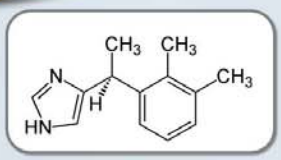
A Population Analysis of Intravenous Dexmedetomidine in Korean

SeungHwan Lee, MD, Bo-Hyung Kim, MD, Donghoon Shin, MD, Min Kyu Park, MD, Sang-Goo Shin, MD, PhD, Kyung-Sang Yu, MD, PhD, In-Jin Jang, MD, PhD
Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea

Introduction

Dexmedetomidine

- A selective alpha2-adrenoreceptor agonist used for sedation in critically ill patients



Objective

- To develop a population pharmacokinetic model of intravenous dexmedetomidine in Korean
- To compare the developed population pharmacokinetic model with previously reported pharmacokinetic data

Method

Population

- Plasma concentrations obtained in a randomized, double-blind, placebo-controlled, phase 1 study with three parallel dose were included in population analysis

Treatment

- Three intravenous dexmedetomidine dosing regimen
  - 3 μg/kg/h for 10 minutes followed by 0.17 μg/kg/h for 50 minutes
  - 6 μg/kg/h for 10 minutes followed by 0.34 μg/kg/h for 50 minutes
  - 3.7 μg/kg/h for 35 minutes followed by 0.7 μg/kg/h for 25 minutes.

Pharmacokinetic sampling

- Pre-dose, 0.17 h, 0.58 h, 0.75 h, 1 h, 1.17 h, 1.33 h, 1.5 h, 2 h, 3 h, 4 h, 7 h, 10 h, 12 h post-dose

Population pharmacokinetics

- Population pharmacokinetic model was developed using NONMEM®, version VI and PsN
- 1- and 2- compartment structural models were tested.
- Sex, height, body weight, age and serum creatinine were tested as covariate.

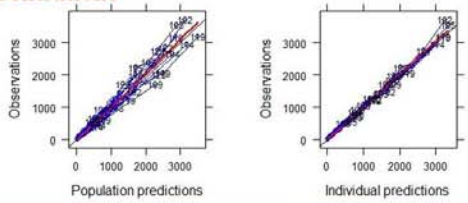
Results

- 208 plasma concentrations from 16 subjects were used in population analysis
- All participants were Korean male subjects. Mean (±SD) age was 26.4 ± 2.7 years, weight was 71.2 ± 8.0 kg and serum creatinine levels were ranged in reference range
- Pharmacokinetics of dexmedetomidine were best described using a two-compartment model with first-order kinetics
- Covaritates (age, weight and serum creatinine level) did not show significant influence on pharmacokinetics of dexmedetomidine

Table1. Pharmacokinetic parameter estimates and standard errors

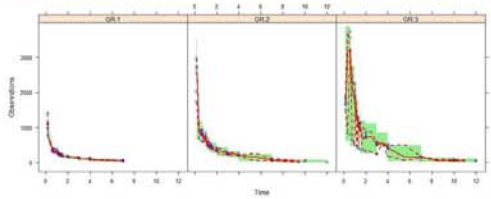
	Typical value estimate	Standard error
Clearance (CL) (L/h)	33.0	0.756
Central volume of distribution (V1) (L)	19.7	0.565
Inter-compartment clearance (Q) (L/h)	65.8	3.41
Peripheral volume of distribution (V2) (L)	61.4	2.47

Figure1. Plots of observed vs. population predicted and observed vs. individual predicted dexmedetomidine concentrations



- Most of the data were within 5th and 95th percentile in visual predictive check (VPC).
- This indicated that the model describes the pharmacokinetics of dexmedetomidine adequately.

Figure2. Plots of visual predictive check based on dexmedetomidine concentration in three dosage group



- The estimate of clearance in Korean was similar to the previously reported clearance in other races and weight-normalized (70kg) estimate in pediatrics.

Conclusion

- A two-compartment model with first-order elimination adequately characterized the pharmacokinetics of dexmedetomidine in Korean.
- Application of population pharmacokinetic model will be helpful for dose selection in clinical use.

Reference

1. Potts, A.L., Dexmedetomidine disposition in children: a population analysis. Paediatr Anaesth, 2008. 18(8): p. 722-30.
2. Fiedler-Kelly, J.B, Population pharmacokinetics of dexmedetomidine during long-term continuous infusion in critically ill patients. Clin. Pharmacol. Ther., 2010. 87, P2 (abstract).