Impact of free fatty acids on prediction of unbound fraction of cefazolin and diazepam in plasma of full-term neonates

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Background

The fraction of drug unbound in plasma (*fu*) is a key parameter in physiologically based pharmacokinetic (PBPK) models and thus requires accurate prediction. Currently, most available models use the equation from McNamara and Alcorn [1] where age related changes in *fu* are due to the ontogeny of plasma proteins. However, this equation assumes the number of binding sites and affinity constant are identical between adults and neonates and therefore does not take into account dynamic changes due to the binding of other age-related components to albumin or α1-acidglycoprotein.

Fatty acid concentrations are elevated during the first week of life and they can bind to plasma albumin. This impact is not usually considered in PBPK models but can be important and potentially affect the *fu* predictions. The aim of this study was to investigate the impact of age-related changes in free fatty acid (FFA) concentration on unbound fraction of the albumin bound drugs cefazolin and diazepam in plasma (*fu*) of full-term neonates.

Methods

Measured values of *fu* for cefazolin and diazepam in full-term neonates were extracted from the literature or through personal communication with authors [2, 3]. The values of *fu* were predicted using the equation below.

$$f_{u,neonate} = \frac{1}{1 + \frac{P_{neonate} \times (1 - f_{u,neadult})}{P_{adult} \times f_{u,adult}}}$$

where $f_{u,neonates}$ and $f_{u,adult}$ are *fu* in neonates and adults respectively and $P_{neonates}$ and P_{adults} are albumin concentrations in neonates and adults, respectively. The measured neonatal $P_{neonates}$ albumin concentrations were compared with model predicted values [4] and in the final prediction the latter albumin concentrations were used.

An exponential decline function was fitted to the measured FFA data in pediatrics and adults to predict the FFA concentration as fraction of adults at each age [5]. Binding of FFA to albumin was accounted for via division of albumin concentration by FFA ontogeny to reflect the available albumin for binding to drugs assuming one to one binding between drug and FFA to albumin. Then *fu* values were predicted for cefazolin and diazepam using the corrected albumin concentration and overlaid with reported values *in vivo*.

Results

Individual *fu* values from 70 full-term neonates for Cefazolin and 5 neonates for diazepam as well as corresponding measured albumin levels were included in the analysis.

The ontogeny function for FFA showed 2-fold higher expression at birth compared to adults and reduced to reach the adult levels by 1 week post natal age (Figure 1).

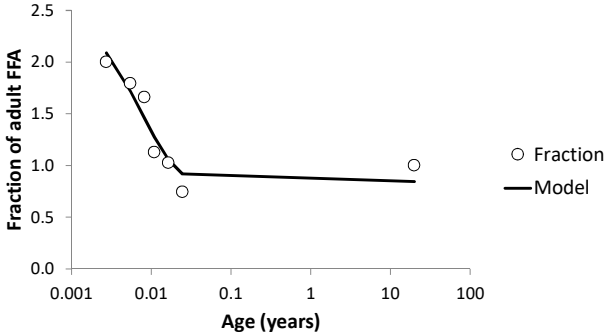

Figure 1. Age-related changes in FFA concentration as a fraction of adults.

Results

Figure 2 shows the predicted values of albumin concentration where within 2-folds of observed data.

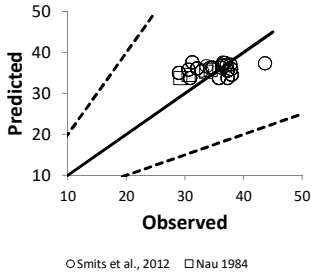

Figure 2. Predicted vs. observed albumin concentration in neonates from references 2 and 3. The black solid line is the line of unity and the dashed lines indicate 2-fold intervals.

The predicted and observed values of *fu* (figure 3) showed a decrease with age in the first few days after birth for both drugs. The mean predicted *vs.* observed *fu* values in all neonates for cefazolin and diazepam in presence of FFA effect were 0.338 vs. 0.389 and 0.043 vs. 0.037, respectively. The corresponding predicted values without FFA effect were 0.305 and 0.031 for cefazolin and diazepam, respectively. Figure 3 shows the predicted (with and without correction for FFA) and observed *fu* values for both drugs. The figure shows the trend of predictions is more reasonable captured when FFA is considered in the model.

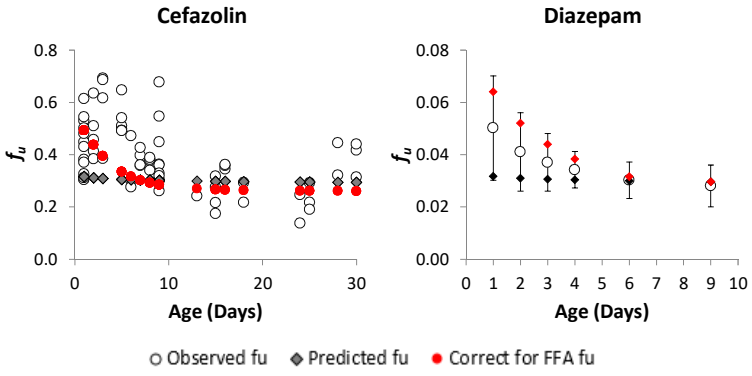

Figure 3. Age-related changes in *fu* for cefazolin and diazepam.

Conclusions

- Accounting for FFA level led to improved predictions of *fu* for cefazolin and improved the shape of profile for diazepam with some improvement in values on early days.
- It is likely that other endogenous mechanisms be involved in binding of drugs especially diazepam.
- There is evidence that the number of binding sites and the affinity constant are different between adults and pediatrics and vary from one drug to another.
- The fetal albumin could also have different affinity for binding to drugs.
- All the above points add complexity to the prediction of *fu*.
- Since *fu* is an important parameter in PBPK models, there are several unknown areas that require further investigation to describe the competitive non-specific binding of FFA to albumin to improve *fu* predictions of drugs in neonates.

References

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