Linking preclinical and clinical whole body physiologically-based pharmacokinetic models with prior distributions in NONMEM

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Background

Compared to empirical compartmental models, physiologically-based pharmacokinetic (PBPK) models provide a more mechanistic description of the behaviour of a compound. Due to the large number of parameters and restricted tissue sampling in human subjects the use of PBPK models to describe pharmacokinetic behaviour in man has been limited. Use of prior information may serve to stabilise the model and allow for parameter estimates to be obtained with clinical data.

Objectives

Formulate a PBPK model using prior information for describing diazepam disposition in the rat and to extrapolate further to describe human pharmacokinetics using clinical data.

Materials and Methods

Diazepam PBPK model in the rat

Tissue and arterial blood concentration-time profiles following a 1 mg/kg intravenous infusion were collected from 24 male Sprague-Dawley rats[1]. The PBPK model comprised 12 tissue compartments and 2 blood compartments (Figure 1). Clearance was assumed to occur entirely from the liver compartment. Equilibrium tissue-to-plasma concentration ratio bound (Kpb), intrinsic clearance (CL_{int}), variability and residual error components for each compartment were included the fraction unbound in plasma (*fu*), the blood-to-plasma concentration ratio (R), and experimentally measured Kpb values[2].

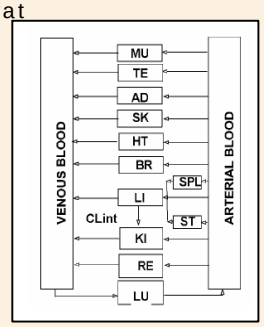

Figure 1: Schematic presentation of the PBPK Model. MUS = muscle, TE = testis, AD = adipose, SK = skin, HT = heart, BR = brain, SPL = splanchnic, ST = stomach, LI = liver, KI = kidney, RE = carcass, LU = lung

Diazepam PBPK model in man

Venous blood samples following a single 7 mg intravenous dose were collected from 12 healthy volunteers. The structure of the PBPK model from the rat was retained. Kpb, CL_{int}, variability and residual error components were estimated from the model. Prior information included the *fu* and R values in man, and equilibrium tissue-to-plasma concentration ratio unbound (Kpub) values from the rat model. Kpub in man were assumed to be identical to Kpub in rats and these values were used as informative priors for making inferences in man.

Use of prior information

Priors were provided for both fixed and random effects and were independent (Table I). No prior was assigned to the residual variance. Prior values for rat Kpb had as a mean the estimate given by a previously determined experimental value and for CL_{int} the prior mean value was based on a NONMEM fit of the plasma data, assuming that hepatic metabolism was the only route of elimination, and re-arranging the well-stirred model only. For the random effects, uninformative priors were defined in NONMEM by setting the degrees of freedom to -1. First-order conditional estimation was used for parameter estimation throughout.

Results

Kpb and CL_{int} values were estimated simultaneously in each model and parameter estimates were in close agreement with experimental prior values[2] and posterior mean values from a Bayesian analysis[1] of the same data (Table 1). The model provided a good overall description of the tissue concentrations in the rat (Figure 2) although there was a degree of over-prediction in the arterial compartment (Figure 3). Plasma concentrations in man were well described by the model (Figure 3).

Table 1: Rat and Human prior and posterior mean estimates for Kpb and CL_{int} together with inter-individual variance for CL_{int}

	Animal PBPK Model						Human PBPK Model			
	Prior Information		WinBUGS Posteriors Mean		NONMEM Parameter Estimates		Prior Information		WinBUGS Posteriors Mean	NONMEM Parameter Estimates
	Prior Means $\bar{\theta}$	Prior SD ¶	Tissue Kp (RSE†)	Residual variance (RSE†)	Tissue Kp (RSE†)	Residual variance (RSE†)	Prior Means $\bar{\theta}$	Prior SD ¶	Tissue Kp (RSE†)	Tissue Kp (RSE†)
LUNG	3.26	0.65	4.49 (0.08)	0.06 (0.16)	4.31 (0.05)	0.05 (0.02)	0.71	0.05	0.70 (0.21)	0.64 (0.30)
SPLANCHNIC	1.85	0.37	3.40 (0.14)	0.53 (0.15)	3.16 (0.12)	0.46 (0.14)	0.53	0.07	0.48 (0.25)	0.37 (0.43)
STOMACH	2.00	0.40	4.79 (0.10)	0.21 (0.15)	4.48 (0.08)	0.18 (0.05)	0.75	0.07	0.76 (0.25)	0.71 (0.33)
LIVER	4.89	0.98	8.59 (0.20)	0.20 (0.22)	6.69 (0.12)	0.16 (0.07)	1.35	0.16	0.66 (0.33)	0.82 (0.23)
BRAIN	1.02	0.20	2.03 (0.11)	0.36 (0.15)	2.02 (0.11)	0.32 (0.10)	0.32	0.04	0.31 (0.19)	0.22 (0.52)
HEART	2.19	0.44	5.38 (0.11)	0.34 (0.16)	4.81 (0.10)	0.31 (0.10)	0.86	0.09	0.82 (0.28)	0.77 (0.31)
KIDNEY	2.30	0.46	4.66 (0.08)	0.08 (0.18)	4.53 (0.06)	0.06 (0.02)	0.73	0.04	0.71 (0.21)	0.69 (0.28)
SKIN	3.37	0.68	2.95 (0.11)	0.18 (0.16)	3.13 (0.11)	0.26 (0.08)	0.46	0.05	0.38 (0.18)	0.25 (0.38)
MUSCLE	1.37	0.27	3.67 (0.09)	0.20 (0.16)	3.35 (0.09)	0.19 (0.06)	0.56	0.05	0.19 (0.16)	0.09 (0.23)
ADIPOSE	12.90	2.56	21.0 (0.14)	0.21 (0.15)	15.8 (0.09)	0.24 (0.07)	3.34	0.44	3.37 (0.09)	3.56 (0.07)
TESTIS	3.00	0.60	4.82 (0.07)	0.07 (0.15)	4.53 (0.06)	0.05 (0.02)	0.76	0.05	0.77 (0.21)	0.76 (0.28)
CARCASS	3.99	-	FIXED	-	3.99	FIXED	2.2	0.8	0.07 (0.43)	0.04 (0.33)
$CL_{intrinsic}$	400.0	277.8	397.5 (0.22)	-	387.6 (0.04)	-	70.8	62.5	75.0 (0.07)	72.2 (0.08)
Ω_{CLint}	0.50	-	0.47 (0.23)	-	0.339 (0.13)	-	0.5	-	0.16 (0.25)	0.10 (0.05)

¶ Standard deviation
† Relative standard error

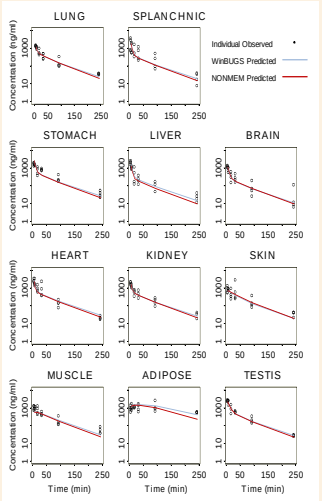

Figure 2: Concentration-time profiles for diazepam disposition in rat tissues

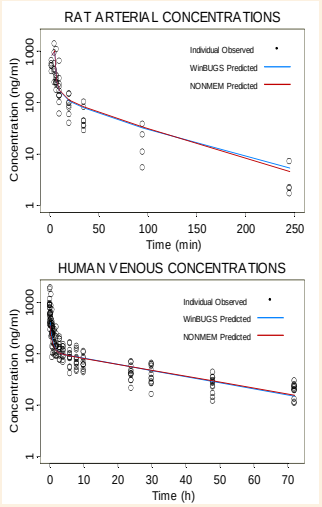

Figure 3: Plasma concentration-time profiles for diazepam in rats (top) and humans (bottom)

Conclusion

Use of prior information allowed parameter estimation from a full PBPK model with limited data. Run time with NONMEM was dramatically reduced when compared to WinBUGS and may allow for a continuous flow of information through the different stages of drug discovery in the future.

References

1. Gueorguieva I, Aarons L, Rowland M. Diazepam Pharmacokinetics from preclinical to Phase I using Bayesian population physiological model with informative prior distributions in WinBugs. J Pharmacokinet Pharmacodyn. 2005 (accepted).
2. Igari Y, Sugiyama Y, Sawada Y, Iga T, Hanano M. Prediction of diazepam disposition in the rat and man by a physiologically based pharmacokinetic model. J Pharmacokinet Biopharm. 1983 Dec;11(6):577-93.