Dexmedetomidine in Patients under Spinal Anesthesia: A Comparison of Clinical Outcomes between Target Controlled Infusion and the Recommended Regimen, Validation of Published Pharmacokinetic Models, and Construction of a New Pharmacokinetic Model

Background: Little information is available on the usefulness of dexmedetomidine target controlled infusion (TCI) and the predictive performances of published pharmacokinetic (PK) models in patients under spinal anesthesia. We examined the difference in clinical outcomes between the recommended regimen (i.e., the dosing manner recommended by drug manufacturers) and TCI. We also validated published pharmacokinetic models and constructed a new PK model in this population.

Methods: After approval by the institutional ethics committee and written informed consent process, 40 patients were randomly allocated to the recommended regimen group (6 mcg/kg/h in 10 min followed by 0.2–0.7 mcg/kg/h) or TCI group (initial target was 1.5 ng/ml using Dyck model [1] with maximum infusion rate of 6 mg/kg/h). Dexmedetomidine was administered after spinal anesthesia. As clinical outcomes, the time to loss of responsiveness, time to recovery, and incidence of circulatory or respiratory depression were recorded as parameters indicating sedation quality. In selected patients, venous blood samples were collected to measure dexmedetomidine concentrations. The predictive performances of six published models [1-6] were evaluated.[7] Population PK parameters were estimated using a nonlinear mixed effect model. NONMEM 7.2, PLT tools (www.pltsoft.com/), and PKPD tools (www.pkpdtools.com/doku.php) were used for PK analysis and simulations.

Results: There were no differences in background characteristics and clinical outcomes between the two groups ($P > 0.05$). The PK dataset contained 84 venous plasma dexmedetomidine concentrations from 16 patients (1 male, 15 female). The age, weight and Body Mass Index ranges were 25–64 yo, 45–71 kg, and 16.9–27.0 kg/m^2 respectively. PK models reported by Hannivoort et al [6] and Lee et al [2] predicted dexmedetomidine concentrations well, although performances of other models were out of the acceptable range (Fig. 1). PKs of dexmedetomidine were described by a 2-compartmental model, with weight and age as significant covariates. The final PK parameter values were as follows: V1 = 22.6 L, V2 = 41.1 L, CL1 = $1.5 \times Age^{-0.23} \times (Weight / 70\ kg)^{0.75}$ L/min and CL2 = 1.2 L/min. The median performance error of the final model was -2% and the median absolute performance error was 11%.

Conclusion: In patients under spinal anesthesia, the clinical outcomes of dexmedetomidine in the TCI group were not significantly different compared with that in the recommended regimen group. The PK model reported by Hannivoort[6] performed the best. A population PK model was developed in this population.

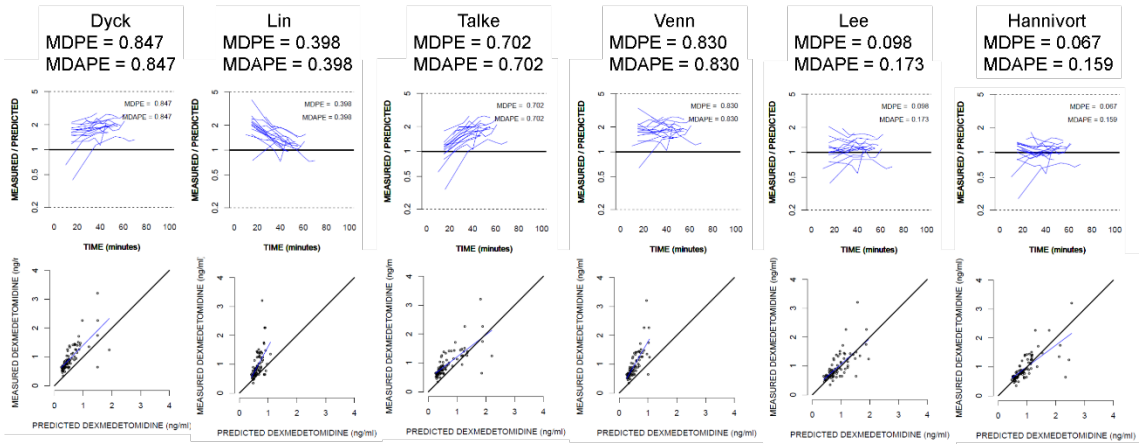

Figure 1. Measured/predicted values vs. time (top panels) and Measured vs. predicted dexmedetomidine concentrations (bottom panels) for six different pharmacokinetic models. MDPE = median performance error, MDAPE = median absolute performance error.

References:

1. Dyck JB et al. Anesthesiology. 1993;78:821-8.
2. Lee S et al. J Clin Pharm Ther. 2012;37:698-703.
3. Lin L et al. Acta Anaesthesiol Scand. 2011;55:359-67.
4. Venn RM et al. Br J Anaesth. 2002;88:669-75.
5. Talke P et al. Anesth Analg. 1997;85:1136-42.
6. Hannivoort LN et al. International Society For Anaesthetic Pharmacology Syllabus. [Abstract]. 2014.
7. Varvel JR et al. J Pharmacokinet Biopharm. 1992;20:63-94.