Poster

[P27-10] P27-10: Pharmacokinetics and pharmacogenetics

Chair: Andrew Somogyi, Australia

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[P27-10-1] Modeling drug transfer over the mammary gland using physicochemical parameters and active transport as descriptors

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Background

Studies about the transfer of drugs into human milk are relatively scarce and often of limited quality. However, knowledge about the transfer of drugs over the mammary gland is of importance because breastfeeding is recommended even when mothers use drugs. Physicochemical parameters like pKa, LogP molecular weight (MW) and protein binding (PB) and pharmacokinetic parameter half-live value (T½) have often been stated as the main drivers for the transfer of drugs into human milk. Previous research showed predictive models, however the validation of these models had serious limitations. We aimed to find linear relationships (R^2>0.6) between physicochemical parameters including T½ and the milk:plasma ratio (MPR) or the relative infant dose (RID).

Methods

We performed univariate and multivariate analyses on a dataset of 195 drugs with information about pKa, LogP, MW, PB and the T1/2 . These values were tested for any relationship with the MPR and the RID using Pearson-Chi square tests, Spearman’ s rho correlation coefficients and one-way ANOVA The MPR and RID data were provided by the research group (Infant Risk Centre of the Texas Tech University, head Prof. Dr. TW Hale). Stratified analysis was conducted to take into account active transport and passive diffusion of the drugs.

Results

All parameters were correlated to at least one other parameter in the dataset. Because of their nonparametric distribution, all original data were log-transformed and categorized in 5 equal sub-groups. After removal of outliers in the dataset, we did not find any significant linear relationships (straightforward linear regression) with either the MPR or the RID, see figures for results of the raw data, categorized into active and passive diffusion of drugs. Multiple linear regression (backward regression) did not reach any significance level. Moreover, a non-linear relationship seems to be more realistic and spline functions may be more appropriate to interpret the data.

Conclusions

We did not find a linear relationship between pKa, LogP, MW, PB and T1/2 and the MPR or RID, active and passive transport taken into account. Further research is necessary to elucidate the relationships between physicochemical parameters and drug transfer over the mammary gland.

Figure 1: Graphical presentation of relationships between physicochemical parameters and MPR of 184 drugs
Zoom image