Development of a novel method for updating the predicted partition coefficient values generated by an existing *in silico* prediction method

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Prediction of partition coefficients

The use of PBPK modelling is becoming an increasingly important step in the drug development process as it aims to reduce the amount of *in vivo* and *in vitro* work needed during the early stages. Tissue-to-plasma partition coefficients (*Kps*) are a vital input parameter for these models, as they help to describe the distribution of a drug within the body, and can be used to predict volume of distribution (V_{ss}). Many *in silico* methods exist in the literature for the prediction of these *Kp* values, with varying degrees of accuracy. Six of these methods have been compared in previous work, with the Rodgers *et al.* method [1,2] found to be the most accurate across all drug classes and in all tissues, and therefore this method has been chosen for further development.

Aims

1) To update the *Kp* predictions generated by the Rodgers *et al.* method in rat by using *in vivo* data and prior knowledge of the prediction error inherent in the method
2) To use these updated *Kps* to produce predicted iv profiles for a variety of drug compounds and compare these to experimental data
3) To use these predicted iv profiles to produce predictions for other pharmacokinetic parameters, such as V_{ss}
4) Expand upon this work by scaling these updated *Kps* into human and using these to produce predictions of iv profiles, V_{ss}, etc.

Method

A covariance matrix was generated from prior knowledge of the prediction error of the Rodgers *et al.* *Kp* predictions when compared to experimental values for a dataset of 88 compounds

Figure 1 describes the process that was then followed to generate predictions for updated *Kps* in rat, and iv profiles and V_{ss} in both rat and human, for a dataset of 25 compounds. These compounds were selected based on the availability of experimental iv data in both rat and human

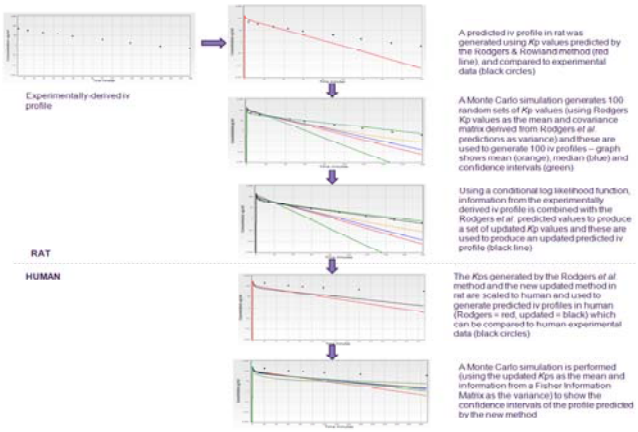

Figure 1. Flowchart describing the process used to improve upon the *Kp* predictions made by the Rodgers *et al.* method for a dataset of 24 compounds.

This work was all performed using the modelling tool AcslX® and an AstraZeneca in-house PBPK model

Results - RAT

Kp values predicted for 25 compounds by the Rodgers *et al.* model and our new method were compared to experimental values obtained from the literature. Accuracy of each of the two methods in comparison to these values is shown in Table 1

	% <2-fold	% 2-5-fold	% >5-fold	afe	aafe	rmse	ccc	mean pred:obs	sd
Rodgers	40.24	33.54	26.22	1.12	3.02	0.62	0.45	3.08	6.40
Updated	32.93	35.98	31.10	1.04	3.56	0.69	0.33	3.52	7.47

Table 1. Comparison of *Kp* predictions in RAT made by the Rodgers *et al.* method and our updated method. Predictions were compared to published experimental results. afe=average fold error, aafe=absolute average fold error, rmse=root mean squared error, ccc=concordance correlation coefficient, pred=predicted, obs=observed, SD=standard deviation.

- Overall, the Rodgers *et al.* method performs better than our updated model at predicting *Kp* values, but our model does produce more accurate predictions in certain tissues such as adipose, liver and brain (*results not shown*)
- V_{ss} prediction was also used as another measure of the accuracy of our updated *Kps* (Table 2), and was calculated using the following equation:

$$V_{ss} = \Sigma(Kp * V_t) + V_p$$

	% <2-fold	% 2-5-fold	% >5-fold	afe	aafe	rmse	ccc	mean pred:obs	sd
Rodgers Vss	40.00	56.00	4.00	1.63	1.96	0.36	0.70	2.00	1.28
Updated Vss	70.83	20.83	8.33	1.38	1.70	0.32	0.51	1.80	1.70

Table 2. Comparison of Vss predictions in RAT made by the Rodgers *et al.* method and our updated method. Predictions were compared to published experimental results.

- Our updated model can now be seen to be outperforming the Rodgers *et al.* model with 30% more predictions falling within 2-fold of experimental values
- These updated *Kps* can now be used within a PBPK model to generate predicted iv profiles and compare these to the profiles predicted using the Rodgers *et al.* *Kp* values (see example in Fig.2)

Figure 2. Experimental iv profile in rat (black circles) compared to the predicted profile generated using the Rodgers *et al.* method (red line) and the predicted profile generated using our updated method (black line) for pentazocine along with the confidence intervals generated by the Rodgers *et al.* method (green lines)

Results - HUMAN

- We can now use the *Kp* values generated by the Rodgers *et al.* method and our updated *Kps*, and scale them to human using *fu* values

$$Kpu_{human} = Kpu_{rat} \qquad Kp_{human} = Kpu_{human} * fu_{human}$$

- These human *Kps* can then be used to predict iv profiles in human and we can then compare our updated method with the Rodgers *et al.* method and experimental data (see pentazocine example in Fig.3)

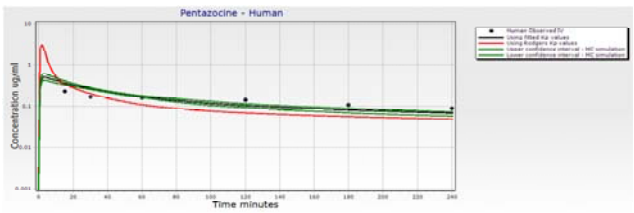

Figure 3. Experimental iv profile in human compared to the predicted profile generated using the Rodgers *et al.* method and the predicted profile generated using our updated method for pentazocine, along with the confidence intervals generated by the new method

- We can now use the predicted human *Kps* to produce predictions for human V_{ss} (Table 3)

	% <2-fold	% 2-5-fold	% >5-fold	afe	aafe	rmse	ccc	mean pred:obs ratio	sd
Rodgers Vss	61.11	33.33	5.56	1.27	2.11	0.38	0.47	1.78	1.68
Updated Vss	58.82	41.18	0.00	1.16	1.75	0.30	0.61	1.45	1.05

Table 3. Comparison of Vss predictions in HUMAN made by the Rodgers *et al.* method and our updated method.

- Our updated method and the Rodgers *et al.* method are very similar in terms of % within 2-fold of experimental values, but a closer look at the statistics shows that our method is more accurate in terms of afe, aafe, rmse, ccc, and mean predicted:observed ratio,
- Our method also produces more accurate predictions of iv profiles (*results not shown*) when compared to the Rodgers *et al.* method

Conclusions & Further Work

Conclusions

A novel method has been described that can generate predicted *Kp* values in rat that are an update of the predictions generated by the Rodgers *et al.* method, by using rat *in vivo* data and information about the error inherent in the Rodgers *et al.* method as prior knowledge

These *Kps* can then be used in a human PBPK model and provide updated predictions for V_{ss} and concentration-time profiles

Further/Ongoing Work

Further investigation of this method using a wider range of compounds (requires large amount of data such as physicochemical properties of drug, rat iv data and human iv data)

Analysis of prediction accuracy of this method for other parameters such as $t_{1/2}$ in both rat and human

Test the effects of removing smaller tissues (e.g. spleen) from the analysis and concentrate on improving the prediction accuracy for the larger tissues, which have a greater influence upon parameters such as V_{ss}

References

[1] Rodgers *et al.* (2005) J Pharm Sci 94(6):1259-1276. [2] Rodgers and Rowland (2006) J Pharm Sci 95(6):1238-1257.

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