

Development of an Optimized Pharmacokinetic Model of Dexmedetomidine Using Target-controlled Infusion in Healthy Volunteers

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ABSTRACT

Background: Several pharmacokinetic models are available for dexmedetomidine, but these have been shown to underestimate plasma concentrations. Most were developed with data from patients during the postoperative phase and/or in intensive care, making them susceptible to errors due to drug interactions. The aim of this study is to improve on existing models using data from healthy volunteers.

Methods: After local ethics committee approval, the authors recruited 18 volunteers, who received a dexmedetomidine target-controlled infusion with increasing target concentrations: 1, 2, 3, 4, 6, and 8 ng/ml, repeated in two sessions, at least 1 week apart. Each level was maintained for 30 min. If one of the predefined safety criteria was breached, the infusion was terminated and the recovery period began. Arterial blood samples were collected at preset times, and NONMEM (Icon plc, Ireland) was used for model development.

Results: The age, weight, and body mass index ranges of the 18 volunteers (9 male and 9 female) were 20 to 70 yr, 51 to 110 kg, and 20.6 to 29.3 kg/m², respectively. A three-compartment allometric model was developed, with the following estimated parameters for an individual of 70 kg: $V_1 = 1.78$ l, $V_2 = 30.3$ l, $V_3 = 52.0$ l, $CL = 0.686$ l/min, $Q_2 = 2.98$ l/min, and $Q_3 = 0.602$ l/min. The predictive performance as calculated by the median absolute performance error and median performance error was better than that of existing models.

Conclusions: Using target-controlled infusion in healthy volunteers, the pharmacokinetics of dexmedetomidine were best described by a three-compartment allometric model. Apart from weight, no other covariates were identified. (*ANESTHESIOLOGY* 2015; 123:357-67)

DEXMEDETOMIDINE is an α_2 -adrenoceptor agonist with sedative, analgesic, and anxiolytic properties. Patients receiving low doses of dexmedetomidine remain rousable despite otherwise appearing to be deeply asleep. This makes it a useful drug for conscious sedation, specific surgical procedures such as awake craniotomies, and sedation in intensive care units (ICUs). In experimental settings, dexmedetomidine is used in the context of “opioid-reducing anesthesia” techniques¹ and to attenuate perioperative inflammatory responses.² To compensate for the rather slow pharmacokinetic profile of the drug, which results in increasing plasma concentrations over time with fixed-rate infusions, target-controlled infusion (TCI) using an accurate pharmacokinetic model is likely to be helpful in managing and titrating sedation by maintaining stable and predictable plasma concentrations.

Few dexmedetomidine pharmacokinetic models have been developed with data from healthy volunteers. The Dyck model combines pharmacokinetic data derived from the studies of plasma concentrations after a bolus dose³ with data acquired during and after a computer-controlled

What We Already Know about This Topic

- Available pharmacokinetic models for dexmedetomidine underestimate plasma concentrations
- No available pharmacokinetic model for dexmedetomidine was able to include weight as a covariate

What This Article Tells Us That Is New

- A pharmacokinetic model for dexmedetomidine was developed using a target-controlled infusion targeting a wide range of concentrations in healthy volunteers of both sexes with a wide range of ages and weights
- The pharmacokinetics of dexmedetomidine was described by a three-compartmental model with only weight as a covariate
- A small initial distribution volume allows better estimates of high peak concentrations after rapid infusion

infusion.⁴ However, this is a very preliminary model, with height as the only covariate, and the model has been shown to be inaccurate at higher target concentrations.⁵ The Dutta model is derived from the data from a healthy population, using computer-controlled infusion with an unpublished

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model.⁶ Venous blood samples were used, although this is likely not an accurate measurement of drug delivery to target organs in non-steady-state conditions, and may have influenced the accuracy of the parameters of the Dutta model. Most of the existing pharmacokinetic models for dexmedetomidine were obtained from trials involving postoperative and/or ICU patients, using either computer-controlled infusion with an unpublished model⁷ or continuous infusion.^{8–10} This approach is sensitive to the influence of confounding drugs such as subtherapeutic levels of anesthetic drugs, additional sedation or analgesia, and other medications. The resulting pharmacokinetic models are thus less applicable to single drug pharmacokinetic modeling. Of the available “ICU” models, the Talke model⁷ is often used, but similar to the Dyck model, it also has been shown to underestimate plasma concentration at higher target concentrations of dexmedetomidine.¹¹ Shafer *et al.*¹² suggested that using TCI administration during model development may provide more appropriate parameters for use in subsequent TCI. Only the Dyck, Dutta, and Talke models used TCI administration (Dutta and Talke used unpublished models) for model development.

For these reasons, we believe that some improvement is desirable for pharmacokinetic models of dexmedetomidine. The aim of this study is to develop a pharmacokinetic model for dexmedetomidine, using TCI administration in healthy volunteers, using data from a population with a wide range of ages and weights and a wide range of drug concentrations.

Materials and Methods

The study was approved by the local Medical Ethics Review Committee (University Medical Center Groningen, Groningen, The Netherlands; Medical Ethics Review Committee number: 2012/400) and was registered in the ClinicalTrials.gov database (NCT01879865). Written informed consent was obtained from 18 healthy volunteers, who were recruited and screened by QPS (a contract research organization based in Groningen, The Netherlands). Subjects were stratified according to age and sex (6 subjects, 3 male and 3 female, for each age group: 18 to 34 yr, 35 to 54 yr, and 55 to 72 yr). Inclusion criteria were American Society of Anesthesiologists physical status I, absence of any medical history of significance, and absence of chronic use of medication (oral contraceptives excluded), alcohol, drugs, or tobacco. Exclusion criteria were known intolerance to dexmedetomidine and body mass index (BMI) less than 18 kg/m² or greater than 30 kg/m². Women who were pregnant or nursing were also excluded. Subjects were instructed not to use medication or drugs in the 2 weeks before the study days, not to drink coffee or alcohol or smoke tobacco in the 2 days before each study day, and to fast from 6 h before the start of the study. To study the intraindividual variability of pharmacokinetic estimations more effectively, the volunteers were enrolled in two separate sessions, at least 1 week and at most

3 weeks apart. We hypothesized that there may be a difference between the first and second sessions due to currently unknown but identifiable causes such as the variation in level of anxiety or adrenergic tone between sessions.

Monitoring

An 18- or 20-gauge IV cannula was placed in a vein on the subject's nondominant arm or hand. A 20-gauge arterial cannula was placed in the radial artery of the same arm under local anesthesia (lidocaine 1%), using the Seldinger technique, and used for continuous arterial blood pressure monitoring and blood sampling. Standard anesthetic monitoring was performed using a Philips MP50 monitor (Philips Healthcare, The Netherlands). Noninvasive blood pressure was measured and recorded at 5-min intervals on the arm opposite the IV and arterial line. All subjects maintained spontaneous ventilation, with a nasal cannula (O₂/CO₂ Nasal Filterline®; Covidien, USA) for oxygen delivery as needed, from 0 to 4 l/min. Capnography was monitored by means of side-stream sampling through the nasal cannula (Microstream® carbon dioxide extension; Philips Healthcare).

All monitored parameters were captured by a computer running RUGLOOP II software (Demed, Belgium). RUGLOOP II also controlled the syringe pump (Orchestra® Module DPS; Orchestra® Base A; Fresenius Kabi, Germany) for dexmedetomidine administration.

Drug Infusion

Dexmedetomidine was delivered through TCI using the Dyck model.⁴ Computer simulations with the Dyck model were performed during study design to determine optimal infusion scheme and sampling times. Various sampling schedules were tested with 10 to 15 samples per patient. In each simulated sampling schedule, samples were included before each increase in target concentration and before the start of the recovery period. For each schedule, 1,000 sets of 20 patients were simulated, taking into account log-normally distributed interindividual variability of 40% and proportional residual variability of 20%. Each dataset was analyzed with NONMEM 7.2 (Icon plc, Ireland) (as described in the section Modeling) assuming log-normally distributed interindividual variability, and its performance was evaluated by calculating the root-mean-squared-error (RMSE, in percentage) of the estimated population values for V₁, CL, and the maximum value of all parameters (V₁, V₂, V₃, CL, Q₂, and Q₃) as measures of the precision of the estimated model parameters. The sampling times were varied until the lowest RMSE values were obtained. These simulations revealed that for more accurate determination of the central volume V₁, a short initial infusion was necessary, followed by the first TCI period starting at 10 min, with sampling times at 2 min and before the first TCI period. With 13 sampling points (excluding blank), the optimal sampling scheme (as described in the section Arterial Blood Sampling

and Dexmedetomidine Analysis) resulted in RMSEs of 23% (V1), 19% (CL), and a maximum of RMSE 36%.

The initial drug infusion was given at $6 \mu\text{g kg}^{-1} \text{h}^{-1}$ for 20 s. To ensure accurate infusion history for the TCI system, this infusion was controlled by the TCI steering algorithm (TCI target set to 1 ng/ml for 20 s, then returned to 0). After 10 min, TCI was restarted with stepwise increasing targets of 1, 2, 3, 4, 6, and 8 ng/ml. Each target was maintained for 30 min.

Because dexmedetomidine bolus doses can induce hypertension and reflex bradycardia, the infusion rate of dexmedetomidine was limited to $6 \mu\text{g kg}^{-1} \text{h}^{-1}$ for the first four steps using a limiting infusion rate algorithm as part of the TCI control system. For 6 and 8 ng/ml, the maximum infusion rate was increased to $10 \mu\text{g kg}^{-1} \text{h}^{-1}$ to facilitate reaching the target within a reasonable time.

The following criteria were used to ensure the safety of the subjects:

- 30% increase from baseline mean arterial blood pressure for more than 5 min;
- 30% decrease from baseline mean arterial blood pressure for more than 5 min;
- Heart rate less than 40 beats/min for more than 5 min;
- Changes in cardiac conduction or cardiac rhythm;
- Inability to maintain a patent airway and/or a decrease of oxygen saturation (SpO_2) less than 93% despite the use of simple airway maneuvers and/or supplementation of up to 4 l/min O_2 via nasal cannula;
- Modified Observer's Assessment of Alertness/Sedation score of 0 (no response to painful stimulus), as assessed before each increase in target concentration.¹³

If any of these criteria were met, or if the last TCI step was completed, dexmedetomidine infusion was halted, and the recovery period started, which lasted 5 h.

Arterial Blood Sampling and Dexmedetomidine Analysis

We performed simulations using the Dyck model to determine optimal sampling times for optimal model parameter estimations. Arterial blood samples were taken at baseline, 2 min after the initial 20-s infusion, before each increase in target concentration (at 10 min and every 30 min thereafter), before the start of the recovery period, and at 2, 5, 10, 20, 60, 120, and 300 min in the recovery period. EDTA tubes (4 ml) were used for blood sample collection. Each sample was stored on ice and centrifuged within 30 min after obtaining the sample. The obtained plasma samples were stored at -80°C until the study was finished.

The samples were analyzed by contract research organization QPS, using reverse-phase high-performance liquid chromatography triple quadrupole mass spectrometry.

Ten microgram of deionized water and 10 μg of internal standard working solution (10 ng/ml of medetomidine- $^{13}\text{C}_3$, [Toronto Research Chemicals, Canada] in deionized water) were added to 100 μl of plasma sample (thawed at room temperature). Protein precipitation was induced by the addition of 300 μl of MeOH (methanol HiPer-Solv Chromanorm gradient grade for high-performance liquid chromatography [Merck, Germany]) and brief vortexing. The samples were centrifuged at 14,000 rpm for 5 min, and the supernatant was transferred to clean 10-ml glass tubes. The solvent was evaporated to dryness in a Turbovap LV evaporator (Zymark; Biotage, Sweden) at 45°C under a gentle stream of nitrogen. The sample residue was redissolved in deionized water:formic acid (100:0.1 v/v):acetonitrile (80:20 v/v) and briefly vortexed. All liquid chromatography-mass spectrometry analysis was conducted on an API 4000 triple quadrupole mass spectrometer (AB SCIEX, Canada) equipped with a type 1100 liquid chromatograph (Agilent, USA) comprising a thermostatted well plate autosampler, a thermostatted column compartment, and a binary pump. Liquid chromatography was done with an xBridge C18 column (3.5 μm , $2.1 \times 50 \text{ mm}$; Waters, The Netherlands) and using an AJO-04286 guard column (Phenomenex, The Netherlands). The autosampler temperature was $+4^\circ\text{C}$, and an injection volume of 10 μl was used. A binary gradient separation at a flow rate of 500 $\mu\text{l}/\text{min}$ was used with solvents A (deionized water:formic acid 100:0.1 v/v) and B (acetonitrile), as follows: 0.00 to 0.20 min 80:20 A:B v/v; 1.00 to 2.00 min 20:80 A:B v/v; 2.10 to 5.00 min 80:20 A:B v/v. The column was kept at 40°C . Tandem mass spectrometry was done by using positive ion turbo ionspray in multiple reaction monitoring mode and using the transitions m/z 201.2 \rightarrow 95.1 for dexmedetomidine and m/z 205.2 \rightarrow 99.0 for medetomidine- $^{13}\text{C}_3$. The spray voltage was 3,000 V, and the probe temperature was 150°C . Other parameters were optimized: collision energy 27 eV, declustering potential 56.0 V, and collision cell exit potential 6.0 V. Nitrogen was used as the collision gas. "Zero air" from a local unit was used for curtain gas, ion source gasses 1 and 2 at 35, 50, and 80 psig, respectively. Quantification range limits for this method were 0.020 to 20 ng/ml.

Modeling

The time course of dexmedetomidine plasma concentration was modeled using a three-compartment mammillary pharmacokinetic model with volumes V_1 , V_2 , and V_3 , elimination clearance CL, and intercompartmental clearances Q_2 and Q_3 . The *a priori* model assumed allometric scaling where volumes scale linearly and clearances scale to the $3/4$ power exponent of the body size descriptor, which was total body weight. Model parameters were estimated relative to a reference subject, a 35-yr-old, 70-kg, and 170-cm individual. Population parameters were assumed to be log-normally distributed and a proportional error model was used for residual error.

During model development, examination of *post hoc* variability was used to guide testing of parameter–covariate relations. Models were compared on the basis of Akaike information criteria (AIC) and performance error as described by Varvel *et al.*¹⁴ using median performance error (MDPE) and median absolute performance error (MDAPE). The performance error was calculated as:

$$PE = \frac{C_{p_{\text{observed}}} - C_{p_{\text{predicted}}}}{C_{p_{\text{predicted}}}} \times 100\%$$

where C_p is dexmedetomidine plasma concentration. We estimated model predictive performance for out-of-sample observations, that is, samples not within the estimation data set using repeated two-fold cross-validation. This involves random partitioning of the observations into two equal (number of individuals) sets: D1 and D2. Model parameters were estimated using D1 and the resulting model was used to predict D2. The process is repeated exchanging D1 and D2. To reduce Monte-Carlo variability due to random partitioning, cross-validation was repeated 10 times, each with different random partitions of D1 and D2. All of the out-of-sample predictions were collected, and MDPE and MDAPE were calculated.

During model building, we required a decrease in AIC of at least 9.2 when adding parameters, corresponding to a relative likelihood (Akaike weight) of greater than 0.99 for the modified model, while removing model parameters required a decrease in AIC. In addition, we required model modifications to decrease MDAPE for the out-of-sample predictions. CIs for population parameters were described using likelihood profiles. We compared the predictive performance of the final model with models by Dyck,⁴ Dutta,⁶ Talke,⁷ Lin,⁸ Venn,⁹ and Välitäto.¹⁰

Results

Forty-three volunteers were screened by QPS. Of these, 26 passed the screening and 18 volunteers were selected to participate, divided into the age–sex–stratified groups. Two subjects (1 male, group: 35 to 54 yr; 1 female, group: 18 to 34 yr) withdrew after the first session, resulting in 34 completed sessions. The age range was 20 to 70 yr, weight range was 51 to 110 kg, and BMI range was 20.6 to 29.3 kg/m². Of the two subjects who had withdrawn after the first session, one reported a hematoma after arterial line placement; the other withdrew due to a headache the night after the first session.

For each step in the infusion stage, the number of completed sessions is as follows (of a total of 34 sessions): 1 ng/ml: 34 sessions; 2 ng/ml: 32 sessions; 3 ng/ml: 19 sessions; 4 ng/ml: 12 sessions; 6 ng/ml: 4 sessions; and 8 ng/ml: 1 session. The reasons for stopping the dexmedetomidine infusions were reaching 8 ng/ml in one session, an Observer's Assessment of Alertness/Sedation score of 0 in 22 sessions, bradycardia in 6 sessions (4 volunteers), hypertension in 2 sessions (2 volunteers), and airway obstruction requiring continuous manual airway maneuvers (jaw thrust, chin lift)

in 3 sessions (2 volunteers). None of the volunteers required any medical intervention at the time of stopping the dexmedetomidine infusion.

Side effects of dexmedetomidine infusions included obstructive apnea in eight subjects (55 to 72 yr age group, as well as two subjects in the 35 to 54 yr age group) requiring some degree of manual airway maneuvers, but no airway devices of any kind were necessary. Five subjects experienced symptomatic orthostatic hypotension, mostly after the end of the study, when they started mobilizing. Slow mobilization and fluid administration (IV or orally) were in most cases sufficient to counter this; however, two subjects required atropine 0.5 mg administration for sustained bradycardia after orthostatic hypotension, and one subject received 5 mg ephedrine to counter the hypotension. Two subjects experienced nausea, one subject also with vomiting. One received only ondansetron 4 mg in one session and the other subject received dexamethasone 5 mg and ondansetron 4 mg in both sessions. These events are likely associated with the hypotensive events. A headache during the following night or day was reported by two subjects.

In total, 408 arterial plasma samples were obtained. One sample result was reported as being lower than, but close to, the lower limit of quantification (0.019 ng/ml) and was treated as a normal observation. Twenty-nine other samples were below the lower limit of quantification. These samples were excluded from analysis. In all, 379 samples were used for analysis. When estimating the *a priori* model, we found that the population variability estimates for Q2 and Q3 were very small and these were fixed to 0. Using compartmental allometry, as described by Eleveld *et al.*,¹⁵ for Q2 and Q3 lead to a small improvement in model performance ($\Delta\text{AIC} = -6.70$; ΔMDAPE [out-of-sample] = -0.23). Also, fixing the population variability of V2 to 0 led to an improved model ($\Delta\text{AIC} = -1.49$; ΔMDAPE [out-of-sample] = -0.05). Covariate search using a two-compartment model did not achieve the same level of performance as the three-compartment model. No other parameter–covariate relations were found to improve the model, neither did using estimated fat-free-mass¹⁶ as body size descriptor. Considering systematic differences in model parameters between the first and second session did not lead to an improved model. Adding interoccasion variance to V1, but not to other parameters, improved model fit ($\Delta\text{AIC} = -14.52$; ΔMDAPE [out-of-sample] = -0.41). The equations of the final model are shown in table 1.

The likelihood profiles (fig. 1) show the parameter CIs for the estimated parameters and suggest that there were no problems with parameter identification. Figure 2 shows the best, median, and worst fits of our model. Population and *post hoc* predictions *versus* time and observed dexmedetomidine concentrations are shown in figure 3.

Discussion

Using TCI administration with a preliminary model in healthy volunteers, the pharmacokinetics of dexmedetomidine were

Table 1. Dexmedetomidine Model Parameters

$V1(l) = 1.78 \times (WT / 70) \times e^{h1} \times e^{h2}$		Variance	CV (%)
$V2(l) = 30.3 \times (WT / 70)$	$\eta 1$ (interindividual)	0.0356	19.0
$V3(l) = 52.0 \times (WT / 70) \times e^{h3}$	$\eta 2$ (interoccasion)	0.273	56.0
$CL(l / min) = 0.686 \times (WT / 70)^{0.75} \times e^{h4}$	$\eta 3$ (interindividual)	0.0635	25.6
$Q2(l / min) = 2.98 \times (V2 / 30.3)^{0.75}$	$\eta 4$ (interindividual)	0.0276	16.7
$Q3(l / min) = 0.602 \times (V3 / 52.0)^{0.75}$			

η_i are normally distributed random variables with a mean of 0 and variances as shown in the table.

CL = elimination clearance; CV = coefficient of variation; Q2–Q3 = intercompartmental clearances between compartment 1 and 2 or 3, respectively; V1–V3 = volume of corresponding compartments; WT = subject weight.

best described by a three-compartmental model with allometric scaling of weight to the volumes and elimination clearance, along with compartmental allometric scaling of the intercompartmental distributions. No other covariates were identified.

We used data from healthy volunteers for our pharmacokinetic study, as volunteer studies provide some unique

possibilities. A major advantage is the absence of adjuvant medication. In a patient population, dexmedetomidine will almost always be coadministered with other drugs, including anesthetic and analgesic drugs, as clinical indications for dexmedetomidine are limited to procedures in the operating room, postanesthesia care unit, and ICU. In our study, we used escape medication in 4 of 34 sessions (11.8%)—2

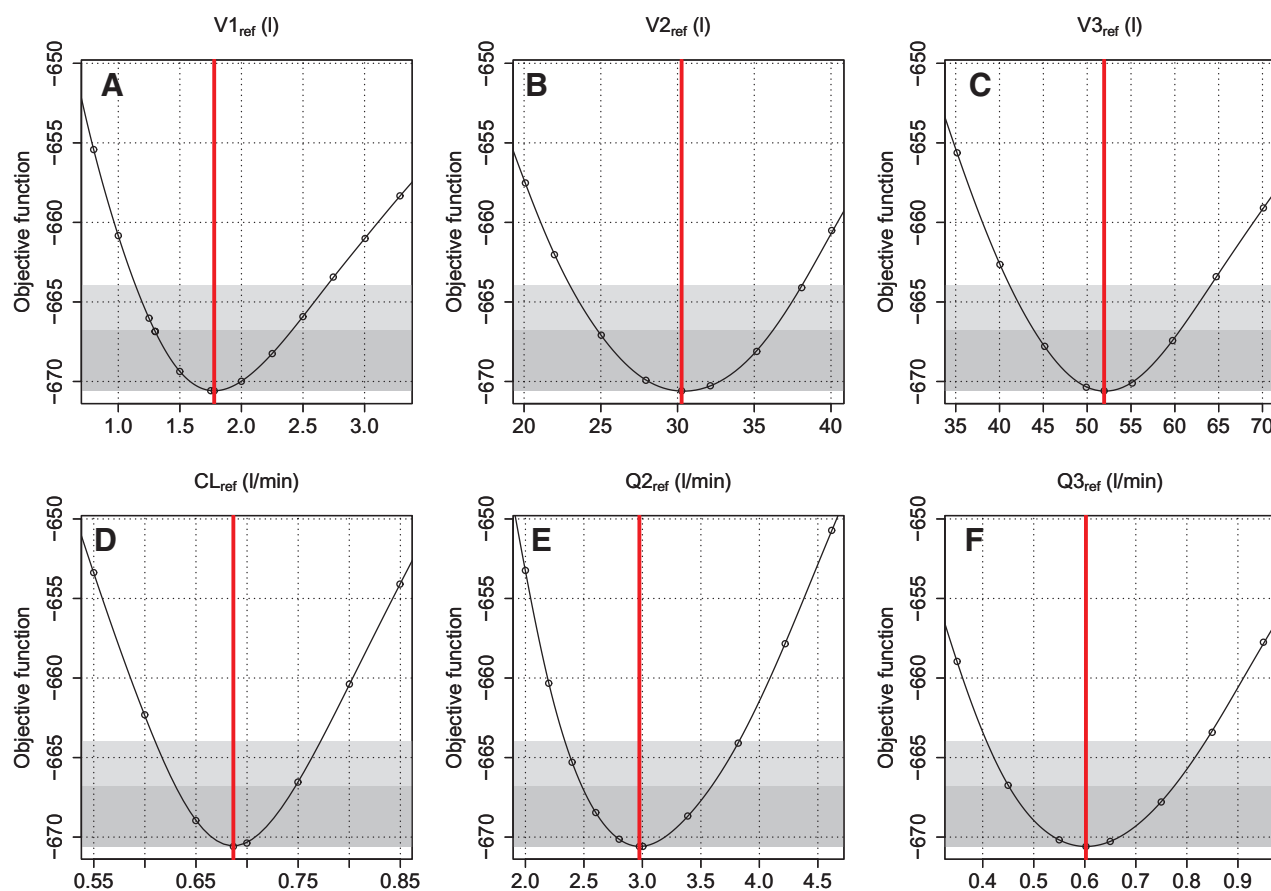


Fig. 1. (A–F) Likelihood profiles show changes in objective function value when fixing model parameters at particular values. The red line is the parameter estimate in the final model. The parameter interval where the likelihood profile is shaded dark gray corresponds to the 95% CI (change in objective function <3.84), and the light gray region corresponds to the 99% CI (change in objective function <6.63). CL = elimination clearance; Q2–Q3 = intercompartmental clearances between compartment 1 and 2 or 3, respectively; V1–V3 = volume of corresponding compartments.

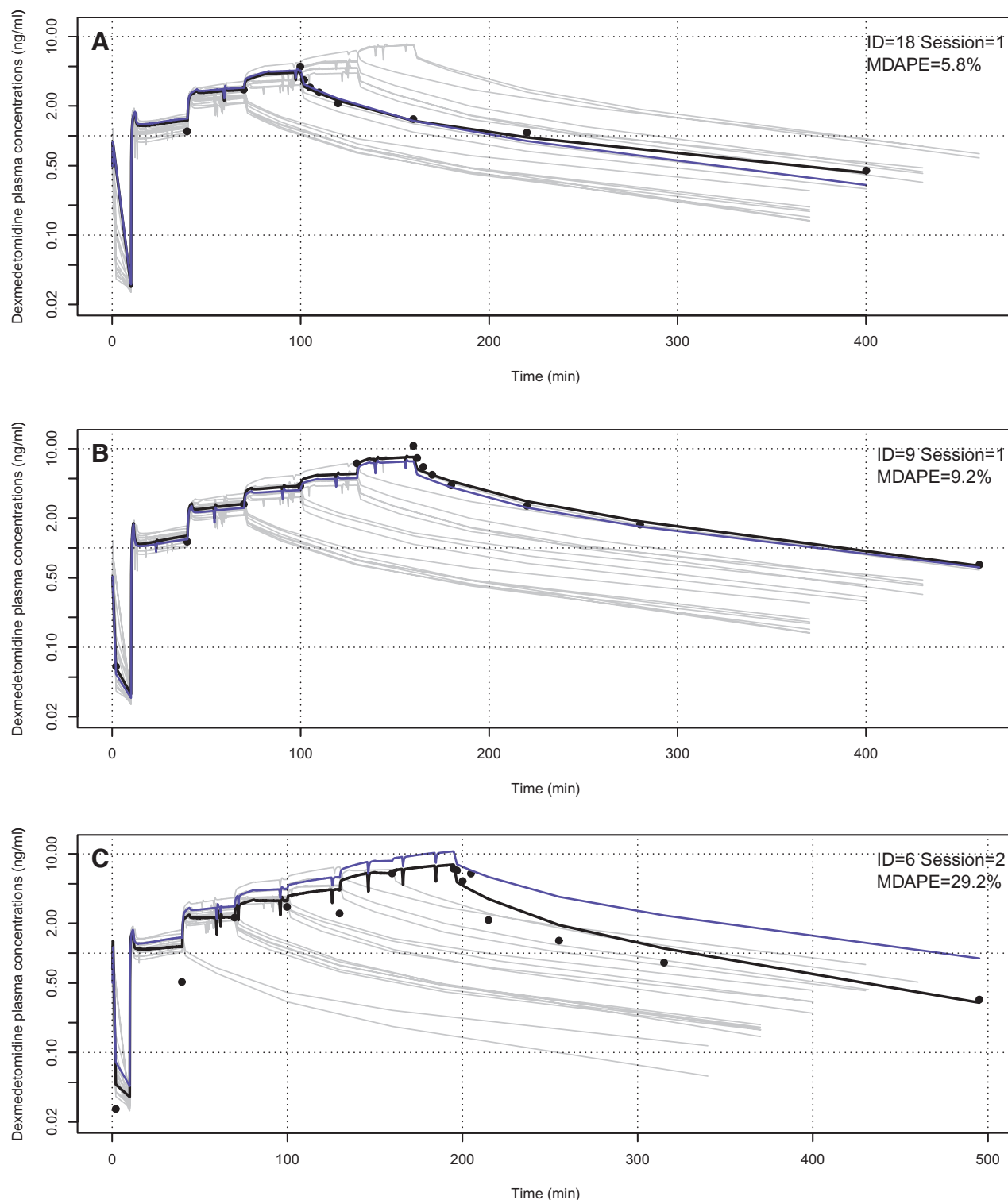


Fig. 2. Observations and predictions for individuals and sessions with the best (A), median (B), and worst (C) median absolute performance error (MDAPE). Filled circles are measured plasma concentrations, the black line is the individual *post hoc* prediction, gray lines are individual *post hoc* predictions for other individuals in the same session, and the blue line is the population prediction. ID = volunteer identification number.

sessions (same volunteer): atropine 0.5 mg IV, dexamethasone 5 mg IV, and ondansetron 4 mg IV; 1 session: ephedrine 5 mg IV; and 1 session: ondansetron 4 mg IV. All of these

were given in the recovery period, most of these (all atropine and ephedrine doses) between 2 and 3.5 h into the recovery period. If there is a pharmacokinetic interaction between any

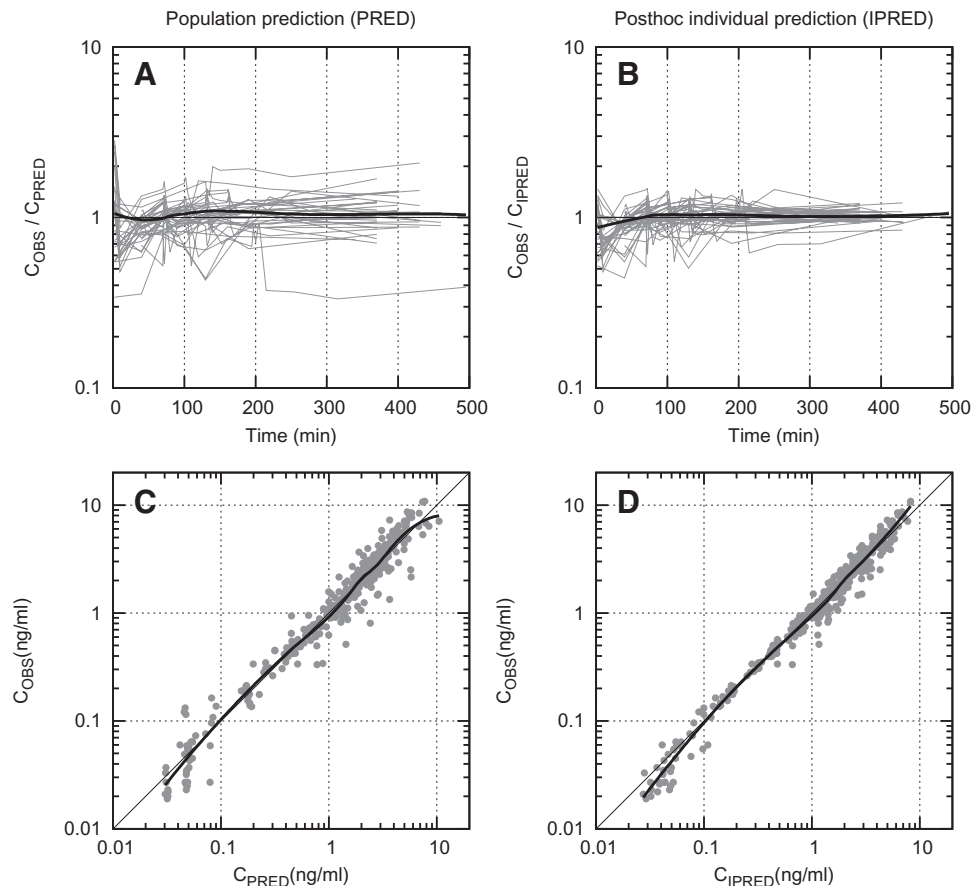


Fig. 3. (A) Population-observed/-predicted plasma dexmedetomidine concentrations versus time. (B) *Post hoc* individual-observed/-predicted plasma dexmedetomidine concentrations versus time. (C) Population-observed versus population-predicted plasma dexmedetomidine concentrations. (D) *Post hoc* individual-observed versus individual-predicted plasma dexmedetomidine concentrations. The black lines are Loess smoothers. C_{IPRED} = *post hoc* individual-predicted plasma concentration; C_{OBS} = observed (measured) plasma concentration; C_{PRED} = population-predicted plasma concentration.

of these drugs and dexmedetomidine, the influence will have been mostly limited to the last plasma sample.

Selecting healthy volunteers also provided us with the opportunity to use a stratified population, with a larger age range. A wide BMI inclusion range gave us a wider range of weights to assess the influence of weight on dexmedetomidine pharmacokinetics. None of the existing models were able to include weight as a covariate, and two models (Dyck and Lin) included height as the only covariate (for CL). Another feature of our model is the use of compartmental allometric scaling,¹⁵ which assumes that intercompartmental clearances, Q2 and Q3, are better scaled to the volumes of their respective compartments, V2 and V3, than with weight. Eleveld *et al.*¹⁵ recently showed significant differences in the pharmacokinetics of propofol in volunteers and patients. It is as of yet unknown whether there is a systematic difference between patients and volunteers for the pharmacokinetics of dexmedetomidine, and whether volunteer models can be extrapolated to patient populations. However, our current investigation does play an important role in making a comparative study possible, by providing a pharmacokinetic model based on volunteers for future comparisons.

In our study, we studied each volunteer twice. This enabled us to determine whether there is interoccasion variability in dexmedetomidine pharmacokinetics. Both sessions were similar in drug dosing scheme and sampling times. It is reasonable to expect subjects to be more anxious or have a higher adrenergic tone during the first session, when they do not know what to expect, compared with the second session. This may cause changes in hemodynamic factors that might influence the pharmacokinetic estimations. Although we found that adding interoccasion variance to V1 had a significant effect on our model performance, we did not find any significant systematic influence of session order on the model parameters, which suggests that variations in stress level that occur systematically between the first and second session probably have only little effect on the pharmacokinetics of dexmedetomidine. Interestingly, for V1, interoccasion variance was greater than interindividual variance, indicating that there are factors changing (nonsystematically) between sessions that have a greater effect on V1 than the differences between individuals. As of yet, we can only guess at what these factors are.

During experiment design, we determined the optimal sampling times, that is, when the pharmacokinetic model parameters could be estimated most precisely, using the

Table 2. Parameters of the Final Model and Dexmedetomidine Models in the Literature, for a 35-yr-old Person with a Height of 170 cm and Weight of 70 kg

	Final Model	Dyck	Dutta	Talke	Lin	Venn	Välitato
V1 (l)	1.78	7.99	13	16.6	63.4	44.1	104
V2 (l)	30.3	13.8	55	85.5	41.3	104.5	—
V3 (l)	52.0	187	—	—	284.3	—	—
CL (l/min)	0.686	0.4177	0.55	0.751	0.694	0.82	0.65
Q2 (l/min)	2.98	2.26	0.833	1.37	2.43	2.255	—
Q3 (l/min)	0.602	1.99	—	—	0.086	—	—

CL = elimination clearance; Q2–Q3 = intercompartmental clearances between compartment 1 and 2 or 3, respectively; V1–V3 = volume of corresponding compartments.

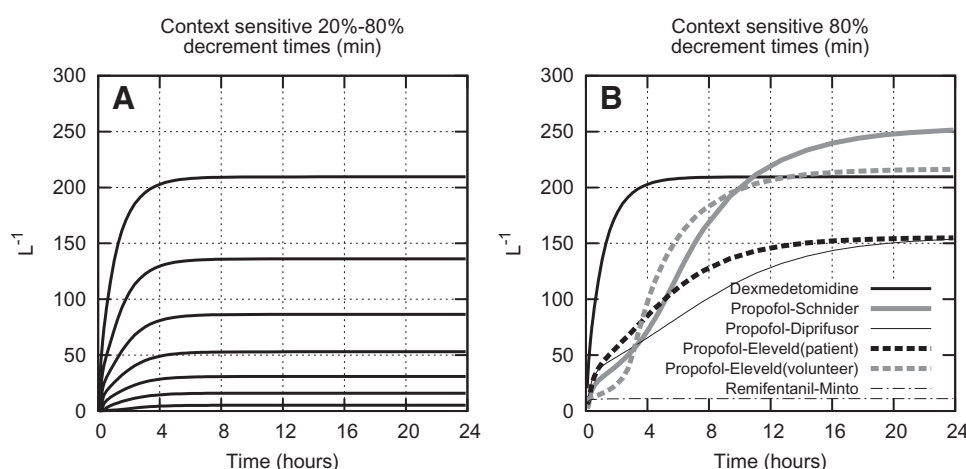


Fig. 4. (A) Context-sensitive 20 (lower line), 30, 40, 50, 60, 70, and 80% (upper line) decrement times for dexmedetomidine. (B) Context-sensitive 80% decrement times for dexmedetomidine, propofol (Diprifusor,¹⁸ Schnider,¹⁹ and Eleveld¹⁵ models), and remifentanyl (Minto²⁰ model).

Dyck model. These simulations revealed that our step-up method, while appropriate for determining V_2 , V_3 , and clearances, allowed poorer determination of the central compartment volume. Therefore, we included a 20-s initial infusion before starting the step-up TCI scheme, which would give us more information on V_1 . The use of a limited infusion rate likely also eliminated, at least in part, potential issues concerning front-end kinetics, as there is no assumption that a bolus dose is distributed instantaneously throughout the vascular system. Avram and Krejcie¹⁷ suggested that three-compartment modeling of drugs given by infusion instead of bolus injection may still estimate front-end kinetics with reasonable accuracy. In several articles referenced by Avram and Krejcie, smaller central compartment volumes have been found with continuous infusions than with bolus injections. In our study, V_1 was 1.78 l (for an individual of 70 kg), which is smaller than V_1 for other models (table 2) thereby modeling the high peak concentrations observed after a fast infusion. Another possible explanation for the smaller V_1 is the effect of the direct vasoconstrictive effect of dexmedetomidine, resulting in a decreased central compartment. Because of our early sampling, this effect may have been more pronounced in the model than for studies with delayed sampling.

The context-sensitive decrement times (fig. 4) of dexmedetomidine plasma concentrations show that the shapes of the graphs are similar for the 20 to 80% decrement times. For infusions shorter than approximately 10 h, the 80% decrement time for dexmedetomidine is longer than those associated with propofol. However, for infusions longer than approximately 12 h, the 80% decrement times for propofol increase substantially, reaching similar values to dexmedetomidine.

Our model has a low bias and high accuracy (table 3, MDPE and MDAPE, respectively), also in cross-validation (out-of-sample). Figure 3 confirms this, as only in the highest concentrations (sparse data), the precision decreases and bias increases. Figure 5 shows the population predictions *versus* time and observed concentrations for previously published dexmedetomidine pharmacokinetic models,^{4,6–10} showing poorer fits for all models compared with our final model. Also, as seen in the C_{obs}/C_{pred} *versus* time graphs in figures 3 and 5, our model predicts initial concentrations more accurately than the existing models, indicating that the accuracy concerning front-end kinetics is acceptable.

Comparison of the final model with the previously published models revealed a lower MDAPE for the new model, both in-sample and with out-of-sample cross-validation

Table 3. MDPE and MDAPE for the Final Model and Models from the Literature

	MDPE (%)	MDAPE (%)
Final model		
In-sample	0.6	14.4
Out-of-sample	0.7	15.7
Dyck	20.7	38.6
Dutta	-26.7	27.7
Talke	4.9	21.0
Lin	22.6	33.7
Venn	23.3	29.6
Välitato	-0.6	36.1

Out-of-sample MD(A)PE was obtained from repeated two-fold cross-validation.

MDAPE = median absolute performance error; MDPE = median performance error.

(table 3). The bias of our model, as estimated with MDPE, was low. Figure 5 and table 3 also show that both “healthy volunteer” models, Dyck (fig. 5, A and G) and Dutta

(fig. 5, B and H), are biased and imprecise, with high MDPE and MDAPE. The Dyck model underestimates the plasma concentrations in the higher concentration ranges, which is likely due to a larger volume of distribution, combined with a higher intercompartmental clearance for the third compartment Q3 (table 2). Underestimation of the Dyck model was previously demonstrated by Hsu *et al.*⁵ and our study confirms this. The Dutta model overestimates plasma concentrations, with the greatest overestimation in the first 50 min of infusion. This may be explained by the relatively low volume of distribution and low intercompartmental clearance. Whether this can be explained by the site of sampling (venous instead of arterial) is unclear. In a study by Persson *et al.*²¹ with ketamine, “venous models” have higher compartment volumes and intercompartmental clearance than “arterial models.” The Talke model performs quite well compared with the other models. The MDPE and MDAPE are only slightly higher than that of our model. The

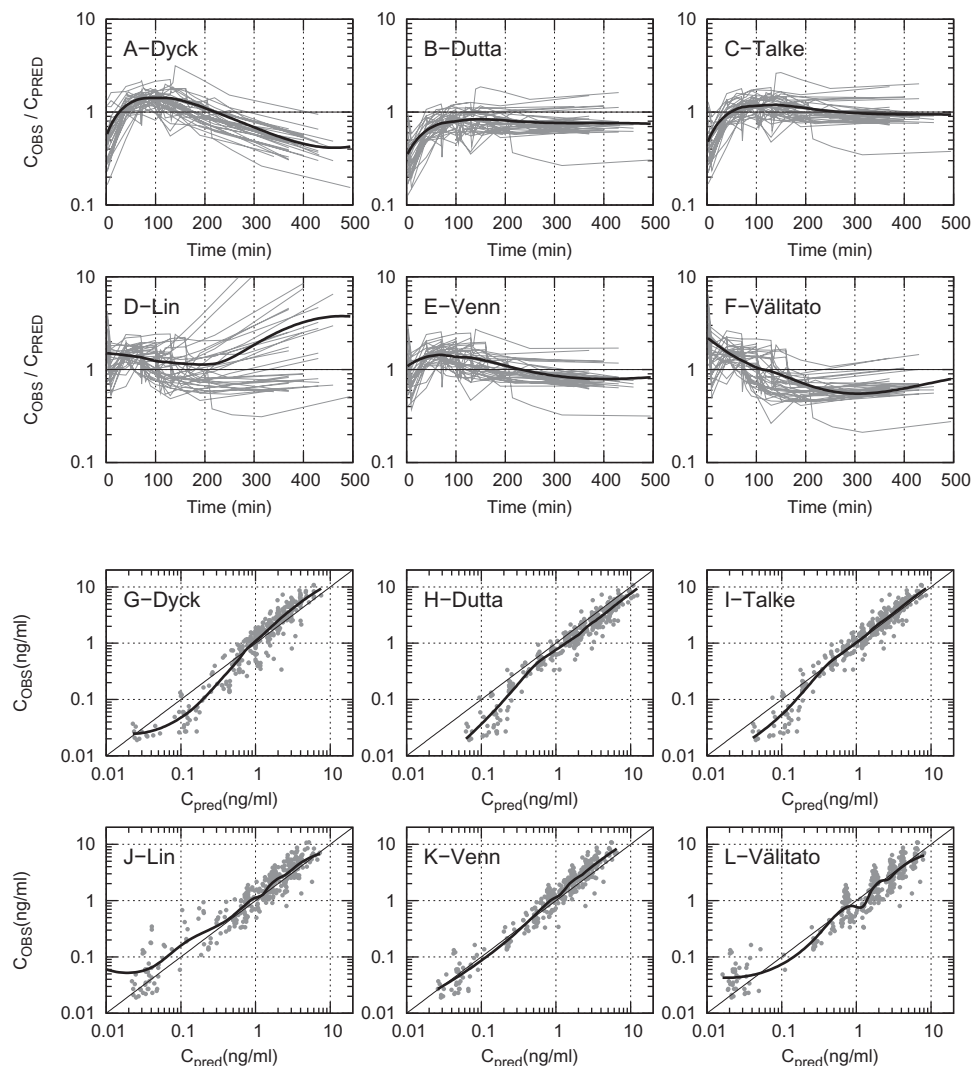


Fig. 5. (A–F) Observed/predicted plasma dexmedetomidine concentrations versus time for existing pharmacokinetic models. (G–L) Observed versus predicted plasma dexmedetomidine concentrations for existing pharmacokinetic models. The black lines are Loess smoothers. C_{OBS} = observed (measured) plasma concentration; C_{PRED} = population-predicted plasma concentration.

C_{obs}/C_{pred} versus time graph for the Talke model shows that initial infusion results in overestimation, whereas later in the period (at higher concentrations), the Talke model underestimates the plasma concentration, which confirms the findings by Snapir *et al.*¹¹ During the last hours of the recovery phase, predictions seem to be quite accurate. The Lin model is very inaccurate and biased, and the volumes of all three compartments are very high in this model. One needs to keep in mind that this model was developed from data of Chinese patients, whereas other models were most likely developed from Caucasian data. It has been suggested that ethnicity may have an important influence on drug pharmacokinetics, especially if the drug is highly protein bound or undergoes hepatic metabolism.²² Because dexmedetomidine is highly bound to plasma albumin (94%) and α_1 -glycoprotein and is metabolized extensively by the liver, this influence may very well be significant between Caucasians and Chinese subjects, as also stated by Lin *et al.*⁸ The Venn model also has a high MDPE and MDAPE. As with the Dyck model, this is likely due to a higher volume of distribution as well as inter-compartmental clearance. The C_{obs} versus C_{pred} graph for the Vältito model (fig. 5L) shows a large spread, but the most illustrative is the C_{obs}/C_{pred} versus time graph (fig. 5F), which shows that there is a large underestimation in the beginning and a large overestimation in the recovery phase. This is not surprising because the Vältito is a one-compartment model and therefore does not describe drug distribution to peripheral compartments. The large (central) compartment results in initially low plasma concentration predictions, whereas the absence of peripheral distribution results in relatively high late-phase predictions. The bias as calculated by the MDPE is very low for this model, as the overestimations and underestimations cancel each other out.

In conclusion, we developed a three-compartmental pharmacokinetic model for dexmedetomidine, derived from data from healthy male and female volunteers for a wide range in age and weight. The model is also reasonably accurate in the early-phase front-end kinetics, while maintaining the simplicity of a standard three-compartment model for easier use in TCI. Before implementation, this model should be validated prospectively to assess the performance in a patient population.

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Competing Interests

The authors declare no competing interests.

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