Modeling Disposition of Sotalol following Intravenous and Oral Administration in Healthy Adult Subjects

S. Ray Chaudhuri, V. Lukacova, W. S. Woltosz
Simulations Plus, Inc. 42505 10th Street West, Lancaster, CA 93534

OBJECTIVE

To simulate and predict the absorption and pharmacokinetics (PK) of sotalol following intravenous (IV) and oral (PO) administrations.

METHODOLOGY

Sotalol is a nonspecific adrenergic beta-antagonist that is used in the treatment of life-threatening arrhythmia [1]. Its absorption, distribution and systemic PK or, collectively, ‘disposition’ was modeled and simulated using GastroPlus™ v7.0 [2]. Biopharmaceutical properties were obtained from in silico predictions [3] and in vitro measurements [4-8] and are listed in Table 1 below.

Systemic PK was simulated using a physiologically based pharmacokinetic (PBPK) model with all perfusion-limited tissues. Human organ weights, volumes, and blood perfusion rates were generated by the built-in age-, gender- and body-weight dependent Population Estimates for Age-Related (PEAR) Physiology™. Tissue/plasma partition coefficients (Kp’s) were calculated using our default modified Rodgers method. Sotalol is cleared predominantly in the kidney. Renal clearance was estimated as the product of fraction of sotalol unbound to blood plasma proteins (fup) and glomerular filtration rate (GFR). The blood-to-plasma concentration ratio (Rbp) of sotalol was fitted to correct for the steady-state volume of distribution (Vss) against observed plasma concentration (Cp-time) data following IV administration of 20 mg sotalol [9]. This systemic PBPK model was further validated by predicting Cp-time profiles after IV administration of four other sotalol doses ranging from 17.375 mg to 139 mg in a different healthy population [10].

The validated PBPK model, combined with the GI absorption (ACAT™) model within GastroPlus, was used to simulate the Cp-time profiles for oral administration of an 80 mg solution [9] and a 100 mg immediate-release tablet [10] of sotalol. The stomach transit time (STT) was fitted to match the relatively late Tmax (~3hrs) in the Cp-time data for the solution dose and then used unchanged to predict the behavior of the tablet administration.

RESULTS & DISCUSSION

Figure 1 shows the simulated Cp-time profile and observed values [9] for 20 mg sotalol administered as a 10-minute IV infusion to healthy male population “D” (n = 7, median age = 22 y, median weight = 79 kg) by fitting the Rbp to 0.89. Figure 2 shows the predicted Cp-time profile and observed values [10] for a 5-minute infusion of 0.25 and 2 mg/kg of sotalol to healthy male population “P” (n = 6, mean age = 23.8 y, mean weight = 69.5 Kg) using the same model built for population “D”.

Table 1. Biopharmaceutical properties of sotalol

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference Solubility (mg/mL)²</td>
<td>16.25 @ pH 8.935</td>
<td>[3]</td>
</tr>
<tr>
<td>Log P</td>
<td>0.24</td>
<td>[4]</td>
</tr>
<tr>
<td>pKa</td>
<td>8.38, 9.47</td>
<td>[5]</td>
</tr>
<tr>
<td>% protein binding</td>
<td>31.0</td>
<td>[6]</td>
</tr>
<tr>
<td>Intestinal Permeability (Pint, cm/s)²</td>
<td>0.9687 x 10⁻⁴</td>
<td>[7-8]</td>
</tr>
</tbody>
</table>

1. Profiles for variation of solubility and logP against varying pH was calculated using both in silico and in vitro methods [3].
2. Mean of reported in vitro values converted to in vivo values using in-house correlation

CONCLUSIONS

• A PBPK-ACAT™ model in GastroPlus was able to simulate the disposition of sotalol (both IV and oral solution doses) in healthy subjects using mainly in silico and in vitro inputs.
• The model successfully predicted the disposition of sotalol (for both IV and oral doses) across multiple dose levels in a different healthy population.

REFERENCES

[1] Drug Bank
[3] ADMET Predictor v5.5