General Approach to Calculation of Tissue:Plasma Partition Coefficients for Physiologically Based Pharmacokinetic (PBPK) Modeling

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Abstract:

Purpose: To conduct a comprehensive evaluation of methods for calculation of tissue/plasma partition coefficients with a focus on correct prediction of volume of distribution and recommendation for a general approach to Kp calculations.

Methods: Kps were calculated by multiple methods for a set of about 80 drugs for which the experimentally determined values in rat were reported in the literature. These included the methods developed by Poulin & Theil [Poulin 2001] and the methods of Rodgers & Rowland [Rodgers 2007], as well as with a correction to the Poulin & Theil method described by Berezhkovskiy [Berezhkovskiy 2004]. In addition, a modified Rodgers & Rowland equation, developed by Simulations Plus, Inc. was included in the comparison.

Results: Among the published approaches, the equations derived by Rodgers and Rowland provided better general predictions for tissue/plasma partition coefficients for the compounds with low to moderate lipophilicity. However, the approach of using different equations for strong bases and for neutrals, acids and weak bases with a hard cutoff at base pKa = 7, as suggested by Rodgers and Rowland, puts a lot of emphasis on the very accurate prediction and measurement of pKa. It also creates a discontinuity in the Kp vs. pKa relationship, which can hardly be physiologically explained. We have modified the Rodgers and Rowland approach by developing a single equation which can be used for all compounds. This approach results in continuous transition of tissue binding from neutrals and weak bases to strong bases.

Conclusions: Our modified Rodgers and Rowland equation accounts for a more mechanistic description of drug binding to individual tissue components. Based on a more physiological explanation of drug binding to individual tissue components, it provides a smooth transition of calculated Kp from weak and moderate bases to strong bases. As a result, possible small errors in prediction or measurement of pKas will have smaller effect on the accuracy of Kp prediction.

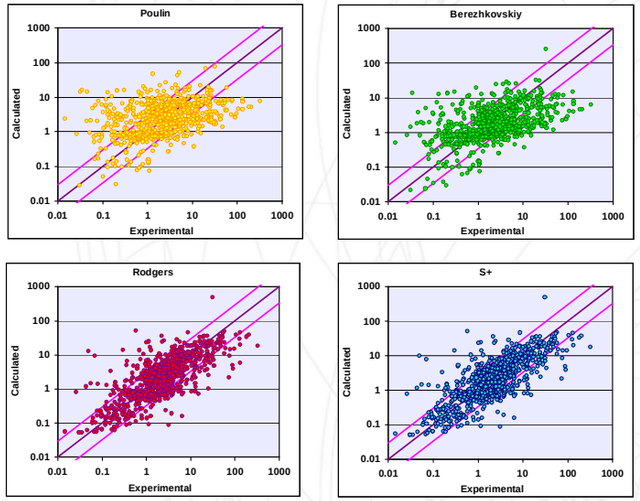
$$Kpu = V_{ew} + \frac{1/X_{[D],iw}}{1/X_{[D],p}} V_{iw} + \left(\frac{P \cdot V_{nlt} + (0.3 \cdot P + 0.7) \cdot V_{pht} \cdot}{1/X_{[D],p}} \right) +$$

$$(Fn + Fa) \cdot \left[\frac{1}{fup} - 1 - \left(\frac{P \cdot V_{nlp} + (0.3 \cdot P + 0.7) \cdot V_{php} \cdot}{1/X_{[D],p}} \right) \right] \cdot RAtp +$$

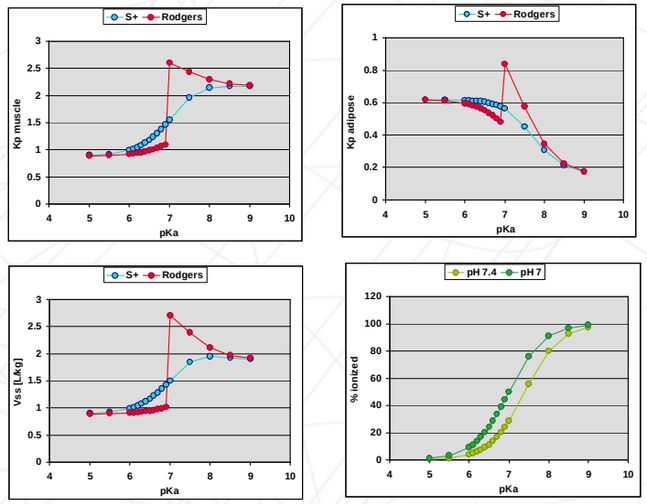
$$(Fc) \cdot \left(\frac{Ka \cdot [AP]_T ((1/X_{[D],IW}) - 1)}{(1/X_{[D],P})} \right)$$

$X_{[D]}$ – neutral fraction in intracellular water (*iw*) and plasma (*p*)
V – volume fraction of extracellular (*ew*) and intracellular (*iw*) water; neutral lipids (*nl*) and phospholipids (*ph*) in plasma (*p*) or tissue (*t*)
P – octanol/water or vegetable oil/water partition coefficient
Ka – drug-acidic phospholipid binding constant
$[AP]_T$ – concentration of acidic phospholipids in tissue
Fup – fraction unbound in plasma
RAtp – tissue/plasma albumin ratio
Fn, Fa, Fc – fraction of drug in neutral, anionic and cationic form at pH = 7.4

Simulations Plus (S+) equation for prediction of tissue:plasma partition coefficients based on the Rodgers equation for Kp prediction. The original method by Rodgers, requiring separate equations for different classes of compounds, was modified into a single equation accounting for all drug interactions with the tissue components. The magnitude of drug interaction with either tissue albumin or tissue acidic phospholipids is given by the actual ionization state of the compound. The S+ equation (1) gives the same (based on Kp comparisons) or better (based on Vss comparison) prediction than the original Rodgers approach; (2) minimizes the effect of possible errors in pKa measurement (or prediction) for bases with pKa ~7; (3) offers a more physiological description of those interactions with tissue components which are ionization-dependent.



Predicted Kps for ~80 compounds [Berezhkovskiy 2004, Poulin 2001, Rodgers 2007 and unpublished Roche measurements] calculated using four mechanistic approaches. Methods accounting also for ionization and interactions with acidic phospholipids (Rodgers and S+) give significantly better predictions than methods accounting only for membrane partitioning and non-specific binding to albumin (Poulin and Berezhkovskiy). In all figures the purple line represents the identity line and magenta lines show the limits of 3-fold prediction error.



Comparison of ionization effect on the Kp for two largest tissues and volume of distribution predicted by Rodgers and S+ method. The profiles were calculated for a model compound with logP = 1, blood-to-plasma ratio = 1, Fup = 1 and a single base pKa ranging from 5 to 9. The two separate Rodgers equations result in discontinuities in Kp and Vss profiles at pKa = 7. The S+ equation provides a smooth transition from a weak base which is mostly in neutral form and interacts with tissue albumin to a strong base which is mostly in ionized form and interacts with tissue acidic phospholipids. Compound which is present as a significant fraction of neutral and cationic form at physiological pH will interact with tissue albumin as well as acidic phospholipids.

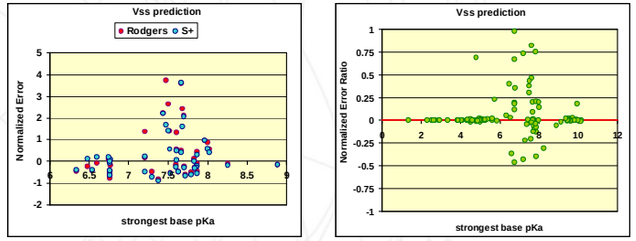
The major differences in prediction of Kps and Vss between the Rodgers and S+ equations will be for compounds with base pKa in the range ~5 to ~8. The set of compounds for which the individual Kp values were available did not contain a sufficient number of compounds with base pKa in this range. The comparison of the performance of the two methods was therefore done on the basis of Vss prediction. The experimental rat Vss values for 215 compounds (Roche compounds) were obtained by non-compartmental analysis of plasma concentration-time profiles after intravenous administration.
For each compound a "normalized error of prediction" was calculated as:

$$NE = \frac{Vss_{pred} - Vss_{exp}}{Vss_{exp}}$$

and "normalized error ratio" was calculated as:

$$NER = \frac{\left(|NE_{Rodgers}| - |NE_{S+}|\right)}{\left(|NE_{Rodgers}| + |NE_{S+}|\right)}$$

The values of NER range from -1 to 1. Positive NER values mean that the S+ equation gave better prediction of Vss than the Rodgers approach (NER value approaching 1 marks compounds where the prediction error from S+ equation was negligible compared to error from Rodgers approach). Negative NER values mean that the Rodgers approach predicted Vss more closely (NER value approaching -1 marks compounds where the prediction error from Rodgers approach was negligible compared to the S+ equation).



Both measures, normalized error and normalized error ratio, indicate slightly better predictions using the S+ equation than using the original Rodgers approach. Both methods, S+ and Rodgers, used adjusted Fup (poster M1313) in the Kp predictions.

References

Berezhkovskiy L.M.; J Pharm Sci 2004, 93:1628-1640
Poulin P., Theil F-P.; J Pharm Sci 2000, 89:16-35
Rodgers T., Rowland M.; J Pharm Sci 2007, 96: 3151-3152
Rodgers T., Rowland M.; J Pharm Sci 2007, 96: 3153-3154

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