Pharmacokinetics of subcutaneously given dexmedetomidine in healthy adult volunteers

Uusalo P¹, Tilli I¹, Aantaa R^{†1}, Scheinin M² and Saari TI¹

¹Anaesthesiology and Intensive Care, University of Turku, Finland

²Pharmacology, Drug Development and Therapeutics, University of Turku, Finland

Background: Patients receiving palliative care often need sedation, and dexmedetomidine has been demonstrated to induce dose-dependent sedation without ventilatory depression. Our aim was to characterize the pharmacokinetics of subcutaneously administered dexmedetomidine in healthy adult volunteers.

Materials and methods:

- 10 volunteers, mean (SD) age 22,6 (2,2) years and body mass index 23,9 (1,5) kg m⁻²
- An open two-period, randomized cross-over design
- 1 µg/kg of dexmedetomidine either intravenously or subcutaneously
- Plasma dexmedetomidine concentrations were measured for 10 h after drug administration with validated HPLC-MS/MS
- Pharmacokinetic variables were calculated with standard non-compartmental methods
- The effects of subcutaneously administered dexmedetomidine on plasma catecholamine levels, vital signs and sedation were measured
- Local and systemic safety and tolerability of subcutaneously administered dexmedetomidine were recorded

Results:

- Mean C_{max} of dexmedetomidine was 2.42 ng/ml and 0.30 ng/ml, after i.v. and s.c. administration, respectively, but after 5 hours, similar plasma concentrations were measured during both phases (Figure 1)
- The mean exposure (AUC_{0-10h}) was 37 % smaller during the s.c. phase, but mean t_{1/2} was longer compared to the i.v. phase (1.9 h vs. 3.8 h) (Table 1)
- Reductions in plasma noradrenaline concentrations were significantly smaller (P = 0.03) after s.c. than after i.v. administration (Figure 2)
- Peak sedative effects were seen 30 min after the start of the i.v. infusion and 90 min after the s.c. administration (Figure 3)
- Subcutaneously administered dexmedetomidine was well tolerated

Conclusions: Dexmedetomidine is rapidly absorbed after subcutaneous administration and causes sedation with minimal sympatholysis.

Figure 1: Mean (SD) dexmedetomidine concentrations in plasma after administration of 1 µg/kg of dexmedetomidine intravenously (closed circles) to eight or subcutaneously (open circles) to ten healthy volunteers.

Table 1: Mean (SD) dexmedetomidine concentrations in plasma after administration of 1 µg/kg of dexmedetomidine intravenously to eight or subcutaneously to ten healthy volunteers.

	Intravenous dexmedetomidine	Subcutaneous dexmedetomidine
C _{max} (ng/ml)	2.4 (0.36)	0.30 (0.10)
t _{max} (min)	-	15 (15-240)
t _{1/2} (min)	113 (15)	230 (53)
AUC _{0-10h} (min ng/l)	2.0 (0.34)	1.2 (0.35)
CL (l/h)	41 (6.5)	54 (21) ¹
Vss (l)	92 (9.9)	286 (81) ²
F	-	61 (15)

All values are mean (SD), except t_{max} (median, range); ¹CL/F, ²Vz/F

Figure 2: Mean (SD) noradrenaline concentrations in plasma after administration of 1 µg/kg of dexmedetomidine intravenously (closed circles) to eight or subcutaneously (open circles) to ten healthy male volunteers.

Figure 3: Self-reported visual analogue scale (VAS) scores (mean and SD) of vigilance and performance after 1 µg/kg intravenous or subcutaneous doses of dexmedetomidine.

[†]Demised

This study was supported by research funds of Turku University Hospital (grant 13821)

Turun yliopisto
University of Turku