Translating Disposition of Sotalol from Healthy Adults to Predict Its Behavior in Pediatric and Adult Subjects with Enhanced and Diminished Renal Clearance

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OBJECTIVE

To extend a physiologically based pharmacokinetic (PBPK) model of sotalol developed in healthy adults to predict its behavior in pediatric subjects and adults with varying degrees of renal clearance (pregnant females with higher clearance as well as patients with renal failure).

METHODOLOGY

Recently, we developed a PBPK model to describe the disposition of sotalol in healthy adult male populations across multiple levels of intravenous (IV) doses using GastroPlus™ [1]. This model, which incorporated the Advanced Compartmental Absorption and Transit (ACAT™) model for absorption, simulated the behavior of sotalol from oral (PO) doses (henceforth, referred to as the 'S+ Sotalol Model'). In this paper, we assess the predictive power of the S+ Sotalol Model (with no change in any biopharmaceutical parameters) in pediatric subjects (range 4 days – 12 years) against reported mean Cp-time data for PO doses (low, medium and high dose level) [2]. The program's built-in Population Estimates for Age-Related Physiology (PEAR™) physiology automatically scaled the glomerular filtration rate (GFR) for the pediatric population. Sotalol is cleared predominantly by the kidney. The current model estimated renal clearance as the product of fraction unbound in plasma (fup) and GFR, thus automatically calculating the renal clearance in different pediatric subjects.

The S+ Sotalol Model was also used to predict sotalol PK in pregnant subjects when administered both as an IV injection and immediate-release tablet [3]. The study reported Cp-time data both during pregnancy and in the postnatal condition. Pregnancy is marked by an increase in GFR, which can be estimated from serum creatinine concentration using a variety of widely accepted correlations [4-5]. Sims et al. [6] reported serum creatinine concentrations during pregnancy and postnatal periods. This data was used to obtain the ratio of GFR in normal and pregnant females using the Modified Diet in Renal Disease (MDRD) formula [4]. This ratio was then used to scale the GFR (original prediction from the default PEAR physiology) for the female population described in [3] and to predict Cp-time profiles for both IV and oral doses with no other parameter changes.

Finally, the S+ Sotalol Model was used to predict sotalol PK in patients with end-stage renal failure [7], characterized by a GFR less than 15 ml/min [5]. As in the other validation examples presented above, no adjustments were made to the biopharmaceutical properties and only the physiology was scaled to represent the given population.

RESULTS & DISCUSSION

Figure 1 shows the simulated Cp-time profile and observed values for oral solution doses of 10, 30 and 70 mg/m^2 body surface area (estimated 5.76, 17.27, and 49.29 mg). All three doses are well-predicted. The degree of slight underprediction decreases with increasing dose.

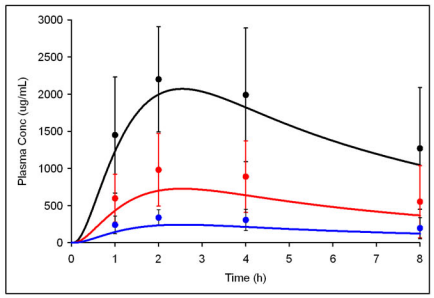

Fig 1. **Predicted** (lines) and observed (points) Cp-time profile for an oral solution of 49.29 (black), 17.27 (red) and 5.76 (blue) mg of sotalol administered to a pediatric population (3.24 ± 4.23 y). Administered doses were estimated from reported body surface areas.

Figure 2 shows simulated Cp-time profiles and observed values for sotalol administered to females in both pregnant and postnatal condition. The model is substantially predictive. It is, again, noteworthy that these are pure predictions from the previously developed S+ Sotalol Model (only physiology was automatically scaled to represent the reported populations) without adjusting any biopharmaceutical parameters.

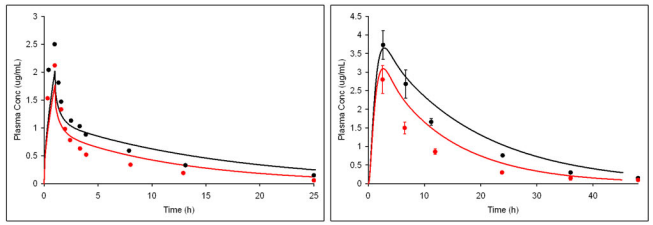

Fig 3. **Predicted** (lines) and observed (points, n = 6) Cp-time profiles for a 100 mg 1-hour IV infusion (left) and a 400 mg immediate-release tablet (right) for females during pregnancy (red, body weight = 81.9 Kg) and postnatal condition (black, body weight = 72.8 Kg).

Figure 3 shows the simulated Cp-time profile and observed values for sotalol administered to patients with end-stage renal failure. The behavior for renal-insufficient patients is overpredicted. However, a closer look at the curve shows that the slope of the simulated line in the clearance phase matches that of the observed points well, but somehow overpredicts the degree of absorption. Whether the absorption of sotalol is somehow hindered in such patients due to additional medications administered or other factors has not yet been investigated.

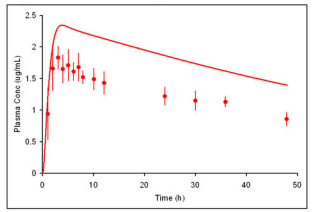

Fig 3. **Predicted** (lines) and observed (points) Cp-time profile for a 160 mg immediate-release tablet of sotalol to patients with end-stage renal failure (red).

CONCLUSIONS

- **A previously developed GastroPlus PBPK model for adults was able to predict the behavior of sotalol in pediatric subjects.**
- **The same model was able to predict sotalol behavior in pregnant females (higher GFR than normal) as well as in patients suffering from end-stage renal insufficiency (very low GFR).**
- **All model applications involved scaling only the physiology with no adjustment of biopharmaceutical properties.**

REFERENCES

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