Pharmaceuticals

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 recommendations for a general approach to Kp calculations.

Methods: Kps were calculated by multiple methods for a set of about 60 drugs for which the experimentally determined values in rat were reported in the literature. These included the methods developed by Poulin & Thiel (Poulin 2001) and the methods of Rodgers & Rowland (Rodgers 2007), as well as a combination in the Poulin & Thiel 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 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 neutral, acidic, and weak bases with a hard cut-off at base pKa ≤ 7, as suggested by Rodgers and Rowland, puts a lot of emphasis on the very accurate predictions and measurement of pKa. It also creates a discontinuity in the log Vss vs. pKa relationship, which can hardly be avoided. Therefore, a new equation has been developed for the purpose, which can be used for all compounds. This approach results in continuous transition of tissue binding from neutral 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 pKa will have smaller effect on the accuracy of Kp prediction.

Predicted Kps for ~60 compounds (Berezhkovskiy 2004, Poulin 2001, Rodgers 2007 and unpublished Roche measurements) calculated using four mechanistic approaches.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+ and S+ + 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 Rodgers represents the identity line and magenta lines show the limits of 3-fold prediction error.

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 ~6. 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:

\[ \text{NER} = \frac{V_{\text{Exp}} - V_{\text{pred}}}{V_{\text{Exp}}} \]

and "normalized error ratio" was calculated as:

\[ \text{NERR} = \frac{V_{\text{Exp}}}{V_{\text{Exp}} - V_{\text{pred}}} \]

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


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