A Mechanistic Model for the Prediction of Human Equilibrium Blood-to-Plasma Concentration Ratio (B/P): Basic and Neutral Drugs.

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Introduction

The equilibrium Blood-to-Plasma concentration ratio (*B/P*) is a widely used parameter for predicting hepatic clearance (CL_h) and equilibrium tissue-to-unbound-plasma partition coefficients (Kp_u).[1,2] When lacking experimental values it is often assumed that *B/P* is 1 (neutrals and bases) or 0.55 (acids and zwitterions) while it has been shown that the use of measured rather than such "rule-of-thumb" *B/P* values *can* significantly alter predicted CL_h[3] or Kp_u.[1] Previously reported *B/P* prediction models have either been difficult for third parties to implement and flawed[4] or the extent of the correlations obtained were quite poor and test set predictions not undertaken[3]. Thus there is a place for alternative tools for the prediction of *B/P*.

Purpose

The first objective is to attempt to improve upon existing *B/P* prediction models while using a minimal set of widely available descriptors so as to facilitate model use at early stages of drug discovery. A second, and constraint on the first, aim is to provide a tool that can be used to aid in the identification of compounds whose Kp_u's are likely to be poorly predicted by the widely used Rodgers and Rowland (R&R)[1] methods on the assumption that outliers to the *B/P* model (identified once measured *B/P* is obtained) may also be outliers to the R&R method. The latter methods require as input log$P_{o:w}$, *pKa*(s), *fu* and, for cations, *B/P* itself where acidic phospholipid (*AP*) binding constants (Ka_{AP}) are frequently back-calculated from *B/P* and then applied to predict the extent of *AP* binding in all other tissues[1]. Thus, with the second objective in mind, it makes sense to use the same properties for building *B/P* prediction models.

Methods

Experimental human *B/P*, *fu*, *pKa* and log$P_{o:w}$ values were collected from in-house databases (including values provided by Simcyp Consortium[5] members) and the literature. The *B/P* values were transformed[3] to erythrocyte-to-plasma-unbound concentration ratios ($K_{e,u}$) - haematocrit (*ht*) was assumed to be 0.45 if not reported. The dataset was divided into two *"training"* subsets *viz* 40 strongly (≥ 95%) ionised bases and 25 predominantly uncharged (≤ 5% ionised) bases or fully neutral drugs (pH 7.4). For each training set *separately* log$K_{e,u}$ was correlated with log$P_{o:w}$ so as to attempt to separate the behaviour of neutral and cationic species[6]. Linear fitting methods were used. Outliers were identified on the basis of 95% confidence bands. With the second objective (above) in mind it makes sense to exclude outliers to the model.

The $K_{e,u}$ of 39 drugs of intermediate ionisation extent was predicted by combining the appropriate predicted strong base $K_{e,u}$ with that predicted for the uncharged species, respectively weighted by the fraction ionised ($f_{ionised}$) or fraction neutral ($f_{neutral}$) at physiological pH.

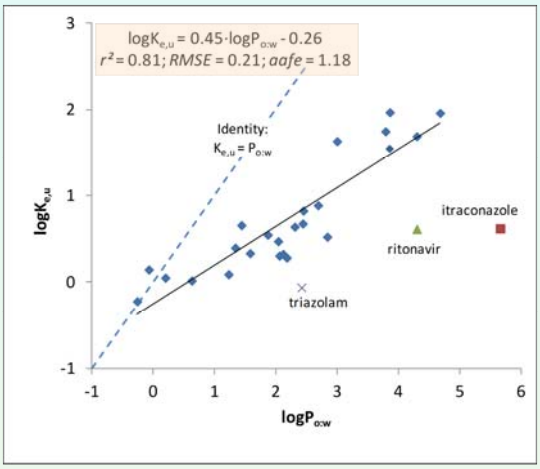
$$\log K_{e,u} = \log\left(f_{ionised} \cdot K_{e,u,basic} + f_{neutral} \cdot K_{e,u,neutral} \right)$$

Model fit and prediction were quantified using *RMSE*, *afe* (average fold error) and *aafe* (absolute *afe*) defined as follows:

$$RMSE = \sqrt{\frac{1}{n} \cdot \sum_{i=1}^{n} (predicted_i - experimental_i)} \qquad afe = 10^{\frac{1}{n}\sum_{i=1}^{n} \log\left(\frac{predicted_i}{experimental_i}\right)}$$

where *predicted* here refers to either a truly predicted value (test set) or a fitted value (training set). For *aafe* calculation the absolute values of log(predicted/experimental) are used.

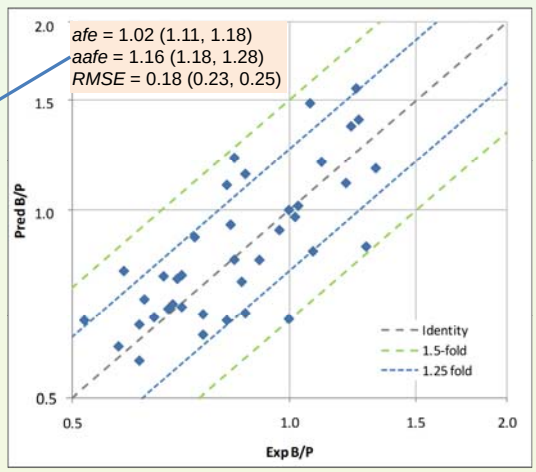
Figure 1: Neutral compound training set: log$K_{e,u}$ *vs.* log$P_{o:w}$.



Results & Discussion

The training set models (bases: r^2 = 0.63, *aafe* = 1.23, *RMSE* = 0.29; neutrals: see Fig 1) have r^2 values somewhat higher than those reported previously[3] (0.38 and 0.44 respectively albeit based on a different but overlapping dataset). Test set *B/P* predictions (Fig. 2) showed improved performance in comparison both to Uchimura *et al.*[3] (their reported equations applied to our dataset) and where the rules-of-thumb are applied (*i.e.*, *B/P* = 1).

Figure 2: Predicted vs. experimental *B/P* for an independent test set of 39 basic compounds of *intermediate* ionisation state at physiological pH (bracketed statistical values refer respectively to predictions made using the model of Uchimura *et al*.[3] and where *B/P* = 1 for all compounds).



Itraconazole (ITZ) (log$P_{o:w}$ = 5.7), ritonavir (RTV) (log$P_{o:w}$ = 4.3) and, to a lesser extent, triazolam (TRZ) (log$P_{o:w}$ = 2.4) are major outliers to the general trend for neutral drugs (Fig. 1) – *Vss* for these compounds are respectively 32, 37 and 3-fold *over-predicted* by the R&R model. This over-prediction might be anticipated from Fig 1; *i.e.*, these compounds lie very much below the trend line. Given the extent of the deviation from trend it is unlikely that error/uncertainty in model inputs (log$P_{o:w}$ etc) is the cause. Thus it seems likely there is an underlying mechanistic explanation for this deviation.

Conclusion

The strong correlations obtained between log$K_{e,u}$ with log$P_{o:w}$ are in contrast to the poorer correlations with log$D_{o:w}$ (pH 7.4) previously reported.[3] This may be the consequence of the clear separation of drugs according to the extent of ionisation. The approach taken is supported by the excellent predictive performance with an independent test set. The models are based upon widely available physicochemical parameters (log$P_{o:w}$, *pKa*, *fu*) and are thus accessible to a wide range of users. The models are to be extended to handle acids and zwitterions and will be updated regularly as further reliable data become available. The model can be used to help assess confidence in mechanistic Kp_u and *Vss* predictions.

References: **1.** Rodgers 2007 *JPharmSci* **24**:918; **2.** Poulin 2011 *ToxicolApplPharmacol* **250**:194; **3.** Uchimura 2010 *BiopharmDrugDisp* **31**:286; **4.** Paixoa 2009 *EurJPharmSci* **36**:544; **5.** www.simcyp.com; **6.** Turner 2006 Poster presented at 9th European ISSX Meeting, Manchester, UK.