PK/PD Model of skin toxicity in animal reported as binary outcome

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Introduction

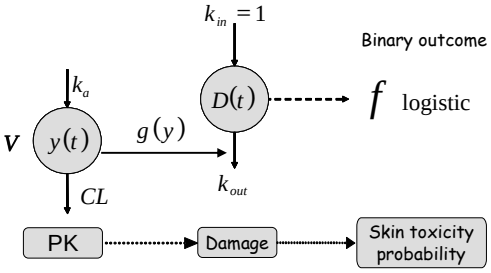
Pharmacokinetics and tolerability of drug X targeting the ERK pathway was investigated in rats (n = 150) in a daily repeated oral dose toxicology study with 4 week recovery period. In order to provide a quantitative basis for preclinical safety assessment in humans, modeling and simulation techniques are applied to analyze the observed data as a binary outcome skin toxicity in animals.

1 – Material and Methods

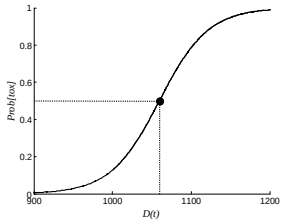
Drug X was administered once daily for 4 weeks orally by gavage at dosage levels 0, 0.25, 1, 4 and 16 mg/kg/day. For each individual, skin toxicity was reported daily as a binary outcome. The number of incidences of skin toxicity was dependant of the administration protocol. Decrease of skin toxicity frequency was observed during the recovery period. PK samples were collected in a satellite group on the first and last administered dose.

A PK/PD model was developed for describing damage kinetics function of time and binary outcome [1]. The structural model was composed of 1) the PK model, 2) the skin damage model and 3) the probabilistic model. For PKs, a 1 compartment model with first order absorption and elimination was used. The skin damage model is an indirect response model. In this model, concentration of the drug blocks damage compartment elimination through a Weibull model (Dc50 parameter as a function of alpha, beta). The damage value serves as independent variable to a Logit function which describes the probability of the toxic outcome. Model parameters were identified to the observed data using population approach with Monolix 3.2 software [2].

2 - PKPD Model



- First level: one compartment PK model with first order absorption and elimination.
- Second level: indirect response model describing the skin damage. The drug levels decrease the recovery rate (kout) through a Weibull function.
- Third level: probabilistic model based on a linear logit regression.
- Monolix 3.2 software was used to identify model parameters by maximizing the likelihood function.
- PK observed drug levels and PD observed skin toxicity were simultaneously processed.



$$g(y) = \exp\left[-(y/\alpha)^{\beta}\right]$$

$$\frac{dD(t)}{dt} = 1 - k_{out} \cdot g(y) \cdot D(t) \qquad D(0) = 1/k_{out}$$

$$\text{logit}\left[\Pr\{\overline{tox}\}\right] = \theta_1 - \theta_2 \cdot \frac{D(t) - D(0)}{D(0)}$$

	Fixed effect	Random effect
PK	k_a CL V	ω_{CL} ω_V
Link	k_{out} α β	$\omega_{k_{out}}$
PD	θ_1 θ_2	×
Res. error	a b	

Structural identifiability conditions force $k_{in} = 1$

3 – Numerical Results

All PK and PD parameters were well identified, with a Dc50 of 0.13 ug/mL and kout of 0.0012 h^{-1}. Gender was identified as a relevant covariate on clearance. An overlay of the predicted probability of skin toxicity and observed frequency for each dosing group showed the model flexibility to describe the observations (VPC). Simulations are done to show risk profile for different protocols.

Estimation of the population parameters

	parameter	r.s.e.(%)	p-value	units
ka :	3.05	-		h-1
CL :	193	7.3		mL/h/kg
beta_CL(Gender_M) :	0.434	24.0	3.5e-005	×
V :	1.2e+003	11.7		mL/kg
alpha :	0.143	0.6		µg/mL
beta :	3.88	0.5		×
kout :	0.00122	5.7		h-1
th1 :	7.73	4.5		×
th2 :	26.4	6.4		×
omega_CL :	0.405	14.8		
omega_V :	0.251	51.8		
omega_kout :	0.287	15.0		
a_1 :	0.0366	7.4		
b_1 :	0.338	7.1		

Estimation of the population parameters by groups

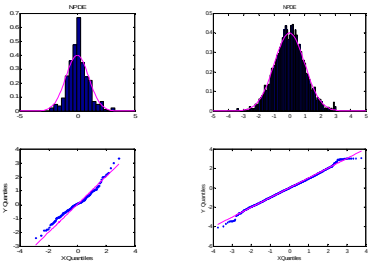
CL_(Gender=F*) :	193	7.3	
CL_(Gender=M) :	298	8.4	

$$Dc50 = \alpha \cdot \log(2)^{1/\beta} = 0.13\,\mu g/mL$$

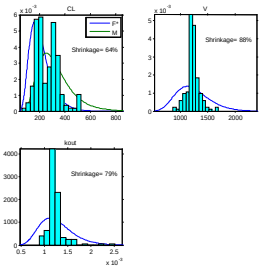
Covariate GENDER influences CL

4 – Graphic validation

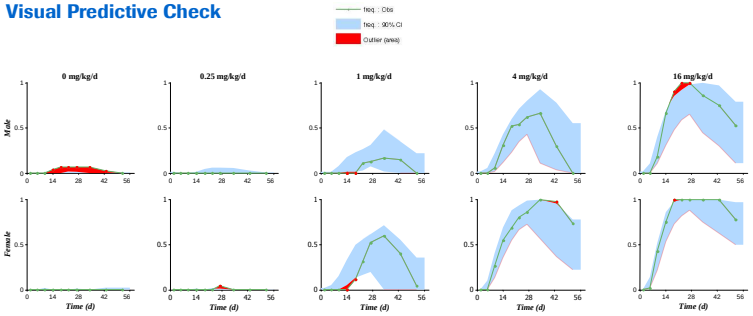
LN inter - individual distribution



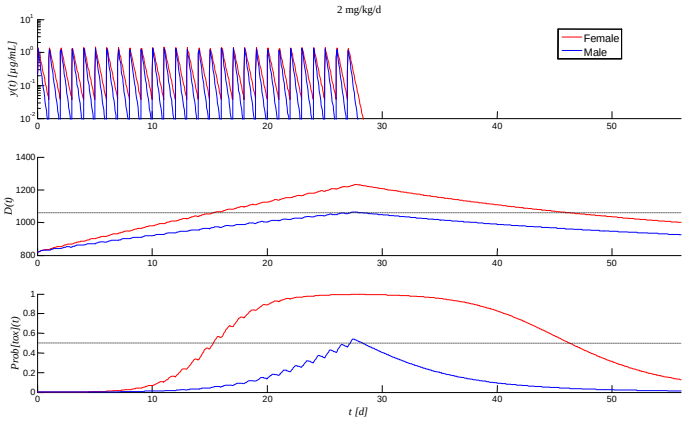
Post - hoc shrinkage



Visual Predictive Check



5 – Simulation



6 - Discussion

- In the dose escalation, females exhibit toxicity earlier than males and with higher associated frequency.
- Gender revealed as a significant covariate in the CL (PK parameter) and it has an indirect impact to the binary outcome in PDs.

Conclusion

The analysis shows PKPD modeling on binary outcome data. Logit model can easily be extended to more categories, describing different grades with ordered categorical data. The same structural model could be applied across various species.

References:
[1] Fiedler-Kelly J. "*PK/PD analysis of binary (logistic) outcome data*" In: Pharmacometrics: The science of quantitative pharmacology, E.I. Ette, P.J. Williams (eds.), John Wiley, 2007, pp 633-654.
[2] Kuhn E., Lavielle M. *"Maximum likelihood estimation in nonlinear mixed effects models"* Computational Statistics and Data Analysis, vol. 49, No. 4, pp 1020-1038, 2005.

Abstract

Objectives: Develop a PK/PD model for skin toxicity in animal and provide a quantitative basis for preclinical safety assessment.
Material and Methods: The PK and tolerability of drug X targeting the ERK pathway was investigated in rats (n = 150) in a repeated oral dose toxicology study with 4 week recovery period. Drug X was administered once daily for 4 weeks orally by gavage at dosage levels 0.25, 1, 4, 16 mg/kg/day. For each individual, the skin toxicity was reported daily as a binary outcome. The number of incidences of skin toxicity was dependant of the administration protocol. Decrease of skin toxicity frequency was observed during the recovery period. PK samples were collected in a satellite group on the first and last administered dose. A PK/PD model was used for describing damage kinetics function of time and binary outcome. The structural model was built of 1) the PK model, 2) the skin damage model and 3) the probabilistic model. For PK a 1 compartment model with first order absorption and elimination was used. The skin damage model is represented by an indirect response model. In this model, concentration of the drug blocks damage compartment elimination through an Imax model (Dc50 parameter). The damage value is the input function to a Logit model which describes the probability of the toxic event function of the damage value. Model parameters were identified to the observed data using population approach with Monolix 3.2 software [1].
Results: All PK and PD parameters were well identified, with a Dc50 of 0.1 ug/ml and kout of 0.0012 h^{-1}. Gender was identified as a relevant covariate on clearance. An overlay of the predicted probability of skin toxicity and observed frequency for each dosing group showed the model flexibility to describe the observations. Simulations are done to show risk profile for different protocols.
Conclusion: This example shows the fit of a PKPD model on binary outcome data. Logit model can easily be extended to more categories, describing different grades with ordered categorical data. The model can be applied across various species.