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Physiologically-based pharmacokinetic (PBPK) model for prediction of midazolam pharmacokinetics after intranasal administration in children

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Abstract:

Purpose: To predict midazolam absorption and pharmacokinetics (PK) after intranasal (*i.n.*) administration in young children.

Methods: The absorption and PK of midazolam were simulated using GastroPlus™ 7.0 (Simulations Plus, Inc., Lancaster, CA). The program's Advanced Compartmental Absorption and Transit (ACAT™) model described the intestinal absorption and gut first pass extraction (FPE) for oral (*p.o.*) doses, coupled with its PBPKPlus™ module for simulation of the PK distribution, liver FPE and systemic clearance, and its Additional Dosage Routes Module (ADRM™) for simulation of absorption after *i.n.* administration. The accuracy of the ACAT model simulations for midazolam in healthy adult volunteers was previously validated by comparing the simulated plasma concentration-time profiles with experimental profiles after intravenous (*i.v.*) and *p.o.* administration. The ADRM module within GastroPlus was used to simulate the absorption after *i.n.* administration in healthy adults and in children (average age 2 years). Built-in age-dependent physiologies of the respiratory system were used to describe nasal absorption in both populations. The initial deposition of the drug was assumed to be 100% in the nose. The permeability through nasal mucosa and systemic absorption rate were fitted to *in vivo* data after *i.n.* administration in adults and, without further adjustments, were used to predict the absorption of midazolam after *i.n.* administration in children.

Results : This PBPK model, when coupled with age-dependent gastrointestinal and respiratory physiologies, was able to account for differences in the absorption and disposition of midazolam between adults and children and resulted in accurate predictions of midazolam exposure after *i.n.* administration in children.

Conclusions: Successful predictions of midazolam disposition in children after *i.v.* and *p.o.* administration were previously reported. The current study validates the utility of a physiologically-based approach for prediction of midazolam disposition in children after an alternative route of administration.

Methods:

Pharmacokinetics:

A PBPK model was used to describe midazolam distribution and PK. Human, adult and pediatric, physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™ module. Tissue/plasma partition coefficients were calculated using a modified Rodgers algorithm [1] based on tissue composition and *in vitro* and *in silico* physicochemical properties (ADMET Predictor™, Simulations Plus, Lancaster, CA).

Metabolic clearances in gut and liver were based on built-in *in vitro* values for the expression levels of 3A4 in each gut compartment and the average expression of 3A4 in liver. Enzyme kinetic constants for 3A4 were *in vitro* values from literature [2].

Gastrointestinal dissolution and absorption:

The ACAT model was used to describe *in vivo* drug dissolution and intestinal absorption. Gastrointestinal physiological parameters (lengths, radii, fluid volumes) were automatically scaled for pediatric subjects.

Nasal absorption:

The pulmonary model within the program's ADRM module was used to describe the absorption of drug from nose after *i.n.*administration. Nasal and pulmonary physiological parameters (absorptive surface area, absorptive layer thickness, etc.) were automatically scaled for pediatric subjects.

Drug permeability through nasal mucosa and rate of drug transfer from nasal epithelial cells to systemic circulation were fitted to Cp-time data obtained after *i.n.* administration in adults [3]. The same parameter values were then linked to pediatric physiology to predict the drug exposure in pediatric subjects after *i.n.* administration [4].

Results:

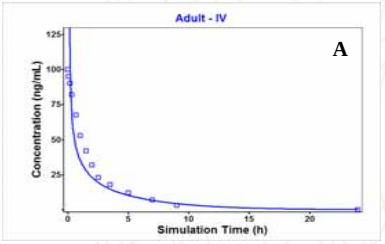
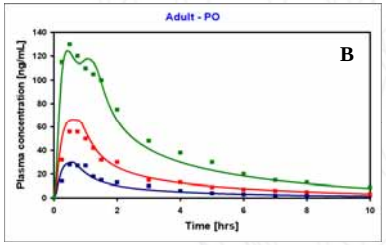


Table 1. Summary of simulated % absorbed, % dosed reaching portal vein and % bioavailable after *p.o.* and *i.n.* administration of 5 mg dose in adults.

Adult	*p.o.* [5 mg dose]	*i.n.* [5 mg dose]
% absorbed from nose	-	65.6
% absorbed from gut	100	33.2
% reaching portal vein	40.5	9.1
% bioavailable	19.4	69.9



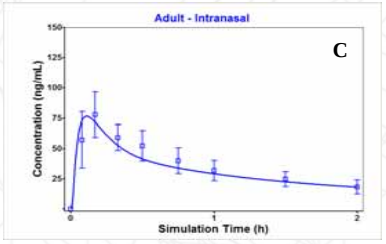


Figure 1. Simulated (lines) and observed (points) Cp-time profiles after A) *i.v.* administration of 5 mg bolus dose [5]; B) *p.o.* administration of 7.5 mg (blue), 15 mg (red) and 30 mg (green) dose [6]; C) *i.n.* administration of 5 mg dose in adults [3]. Common model parameters are identical across all simulations.

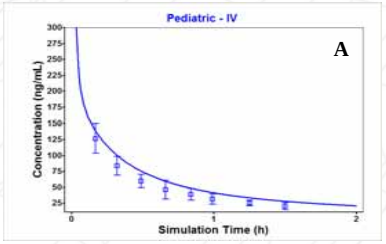
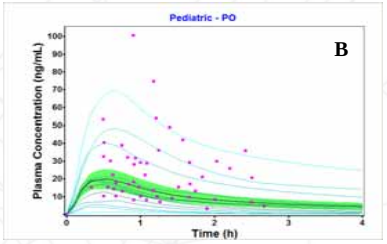


Table 2. Summary of simulated % absorbed, % reaching portal vein and % bioavailable after *p.o.* and *i.n.* administration of 0.1 mg/kg dose in pediatric subjects (2 years old, 12 kg).

Pediatric	*p.o.* [1.2 mg dose]	*i.n.* [1.2 mg dose]
% absorbed from nose	-	65.7
% absorbed from gut	100	33.9
% reaching portal vein	21.2	4.8
% bioavailable	10.6	68.1



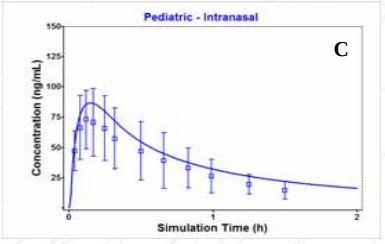


Figure 2. Simulated (lines) and observed (points) Cp-time profiles after A) *i.v.* administration of 0.1 mg/kg bolus dose [4]; B) *p.o.* administration of *0.1* mg/kg dose [7]; C) *i.n.* administration of 0.1 mg/kg dose in children [4]. Common model parameters are identical across all simulations.

Conclusions:

- A PBPK model combined with *in silico* or *in vitro* parameters describing the drug's physicochemical and biopharmaceutical properties along with *in vitro* parameters describing the drug's metabolic stability correctly described PK after *i.v.* administration in adults and children.
- The ACAT model, which incorporates enzyme distributions in the liver and the gastrointestinal tract, correctly described the drug's absorption and intestinal metabolism in adults and children.
- The intranasal-pulmonary model calibrated using *in vivo* data from adults correctly predicted exposure after *i.n.* administration in children.
- The approach of utilizing PBPK modeling and *in vivo* data in adults to predict PK in pediatric populations can be successfully applied to variety of dosage forms if relevant physiological information is available.

References:

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