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Prospective evaluation of a population pharmacokinetic model of pantoprazole for obese children

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Describe role of Submitting/Presenting Trainee in this project (limit 150 words):
Trainee was responsible for data extraction from the available literature, computer simulation, evaluation of model performance, data analysis and interpretation.

Background:

Proton pump inhibitors are commonly prescribed medications for children. Current dosing of proton pump inhibitors (PPIs) relies on weight-based strategies (e.g., mg/kg, weight-tiered). Such dose selection may not be appropriate for obese children, as it does not take into account obesity-related changes in physiology that can affect systemic exposure to drugs. Since obese children are 6-times more likely to suffer from gastroesophageal reflux disease, and PPIs have become some of the most commonly prescribed drugs to children, there is a critical need to characterize the drivers of variability in systemic exposure to PPIs, other than pharmacogenetic (i.e., CYP2C19 genotype), for obese children.

Objectives/Goal:

We recently published a population pharmacokinetic (PK) model for the disposition of the PPI pantoprazole (PAN) in obese children. The objective of this investigation was to evaluate the predictive performance of this computer model in an independent cohort of normal weight, overweight and obese children.

Methods/Design:

A 2-compartment structural model, modified to exclude transit compartments for delayed absorption, was used to predict the PK of PAN oral suspension, immediate release (k_a=7.3 hr^{-1}). Calculated population parameters and covariate relationships (e.g., weight, CYP2C19 genotype)

were extracted. Predictions were based on dose, sampling times, and covariates from 57 children (6-17 years; 21% obese, 28% overweight) who received a single dose PAN and had plasma PAN concentrations collected at 10 time-points over 8 hours. Model predictive performance was assessed visually and by relative root mean squared error (RMSE), with mean ratio of predicted-to-observed area under the concentration time curve (AUC) compared via one-way ANOVA across weight groups, defined by body mass index (BMI) for age (10-84th percentile normal-weight, 85-94th percentile overweight, ≥95th percentile obese; α=0.05, R).

Results:

The model generally over-predicted observed PAN concentrations (RMSE 194%). Ratios of predicted versus observed AUC were not significantly different among obese, overweight and normal-weight children (1.5 vs. 1.7 vs. 2.2, p=0.06); however, a trend toward better model prediction was observed in the subset of obese children.

Conclusions:

Observed PAN PK deviated from model predictions, which may be due to differences in PAN formulation (delayed vs. immediate release) between studies. Formulation effect is being addressed in an ongoing study of a delayed release PAN, with plans to use the data generated to refine our model. Ultimately, the findings of these studies will aid in appropriate dose selection of PAN and other PPIs to prevent over- or under-dosing.