Simulating the Disposition of Triamcinolone Acetonide following Oral and Pulmonary Administration

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INTRODUCTION & METHODOLOGY

Absorption, distribution and clearance of triamcinolone acetonide (TA) from oral and pulmonary administrations have been simulated using GastroPlus™.[1]. Simulation of orally administered doses and swallowed portions of inhaled doses were simulated using the Advanced Compartmental Absorption and Transit (ACAT™) model within GastroPlus. The pulmonary delivery and pharmacokinetics model within GastroPlus (shown in Figure 1) has been used in earlier studies[3-8]. The model accounts for:

- mucociliary transit
- dissolution/ precipitation
- absorption into pulmonary cells
- nonspecific binding in mucus/ surfactant layers and cells
- (linear) metabolism
- transfer into the systemic circulation
- partial swallowing of the inhaled dose

Biopharmaceutical properties for TA (MW = 434.5) were generated using ADMET Predictor™ v5.0[2] or obtained from the literature[9-15]. Human lung physiological parameters (surface area, thickness, and volume for the mucus and cell) for each compartment were obtained from the literature[16-18]. Observed plasma concentration-time (Cp-time) profiles from a 2 mg intravenous (IV) bolus dose in humans (mean age = 29 years, mean weight = 81 kg) were used to fit a two-compartment PK model (using the PKPlus™ module of GastroPlus). The lumped systemic clearance was subsequently replaced by a Michaelis-Menten CYP3A4 clearance model for TA both in the liver and the GI tract. The K_m was artificially set to a high value to represent nonsaturable conditions and the V_{max} was fitted to the IV data. This PK model was used to describe systemic PK for all subsequent simulations. All oral and pulmonary simulations used the default human fasted state ACAT. Gut metabolism was described using the liver K_m and V_{max} values, with V_{max} scaled in proportion to the ratio of the amount of CYP3A4 in gut and liver. Intestinal permeability was adjusted to match the oral Cp-time slope prior to C_{max}. For pulmonary simulations, human lung physiological compartment parameters were obtained from the literature. Although particle size distribution was not reported, it was obtained from an independent source for the same device[19], and was used to calculate the fraction of the dose deposited in each lung compartment and fraction exhaled according to the built-in ICRP 66 model. A single value for the systemic absorption rate coefficient and linear metabolic clearance (representing possible metabolism, degradation, phagocytosis etc.) in all lung compartments was the only parameter fitted to match the pulmonary data.

RESULTS & DISCUSSION

Figure 2 shows the fitted Cp-time profile (along with parameter values for 2 compartment PK and CYP3A4) and observed[20] values for TA administered as an IV bolus to healthy volunteers. Figure 3 gives a comparison of the observed[20] and simulated Cp-time profiles for the 5 mg oral dose. The value of intestinal permeability was 1.0 x 10-4 cm/s. For the oral administration, the percents of administered dose that was absorbed, (Fa%), reached the portal vein (FDp%) and was bioavailable (F%) were 99.5, 42.4 and 22.2, respectively. Figure 4 gives a comparison of observed[20] and simulated Cp-time profiles for the 2 mg inhaled dose. In this case, the systemic absorption rate coefficient in lung compartment was the only parameter that was fitted. The same value was used in all pulmonary compartments. For the inhaled dose, **lung Fa%** (percent absorbed from the lung), **gut Fa%** (percent absorbed from the gut) and **FDp% was 41.9, 24.0 and 9.8** respectively. Correspondingly, **lung F%** (contribution from the lung) and **gut F%** (contribution from the gut) **was 14.0 and 5.1**, respectively, with a **total bioavailability of 19.1%**. Even though the total Fa% is ~34% lower after inhaled administration, the overall bioavailability is comparable to the oral dose due to significant gut and liver first pass extraction of the dose absorbed from the gut.

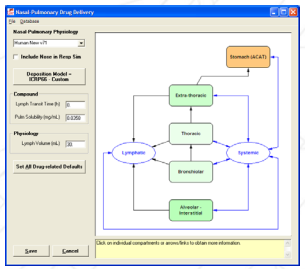

Fig 1. Nasal-Pulmonary Drug Delivery editor within the GastroPlus Additional Dosage Routes Module (ADRM)

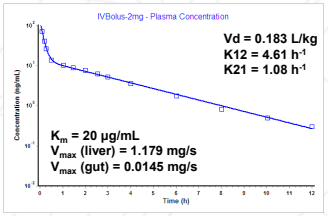

Fig 2. Simulated (line) and observed (points) Cp-time profile for an i.v. bolus dose of 2 mg TA. Image is shown in logarithmic scale.

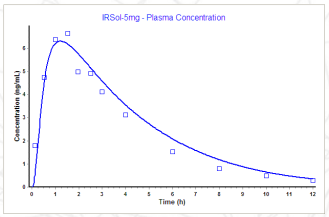

Fig 3. Simulated (line) and observed (points) Cp-time profile for an oral solution dose of 5 mg TA. Image is shown in linear scale.

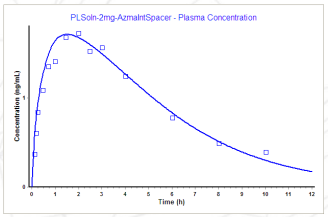

Fig 4. Simulated (line) and observed (points) Cp-time profile for an inhaled administration of 2 mg TA. Image is shown in linear scale.

CONCLUSIONS

- GastroPlus successfully simulated the IV and oral administration of TA.
- The physiologically based nasal-pulmonary absorption and PK model for TA provides reasonable agreement between observed and simulated plasma concentration-time data, with fitting of only one pulmonary parameter – the systemic absorption rate constant (uniform value used across all compartments)
- Information such as particle size and its distribution was not reported for the administered formulation, which may, in turn, affect the regional distribution of the inhaled dose into different pulmonary compartments. Routine measurement and reporting of this information would help to avoid incorporating unknown factors in the mechanistic understanding of inhaled administrations.

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