as NICE) are also very interested in the comparison of new therapies with existing treatments for healthcare cost containment. Any organization that intends using these databases as 'legacy' systems that are available for input and use by multiple users needs to take time to carefully consider the processes and infrastructure to ensure reliability and quality. At Novartis, an IT infrastructure that uses publicly accessible open source database systems is planned and will be presented in this poster.

Objectives: To solicit feedback and discussion on the establishment of an infrastructure for building, maintaining and modeling summary-level literature data from the published literature publications.

Methods: A clear 7 step process has been identified.

1. Identify the key characteristic endpoint for an indication,.
2. Identify the relevant publications
3. Define the data specification for the indication
4. Load the relevant data from the identified publications
5. Quality control the loading of the data
6. Publish the database
7. Revise and update the database on an ongoing basis

Results: Several indication specific databases have been developed (diabetes, respiratory), while some have been commercially acquired. The partnership with GvKBio for data extraction has been established and has proved very effective.

Conclusions: A clear methodology has been defined and the effort required to set up an indication specific database has been established. The next step is to industrialize the process by establishing a central database that will hold all the information and support the acquisition process.

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Carmen Navarro Bioequivalence Trials Simulation to Select the Best Analyte for Drugs with Presystemic Intestinal and Hepatic Metabolism.

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Objectives: The aim of this work is to evaluate the chemical substance (parent drug or metabolite) more suitable for BE analysis. The semi-physiological model includes pre-systemic intestinal metabolism with efflux transporter from enterocyte to lumen in addition to the previous model (1, 2). Simulations about class I drugs undergoing saturable and non saturable metabolic clearance were performed.

Methods: The studies were simulated using NONMEM VI. A semi-physiological model was developed, including dissolution compartment, operative absorption time, efflux transport in gut, pre-systemic metabolism in gut and liver in addition to systemic metabolism. Four scenarios were simulated by combining high and low intrinsic clearance in liver or gut, and were evaluated at saturable and non-saturable conditions. Parent drug and metabolite plasma profiles were simulated for both, reference and test. Afterward AUC and Cmax were calculated to assess the ratios between reference and test.

To simulate the test and reference formulations, different scenarios were performed by varying the values of in vivo dissolution rate constant in lumen.

Results: Results of all simulations will be presented as percentage of BE success for the metabolite and the parent drug. In absence of efflux transport and non-saturable conditions, there are small differences between parent drug and metabolite in AUC and Cmax ratios, but when the metabolism becomes saturable, metabolite AUC and Cmax ratios are higher than 0.8 even when dissolution constant of test formulation is 12% of reference formulation, whereas parent drug is affected by formulation quality.

Conclusions: This work shows the differences between high and low intestinal or hepatic metabolism concerning the AUC and Cmax ratios, demonstrating that the parent drug is the most sensible moiety in most scenarios.

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Didier Renard Using desirability indices for decision making in drug development

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Objectives: The clinical utility index (CUI) has been proposed as an integrated measure of clinical benefit/risk [1] [2]. Its usage has focused on characterizing optimal dose ranges and selecting compounds when decisions are based on multiple attributes (e.g., safety and efficacy outcomes, quality of life benefits, drugability properties, etc.). By definition the CUI is a weighted sum and requires defining utility functions to represent expected clinical value of possible outcomes. We propose using the desirability index (DI) [3] as an alternative measure to the CUI.

Methods: Desirability concepts have been developed for the optimization of complex industrial processes which involve competing properties. The weighted geometric mean is a popular choice as a summary measure in this context and one of its features naturally translates to drug development applications, namely that if one of the process' attributes is unacceptable, the process as a whole becomes unacceptable. In our approach DI is derived while accounting for two sources of uncertainty: variability in estimated dose-response relationships and random variation in desirability functions, which are inherently subjective, in order to achieve a more robust assessment. These naturally lend themselves to a Bayesian decision-analytic framework, where the desirability index acts as a gain function. The distribution of DI can easily be obtained through simulation-based methods, either in a Bayesian or frequentist setting.

Results: We highlight some limitations of CUI and show how it can be framed within a broader desirability context. We illustrate the dose optimization and compound comparison problems using a (blinded) case study where one wants to optimize on a single efficacy and single safety outcome. We also illustrate how weights can be employed to generate a desirability surface that better reflects the risk-benefit assessment through equi-desirable contours.

Conclusions: Desirability indices provide a general and flexible framework to extend CUI as an integrated measure of clinical benefit/risk and support dose and compound decisions in drug development.

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Soundos Saleh Matching PBPK and NONMEM pharmacokinetics descriptions to understand and extrapolate - case study ciprofloxacin

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Objectives: Ciprofloxacin is a member of the fluoroquinolone class of antibiotics. Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria drug and it is first choice in the treatment of presumed or confirmed pneumonia secondary to Streptococcus pneumonia. Ciprofloxacin is applied to proven uncomplicated and complicated urinary tract infections. Being more than 20 years on the market available knowledge of ciprofloxacin was combined as a case study to elucidate the potential of PK modeling and simulation for the use in clinical development and PK/PD analysis.

Method: Data for approved oral, intravenous application and inhalation route were matched from several sources of clinical and preclinical studies. The basic techniques of NCA as well as compartmental analysis were complemented by population analysis in healthy volunteers as well as in patients. Basic understanding of model mechanism was collected regarding the oral absorption, systemic distribution as well as metabolic and excretory elimination. The descriptive view achieved by retrospective analysis described the data well and allowed suitable predictions (e.g. pediatrics). PB/PK was applied to better understand the physiological and pathophysiological behavior and to get knowledge about the drug exposure at the site of infection. Not only distribution to organs but also accumulation due to the presence of incorporating cells could be described.

Results: Applying PK knowledge from different evaluation and simulation tools joint perspective powerful instrument to predict therapeutic efficacy. The quantification of these processes led to the understanding, interpretation and prediction of ciprofloxacin plasma concentration-time profiles. The possibility to predict tissue concentration enabled model-based PK/PD predictions for populations of interest which can not covered by available clinical data.

Conclusion: When appropriate workflows can be established the different methods from the toolbox of pharmacokinetics complement retrospective analysis, physiological understanding and prospective simulations.

Nelleke Snelder A proposal for implementation of the Markov property into a continuous time transition state model in NONMEM

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Objectives: Repeated measures of ordered categorical data are typically described in NONMEM using proportional odds models. These models often result in an adequate description of the data. However, a limitation of proportional odds models is the underlying assumption that, given the random effects, the observations are independent. In specific situations this may result in an overestimation of inter-individual variability, resulting in individual profiles that are physiologically implausible [1]. When dependency between observations is an issue, Markov models are better suited than proportional odds models since they inherently assume that future events depend on present events. Initially, this property was implemented in a hybrid model, a proportional odds model where the probabilities are dependent on the preceding stage through a first order Markov element [2]. As this model is discrete in time the sampling scheme can play an important role. Therefore, we have further developed this model by implementing the Markov property in a continuous time transition state model in NONMEM using the Kolmogorov backward equations [3].

Methods: Categorical measurements from the monosodium iodoacetate induced arthritis model were described by a proportional odds model and by a transition state model including the Markov property. The transition state model was implemented using ordinary differential equations such that each differential equation represented the probability for a certain category. The Markov property was implemented using the Kolmogorov backward equations. Subsequently, simulations were performed with both models and a comparison was made between the simulated and original data.

Results: Both models resulted in a comparable description of the population data. However, the transition state model with the Markov property resulted in a better prediction of the individual data as demonstrated by simulations.

Conclusion: The Markov property was successfully implemented in a transition state model in NONMEM using the Kolmogorov backward equations. Simulations with this model resulted in physiologically plausible individual profiles. Moreover, as the transition state model including the Markov property is continuous in time the influence of the sampling scheme on the parameter estimates is less as compared to the hybrid model. As a result, this model has better properties to simulate observations from different sampling schemes.

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Ashley Strougo Mechanism-based pharmacokinetic modelling to describe the effect of protein binding on the pharmacokinetics of solifenacin

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Background and objectives: Solifenacin succinate is a muscarinic receptor antagonist used for the symptomatic treatment of overactive bladder (OAB). The parent compound extensively binds to α1-acid glycoprotein (AGP). To explore and quantify the influence of protein binding on the pharmacokinetics (PK) of solifenacin, we aimed to develop a mechanism-based PK model.

Methods: The "law of mass action" was used to describe the reversible solifenacin-AGP and solifenacin-albumin binding. The model also included binding of free solifenacin to a virtual binding compartment (VBC) positioned outside the plasma. In addition, a physiological expression was included into the model in order to relate the volume of distribution (Vd) to its physiological determinants. Total, free, AGP and albumin plasma concentration data from three clinical trials in healthy, elderly, renal and hepatic impaired subjects were used to parameterize the model with NONMEM VI. The model was externally validated on data from patients with OAB.

Results: A two-compartment model including protein binding best described the PK of total and free plasma concentrations of solifenacin. Based on individual plasma-AGP (range 26 - 181 mg/dL) and plasma-albumin (range 2.5 - 5.1 g/dL), free fraction was estimated as 0.0204 (range 0.00108 - 0.0411). The effect of free fraction on Vd (578 L; range 345 - 1151 L) and clearance (5.84 L/h; range 2.26 - 20.5 L/h) could also be quantified. Model evaluation by means of an internal and external visual predictive check showed satisfactory results.

Conclusions: A mechanism-based PK model was successfully developed allowing us to explore and quantify the influence of protein binding on the PK of solifenacin. This model constitutes a theoretical framework that could be applied to other drugs. In addition, it could be used to determine the influence of protein binding and body composition on the PK and pharmacodynamics of solifenacin.

Dalia Vasquez Population Pharmacokinetic-pharmacodynamic modeling of the Analgesic Effects of Lumiracoxib, a selective inhibitor of the enzyme COX2 in the Rat

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Objectives: Lumiracoxib (LMX) is the most selective of the commercially available COX_2 inhibitors (coxibs) [1]. Several coxibs have been withdrawn from the market due to unexpected side effects [2]. It has been pointed, that such withdrawals were due to insufficient information on the pharmacology of these drugs at the time of commercialization, and could be avoided if an adequate strategy, including pharmacokinetic-pharmacodynamic (PKPD) modeling, had been followed [3]. Therefore the objective of this study was to establish a PK/PD model for the analgesic effects of LMX in the rat, and characterize the *in vivo* concentration-response relationship of this drug.

Methods: Female Wistar (180-200 gr) rats received a subcutaneous injection of saline solution or carrageenan into the plantar surface of the right hind paw to induce inflammation and hyperalgesia. Experiment I: fasted rats received the carrageenan insult followed by oral administration of vehicle, 1, 3, 10 or 30mg/kg LMX dose. Plasma drug concentration was determined and the antihyperalgesic response was measured as the latency time (LT) to express a nociceptive behavior. Experiment II: rats were administered with vehicle, 10 or 30mg/kg oral dose of LMX at 4 h after carrageenan administration. The PK/PD modeling of the antinociceptive response was performed sequentially using a population approach (NONMEM VI).

Results: A two-compartment model described the plasma disposition of LMX. An input model, considering a lag time and a decrease of the relative bioavailability with the administered dose, was suitable to describe the absorption process. The response was predicted according with the following expression: $LT_{(t)}=LT_0/(1+MED_t)$, where LT_0 is the baseline response and MED represents the level of inflammatory mediators. The time course of MED was assumed be equal to the time course of COX_2, calculated according with the formula: $dCOX_2/dt=k_{Scox2(t)}-k_{D\_COX2}xCOX_2$. The effect of LMX was considered by a reversible inhibition of the COX_2 activity. The value of the *in vivo* estimate of the dissociation equilibrium constant (KD) of the COX_2-LMX complex was 0.25 µg/mL.

Conclusions: The developed model was suitable to describe the time course of the pharmacological response of LMX according to its mechanism of action and its pharmacokinetics. PK/PD modeling thus is a useful tool to improve our understanding of the *in vivo* pharmacology of coxibs, and thus to optimize the therapeutic use of these agents.

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James Yates Validation of in vivo Mouse PK Assay by Mixed Effects Modelling: Estimation of between-study variability.

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Objectives: A capillary bleed sampling technique was evaluated in-house. This technique allowed the sampling of multiple time points from a single mouse. The reproducibility of the data produced by this technique was investigated by carrying out a number of *in vivo* studies. The variability in the data may then be partitioned into inter-study and inter-animal. A particular compound was chosen for its well-defined 2-compartmental kinetics. Reproducibility, at least for this compound, would be assessed if the majority of variability could be assigned to inter-animal variability rather than inter-study variability. To achieve these objectives the data were analysed in NONMEM VI, the NLME toolbox in R and WinBUGS for a comparison of results.

Methods: The NONMEM analysis was performed using the FOCE method. The NLME tool in R uses the Lindstrom-Bates method [1] which is similar to FOCE because it linearises about the current individual estimate. WinBUGS was used with uninformative priors and five independent chains. The latter two methods allow the construction of a multi-level mixed effects model. The implementation of inter-study and inter-individual variability in NONMEM was as described in the literature[2].

Results: The data set contained profiles of 48 animals over 7 studies; each individual profile contained a maximum of 5 time points. The results from NONMEM suggested that the inter-animal variability was large (~70% CV on each parameter) whereas there was very little evidence of inter-study variability except for on the volume of the peripheral compartment. The NLME results were qualitatively very similar with the majority of variance at the inter-animal level, except for a moderate variability at the study level on the inter-compartmental flow. This is possibly due to drug being detectable in some animals at 24hrs and not in others. The NLME results did show some sensitivity to initial parameter values. The WinBUGS output allocated variance more evenly across the inter-animal and inter-study levels, with more variance at the inter-animal level.

Conclusions: The analysis is readily applicable, though there are a number of pitfalls - especially with respect to the NONMEM implementation of the statistical models. The results also show that with this quantity of data different conclusions may be reached by using different methods. The results however point towards a more sophisticated use of data when planning drug discovery life-phase activities.

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Balaji Agoram A Physiologically-Based Mathematical Model to Predict Lung Retention and Inhaled Pharmacokinetics of Therapeutic Candidates

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Objectives: Retention within the lung tissue is widely believed to enhance the duration of action of inhaled therapeutics. However, the physicochemical factors that influence lung retention are not fully understood; hence rational design of potentially lung-retained inhaled molecules faces substantial hurdles.

The main aim of this work is to develop an *in silico* approach for designing lung retention. The specific objectives are: (1) integrate *in vivo* processes such as dissolution, retention, absorption, and systemic elimination of inhaled compounds quantitatively within a physiologically-based mathematical model with physicochemical determinants, (2) evaluate the model by comparing predictions of retention with experimental rat data for seven inhaled compounds and (3) create a user-friendly software package implementation of the model.

Methods: The model is based on a system of 15 ordinary differential equations describing drug dissolution, absorption across lung epithelium, lung tissue binding, systemic distribution and elimination processes. *In vitro* permeability and tissue binding data were generated for 7 small molecule compounds of widely different physicochemical characteristics and target mechanisms using Caco-2 systems and rat lung tissue. Plasma concentration data were also generated for these compounds in rats after intravenous (IV) and intratracheal (IT) solution dosing. Stochastic model simulations, accounting for uncertainty in model parameters such as permeability and tissue distribution, were performed to predict PK of IT compared to IV dosing. Retention of compound in the lung was assessed based on a visual examination of predicted lung and plasma IT PK profile compared to the IV profile. The model was implemented using SAAMII programming language.

Results: The model predictions were classified as either high or low confidence based on the width of predicted confidence intervals. Among high confidence predictions (5/7 candidates), all predictions of lung retention and lack thereof were accurate. Among low confidence predictions (2/7 candidates), 1 prediction of retention was accurate.

Conclusions: A mathematical model representing physiological processes during inhaled absorption has been developed and accurately predicts lung tissue retention in rats for the range of molecules tested. The model has the potential to substantially impact inhaled drug discovery and hence "inhalation by design" paradigm. The model has been implemented in a user-friendly software package.

Corina Becker Whole-Body Physiologically-Based Pharmacokinetic (WB-PBPK) Modeling of Moxifloxacin (MFX) to Support a Translational Approach in Pediatric Study Design

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Objectives: Pediatric development strategies requested by FDA and EMEA aim for dosing recommendations to maintain efficacy and safety in different age groups. Since established PK methods such as simple allometric scaling show limited predictive power, an alternative approach is applied to design clinical studies in children: the use of a pediatric PBPK model for MFX paying attention to developmental changes.

Methods: An adult WB-PBPK model for MFX is built using the software PK-Sim®. When the simulated plasma concentration-time profiles and clearance pathways reflect adequately the observed data from adults, the physiological and ontogenic changes and the clearance pathways of MFX are scaled to the respective ages using the Clearance Scaling Module of PK-Sim®. The Population Module of PK-Sim® is used to build virtual populations of children from 18 to 0.5 years categorized according to the ICH11 classification. Concentration-time profiles in the different pediatric populations are predicted by the pediatric WB-PBPK model. Based on the predictions, and derived PK parameters, dose and dosing scheme recommendations are developed to maintain exposure and maximum concentrations limits known for efficacy (AUC) and safety (Cmax) in adults.

Results: The WB-PBPK model provides an accurate description of the experimental PK data of MFX in adults. In preschool children and infants between 25 to 80% higher mg/kg doses and/or shorter dosing intervals than those recommended in adults are required to achieve equivalent exposure to adults. The results obtained from the pediatric PBPK model are used to plan first studies in pediatric patients.

Conclusions: The WB-PBPK predictions of pediatric populations enable the rationale knowledge-based development of study designs. The approach uses drug-independent prior information about developmental differences between the pediatric populations and adults. It suited for iterative continuous validation and refinement when clinical data of MFX in pediatric patients becomes available. This knowledge-driven approach strengthens the scientific basis of the pediatric development and is well suited for continuous trial support.

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S. Y. Amy Cheung Development of a closed loop whole body (WB) physiologically based pharmacokinetic model (PBPK) of beta-blockers in the rat

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Objective: To develop a closed loop (CDL) WBPBPK model to investigate the *in vivo* pharmacokinetics of some beta-blockers from rat data. Some tissues exhibit slow equilibration with blood levels which suggests permeability limited (PML) kinetics. Therefore tissue models representing this process must be developed.

Method: 12 tissues (adipose, bone, brain, gut, heart, kidney, liver, lung, muscle, skin, testes & thymus) and arterial blood of rats for 15 beta-blocker compounds (R- and S- acebutolol, betaxolol, bisoprolol, metoprolol, oxprenolol, propranolol, pindolol & S- timolol) were previously collected. Open loop (OPL) modelling [1], also called the forcing function approach [2], allows the estimation of partition coefficients (K_p) in a PBPK model for individual well-stirred tissues by using the known arterial concentration-time profile as a driving function together with the physiological information of tissue volumes and tissue blood flow rate, assuming perfusion limited (PFL) kinetics. This results in a 1 compartment tissue model. For certain tissues, PML kinetics is modelled by 2 compartments with the rate of exchange between vasculature and tissue controlled by permeability (PST). These findings necessitated the incorporation of certain PML tissues into the closed loop WBPBPK model of each compound. The estimated K_p values with its %SE from the OPL modelling was then used together with the prior function subroutine [3] in NONMEM to develop a WBPBPK model. In the CDL modelling, all tissue K_ps of a compound are estimated simultaneously.

Results: The K_p estimates for S-acebutalol are compared to the steady state (SS) values in the table below as an example. The CDL PML K_p estimates more closely reflect the SS estimates than the CDL PFL estimates. The difference in objective function (OBJ FN) values indicates the model fit of the permeability incorporated WBPBPK model is also better than the perfusion limited model.

Tissues	SS	CDL PFL	CDL PML
Lung	6.07	5.81	5.31
Gut	90.4	0.127	150
Gut PST	NA	NA	1.78
Thymus	4.35	2.94	2.83
Liver	24.6	1.72	9.78
Brain	0.356	0.202	0.165
Heart	4.29	7.10	6.89
Kidneys	31.4	13.2	12.8

Skin	2.45	8.50	7.69
Muscle	4.06	5.53	4.81
Adipose	0.772	0.553	0.470
Testis	2.50	3.25	3.39
Testis PST	NA	NA	0.0513
Bone	0.0436	0.422	0.0373
OBJ FN	NA	1240	461

Conclusion: These results show the importance of using the information obtained in OPL modelling in the development of a WBPBPK model using the prior function subroutine in NONMEM. This also demonstrates that PML kinetics must be incorporated into the model.

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Brenda de Winter Mechanism-based pharmacokinetic modelling of protein binding of mycophenolic acid and its glucuronide metabolite in renal transplant recipients

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Introduction: Mycophenolic acid (MPA), the active compound of mycophenolate mofetil (MMF), is used to prevent rejection in renal transplant recipients. MPA is mainly glucuronidated to the metabolite MPAG, which exhibits enterohepatic recirculation (EHC). Both drug are highly protein bounded, MPA for 97% and MPAG for 82%. Low plasma albumin levels, impaired renal function and coadministration of ciclosporin (CsA) are associated with increased clearance of total MPA (tMPA). Decreased tMPA exposure is correlated with a higher risk for acute rejection, whereas increased unbound MPA (fMPA) exposure may produce side effects.

Objectives: A mechanism-based population PK model was developed describing the relationship between dose and tMPA, fMPA, tMPAG and fMPAG and the influence of renal function, plasma albumin levels and cotreatment with CsA on this relationship.

Methods: tMPA, fMPA, tMPAG and fMPAG concentration-time profiles of renal transplant recipients cotreated with CsA (n=48) and tacrolimus (n=45) were analysed retrospectively using NONMEM.

Results: A 2- and 1- compartment model were used to describe the PK of fMPA and fMPAG, respectively. MPA and MPAG were allowed to competitively bind with albumine (bMPA and bMPAG). tMPA and tMPAG were modelled as fMPA+bMPA and fMPAG+bMPAG, respectively. In the model clearance of fMPAG decreased when creatinine clearance (CrCL) was reduced ($p<0.001$). In this situation the mechanistic model adequately described how increasing fMPAG concentrations decrease tMPA AUC due to displacement of MPA from the binding sites. With a MMF dose of 1000 mg and CsA cotreatment fMPA AUC decreased from 2.5 to 2.3 mmol*h/L and tMPA AUC from 69 to 56 mmol*h/L due to a decrease in CrCL from 50 to 10 mL/min. fMPA clearance remained unchanged. Albumine was correlated with the maximum number of binding sites available for MPA and MPAG ($p<0.001$). A decrease in plasma albumin levels from 0.5 to 0.4 mmol/L resulted in 27% reduction of tMPA AUC, whereas the reduction in fMPA AUC was less (8%). EHC, decreased due to CsA cotreatment ($p<0.001$), was modelled by transportation of fMPAG to the gall bladder.

Conclusion: A mechanistic PK model has been developed which describes the relationship between dose and both free and total MPA exposure. The model adequately describes the influence of renal function, plasma albumin and CsA co-medication. This model may be used to further explore the relationship between dose and both therapeutic efficacy and toxicity.

Gemma Dickinson Prediction of a Metabolic Drug-Drug Interaction in a Virtual Human Population using in vitro Enzyme Kinetic Information

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Introduction: The quantitative prediction of metabolic drug-drug interactions (mDDI) is of clinical benefit. In cases where there is potential for an interaction, in vitro ADME properties may be extrapolated to predict in vivo ADME behaviour in simulated virtual populations. These simulations can provide a valuable tool in the assessment of the probability of an mDDI and may facilitate the identification of patients most at risk of experiencing such interactions. Predictions such as these can assist in the design of clinical DDI studies and help make go/no go decisions.

Methods: An in vivo study was carried out to assess the interaction of the compound with ketoconazole. It was assumed that the substrate compound was metabolised entirely by CYP3A4 and 2C19 and *in vitro* kinetic data were obtained from various sources. Virtual trials (n = 10) were simulated (Simcyp Version 7.0, www.Simcyp.com), that mimicked the design of the *in vivo* study.

Results: In the *in vivo* study, observed changes in the area under the concentration-time curve (AUC) and the maximum substrate concentration (Cmax) were 4.5 and 2.5, respectively. Predicted values from the 10 simulated trials were an AUC ratio of 2.5 (range; 1.2 to 7.7) and a Cmax ratio of 1.5 (range; 1.1 to 2.9). The mean fold error in the prediction of Cmax ratios was 1.5 with 10/10 predicted values within 2-fold of the observed data. The corresponding mean fold error for AUC ratio was 2 with 7/10 predicted values within 2-fold of the predicted data.

Conclusions: IVIVE is a useful tool for assessing mDDI in early drug development; it was used successfully in the current study to accurately predict the interaction of a Lilly compound with ketoconazole. The simulations indicated a potentially significant interaction that was confirmed with *in vivo* studies.

Andrea Edginton Parameterization of a physiologically-based pharmacokinetic (PBPK) model for the simulation of ibuprofen pharmacokinetics under exercise and heat stress with validation from clinical data

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Objectives: Military personnel in areas such as the Middle East are subject to heat and exercise stress. The need for altered dosing of medications in this sub-population may be required to maintain therapeutic plasma concentrations. This study aims to parameterize a physiologically-based pharmacokinetic (PBPK) model using ibuprofen as a proof-of-concept allowing for changes in physiological parameters associated with operational stresses using clinical data for model evaluation.

Methods: PBPK models for R- and S-ibuprofen were built using PK-Sim®. Model coupling in MoBi® allowed for the R- to S-ibuprofen chiral inversion to be described. Literature information on the physiological changes associated with heat and exercise stress were incorporated to simulate these conditions. These included changes in cardiac output, hematocrit, organ-specific blood flows and albumin concentrations. A prospective pharmacokinetic clinical trial was completed by DRDC where volunteers were subjected to exercise (15 minute walk, 5 minute rest for 2.5 hours at 42oC followed by 6 hours at 42oC) following per oral administration of 400 mg racemic ibuprofen. R- and S-ibuprofen plasma concentrations were determined by UPLC/MS/MS. Thus far, simulated pharmacokinetic profiles generated from the PBPK model were tested against the clinical data from the pilot study to evaluate changes in relevant pharmacokinetic parameters such as R- and S-ibuprofen half-life and area under the plasma concentration vs. time profile.

Results: 4 volunteers completed the pilot study and contributed 47 ibuprofen concentrations. Half-life [mean (CV%); S-IBU 2.1 (4) h, R-IBU 2.5 (32) h] and AUCt_end [S-IBU 2912 (18) mg*min/L, R-IBU 1099 (26) mg*min/L] were obtained. Ibuprofen pharmacokinetics in the volunteers was similar to that from non-stressed individuals in the literature. The PBPK model altered for operational stress (e.g. reduced portal flow, increased muscle and skin flow, increased hematocrit) echoed results from the clinical trial simulating no changes in ibuprofen pharmacokinetics.

Conclusion: A PBPK model parameterized to simulate changes in drug pharmacokinetics under operational stress echoed the results from the pilot clinical trial such that ibuprofen pharmacokinetics were consistent with non-stress individuals from the literature. A full scale trial is ongoing using each volunteer as their own control (non-stress arm) to further elucidate potential drug pharmacokinetic changes and to provide data for model evaluation. The model will also be used to focus resources with respect to future clinical trials to rank those commonly used drugs in the field that have the greatest chance of requiring dose adjustment.

Cecile GERARD Link between cyclosporin exposure in tissues and graft versus host disease in paediatric bone marrow transplantation: analysis by a PBPK model

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Objectives: In bone marrow transplantation (BMT), cyclosporin is used to prevent the graft versus host disease (GVHD). A retrospective analysis of clinical data showed different patterns of cyclosporin anti-GVHD effect depending on its mode of administration. Non-linearity in cyclosporin distribution may be an explanation. The objective of this study was to link the occurrence of GVHD to cyclosporin exposure in blood, target organs of GVHD (skin, liver and intestine) and also bone marrow and thymus (effect of cyclosporin on T lymphocytes).

Method: Using a PBPK model of cyclosporin disposition in children (see companion abstract), AUC in blood and organs were calculated for 61 paediatrics patients (31 with intermittent 2 h every 12 h infusions and 30 with continuous infusion) undergoing BMT. The influence of cyclosporin exposure on the probabilities of GVHD (grade > 0) and GVHD in skin, liver and intestine (score > 0) were assessed by binary logistic regression (SPSS V.17 software).

Results: Severe GVHD (grade III and IV) and cutaneous GVHD were significantly more frequent after continuous infusion than after intermittent infusions (17 vs 0 % and 89 vs 59 % respectively). Mean time to GVHD was 13 (intermittent) and 18 days (continuous). Mean cyclosporin dose at day 1 was 3.71 mg/kg (intermittent) and 3.55 mg/kg (continuous). There was no link between blood cyclosporin AUC and the occurrence of GVHD. There were significant links between AUCs in bone (including bone marrow) or thymus at the beginning of the treatment (0-24h) and the occurrence of GVHD ($p < 0.05$ in each case). The ratio of mean AUCs (no GVHD / GVHD) was 1.26 for bone and 1.13 for thymus. AUC in skin and intestine (0-12h) were a significant covariate of cutaneous GVHD and intestinal GVHD, respectively. The ratio of mean AUCs (no GVHD / GVHD) was 1.23 for skin and 1.21 for intestine. Cyclosporin infusion duration was not a significant covariate of the occurrence of GVHD once AUCs were taken into account.

Conclusions: In BMT, cyclosporin exposure in blood on day 1 was not a predictor of GVHD occurrence contrary to exposures in bone and thymus, which show the interest of the PBPK model. Differences in the pattern of GVHD depend only on differences in drug exposure in target tissues and not of duration of infusion per se. Non-linearity in tissue distribution explain these differences. The strong influence of cyclosporin exposure at day 1 confirms the importance of decreasing the activation of T-cells from the graft.

Cecile GERARD Influence of cyclosporin infusion duration on efficacy in paediatric bone marrow transplantation: analysis by a PBPK model

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Objectives: In bone marrow transplantation (BMT), cyclosporin is used to prevent the graft versus host disease (GVHD). In our hospital, more frequent and severe GVHD were observed with continuous infusion than with twice daily infusion (2 h every 12 h), given the same daily dose (mg/kg). The team of Rowland has built a physiologically based pharmacokinetic (PBPK) model of cyclosporin in rats and clearly showed that cyclosporin distribution presents several sources of non-linearity [1]. Our hypothesis is that the difference of efficacy of cyclosporin between both types of infusion is linked to a difference of tissue distribution of the target organs of GVHD (skin, intestine and liver). The objective of this study was to compare, with a global PBPK model, exposure of these organs to cyclosporin for each type of infusion.

Method: The rat PBPK model of Rowland was scaled up to human adult and adjusted to children. The scaling was based on physiological data and allometric equations. The model was implemented in ADAPT II. The paediatric PBPK model was fitted individually (bayesian MAP estimator) to cyclosporin blood concentrations from 61 paediatric patients (31 and 30 with intermittent and continuous infusion, respectively). Both groups were comparable for demographics, initial dosing regimen and BMT indication. Using the adjusted PBPK model, the AUC in blood and target organs were calculated for each child.

Results: Kinetic profiles simulated in blood and all organs with the rat PBPK model were similar to the experimental data [1]. The model in children was improved by modifying the mean value of CLint. With the final model, the weighted residuals were normally distributed, with 100 % in the range [-3;+3]. The study showed that mean AUCs were significantly greater for the blood and GVHD targeted organs at the beginning of the treatment (0-24 hours) when cyclosporin was administered by intermittent rather than continuous infusion ($p < 0.05$ in each case). The ratio of mean AUCs 0-24h (intermittent / continuous) was 1.25 (blood), 1.42 (skin), 1.10 (gut), 1.25 (liver).

Conclusions: The PBPK model in children showed that the exposition by cyclosporin was more important in the GVHD target organs when it was administered by intermittent infusion, which is consistent with the greater efficacy of intermittent infusion in prevention of GVHD.

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Hannah Jones Use of PBPK modelling in drug discovery at Pfizer

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Objectives: Physiologically-based pharmacokinetic (PBPK) models are composed of a series of differential equations and have been implemented in a number of commercial software packages. Integration of species and compound specific data into these models allow for the prediction of plasma and tissue concentration time profiles after intravenous and oral administration of compounds to animals and humans. The aim of this work was to prospectively explore the utility of such models in a drug discovery setting.

Methods: The PBPK strategy proposed by Jones et al., 2006 and validated by De Buck et al., 2007 was followed in all cases. The following applications were investigated: 1. simulation of human PK; 2. simulation of food effects in human and 3. simulation of high dose preclinical TK exposure.

Results: In the majority of cases, the PBPK models (as implemented in GastroPlus™) together with the relevant input data were able to accurately predict the PK of the compounds studied in the presence and absence of food. Prediction accuracy tended to decrease with increasing dose as a result of saturable clearance mechanisms that were not incorporated into the model.

Conclusions: PBPK models were used to enable the early integration of a wide variety of preclinical data into a mechanistic quantitative framework, allowing the scientist to gain insights into the properties of a compound, ultimately guiding experimental efforts and enabling effective design of clinical studies.

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Klaas Prins Characterization of the population pharmacokinetics of UK-369,003 using a semi-mechanistic model

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Objectives: Repeated dosing of a PDE5-inhibitor, UK-369,003, indicated that the plasma exposure dose-dependently decreased to equilibrate between 1 and 2 weeks after start of treatment. This suggested auto-induction of clearance, although the mechanism by which (hepatic or gastrointestinal clearance) was unclear. A semi-mechanistic model was developed to characterize UK-369,003 pharmacokinetics (PK) following single dose intravenous (IV) administration and single and multiple doses of a modified release (MR) formulation by determining if and to what extent the dose-disproportional PK was due to hepatic and/or gastrointestinal enzyme induction.

Methods: The PK data set consisted of 6602 plasma concentrations from 610 subjects from 7 dense PK sample phase I studies (3463 concentrations) and 2 sparse PK sample phase II studies (3139 concentrations). A semi-mechanistic model allowing partitioning of induction of clearance between the gut wall and liver clearance [1] was fitted to the data in NONMEM VI. The PK model featured a tablet release into the depot compartment followed by a first-order absorption process into the liver compartment, where the fraction absorbed was estimated. The liver compartment was linked to the central (sampling) compartment with a bi-directional blood flow and a peripheral compartment completed the 2 compartment disposition model. The intrinsic hepatic clearance was assumed to be proportional to the metabolic enzyme amount in a turnover model, where a power model described the relationship between dose and enzyme production rate. Interoccasion variability was allowed for the absorption component of the PK model.

Results: The model fit suggested that the induction of intrinsic clearance was entirely hepatic and neglible contribution of gut wall induction was observed. The half-life of the enzyme induction was estimated at 64 hr, which is consistent with half lives of ~70 hr reported in the literature [1,2]. UK-369,003 metabolism in the liver was estimated to approximately proportionally increase with dose, and resulted in a near doubling of hepatic clearance at 200mg as compared to 10mg at steady state. Age was found to decrease intrinsic clearance (~10% reduction for a 80-yr old compared to a 20-yr old) albeit this relationship came with substantial uncertainty.

Conclusion: UK-369,003 plasma concentrations across time and dose were adequately described by a semi-mechanistic model, which includes a dose-dependent auto-induction of hepatic clearance.

References:

[1] Magnusson, M.O., Dahl M-L, et al. Clin. Pharmacol. Ther. 84, 52-62 (2008)
[2] Ghanbari, F. et al. Curr. Drug Metab. 7, 315-334 (2006).

Anastassia Viglinskaya A physiology-based pharmacokinetic model describing the disposition of a novel selective anxiolytic drug afobazole and its metabolites in rats.

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Objectives: The purpose of this study was to model the pharmacokinetics of a novel selective anxiolytic drug afobazole [2-(2-morpholinoethylthio)-5-ethoxybenzimidazole dihydrocloride] and its metabolites in rats using physiology-based (PBPK) modeling approaches.

Methods: We examined in vivo metabolism and the pharmacokinetics of Afobazole and its metabolites in rats as a component of its preclinical development by a validated HPLC/MS/MS method. 160 male Wistar rats were randomly assigned to treatment groups and received either an i.p. and a p.o. dose of Afobazole at a dose level of 25 mg/kg. The model was constructed using the Windows version of WinSAAM software, a general equation-solving package that has been developed. Thus, the physiological processes responsible for afobazole pharmacokinetic characteristics were assessed.

Results: Afobazole demonstrated a large-scale volume of distribution (range, 7.11-23.5 l/kg), a rapid clearance (range, 15.04-30.9 l/hr/kg), and a terminal half-life 0.33 h (for its metabolites ranging from 0.40 to 0.44 h) after i.p. dosage. Afobazole is characterized by the expressed ability to penetrate organs and tissues. Afobazole is rapidly absorbed, cleared and extensively metabolized in rats.

Conclusions: PK model of a novel selective anxiolytic drug afobazole and its metabolites based on physiological modeling adequately described the observed plasma and organ concentration data and the estimated parameters are consistent with the previously available data.