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

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OBJECTIVE

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

METHODOLOGY

Budesonide is a glucocorticosteroid with high local anti-inflammatory effects. Its absorption, distribution, and systemic PK or, collectively, 'disposition' was modeled and simulated using GastroPlus™ v8.5 [1]. Biopharmaceutical properties were obtained from *in silico* predictions [2] and *in vitro* measurements [3-5] 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 the default Lukacova method [6]. Budesonide is cleared predominantly by CYP3A4, which is abundant in both liver and GI tract. A linear systemic (liver) clearance (CL) was fitted against the observed plasma concentration-time (Cp-time) profiles following IV infusion of 0.1 mg budesonide [7] in healthy male subjects. The minor contribution to renal clearance was estimated using the fraction of budesonide unbound in blood plasma (fup) and glomerular filtration rate (GFR). This systemic PBPK model was further validated by predicting the Cp-time profile after IV infusion of 1 mg of budesonide in a different (mixed gender) population [8]. For, the latter, a higher liver clearance was used to represent increased expression of CYP3A4 in female livers [9]

The validated PBPK model, combined with the GI absorption (ACAT™) model within GastroPlus was used to simulate the Cp-time profile after PO administration of a 4 mg budesonide immediate-release tablet [10]. The *in vivo* GI permeability was obtained by converting the *in vitro* measurement in Pgp-inhibited Caco-2 cells using the built-in Absorption Systems correlation [1]. For the PO dose, the only adjusted parameters were a fixed intestinal first-pass extraction (FPE) against its Cp-time profile (at the lack of *in silico* or *in vitro* estimations) and the stomach transit time (as reported in the study [10]).

Table 1. Biopharmaceutical properties of budesonide

Physicochemical Properties for budesonide	Value	Source
Log P	2.39	[2]
pKa	none	
Reference Solubility (mg/mL)*	0.028 @ pH = 7	[3]
% plasma protein binding	32.0	[4]
Blood: plasma concentration ratio	0.76	[2]
Intestinal Permeability (P_{eff}, cm/s)[2]	2.488 x 10^{-4}	[5]

Profiles for variation of solubility and logD against varying pH were calculated using both *in silico* and *in vitro* inputs [2-3]

RESULTS & DISCUSSION

Figure 1 shows the simulated Cp-time profile and observed values [7] for 0.1 mg budesonide administered as a 5-minute IV infusion to healthy male population (n = 4, mean age = 34 y, mean weight = 79 Kg) using a fitted unbound intrinsic liver CL of 1200 L/h, which translates to a systemic liver clearance of 43.4 L/h. Figure 2 shows the same for 1 mg budesonide [8] administered as a 5-minute IV infusion to a mixed population (n = 24, F:M = 1:1, mean age = 39 y, mean weight = 68 Kg) using a higher Clint of 2108.5 L/h (to account for higher CYP3A4 expression in females).

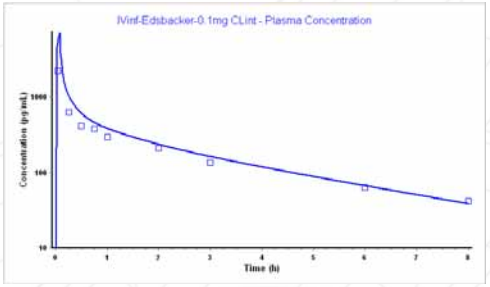

Fig 1. **Simulated** (line) and observed (points) Cp-time profile for 5-minute IV infusion of 0.1 mg budesonide. Image is shown in semi-logarithmic scale

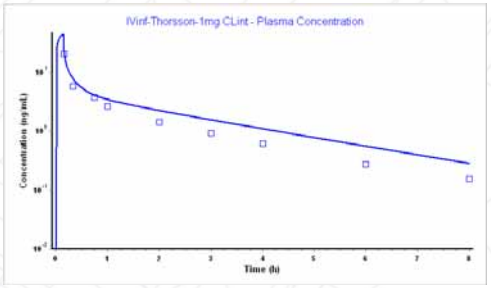

Fig 2. **Predicted** (line) and observed (points) Cp-time profile for 5-minute IV infusion of 1 mg budesonide. Image is shown in semi-logarithmic scale

Figure 3 shows the simulated Cp-time profile and observed values for 4 mg of budesonide administered as an immediate-release tablet to a mixed population (n = 5, F:M = 3:2, mean age = 34 y, mean weight = 79 Kg). Weighted average of male and female Clint (2290 L/h) was used. Fitted fixed intestinal FPE was 7% and stomach transit time was 4 h.

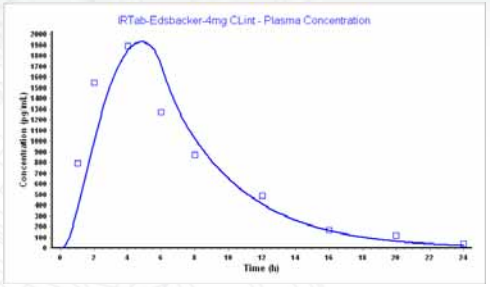

Fig 3. **Simulated** (line) and observed (points) Cp-time profile for an oral administration of a 4 mg immediate-release tablet with 200 mL water in fed condition.

CONCLUSIONS

- **A PBPK-ACAT model in GastroPlus was able to simulate the disposition of budesonide (both IV and oral solution doses) in human subjects using mainly *in silico* and *in vitro* inputs.**
- **The model successfully predicted the IV disposition of budesonide across multiple dose levels in different human populations.**

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