Application of a Respiratory PBPK Model for Predicting Deposition and Disposition following Inhaled Administration of Morphine

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

OBJECTIVE

Demonstrate the pulmonary component of the GastroPlus™ Additional Dosage Routes Module™ (ADRM) simulation to develop a pharmacokinetic (PK) and pharmacodynamic (PD) model for inhaled administration of morphine in humans.

METHODOLOGY

The GastroPlus[1] pulmonary model, shown in Figure 1, has been used in earlier studies[2-4]. The model accounts for:

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

Swallowed portions of the inhaled dose have been accounted for using the Advanced Compartmental Absorption and Transit (ACAT™) model within GastroPlus. Human lung physiological parameters (surface area, thickness and volume for the mucus and cell) for each compartment were obtained from the literature[5-7]. Three-compartment PK parameters were fitted to observed Cp–time profiles from a 7-minute 8.8 mg *i.v.* infusion dose in healthy human subjects[8] using the PKPlus™ module within GastroPlus. Physicochemical properties were obtained from *in vitro* measurements[9] or *in silico* predictions[10]. Pulmonary permeability and systemic absorption rate was adjusted against the reported *in vivo* inhaled data. Fixed liver first-pass extraction (76.2%)[11] was used in all simulations. Deposition fractions in the lung compartments were calculated both by the built-in ICRP 66[5] algorithm and an external Multiple Path Particle Dosimetry (MPPD) Model[12] assuming complete mouth breathing. Particle diameter of 2.96 µm with a geometric standard deviation of 1.24 µm, reported for AERx devices[13], was used to calculate deposition fractions, with an airflow rate of 73 L/min[8]. Observed pharmacodynamic (PD) data for pupil diameter was fitted to the PK model using the PDPlus™ module of GastroPlus.

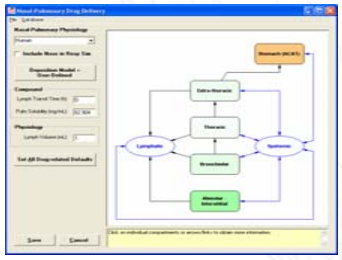

Fig 1. Nasal-Pulmonary Drug Delivery editor within the GastroPlus Additional Dosage Routes Module (ADRM)

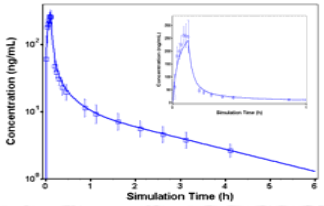

Fig 2. Simulated (line) and observed (points) Cp-time profile for 7-minute i.v. infusion of 8.8 mg morphine. Inset shows the same image on a linear scale (up to 1 h).

RESULTS & DISCUSSION

Figure 2 shows the fitted Cp-time profile and observed values for morphine administered as an IV infusion to 13 healthy volunteers. Deposition fractions from the ICRP 66 and MPPD algorithms are shown in Figure 3. A direct comparison of ICRP 66 and MPPD algorithms is difficult owing to their different approaches. While ICRP 66 treats the lung as a collection of 4 compartments (5 with nose), MPPD adopts a generational approach and finally lumps the generations into 3 distinct compartments: Head, TB and P. Extrapolating 3 MPPD compartments into 4 ICRP 66 compartments can result in significant differences in predicted deposition fractions. ICRP 66 and MPPD algorithms generated exhaled fractions of 39% and 45%, comparable to the reported value of 47%[8]. Although the two algorithms calculated different deposition fractions, the differences did not have a significant effect on the simulated Cp-time profile (Figure 3).

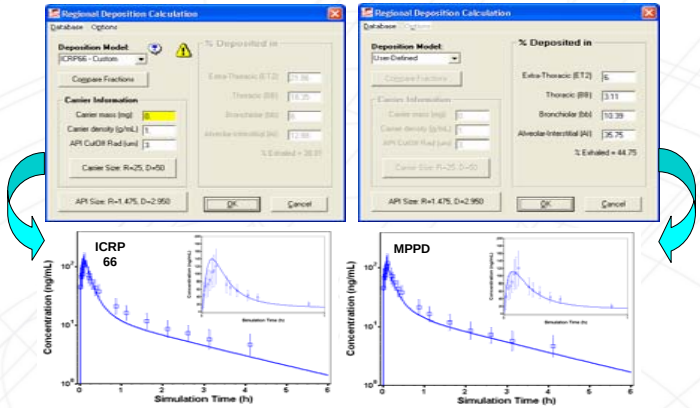

Fig 3. Simulated (line) and observed (points) plasma concentration-time profile for 17.6 mg of inhaled aerosolized morphine resulting from initial deposition fractions generated by the ICRP 66 and MPPD algorithms. Inset shows the same image on a linear scale (up to 1 hr).

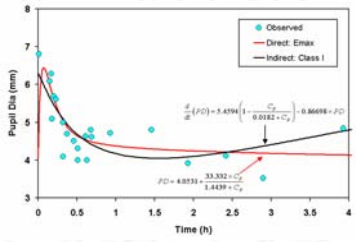

Fig 4. Simulated (line) and observed (points) PD effect-time profile corresponding to the inhaled administration of aerosolized morphine for subject # 5 in the study conducted by Dershwtitz et al[8].

RESULTS & DISCUSSION (Contd.)

Figure 4 shows the PD effect (pupil diameter) for subject # 5 and models built using direct (Emax) and indirect (Class I) models. A direct linear model performed similar to the Emax model and hence is not shown here. The subjects showed a wide variability of PD effect, which can be attributed to a variability in PK[8]. Although PD effect data were reported for individuals, lack of individual PK data precluded the possibility of extending the model to other subjects.

CONCLUSIONS

- Deposition fractions generated from ICRP 66 and MPPD algorithms predict exhaled fractions comparable to those reported for the AERx device.
- The physiologically based nasal-pulmonary absorption and PK model for morphine provides reasonable agreement between observed and simulated plasma concentration-time data, with fitting of only pulmonary absorption parameters (uniform value used across all compartments)
- The inhaled model results in a reasonable PKPD model for morphine for a random subject. Variability in the observed data precluded any possibility of average or collective analysis.

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