Impact of Partition Coefficient Prediction Methods on PBPK Model Output Using a Unified Tissue Composition

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Abstract

Objectives: Tissue:plasma partition coefficients are critical parameters in physiologically-based pharmacokinetic (PBPK) models, yet the coefficients are challenging to measure in vivo. Several mechanistic-based methods have been developed to calculate partition coefficients using tissue composition information and the compound's physicochemical properties. However, the impact of using different methods on model predictions was not adequately quantified. Furthermore, the inconsistency in the tissue composition information used by each method adds another level of complexity that needs to be sorted out before a reliable comparison between the methods can be assessed.

Methods: This study proposed a unified tissue composition for humans that was used as input for five common calculation methods. The methods were implemented in R and were used to calculate partition coefficients for 11 drugs, classified as strong bases (metoprolol and caffeine), weak bases (voriconazole, alfentanil, nevirapine, and midazolam), acids (thiopental and nifedipine), neutrals (digoxin and artemether), and zwitterions (ofloxacin). PBPK models were developed for each drug using the open-source R package mrgsolve. PBPK model predictions using each partition coefficient method were then compared to observed plasma concentrations for each drug. The accuracy of each PBPK model output was assessed using the percent RMSE, AUC percent error, and half-life percent error. Monte Carlo simulations were used to investigate the impact of interindividual variability in tissue composition values and physicochemical parameter uncertainty on PBPK model output using each partition coefficient method for voriconazole.

Results: The developed tissue composition database was implemented in all calculation methods, and the resulting partition coefficients showed acceptable correlations with those predicted using the reference tissue compositions (PCC range for human reference tissue compositions: 0.80 – 1.00). The analysis highlighted the importance of using a unified tissue composition for reliable comparison between the partition coefficient calculation methods and that no single one of these methods consistently yielded the most accurate PBPK model output. For example, the ofloxacin RMSE ranged between 6.38% and 24.0%, AUC error ranged between 12.8% and 25.4%, and half-life error ranged between 19.3% and 59.8%. The errors for the other drugs were comparable to those for ofloxacin, except for a few outliers. In particular, a RMSE for nifedipine was 1270%, and an AUC error for nevirapine was 4170%. The analysis also showed the relatively large impact of interindividual variability and physicochemical uncertainty on partition coefficient predictions, and, hence, on the PBPK model output.

Conclusions: PBPK model outputs using all partition coefficient methods should be considered during drug development, and a partition coefficient method may be selected as part of the model optimization process. The impact of interindividual variability and physicochemical uncertainty should be considered when choosing a partition coefficient method during PBPK model construction.

Methods

Partition coefficient prediction methods:

- Poulin and Theil [2] (PT)
- Berezhkovskiy [3] (Berez)
- Rodgers and Rowland [4, 5] (RR)
- Schmitt [6]
- PK-Sim Standard [7]

1. Development of a unified tissue composition:

- Information from several sources was combined to avoid biasing the evaluation of the partition coefficient methods [2, 4, 5, 7, 8].

2. General PBPK model framework:

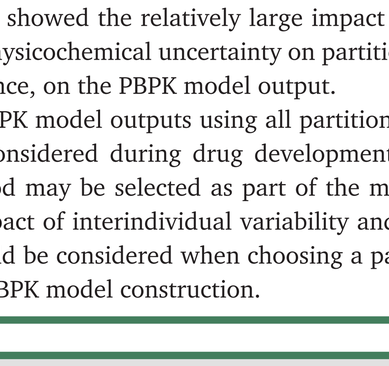

Figure 1: Schematic for the general, flow-limited, physiologically-based pharmacokinetic model.

3. Evaluation of PBPK model predictions:

- The PBPK model was simulated for 11 drugs using each of the partition coefficient methods.
- PBPK model accuracy was assessed using percent RMSE, AUC percent error, and half-life percent error.

4. Investigation of interindividual variability/uncertainty:

- The voriconazole PBPK model was used to investigate the impact of interindividual variability/uncertainty through the simulation of 1000 theoretical individuals.
- Each tissue composition value was sampled from a truncated normal distribution with coefficients of variation reported by Ruark and co-workers [8].
- Each physicochemical value was sampled from a uniform distribution with bounds ± 50% of the reported value.

Results

Table 1: Unified tissue composition values are from Ruark and co-workers unless indicated otherwise [8]. Subscripts indicate fractional volume of: $_{pr}$ proteins; $_{pl}$ phospholipids; $_{nl}$ neutral lipids; $_{npl}$ neutral phospholipids; $_{apl}$ acidic phospholipids; $_{ew}$ extracellular water; $_{iw}$ intracellular water; AR albumin ratio; LR lipoprotein ratio.

Tissue	f_{water}	f_{lipid}	f_{pr}	f_{pl} [2]	f_{nl}	f_{npl}	f_{apl}	pH [6]	f_{ew} [4]	f_{iw} [4]	AR [4]	LR [4]
Bone	0.446 [4]	0.268 [7]	0.268 [7]	0.0011	0.074 [2]	0.0016 [5]	8E-04 [7]	7	0.1	0.346	0.1	0.05
Brain	0.782 [4]	0.107	0.08	0.0565	0.045	0.0553	0.02022	7.1	0.162	0.62	0.048	0.041
Adipose	0.152 [4]	0.8	0.05	0.002	0.798	0.0478	0.0067	7.1	0.135	0.017	0.049	0.069
Heart	0.776 [4]	0.1	0.17	0.0166	0.089	0.0079	0.00309	7.1	0.32	0.456	0.157	0.16
Kidney	0.756 [4]	0.052	0.17	0.0162	0.036	0.0166	0.00387	7.22	0.273	0.483	0.13	0.137
Gut	0.757 [4]	0.062 [7]	0.133 [7]	0.0163	0.0487 [2]	0.0124 [5]	3.5E-03 [7]	7.4	0.282	0.475	0.158	0.141
Liver	0.734 [4]	0.067	0.18	0.0252	0.037	0.0115	0.00258	7.23	0.161	0.573	0.086	0.161
Lung	0.782 [4]	0.01	0.18	0.009	0.003	0.0056	0.0014	6.6	0.336	0.446	0.212	0.168
Muscle	0.748 [4]	0.019	0.17	0.0072	0.013	0.0092	0.0019	6.81	0.118	0.63	0.064	0.059
Skin	0.673 [4]	0.1	0.29	0.0111	0.036	0.0502	0.01382	7	0.382	0.291	0.277	0.096
Spleen	0.786 [4]	0.028	0.19	0.0198	0.014	0.0103	0.00191	7	0.207	0.579	0.097	0.207
Plasma	0.928	0.009	0.07	0.00225	0.003	0.005	9.70E-04	7.3	-	-	0.029	6.00E-04
RBCs	0.663	0.005	0.33	-	0.002	0.0025	5.00E-05	7.2	-	0.663	-	-

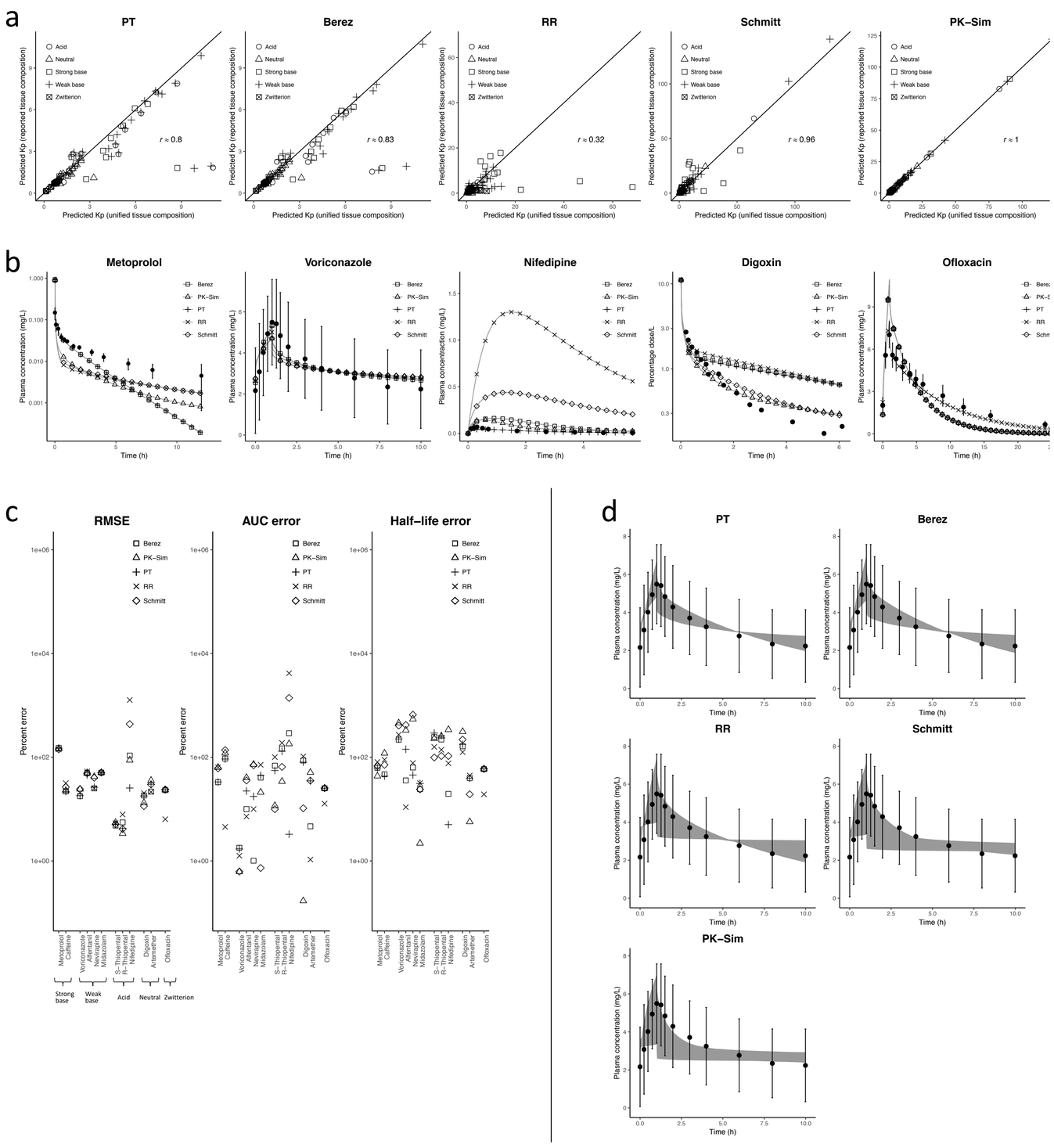

Figure 2: (a) Comparison between predicted tissue:plasma partition coefficients using the unified tissue composition and the reported tissue compositions. The PCC for each method is denoted by r. (b) Comparison between PBPK model prediction curves for each method and observed data for metoprolol (10 mg IV), voriconazole (4 mg/kg IV infusion), nifedipine (10 mg PO), digoxin (0.013 mg IV), and ofloxacin (400 mg IV). (c) Comparison of the RMSE, AUC, and half-life log percent errors for each partition coefficient method and each drug. Drugs are organized by type. (d) The shaded regions indicate the 95% prediction interval of 1000 sampled patients for the voriconazole PBPK model predictions. Dots indicate the mean and error bars indicate the standard deviation of the observed plasma concentration.

Conclusions

- A controlled, traceable set of unified tissue composition values was proposed to provide reliable comparisons between the partition coefficient prediction methods.
- Errors in predictions were seemingly random across each partition coefficient prediction method, even when considered by the acid-base category. This may warrant that the sensitivity of the PBPK model outputs using all partition coefficient methods should be considered during drug development.
- The simulations based on the voriconazole PBPK model that included interindividual variability/uncertainty indicated that such sources of variability should be considered when evaluating PBPK model predictive performance for each partition coefficient estimation method.

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