

Population pharmacokinetics of dexmedetomidine during long-term sedation in intensive care patients

T. Iirola^{1*†}, H. Ihmsen^{2†}, R. Laitio¹, E. Kentala¹, R. Aantaa¹, J.-P. Kurvinen³, M. Scheinin³, H. Schwilden², J. Schüttler² and K. T. Olkkola¹

¹ Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine, University of Turku and Turku University Hospital, Turku, Finland

² Department of Anesthesiology, University of Erlangen-Nürnberg, Erlangen, Germany

³ Department of Pharmacology, Drug Development and Therapeutics, University of Turku and Unit of Clinical Pharmacology, TYKSLAB, Turku, Finland

* Corresponding author. E-mail: tirola@utu.fi

Editor's key points

- Dexmedetomidine is widely used for sedation in the intensive care unit.
- There are few data on factors affecting its pharmacokinetics in this setting.
- Dexmedetomidine pharmacokinetics was affected by low cardiac output, increasing age, and low plasma albumin.
- Elimination half-life and context-sensitive half-time are prolonged in the elderly and by hypoalbuminaemia.

Background. Dexmedetomidine is a highly selective and potent α_2 -adrenoceptor agonist registered for sedation of patients in intensive care units. There is little information on factors possibly affecting its pharmacokinetics during long drug infusions in critically ill patients. We characterized the pharmacokinetics of dexmedetomidine in critically ill patients during long-term sedation using a population pharmacokinetic approach.

Methods. Twenty-one intensive care patients requiring sedation and mechanical ventilation received dexmedetomidine with a loading dose of 3–6 $\mu\text{g kg}^{-1} \text{h}^{-1}$ in 10 min and a maintenance dose of 0.1–2.5 $\mu\text{g kg}^{-1} \text{h}^{-1}$ for a median duration of 96 h (range, 20–571 h). Cardiac output (CO), laboratory and respiratory parameters, and dexmedetomidine concentrations in arterial plasma were measured. The pharmacokinetics was determined by population analysis using linear multicompartment models.

Results. The pharmacokinetics of dexmedetomidine was best described by a two-compartment model. The population values (95% confidence interval) for elimination clearance, inter-compartmental clearance, central volume of distribution, and volume of distribution at steady state were 57.0 (42.1, 65.6), 183 (157, 212) litre h^{-1} , 12.3 (7.6, 17.0), and 132 (96, 189) litre. Dexmedetomidine clearance decreased with decreasing CO and with increasing age, whereas its volume of distribution at steady state was increased in patients with low plasma albumin concentration.

Conclusions. The population pharmacokinetics of dexmedetomidine was generally in line with results from previous studies. In elderly patients and in patients with hypoalbuminaemia, the elimination half-life and the context-sensitive half-time of dexmedetomidine were prolonged.

Keywords: dexmedetomidine; intensive care; pharmacokinetics; population

Accepted for publication: 4 November 2011

Patients treated in intensive care units (ICUs) often require sedation and analgesia to tolerate the tracheal tube, artificial ventilation, and other procedures. However, sedation regimens may have adverse effects on recovery.¹ An ideal sedative agent should have minimal cardiovascular and respiratory side-effects, rapid onset and offset of action, no accumulation in renal or hepatic dysfunction, no active metabolites, and no adverse interactions with other drugs used in intensive care.

No currently available drug completely fulfils the properties of an ideal sedative for intensive care. Dexmedetomidine is a highly selective, potent α_2 -adrenoceptor agonist

registered for sedation of initially intubated patients in ICUs and sedation of non-intubated patients before and/or during surgical and other procedures. In addition to providing sedation and anxiolysis, α_2 -agonists have analgesic qualities and reduce stress responses to surgery and intensive care procedures.² Although the pharmacokinetics of dexmedetomidine have been investigated also in the ICU setting,³ there is no information on its pharmacokinetics after long-lasting (>48 h) infusions and only little information on factors affecting its pharmacokinetics in critically ill patients. Inclusion of covariates can help individualize dosing and might be particularly useful for model-based administration

[†]These authors contributed equally to this work.

like target-controlled infusion.⁴ The aim of this explorative study was to investigate the pharmacokinetics of dexmedetomidine during long-term sedation in ICU patients with special regard to covariate effects using a population pharmacokinetic approach, with the hypothesis that inclusion of covariates would significantly improve the accuracy of the pharmacokinetic model.

Methods

Subjects

This study (EudraCT number 2007-002932-27/ClinicalTrials.gov identifier NCT00714857) was conducted in the ICU of Turku University Hospital (Finland). It was approved by the Ethics Committee of the Hospital District of Southwest Finland and by the Finnish Medicines Agency. It was conducted according to the revised Declaration of Helsinki of the World Medical Association and ICH GCP guidelines for good clinical trial practice.

Study design

All patients older than 18 yr and needing light to moderate sedation for at least 48 h were eligible for the study. Written informed consent was obtained from legal representatives of potential study subjects. Patients with a history of intolerance to dexmedetomidine or related compounds and additives or with significant haematological, endocrine, metabolic, or gastrointestinal disease were excluded.

Study treatment

Subjects received a loading dose of 3–6 $\mu\text{g kg}^{-1} \text{h}^{-1}$ dexmedetomidine (dexmedetomidine 100 $\mu\text{g ml}^{-1}$, Precedex[®] Abbott Laboratories, North Chicago, IL, USA) in 10 min followed by continuous infusion of 0.1–2.5 $\mu\text{g kg}^{-1} \text{h}^{-1}$ for as long as the responsible physician deemed necessary. The dosage was selected on the basis of clinical need and was adjusted as considered necessary to maintain optimal sedation. As concomitant treatment, subjects received standard care of the unit, which included administration of oxycodone, fentanyl, or remifentanyl for pain relief and propofol, midazolam, lorazepam, or haloperidol for control of the level of consciousness. Heart rate and systolic and diastolic arterial pressure were continuously monitored. Cardiac output (CO) was determined intermittently using the thermodilution method shortly before and 0.5, 1, and 2 h after the start of the dexmedetomidine infusion, and then at least three times daily simultaneously with blood sampling, for as long as the subject had a pulmonary artery catheter.

Blood sampling and drug analysis

Arterial blood samples (2 ml) were collected into EDTA tubes immediately before the loading dose and 5, 7.5, 10, 15, 20, 30, 45, 60, 90, and 120 min after commencement of the dexmedetomidine infusion. Thereafter, samples were collected three times daily at 6–10 h intervals. Samples were kept at +4°C until centrifugation, and plasma was frozen at –30°C

immediately after separation. The samples were later stored at –70°C until analysis. Blood sampling for other laboratory parameters was performed as part of the routine care, usually in the mornings.

The reference compound in the drug concentration analysis was dexmedetomidine HCl and the internal standard was deuterated medetomidine (²H₆-medetomidine HCl), both provided by Orion Pharma (Espoo, Finland). Sample preparation was performed using solid-phase extraction. Plasma aliquots of 0.10 ml were mixed with 0.85 ml of 0.1% formic acid in water and 50 μl of internal standard solution and extracted with Sep-Pak[®] Vac 1cc (100 mg) tC18 cartridges (Waters Corporation, Milford, MA, USA). After loading, the cartridges were washed with 1.5 ml of 20% methanol in water and dried with air for about 10 s. Elution was with 1.0 ml of a 1:1 mixture of methanol and acetonitrile. Extracts were evaporated to dryness with a gentle stream of nitrogen and the dry residue was dissolved in 0.10 ml of a solution containing 0.1% formic acid and water, methanol, and acetonitrile in equal proportions.

Isocratic HPLC separation was performed with a Phenomenex Gemini C₁₈ 150 × 2.0 mm (5 μm) column (Torrance, CA, USA) and a mobile phase consisting of methanol and 0.1% formic acid in water (140:80; flow rate 220 $\mu\text{l min}^{-1}$) at 28°C. Mass spectrometric detection was carried out with an Applied Biosystems API 4000 triple-quadrupole instrument (AB SCIEX, Foster City, CA, USA), using positive ion spray ionization and multiple reaction monitoring. The needle potential was set to 5.3 kV, the temperature of the heated purified air was 500°C, and the flow was set to 40. The declustering potential was set to 62 V and entrance potential to 10 V. The collision energy was set to 30 V. Nebulizer gas (purified air) was set to 40, curtain gas (nitrogen) was set to 35, and collision gas (nitrogen) was set to 4.0. The precursor ion–fragment ion pairs detected were m/z 201.1–95.0 for dexmedetomidine and m/z 206.2–95.1 for the internal standard. Quantitation was based on peak area ratios of the analyte and the internal standard. Data collection and analysis were done with Applied Biosystems Analyst 1.4.1 software.

The assay was validated in the context of a previous study.⁵ It was linear over a concentration range from 0.020 to 10.0 ng ml^{-1} . Within-run precision was assessed using six determinations per dexmedetomidine concentration at four concentrations (0.020, 0.060, 0.90, and 8.0 ng ml^{-1}) and was found to be acceptable (the coefficient of variation was 9.5% at 0.020 ng ml^{-1} and 1–3% at other concentrations). The between-batch precision was also evaluated at the same concentrations and was found to be excellent (the coefficient of variation was 4% at 0.020 ng ml^{-1} and 1–4% at the other concentrations).

Pharmacokinetic analysis

The time courses of the dexmedetomidine concentrations were analysed using a linear mammillary model with two or three compartments, using non-linear mixed-effect

modelling (NONMEM 7.1.2, ICON Development Solutions, Ellicott City, MD, USA).⁶ Pharmacokinetic models were parameterized using elimination and inter-compartmental (distributional) clearances and volumes of distribution. The inter-individual variability of the pharmacokinetic parameters was modelled by exponential random effects: $\theta_i = \theta_{POP} \times e^{\eta_i}$, where θ_i is the parameter value in the i th subject, θ_{POP} is the population value of this parameter, and η is a random variable with a mean of zero and a variance of ω_i^2 . The residual intra-individual variance was modelled using a combined proportional and additive error model: $C_{mij} = C_{prij} + C_{prij} \cdot \varepsilon_{ij1} + \varepsilon_{ij2}$, where C_{mij} is the j th measured concentration in the i th subject, C_{prij} is the corresponding predicted value, and ε_1 and ε_2 are random variables with means of zero and variances of σ_1^2 and σ_2^2 . The first-order conditional estimates algorithm with η - ε interaction was used.

Statistical analysis

Goodness of fit was judged by residual plots, by the objective function value (OFV) which is minimized in the fitting procedure, and by the median prediction error, MDPE=median{PE_{ij}}, and the median absolute prediction error, MDAPE=median{|PE_{ij}|}, where PE_{ij} is the prediction error PE_{ij} = (C_{mij} - C_{prij})/C_{prij}. Statistical comparison of the two models was performed using the difference in the OFV (Δ OFV). In order to consider multiple testing, we used a more conservative significance level of $P < 0.01$ which corresponds to Δ OFV > 6.6 for one degree of freedom.

Covariate analysis

We evaluated the effects of subject age, sex, body mass, height, BMI, and lean body mass on dexmedetomidine pharmacokinetics. We further investigated the effects of CO, plasma bilirubin and albumin concentrations, PaO₂/FIO₂, and renal replacement therapy. Renal function was assessed by estimating the glomerular filtration rate (GFR) from creatinine concentrations, using the formula⁷

$$\text{GFR} = 186 \times 88.4^{1.154} \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} (\times 0.742 \text{ if female})$$

First, the model was estimated without covariates. The individual Bayesian estimates of the model parameters were plotted against the covariates and assessed for a covariate influence using linear regression. Covariates with an effect on a model parameter were then included step by step in the model, using a linear relationship which was centred around the median value of the covariate:

$$\theta_i = \hat{\theta} \times \left(1 + \theta_{cov} \times \frac{\text{COV}_i - \text{COV}_{\text{median}}}{\text{COV}_{\text{median}}} \right)$$

where $\hat{\theta}$ is the value of the parameter θ in the 'average' subject with a covariate value equal to the median value COV_{median} of the studied individuals. COV_{*i*} denotes the individual value of the covariate and θ_{cov} is the covariate

parameter that quantifies the magnitude of the covariate effect. For those covariates with multiple measurements within a subject (albumin concentration, GFR, PaO₂/FIO₂, CO, etc.), each measurement was used in the modelling assuming a stepwise change, that is, that the value remained constant between two measurements. A covariate effect was assumed to be significant if the OFV was significantly improved and if the 95% confidence interval (CI) of θ_{cov} did not include zero. After the full model with all covariate effects was developed, each covariate effect was tested again for significance by fixing the corresponding parameter $\theta_{cov} = 0$.

Model validation and simulations

For model validation and in order to obtain non-parametric 95% CIs of the model parameters, we performed a bootstrap analysis with 1000 replicates (by subject with replacement). To illustrate the covariate effects, we estimated the time for a 50% concentration decrement after the termination of the continuous drug infusion (context-sensitive half-time)⁸ for fictive subjects having different covariate values, based on the 25%, 50%, and 75% quartiles of the covariate distributions within the study population. In order to compare our results with those of previous studies, we further estimated the context-sensitive half-time for a typical subject of this study population (age: 60 yr, albumin concentration: 14 g litre⁻¹, height: 174 cm) using pharmacokinetic models of dexmedetomidine reported in the literature.^{3 9-11}

Results

Twenty-one ICU patients were included in the study and 534 blood samples were drawn for determination of dexmedetomidine concentrations (Fig. 1). The median duration of dexmedetomidine infusions was 96 h (range, 20–571 h). The subject characteristics and sedation data are summarized in Table 1.

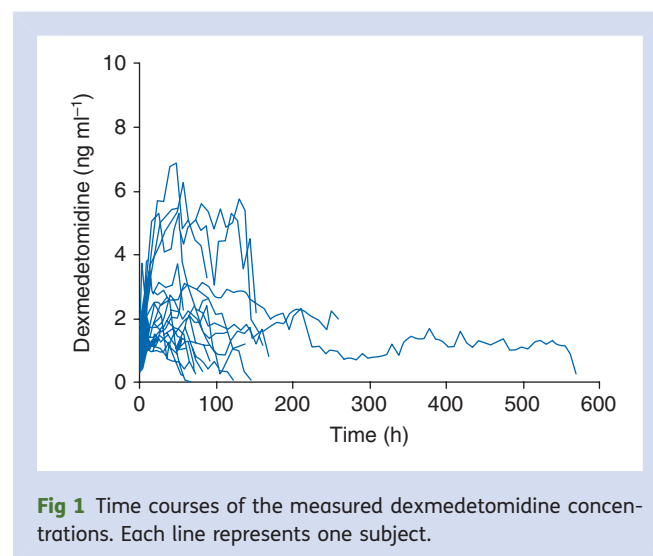
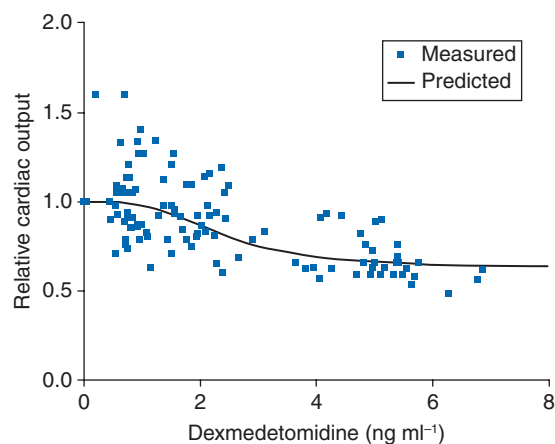


Fig 1 Time courses of the measured dexmedetomidine concentrations. Each line represents one subject.

Table 1 Subject and sedation characteristics. Values are reported as median (range) unless specified otherwise

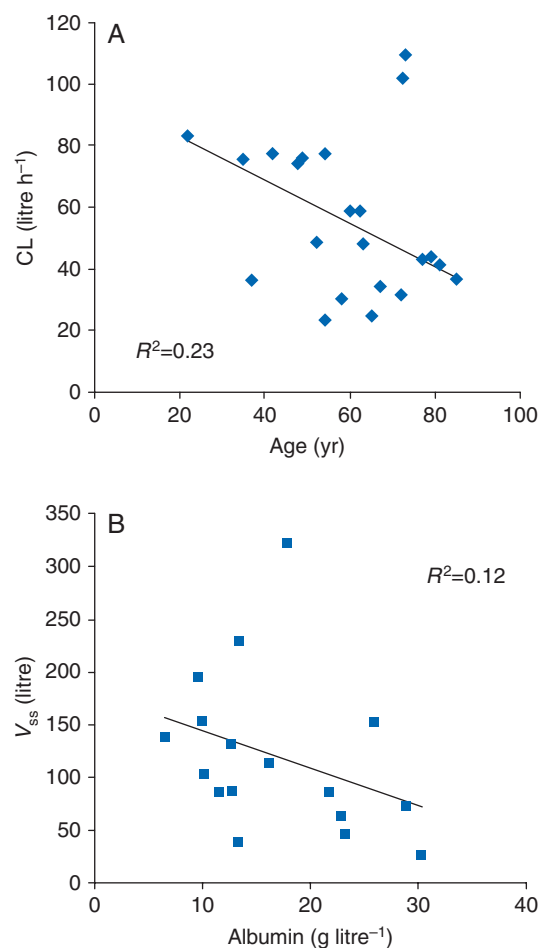
Characteristic	Value
Sex (male/female; n)	16/5
Age (yr)	60 (22–85)
Body weight (kg)	85 (53–120)
Height (cm)	174 (160–181)
BMI (kg m ⁻²)	27.8 (19.9–37.0)
Lean body mass (kg)	60 (41–75)
Plasma albumin (g litre ⁻¹)	13.5 (6.6–30.3)
Plasma bilirubin (μmol litre ⁻¹)	10.2 (0–90)
Plasma creatinine (μmol litre ⁻¹)	72 (32.6–232)
<i>P</i> a _{O₂} / <i>F</i> iO ₂ (kPa)	28.8 (15.8–50.2)
Duration of dexmedetomidine infusion (h)	96 (20–571)
Infusion rate of dexmedetomidine (μg kg ⁻¹ h ⁻¹)	1.25 (0.57–2.12)

**Fig 2** Baseline-normalized relative CO (baseline=1) vs measured dexmedetomidine concentration. The solid black line shows the prediction of the sigmoid model, fitted to the data.

A two-compartment model was adequate to describe the pharmacokinetics of dexmedetomidine. A three-compartment model yielded only a slightly better fit ($\Delta\text{OFV}=12.3$, $P=0.015$) with large standard errors and large inter-individual variances.

Covariate effects

The covariates of body weight, height, BMI, lean body mass, and sex had no significant effects on dexmedetomidine pharmacokinetics. Only eight subjects had enough data for the assessment of the effect of CO on the model. As dexmedetomidine itself reduces CO,¹² we used the following approach: the normalized measured cardiac output $\text{RCO}=\text{CO}/\text{CO}_{\text{baseline}}$ was plotted against the corresponding measured dexmedetomidine concentration (Fig. 2), and a sigmoid

**Fig 3** Scatter plots of the individual Bayesian estimates of clearance vs age (A) and of volume of distribution at steady-state vs albumin concentration (B). Each data point represents one subject. In four subjects, no albumin concentrations were available. Multiple albumin concentration measurements within one subject were averaged. The solid black line was obtained by linear regression analysis; R^2 is the corresponding regression coefficient.

function was fitted to the data by population analysis: $\text{RCO} = 1 - 0.37 \times C^{3.15} / (C^{3.15} + 2.40^{3.15})$.

For those subjects without CO measurements, estimates of RCO were calculated for each measured dexmedetomidine concentration using this formula. Dexmedetomidine clearance significantly decreased with decreasing RCO, and a non-linear relationship described best the CO effect on clearance:

$$\text{CL} = \hat{\text{CL}} \times \text{RCO}^{0.5} \quad (\Delta\text{OFV} = 142.9, P < 0.0001)$$

Dexmedetomidine clearance decreased with age (Fig. 3A, $\Delta\text{OFV}=6.9$, $P=0.009$), whereas the other parameters did not show significant age effects. Dexmedetomidine clearance also decreased slightly with decreasing GFR. Age and GFR are, however, strongly intercorrelated as the formula

used to estimate GFR includes age. We therefore decided to use only age but not GFR as a covariate for clearance.

The distribution volume at steady state, V_{ss} , showed a significant increase with decreasing albumin concentrations (Fig. 3B, $\Delta OFV=9.7$, $P=0.002$), whereas the other parameters did not show significant albumin effects. V_{ss} also increased with decreasing Pa_{O_2}/F_{IO_2} , but as the albumin concentration and Pa_{O_2}/F_{IO_2} were positively associated in our subjects ($r=0.70$), we decided to use only the albumin concentration as a covariate for V_{ss} .

Plasma bilirubin concentrations had no significant influence on dexmedetomidine pharmacokinetics. Three subjects received renal replacement therapy with haemodialysis or haemodiafiltration, but this had no significant effect on the pharmacokinetics of dexmedetomidine.

Thus, the final pharmacokinetic model was as follows:

$$CL = \theta_1 \times \left(1 + \theta_6 \frac{\text{age} - 60}{60}\right) \times RCO^{0.5}$$

$$Q = \theta_2$$

$$V_1 = \theta_3$$

$$V_{ss} = \theta_4 \times \left(1 + \theta_7 \frac{\text{albumin} - 14}{14}\right)$$

with the albumin concentration measured in g litre⁻¹. The parameter estimates for this final model are summarized in Table 2, and Figure 4 shows the plot of the measured concentrations vs the individual and population predictions. For the average subjects of this study, the half-lives of dexmedetomidine (95% CI) were $t_{1/2\alpha}=2.0$ (1.2, 2.8) min and $t_{1/2\beta}=122$ (86, 192) min. Comparing the final model with the simple two-compartment model without any covariates,

the MDPE decreased from -5.9% to -3.7% , and the MDAPE decreased from 33.5% to 21.7%.

Simulations

To illustrate the covariate effects, we simulated the pharmacokinetic parameters and the context-sensitive half-time for fictive subjects of different ages and having different albumin concentrations. Table 3 and Figure 5 show that the elimination half-life and the context-sensitive half-life of dexmedetomidine were increased in elderly patients and also in patients with a low albumin concentration. Simulations of the context-sensitive half-times for a typical subject calculated with the final pharmacokinetic model of this study and with pharmacokinetic models from the literature yielded similar results for the different models, with the exception of the model by Dyck and colleagues⁹ which predicted a much longer context-sensitive half-time (Fig. 6).

Haemodynamics

During the first 24 h of dexmedetomidine infusion, the average heart rate decreased, whereas the averages of systolic and diastolic arterial pressure remained constant throughout the study (Fig. 7). The maximum decreases/increases in heart rate in an individual subject [mean (sd)] were 32 (16)% and 37 (43)%, respectively. The maximum decreases/increases in systolic arterial pressure in an individual subject were 29 (11)% and 41 (21)%, respectively. The maximum decreases/increases in diastolic arterial pressure in an individual subject were 28 (11)% and 39 (19)%, respectively.

Table 2 Results of the pharmacokinetic modelling. CL, total body clearance; Q, inter-compartmental clearance; V_1 , central volume of distribution; V_{ss} , steady-state volume of distribution

Variable	Estimate	SE	Bootstrap median	Bootstrap 95% CI
Population parameters				
$\theta_1 = \hat{CL}$ (litre h ⁻¹)	57.0	5.5	57.4	(42.1, 65.6)
$\theta_2 = \hat{Q}$ (litre h ⁻¹)	183	13	191	(157, 212)
$\theta_3 = \hat{V}_1$ (litre)	12.3	1.7	12.0	(7.6, 17.0)
$\theta_4 = \hat{V}_{ss}$ (litre)	132	20	128	(96, 189)
Covariate effects				
θ_5 (cardiac output on CL)	1.24	0.38	1.15	(0.34, 1.90)
θ_6 (age on CL)	-0.78	0.24	-0.73	(-1.26, -0.18)
θ_7 (albumin on V_{ss})	-0.51	0.02	-0.51	(-0.72, -0.07)
Inter-individual variability				
CL (%)	33.5	5.8	32.0	(21.7, 44.9)
Q (%)	25.1	5.2	23.9	(0.3, 35.5)
V_1 (%)	53.4	11.4	51.6	(30.2, 80.5)
V_{ss} (%)	65.0	9.8	60.7	(44.3, 80.9)
Residual variability				
Additive (ng ml ⁻¹)	0.017	0.003	0.017	(0.001, 0.025)
Proportional (%)	16.0	1.6	15.9	(12.9, 18.5)

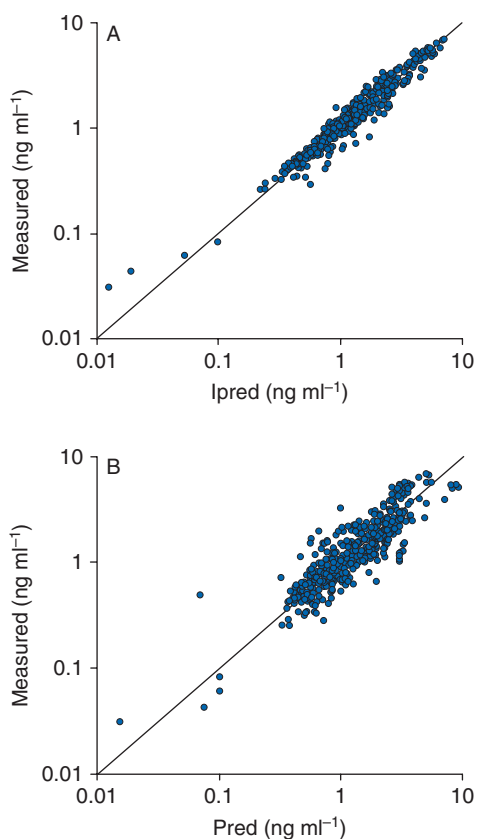


Fig 4 Measured dexmedetomidine concentrations vs the individual Bayesian predictions (A) and the population predictions (B), as obtained with the final pharmacokinetic model. The solid black line is the line of identity (measured=predicted).

Table 3 Subject characteristics used for simulation of context-sensitive half-life. CL, total body clearance; V_{ss} , steady-state volume of distribution; $t_{1/2\beta}$, elimination half-life

Characteristics	Age (yr)	Albumin (g litre ⁻¹)	CL (litre h ⁻¹)	V_{ss} (litre)	$t_{1/2\beta}$ (min)
Average age; average albumin	60	14	57.0	132	122
Younger; average albumin	40	14	71.8	132	102
Elderly; average albumin	80	14	42.2	132	155
Average age; lower albumin	60	10	57.0	151	140
Average age; higher albumin	60	20	57.0	103	94

Discussion

We investigated the pharmacokinetics of dexmedetomidine during long-term sedation in adult intensive care patients with a focus on the effects of covariates. Dexmedetomidine

concentrations could be adequately described by a two-compartment model with significant covariate effects mainly influencing the elimination clearance and the volume of distribution at steady state. That a three-compartment model was not superior to the two-compartment model might largely have been caused by the limitation that, due to practical reasons, the last blood sample was drawn only a few hours after or in some cases even shortly before discontinuing the dexmedetomidine infusion. Interestingly, in another study conducted in intensive care patients, dexmedetomidine pharmacokinetics could also be adequately described by a two-compartment model, even if the last sample was taken 24 h after the end of the infusion.³ In that study, the authors reported an elimination clearance rate of 49.2 litre h⁻¹, a distribution clearance rate of 135 litre h⁻¹, a volume of distribution of 149 litre, and an elimination half-life of 3 h, which are similar to those found in our study. The current estimates of the pharmacokinetic variables are also quite close to the values observed earlier in female surgical patients undergoing transsphenoidal pituitary hypophysectomy.¹¹ For the central volume of distribution, the values reported in the literature show a broad range from 8.0 litre in the study of Dyck and colleagues⁹ up to 63.4 litre in the study of Lin and colleagues.¹⁰ The estimate of 12.3 litre in the present study is within this range, and one has to consider that the estimate of V_1 depends on the sampling site (arterial or venous), on the time of the first samples, and on the administration scheme (bolus or infusion).

The context-sensitive half-times predicted by the models from different studies were quite similar (Fig. 6), with the exception of the study by Dyck and colleagues.⁹ The much longer context-sensitive half-time obtained with this model was mainly caused by the very small value of 27.0 litre h⁻¹ for the elimination clearance. However, experimental design strongly affects the pharmacokinetic estimates. In the study by Dyck and colleagues,⁹ sampling was performed until 24 h after stopping of infusion with high time resolution, whereas in most other studies, sampling periods have been shorter. Interestingly, the context-sensitive half-time obtained with the pharmacokinetic parameters of Venn and colleagues³ was similar to our results, although they also sampled for 24 h after stopping infusion, but with lesser time resolution than Dyck and colleagues.⁹

Whereas the results for the 'average' subject in the present study are quite similar to those of previous studies, the covariate effects are to some extent novel findings. Only very few covariate effects have been identified in previous studies: no effects of age, sex, body weight, lean body mass, and body surface area have been reported. Whereas Dyck and colleagues⁹ found only a small effect of height on dexmedetomidine clearance, the recent study of Lin and colleagues¹⁰ reported a distinct increase in dexmedetomidine clearance with height. The influence of height was described by a power model: $CL=0.47*(height/160\text{ cm})^{6.42}$, which means that for a subject of 180 cm, dexmedetomidine clearance would be more than twice the value for a subject

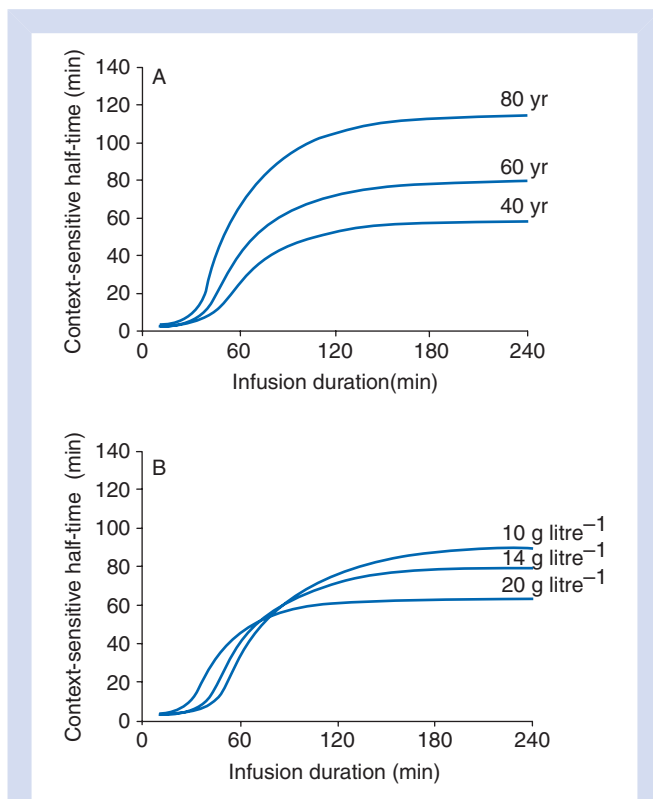


Fig 5 Simulations of the time for a 50% concentration decrement after termination of a continuous drug infusion (context-sensitive half-time) for fictive subjects having (A) different age and an equal plasma albumin concentration of 14 g litre⁻¹, and (B) different albumin concentration and an equal age of 60 yr (Table 3).

of 160 cm. Unfortunately, the authors did not report a standard error or a CI for the very large exponent, so that one cannot judge the reliability of this model. The large height effect may also in part be explained by ethnic differences, as this study was conducted in China. Some studies included too few subjects to detect covariate effects with modest effect sizes.³ In the study of Dyck and colleagues,⁹ the range of the healthy volunteer subjects' characteristics (27–44 yr, 60–98 kg, $n=16$) was rather small. The present study included more subjects ($n=21$) with a broader range of covariate values. In our study, there was a positive association of CO with dexmedetomidine clearance, which supports the assumption that hepatic blood flow influences the clearance of dexmedetomidine.¹²

Other studies give little information on the effects of laboratory covariates describing organ function (albumin, bilirubin, creatinine) and respiratory function on the pharmacokinetics of dexmedetomidine. De Wolf and colleagues¹³ studied the effect of renal impairment in otherwise healthy subjects and found no difference between the control group with an average creatinine clearance of 122 ml min⁻¹ and the diseased group with a mean creatinine clearance of 21 ml min⁻¹. We observed a slight effect of renal impairment, as assessed by GFR, on dexmedetomidine

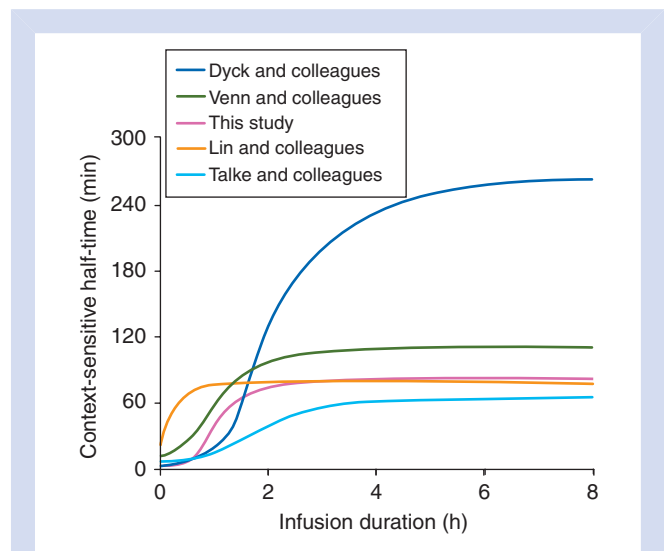


Fig 6 Simulations of the time for a 50% concentration decrement after termination of a continuous drug infusion (context-sensitive half-time) for a typical subject of this study (age: 60 yr, albumin concentration: 14 g litre⁻¹, height: 174 cm) using the pharmacokinetic models of this study and of the studies by Lin and colleagues,¹⁰ Dyck and colleagues,⁹ Talke and colleagues,¹¹ and Venn and colleagues.³

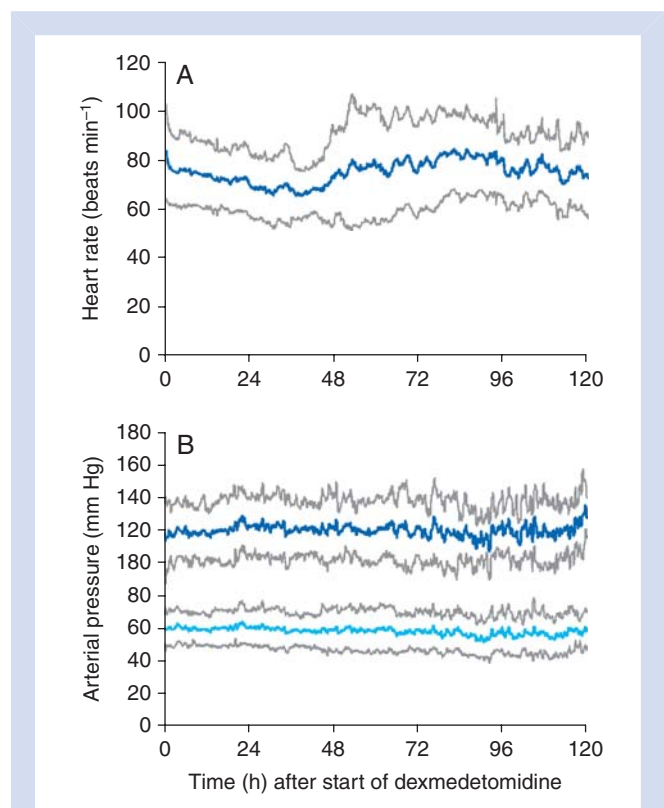


Fig 7 Time courses of heart rate (A) and of systolic (dark blue) and diastolic (light blue) arterial pressure during dexmedetomidine infusion (B). Data are shown as mean (SD).

clearance. GFR was, however, not included in the model, as drug clearance decreased with age and GFR was estimated using a formula which includes age. Thus, one cannot clearly distinguish between the age effect and the effect of renal impairment. Decreasing clearance of dexmedetomidine with age has not been reported previously, but at close inspection of the data of Venn and colleagues,³ dexmedetomidine clearance appears to decrease from 72.3 litre h⁻¹ in the youngest subject of 35 yr to 37.7 litre h⁻¹ in the oldest subject aged 80 yr, with a negative correlation ($r = -0.71$, $P = 0.02$) between age and clearance.

The effect of albumin concentration on the volume of distribution of dexmedetomidine could reflect altered protein binding in plasma. Dexmedetomidine is rather highly (94%) bound to plasma proteins,¹⁴ and a decreased albumin concentration would cause a higher proportion of unbound dexmedetomidine in blood, which then results in a larger volume of distribution. Clearance of dexmedetomidine, on the other hand, was not associated with the albumin concentration, which might be explained by dexmedetomidine being a high-extraction drug, the clearance of which is mainly determined by liver blood flow but less by protein binding.¹²

Interestingly, there was no association between the plasma bilirubin concentration and dexmedetomidine clearance, although dexmedetomidine is mainly metabolized by the liver. The most probable reason for this is that plasma bilirubin is only a weak indicator of liver function. Furthermore, for a high-extraction drug like dexmedetomidine, hepatic clearance is mainly determined by liver blood flow and less by intrinsic liver function. Additionally, our study did not include patients with severely impaired liver function.

The clinical relevance of the covariate effects was studied by simulations. The simulations demonstrated that in elderly patients and in patients with hypoalbuminaemia, the terminal half-life and context-sensitive half-time of dexmedetomidine are prolonged (Table 3 and Fig. 5). This could result in prolonged sedation. For long-term drug dosing, the most important parameter is the elimination clearance as the infusion rate at steady state is given by $I_{ss} = C_{target} \times CL$, where C_{target} is the targeted plasma concentration. Table 3 shows that clearance in an 80-yr-old subject was about 25% smaller than in a 60-yr-old. Consequently, the steady-state infusion rate for elderly patients should be reduced to achieve similar dexmedetomidine concentrations. One should be aware of potentially increased pharmacodynamic effects and longer lasting action when prescribing dexmedetomidine to elderly patients or to patients with marked hypoalbuminaemia.

Hypotension and bradycardia have been reported in association with dexmedetomidine infusions.¹⁵ Additionally, transient hypertension has been observed primarily during the loading phase.¹⁶ Previous studies on the haemodynamic effects of dexmedetomidine have reported an average maximum decrease in heart rate of 29%¹⁷ and a maximum decrease in mean arterial pressure of 27%.¹⁶ Similarly, the heart rate of our subjects decreased after starting the dexmedetomidine infusion, but we observed no changes in

average arterial pressures. However, one of the aims in intensive care is to keep haemodynamics stable using various methods, and therefore, we do not know whether the stability of arterial pressure is associated with the use of dexmedetomidine or other interventions. Therefore, one should not draw any definitive conclusions on the haemodynamic effects of dexmedetomidine based on the current study.

The present study has several limitations. First, the short post-infusion sampling period did not allow the use of a three-compartment model, which might generally be more adequate to characterize the pharmacokinetics of dexmedetomidine. Secondly, the covariates of the subjects were partially inter-correlated, so that one cannot directly say which physiological mechanisms relate to each of the covariate effects. Therefore, the sum of these covariate effects might be regarded as a descriptor of the general condition of the subject, including the effect of age. One should also not extrapolate the covariate effects beyond the ranges of the characteristics of the subjects and the sedation regimens within this study. Thirdly, one has to consider possible drug interactions. In the present study, the large number of concomitantly administered drugs made it impossible to systematically evaluate the possible effects of concomitant medications on the pharmacokinetics or pharmacodynamics of dexmedetomidine. Although the MDPE could be reduced from -5.9% to -3.7% by including covariate effects, the remaining residual bias for the final population model indicates that some unexplained covariate effects might exist. However, we did not want to include covariate effects that were hard to justify on a physiological basis, such as the effect of $Pa_{O_2}/F_{I_{O_2}}$ on the steady-state volume of distribution.

In conclusion, even after long-term sedation of several days, the average population pharmacokinetics of dexmedetomidine in ill ICU subjects was similar to that found in studies of much shorter duration. Age and plasma albumin concentrations influenced the pharmacokinetics of dexmedetomidine such that elderly subjects showed decreased drug clearance and subjects with hypoalbuminaemia showed an increased volume of distribution, both of which caused prolongation of elimination half-life. The results of this study should help to generate hypothesis-based studies in order to test the clinical relevance of these findings.

Acknowledgements

The nurses of the intensive care unit are acknowledged for their invaluable help in collection of blood samples during night-time.

Declaration of interest

T.I., R.L., E.K., R.A., and K.T.O. have ongoing contract research relationships with Orion Corporation (Espoo, Finland), the original developer of dexmedetomidine. T.I. has received speaker fees from Orion Corporation. R.A. has been a paid consultant for Orion Corporation and Abbott Laboratories (Abbott Park, IL, USA), the original co-developers of

dexmedetomidine, as well as for Hospira (Lake Forest, IL, USA). Hospira has a license agreement with Orion Corporation concerning dexmedetomidine (Precedex®). J.-P.K. has been engaged in contract research for Orion Corporation and Hospira. The laboratory of M.S. has contract research relationships with Orion Corporation and Hospira. M.S. has also received speaker fees and consulting fees from Orion Corporation.

Funding

This work was supported by Turku University Hospital research funds (grant number 13821), Turku, Finland.

References

- Devlin JW, Mallow-Corbett S, Riker RR. Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. *Crit Care Med* 2010; **38**: S231–43
- Hayashi Y, Maze M. Alpha 2 adrenoceptor agonists and anaesthesia. *Br J Anaesth* 1993; **71**: 108–18
- Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. *Br J Anaesth* 2002; **88**: 669–75
- Struys MM, Sahinovic M, Lichtenbelt BJ, Vereecke HE, Absalom AR. Optimizing intravenous drug administration by applying pharmacokinetic/pharmacodynamic concepts. *Br J Anaesth* 2011; **107**: 38–47
- Snapir A, Posti J, Kentala E, et al. Effects of low and high plasma concentrations of dexmedetomidine on myocardial perfusion and cardiac function in healthy male subjects. *Anesthesiology* 2006; **105**: 902–10
- Beal S, Sheiner LB, Boeckmann A, Bauer RJ. *NONMEM User's Guides* (1989–2009). Ellicott City, MD: Icon Development Solutions, 2009
- Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; **139**: 137–47
- Hughes MA, Glass PS, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* 1992; **76**: 334–41
- Dyck JB, Maze M, Haack C, Azarnoff DL, Vuorilehto L, Shafer SL. Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology* 1993; **78**: 821–8
- Lin L, Guo X, Zhang MZ, Qu CJ, Sun Y, Bai J. Pharmacokinetics of dexmedetomidine in Chinese post-surgical intensive care unit patients. *Acta Anaesthesiol Scand* 2011; **55**: 359–67
- Talke P, Richardson CA, Scheinin M, Fisher DM. Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. *Anesth Analg* 1997; **85**: 1136–42
- Dutta S, Lal R, Karol MD, Cohen T, Ebert T. Influence of cardiac output on dexmedetomidine pharmacokinetics. *J Pharm Sci* 2000; **89**: 519–27
- De Wolf AM, Fragen RJ, Avram MJ, Fitzgerald PC, Rahimi-Danesh F. The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. *Anesth Analg* 2001; **93**: 1205–9
- Karol MD, Maze M. Pharmacokinetics and interaction pharmacodynamics of dexmedetomidine in humans. *Bailliere's Best Pract Res Clin Anaesthesiol* 2000; **14**: 261–9
- Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: a review of clinical applications. *Curr Opin Anaesthesiol* 2008; **21**: 457–61
- Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; **77**: 1134–42
- Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colino MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology* 2000; **93**: 382–94