Development of an Optimized Pharmacokinetic Model for Dexmedetomidine in Healthy Volunteers

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Background: Dexmedetomidine is an α_2-adrenoceptor agonist with sedative, analgesic and anxiolytic properties. Several pharmacokinetic (PK) models have been developed, but they tend to either underestimate plasma concentrations in the higher ranges[1, 2], or were developed with data from postoperative and/or intensive care patients which makes them susceptible to errors due to interactions with other medications. The goal of our study was to improve on the existing models in healthy volunteers.

Methods: After local ethics committee approval, we recruited 18 volunteers. Over two sessions, at least one week apart, they received a dexmedetomidine target controlled infusion (TCI) applied using the Dyck model[3]. A 20-second starting infusion at 6 mg/kg/h was administered. Ten minutes after this initial infusion, the target concentrations were increased step-wise in the following sequence: 1, 2, 3, 4, 6 and 8 ng/ml. Each level was maintained for 30 minutes. If the volunteer breached one of the pre-defined safety criteria, infusion was terminated and the recovery period began. Arterial blood samples were collected at 2 minutes after initial infusion; before each increase in target concentration, and at 2, 5, 10, 20, 60, 120 and 300 minutes in the recovery period. NONMEM 7.3 (ICON plc, Dublin, Ireland) was used for model development.

Results: The dataset contains 379 arterial plasma dexmedetomidine concentration observations from 18 individuals (9 male, 9 female). The age, weight and BMI ranges were 20-70 years, 51-110 kg and 20.6-29.3 kg/m^2 respectively. The parameters of the final model are shown to the right, where η is a normally distributed random variable with a mean of 0 and estimated variances of: $\boldsymbol{\eta 1} = 0.473$, $\boldsymbol{\eta 2} = 0.0568$ and $\boldsymbol{\eta 3} = 0.0273$. The population and post-hoc predictions vs. time are shown in Figure 1. The median absolute performance error of the population model, as described by Varvel[4], was 14.5%, the median performance error was 1.1%.

$$V1\ (L) = 1.83 \cdot (WT/70) \cdot e^{\eta 1}$$
$$V2\ (L) = 27.8 \cdot (WT/70)$$
$$V3\ (L) = 54.4 \cdot (WT/70) \cdot e^{\eta 2}$$
$$CL\ (L/min) = 0.695 \cdot (WT/70)^{0.75} \cdot e^{\eta 3}$$
$$Q2\ (L/min) = 3.25 \cdot (V2/27.8)^{0.75}$$
$$Q3\ (L/min) = 0.689 \cdot (V3/54.4)^{0.75}$$

Conclusion: Using TCI in healthy volunteers, the pharmacokinetics of dexmedetomidine were best described by a three-compartmental model. Weight but not age or gender were found to be significant covariates.

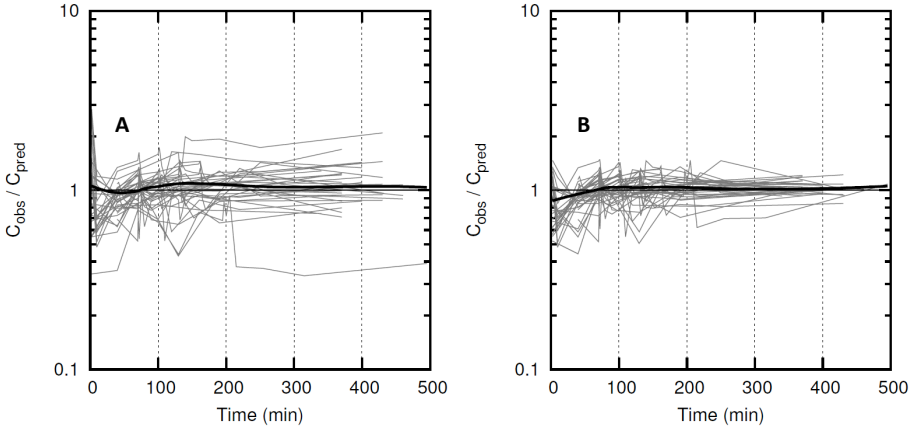

Figure 1: Observed/population predicted (A) and observed/post-hoc predicted (B) plasma concentrations vs. time.

References:

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