Title: Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine

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Abbreviated title: Pharmacology of intranasal and intravenous dexmedetomidine

Abstract

Background: Intranasal dexmedetomidine produces safe, effective sedation in children and adults. It may be administered by drops from a syringe or by nasal mucosal atomisation (MAD Nasal™).

Methods: This prospective, three-period, crossover, double-blind study compared the pharmacokinetic (PK) and pharmacodynamic (PD) profile of intravenous and these two different modes of administration. In each session each subject received 1 μg kg^{-1} dexmedetomidine either intravenous, intranasal with the atomiser or intranasal by drops. Dexmedetomidine plasma concentration and Ramsay sedation score were used for PK/PD modelling by NONMEM.

Results: The intravenous route had a significantly faster onset (15 min, 95%CI 15-20 min) compared to intranasal routes by atomiser (47.5 min, 95%CI 25-135 min), and by drops (60 min, 95%CI 30-75 min), (P<0.001). There was no significant difference in sedation duration across the three treatment groups (P=0.88) nor in the median onset time between the two modes of intranasal administration (P=0.94). A 2-compartment disposition model, with transit intranasal absorption and clearance driven by cardiac output using the well-stirred liver model, was the final PK model. Intranasal bioavailability was estimated to be 40.6% (95%CI 34.7-54.4%) and 40.7% (95%CI 36.5-53.2%) for atomisation and drops respectively. Sedation score was modelled via a sigmoidal E_{max} model driven by an effect compartment. The effect compartment had an equilibration half time 3.3 (95%CI 1.8-4.7) min^{-1}, and the EC50 was estimated to be 903 (95%CI 450-2344) pg ml^{-1}.

Conclusions: There is no difference in bioavailability with atomisation or nasal drops. A similar degree of sedation can be achieved by either method.

Keywords

pharmacokinetics; pharmacodynamics; α2-agonists, dexmedetomidine; administration, intranasal; NONMEM

Clinical Trial Number

HKUCTR-1617: http://www.hkuctr.com/Study/Show/c33056e7e147453fa2b2a580b15e9298

Introduction

Dexmedetomidine is a highly selective alpha-2 adrenergic receptor antagonist that acts on the locus ceruleus[1] to produce dose dependent sedation with no respiratory depression and only modest haemodynamic effects.[2, 3] The intravenous formulation is also efficacious when administered by the intranasal route in both children[4-8] and adults.[9, 10] Since this is not associated with any unpleasant sensation, there is increasing use for paediatric premedication and procedural sedation.[5, 11]

There is one report on the bioavailability (65%) of intranasal dexmedetomidine in healthy volunteers,[12] performed with a special nasal pump and a highly concentrated veterinary formulation of dexmedetomidine (84 mcg in 0.2 ml). Since neither the nasal pump nor the veterinary formulation are available for human use, these data cannot be applied to clinical practice where intranasal dexmedetomidine is usually administered by drops with a 1-ml tuberculin syringe or by using a nasal mucosal atomisation device (MAD Nasal™, Wolfe Tory Medical Inc., Salt Lake City, UT, USA).

The aim of this study was to evaluate the pharmacokinetics and pharmacodynamics of dexmedetomidine with these two intranasal modes of administration in healthy volunteers and compare this with intravenous administration.

Methods

The study was approved by the Institutional Review Board of the University of Hong Kong (UW 12-373) and was registered with Hong Kong Clinical Trials Registry (HKCTR-1617). Written, informed consent was obtained from all subjects before the study started. Healthy adults with American Society of Anesthesiologists (ASA) physical status class I were recruited. Exclusion criteria included body mass index > 30 kg m^{-2}, history of intolerance to the study drug or related compounds, concomitant drug therapy of any kind except paracetamol in the 14 days prior to the study, previous or present alcoholism, drug abuse, cigarette smoking, and abnormal electrocardiograph. All participants were requested to refrain from the use of any herbal medicine, any medications and some natural products (including grapefruit products) for at least 14 days, and alcohol and caffeine-containing products for at least 24 hours.

This was a three-period, crossover, study. Eight subjects, 7 males and 1 female, aged from 29 to 42 years with body mass index (BMI) ranging from 19.1 to 28.5 kg m^{-2} were recruited and attended 3 study sessions. The study was double-blind to avoid bias during assessment of sedation status by both subjects and observers. All subjects received intravenous drug/placebo and one mode of intranasal drug/placebo administration at the beginning of each study session. A crossover study design was used to reduce inter-individual variability. As there were three treatment periods for each subject and two possible routes of intranasal placebo whenever a subject received intravenous dexmedetomidine, the possible number of treatments with different assignment of intranasal placebo would be 12. However, whenever the intranasal route, be it placebo or active drug, were the same for the first two treatment periods, it would be possible for the subjects and investigators to guess the route of active drug administration on the third study period. Therefore, eliminating those treatment and intranasal placebo combinations, the possible number of treatments was 8. All subjects were randomly assigned to one of the 8 possible treatment orders. Two independent anaesthesiologists who were not involved in data collection and drug administration were responsible for drug and placebo preparation during each study session. All syringes were labelled with the subjects' name and identification number and were verified before drug administration during each study session. The study drugs were administered by investigators who were blinded to treatment allocation.

The order of drug administration was randomly assigned once the subject was recruited into the study with a

washout period of at least 7 days. In each of these sessions each subject received 1 μg kg^{-1}dexmedetomidine either intravenous, intranasal by atomiser or intranasal by drops. Intravenous dexmedetomidine was prepared in 50 ml 0.9% saline and was administered via a 20G intravenous cannula over 10 minutes with a programmable syringe pump. When intranasal dexmedetomidine was administered by atomisation or by drops, the parenteral formulation of undiluted dexmedetomidine (100 μg ml^{-1}) at 1 μg kg^{-1} was used and drawn up in tuberculin (1 ml) syringes. When atomisation was used to deliver dexmedetomidine, the dead space of the atomiser was filled with dexmedetomidine before the drug was administered. An equal volume of drug was given via the two nostrils when the drug was administered intranasally. Atomisation was performed with the subject sitting up with a slight backward head tilt as this allows optimal spread and absorption of atomized solutions.[5] When the intranasal drug was administered by drops, subjects were asked to lie flat so that the solution could be dripped into the nostrils.

On the study day the subjects were fasted from midnight until 3 hours after the study drug administration. During this period water intake was allowed. Two 20G intravenous catheters, one on each upper limb, were inserted at the commencement of each session. One intravenous access was used for drug or placebo administration and the other for blood sampling. The study drug was administered after recording baseline pulse rate (PR), non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), oxygen saturation (SpO_2) and sedation status. SpO_2 and pulse rate were monitored continuously for the first 3 hours, while blood pressure and sedation status were recorded every 5 minutes. Subjects were allowed to ambulate, eat and drink after the third hour of investigation. After the third hour SBP, DBP, PR, SpO_2 and sedation status were monitored and recorded every hour.

Sedation status was assessed by a blinded observer using the Ramsay sedation scale (**Table S1**) every 5 minutes for the first three hours, then every 30 minutes for the subsequent 5 hours. Any changes in blood pressure or heart rate of greater than 20% in magnitude from baseline measurements were reported and managed by on site anaesthesiologists. Intravenous fluid administration and vasoactive drugs were readily available. Other discomfort or suspected side effects of study drugs were to be reported to investigators during and up to 48 hours after the study period.

A venous cannula flushed with heparinized saline (10 units ml^{-1}) was used for blood sampling. Two mL

venous blood samples were collected immediately prior to administration of dexmedetomidine (baseline) and thereafter at 5, 7.5, 10, 15, 20, 30, and 45 minutes and 1, 1.5, 2, and 3, 4, 5, 6 and 8 h to determine concentrations of dexmedetomidine. Plasma was separated by centrifuging and was stored at -20^{o}C until batch analysis.

A validated analytical method was developed with reference to a previously reported method[13] to analyse all the plasma samples. 200 µl plasma was extracted with ammonium acetate using diethyl ether and reconstituted by 50 µl of the mixture of 0.07% formic acid in water and acetonitrile (80:20). The ultra-performance liquid chromatography system, Waters ACQUITY UPLC system (Waters, Milford, MA, USA), equipped with ACQUITY UPLC BEH C18 Column, 130Å, 1.7 µm, 3 mm X 50 mm, and a guard column ACQUITY UPLC BEH C18 VanGuard Pre-column, 130Å, 1.7 µm, 2.1 mm was used to perform chromatographic separation, and a tandem mass spectrometer (AB Sciex 6500 QTRAP) was used for detection. The mobile phase system was a gradient program consisting of formic acid in water (A) and acetonitrile (B) with a flow rate 0.5

ml min^{-1}. The gradient program was as follows: 0-0.5 min 90%A, 0.5-4.0min gradually changed to 1% A, 4.5-5.0 min returned back to 90% A, 5.0-6.5 min maintained at 90% A. The method showed good linearity from 8.3 to 4230.7 pg ml^{-1} dexmedetomidine (r^2=0.9999) with a lower limit of quantitation (LLOQ) 8.3 pg ml^{-1}. The matrix effect introduced by 6 batches of blank plasma on the peak area of dexmedetomidine and internal standard, was less than 20% at three QC concentration levels (1692.3, 423.1, and 21.1 pg ml^{-1}). The intra and inter-day precision, expressed as coefficient of variation, was less than 15%. The accuracy of the method was within the range of 85-115 %. All plasma samples collected were analysed, following the validation method, and finished within one month. The concentration of each plasma sample was calculated based on a calibration curve obtained in the method validation.

Pharmacokinetic analysis

Compartmental PK model building began with intravenous data only, and a visible change in elimination rate seeming to coincide with heart rate led us to test the model derived by Dutta S. et al. [14] whereby clearance is driven by the well-stirred hepatic model (Equation(1)). Cardiac output was estimated as heart

rate times stroke volume (Equation (2)). [15] [16] The stroke volume was fixed to 70 ml as it has been proven that the stroke volume of healthy adults would not be affected by dexmedetomidine if the plasma concentration is below 5 ng.ml^{-1}. [2] Then hepatic blood flow was set to be 30% of cardiac output (Equation (3)). [17]

$$Cl = \frac{QH \cdot f_{UB}}{\frac{QH}{Cl_0} + f_{UB}} \cdot \frac{CB}{CP} \quad (1)$$

$$Cardiac\ Output(L/h) = Heart\ Rate(beats/h) \times Stroke\ Volume(L) \quad (2)$$

$$QH = Cardiac\ Output \times 30\% \quad (3)$$

where Cl_0 represents intrinsic clearance, QH is hepatic blood flow. C_B is concentration in blood, C_P is concentration in plasma, and C_B/C_P represents the dexmedetomidine blood/plasma concentration ratio. f_{UB} is fraction unbound in blood, calculated by fraction unbound in plasma f_{UP} over C_B/C_P , the value of which were fixed to 0.0602 and 0.704 respectively, as reported previously. [14]

Intranasal data was then incorporated to characterize absorption with the two modes of intranasal administration. A single first-order absorption with lag time, two parallel first order absorptions (rapid and slow) absorption with lag times, and the transit compartment model where the drug amount in the absorption compartment calculated by Equation (4) [18], were tested. Non-compartmental analysis was also performed using PKSolver. [19]

$$\frac{dA(a)}{dt} = Dose \cdot \mathrm{F} \cdot k_{tr} \cdot \frac{e^{-k_{tr}*t} \cdot (k_{tr} \cdot t)^n}{\sqrt{2\pi} \cdot n^{n+0.5} \cdot e^{-n}} - ka \cdot A(a) \quad (4)$$

where $A(a)$ is the drug amount in the absorption compartment, t is time, F stands for bioavailability after intranasal administration, k_{tr} is the transit rate constant from $(n-1)$th compartment to the nth compartment, n is the number of transit compartments, and ka is absorption rate constant.

Pharmacodynamic analysis

Ramsay sedation score was modelled as a time-varying ordered categorical variable, with the relationship between the probability of score at each time point and concentration being estimated with a sigmoidal E_{max} model. The observed delay between circulating concentration and observed effect was modelled by using an effect compartment with first-order equilibration rate k_{eo}. The possible relatedness of the score at a given time point with the preceding score was modelled using a Markov model.[20] Probabilities for sedation score greater or equal to n (SS≥n) given a preceding observation of m (PSS=m) was expressed by Equation (5)

$$PGE\ n,m = P(SS \geq n|PSS = m) = \frac{1}{1+e^{-logn,m}} \quad (5)$$

where log(n,m), the logits for SS≥n given PSS=m, was calculated by Equation (6)

$$logn,m = logit[p(SS \geq n|PSS = m)] = \sum_{k=1}^{i} Bk,m + Drug + \eta \quad (6)$$

where

$$\text{Drug} = \text{Emax} * \frac{CE^{\gamma}}{EC50^{\gamma} + CE^{\gamma}} \quad (7)$$

where $B_{k,m}$ (k=1,2,3,4) is the baseline values for sedation score k given a previous observation m. η is the between subject variability assumed to be normally distributed with mean 0 and variance ω^2. *CE* is the drug concentration in effect compartment.

Finally, probabilities for sedation score n given a previous observation of m can be calculated by Equation (8).

$$Pn,m = PGE(n,m) - PGE(n+1,m) \quad (8)$$

A simulation study was performed to investigate the probability of each sedation level over time in each group and the onset time of each individual.

Onset of sedation was defined as the first time point when the Ramsay Sedation score was ≥ 5 and wake up time defined as the first time point when the Ramsay Sedation score was ≤ 2 after onset. These values were chosen to reflect the level of sedation required for subjects to undergo invasive procedures and the level of

alertness before they could be safely discharged in a clinical setting. The observed onset time and duration of sedation were also analysed by log-rank and the Kaplan Meier method.

All PK/PD modelling was performed with NONMEM 7.3.0 (ICON Development Solutions, Hanover, MD, USA) and Pirana 2.9.2 (Pirana Software & Consulting BV, Amsterdam, the Netherlands), using first-order conditional estimation method with the interaction (FOCEI) method for PK models and Laplacian method for PD models. The inter-individual variability (IIV), inter-occasional variability (IOV) on structural parameters and residual error were evaluated. The PD model was constructed using the sequential approach where individual PK parameters (IPP) were fixed to the post hoc values obtained from the final PK model. Different models were evaluated by Goodness-of-fit (GOF) and statistical significance in objective-function-value (OFV) change. R 3.2.2 was used for graphical plots. [21]

Results

All eight subjects completed three study sessions. ANOVA for a 3x3 crossover trial revealed no sequence, period or carry over effects on AUC for dexmedetomidine time - plasma concentration, Ramsay sedation scores, blood pressure, heart rate and SpO_2. Observed plasma concentration, Ramsay sedation score, and change in heart rate, SBP are presented in **Figure 1**.

A two-compartment model, with well-stirred model for clearance and transit compartment model for absorption, best described dexmedetomidine PK. After introducing the well-stirred model to describe the relationship between clearance - hepatic blood flow - cardiac output - heart rate, a significant improvement in modelling was observed (-ΔOFV: 10.8, P<0.05). The estimated typical intrinsic clearance was 2320 l h^{-1} with inter-individual variability 108.2%, which was reasonably similar to 1800 (1100) l h^{-1} reported by Dutta S. et al.[14] Baseline clearance varied from 24.7 to 59.4 l h^{-1}, which were similar to previous reported values.[13 23 24] Derived from equation (1-3), clearance decreased up to around 40% as dexmedetomidine plasma concentration increases. The heart rate reached its lowest value at around 2 hours after dosing, and gradually rebounded to the baseline afterwards as plasma concentration decreased (**Figure 1** (c)). A similar trend was observed in the predicted clearance and hepatic blood flow (figure not shown).

The transit model improved the goodness-of-fit and decreased OFV, compared with first-order absorption with lag time model (-ΔOFV: 55.3, P<0.05) and two parallel absorption model (-ΔOFV: 18.2, P<0.05). The mean transit time (MTT) were 10.74 min and 10.02 min, and the absorption rate constant (k_a) was 0.855h^{-1} and 0.722h^{-1} for intranasal by atomiser and intranasal by drops, respectively. The bioavailability was 40.6% (IIV 35.1%) and 40.7% (IIV 31.9%) for intranasal atomisation and by drops, respectively. Parameter estimates for the final pharmacokinetic model are given in **Table 1**. Goodness-of-plots and visual predictive checks are presented in **Figure 2**. The individual plot of observed and predicted plasma concentration over time is presented in **Figure S1**.

As there was no sedation score 1 (anxious or restless or both) recorded in this study, the functional minimum score was 2 (cooperative, orientated and tranquil). Application of the hypothetical effect compartment decreased the OFV significantly (-ΔOFV: 233.3, P<0.05) compared to a model without effect compartment. Introducing a baseline E_0 into the E_{max} model did not improve model fit (-ΔOFV: 0). Thus we used the

sigmoidal E_{max} model to describe impact of concentration in the effect compartment on probability of sedation score. Finally, the PD model was further improved by introducing the Markov elements (-ΔOFV: 818.5, P<0.05), with better visual predictive check results. The parameter estimates of the final pharmacodynamic model are shown in **Table 3**. The value of k_{eo} was 12.6 h^{-1}, corresponding to a rapid effect delay of 3.3 min. The administration route showed no significant impact on the k_{eo}, as no significant inter-occasional variability was found. EC50 was 903 pg ml^{-1} with inter-individual variability of 36.6%. The categorical visual predictive check plot (**Figure S2** in supplementary information) shows that the probability of each sedation score over time can be well predicted by the PD model. The simulated probability of being sedated (sedation score ≥ 5) over time after administration of 1μg kg^{-1} dexmedetomidine by intravenous or intranasal routes is shown in **Figure 3**. A schematic diagram of the final PK and PD model is shown in **Figure S4** in supplementary information and the key model selection steps were listed in **Table S3**.

Statistical analysis of the raw data showed that the median time to onset of sedation was 15 (95% CI 15-20), 47.5 (95% CI 25-135) and 60 (95% CI 30-75) minutes for intravenous, intranasal by atomiser and intranasal by drops, respectively (**Table 2**). The intravenous route has a significantly faster onset when compared to atomiser and drops (P<0.001 and P<0.001, respectively) while there was no difference in sedation onset between the atomiser and drops. The median duration of sedation was 202.5 (95% CI 105-225), 147.5 (95% CI 65-220) and 170 (95%CI 155-180) minutes for intravenous, intranasal by atomiser and intranasal by drops, respectively (**Table 2**). There was no difference in the median duration of sedation (P=0.88). The model predicted individual onset time was presented in **Figure S3**.

Both intranasal and intravenous dexmedetomidine were well tolerated with no reported irritation or pain associated with administration of the drug. There were decreases in blood pressure and heart rate after administration in all three treatment groups. However, they were not associated with any subjective symptoms and did not require intervention or treatment.

Discussion

We have shown that bioavailability does not differ whenever intranasal dexmedetomidine is given by simple drops or by an atomisation device, and there is no significant difference in their pharmacokinetic or pharmacodynamic profiles. A recent prospective, randomized, controlled trial comparing the two modes of intranasal dexmedetomidine in children undergoing transthoracic echocardiography also showed similar clinical effects with these two modes of administration.[25] The dose used in this adult study was 1 μg kg^{-1} whereas the dose used in the paediatric clinical trial was 3 μg kg^{-1}. In both studies the undiluted intravenous formulation was used, hence the volume of drug administration correlates with the drug dose. Compared to children, adults should have a larger surface area for intranasal drug absorption, yet atomisation did not result in improved bioavailability. Atomisation also does not improve clinical effectiveness when the dose is relatively larger in children. To date we have no information on the bioavailability when using higher doses of intranasal dexmedetomidine in adults and children.

In this study the bioavailability of both intranasal routes was lower than that estimated by Iirola and colleagues.[12] This could be secondary to the difference in formulation as the veterinary formulation was much more concentrated which should result in better absorption. In order to produce a fine mist with the atomisation device one needs to apply brisk high pressure to the atomiser. The drug deposition pattern during intranasal administration with a nasal cast silicone model has been studied,[26] and it has been suggested that the administration angle is a critical factor in optimizing drug deposition , with an administration angle >60^{o} and slight head tilt best. Whether this will translate to the clinical effect would be an interesting subject of research. However, it would be difficult to control the angle of administration in the clinical setting especially in children. The population mean bioavailability is 40.7% (95% CI 36.5%-53.2%) and 40.6% (95% CI 34.7%-54.4%) for intranasal by drops and intranasal by atomiser. The corresponding geometric mean of bioavailability obtained in non-compartmental analysis is 51.2% (95% CI 31.7%-88.7%) and 48.2% (95% CI 37.4%-69.5%), respectively. The discrepancy might be as a result of high between subject variability and small number of subjects. Also, NCA analysis, without considering non-linear pharmacokinetics or assay error, might introduce bias in AUC and bioavailability calculation.[27, 28]

The plasma dexmedetomidine concentration associated with a loading dose and constant infusion of dexmedetomidine has been studied in patients in critical care.[29] With a loading dose of 0.5-1 μg kg^{-1} over 10 minutes and an infusion rate of 0.1-2.5 μg kg^{-1} h^{-1}, the resulting constant plasma dexmedetomidine concentrations were generally higher than 1 ng ml^{-1} and these concentrations were correlated with light to moderate sedation. We have shown that 1 μg kg^{-1} of intranasal dexmedetomidine results in a median peak plasma concentration of 0.28 and 0.25 ng ml^{-1} for atomiser and drops, respectively (**Table S2** in supplementary information); these levels are lower than those resulting from constant intravenous infusion. Future pharmacokinetic studies would be useful to determine whether increasing the dose of intranasal dexmedetomidine will increase systemic absorption to an extent that mimics the concentration resulting from intravenous infusion.

The arteriovenous concentration difference and its effect on pharmacokinetics and pharmacodynamics of dexmedetomidine is unclear. One study using arterial concentration for PK modelling found similar central clearance yet different distribution volume comparing to those using venous concentration data. [30]

The suggested physiological covariates include body weight, [30] age,[29] height,[31] albumin level,[23] cardiac output, [14] and co-existent pathology.[22] No significant covariate was found in our study, which was probably due to the narrow range of these covariates and small sample size. Future studies could explore possible covariates that are correlated with the intrinsic clearance.

Intranasal dexmedetomidine is associated with a slower and more gradual onset than intravenous administration. Although intravenous administration results in much higher peak plasma concentrations and earlier onset, the depth of sedation is similar once it occurs. A more gradual onset may actually be desirable in avoiding the alpha-1 agonist effects seen with rapid intravenous administration (hypertension and bradycardia). While there is no significant difference in the parameter estimates, the probability of being sedated after intranasal by atomiser administration is higher than that after intranasal by drop administration. The clinical relevance can be further investigated.

Conclusion

The bioavailability of intranasal dexmedetomidine by atomiser and by drops is approximately 40% in

healthy adult volunteers with an inter-individual variability of around 30%. The pharmacokinetic and pharmacodynamic profiles of the two modes of administration are similar and both are equally effective in inducing adequate sedation.

Authors Contribution

A.L.: Performed original literature search, developed methodology and performed quantification of dexmedetomidine, performed pharmacokinetic/pharmacodynamic modelling and prepare first draft of manuscript and revision.

V.M.Y.: Conceived the idea, performed original literature search, set up experimental design, organized, coordinated the investigation, subjects recruitment and data collection, data analysis and manuscript preparation and revision wrote the clinical in the IRB and funding.

S.G.D.: Performed literature search, advised and developed methodology for quantification of dexmedetomidine, advised on data analysis of pharmacokinetic parameters, wrote the PK sampling program and analysis in the IRB and funding.

Y.C.S.: Supervised pharmacokinetic/pharmacodynamic modelling, critical advice on the manuscript

J.F.S.: Conceived the idea of and supervised pharmacokinetic/pharmacodynamic modelling, critical advice on the manuscript

P.C.K.: Responsible for blinding and drug preparation, performed literature search, advised and developed methodology for quantification of dexmedetomidine, advised on data analysis of pharmacokinetic parameters

M.K.M.L.: Performed literature search, responsible for study coordination, subjects recruitment, data collection, data analysis and manuscript preparation

A.S.L.: Performed literature search, responsible for study coordination, subjects recruitment, data collection, data analysis and manuscript preparation

I.C.W.: Critical revision and advice of the research protocol and manuscript

M.G.I.: Critical revision and development of the research protocol. Writing the manuscript

All authors approved this version of the manuscript be published; and all authors agreed to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Table 1 Parameter estimates from the final pharmacokinetic model

Parameters	Estimates	
	Fixed Effects (RSE)	Inter-individual variability (%) (RSE)[Shrinkage]
Disposition		
Cl_0 ($l \cdot h^{-1}$)	2320(58.3%)	108.2 (72.2%) [4%]
Cl at t_0 ($l \cdot h^{-1}$) *	38.4 (4.4%) range 24.7-59.4	
V_1 (*l*)	15.3 (19.1%)	49.8 (60.8%) [1%]
Cl_2 ($l \cdot h^{-1}$)	93.7 (20.0%)	50.1 (52.3%) [1%]
V_2 (*l*)	53.5 (8.9%)	21.4 (42.1%) [5%]
Absorption-intranasal by atomiser		
k_a (h^{-1})	0.857 (14.2%)	41.1 (48.9%) [8%]
MTT (h)	0.176 (18.7%)	61.2 (85.0%) [7%]
n	0.42 (43.1%)	101.5 (50.0%) [27%]
F(%)	40.6 (15.2%)	35.1 (58.4%) [3%]
Absorption-intranasal by drops		
k_a (h^{-1})	0.725 (10.5%)	29.2 (32.9%) [10%]
MTT (h)	0.163 (19.6%)	47.4 (55.1%) [12%]
n	0.371 (73.4%)	151.3 (56%) [6%]
F(%)	40.7 (12.2%)	31.9 (41.2%) [15%]
Residual Error		
Proportional	0.0399 (16.4%) [12%]	
Additive	72 (47.0%) [9%]	

RSE: relative standard error obtained in 500 times bootstrap results.
Cl_0: intrinsic clearance; Cl_2: inter-compartmental clearance. V_1 *and* V_2: central volume and peripheral compartment volume.
k_a: absorption rate constant from depot compartment to central compartment.
MTT: mean transit time to depot compartment. n: number of transit. compartment.
F: bioavailability after intranasal administration.
*Cl: central clearance, derived from Cl_0 and baseline heart rate using equation (1-3).

Table 2 Log-rank analysis of sedation onset time and duration for three routes of administration. Values in median (95% CI)

	Intravenous (n=8)	Atomiser (n=8)	Drops (n=8)	P
Onset time (min)	15 (15-20)	47.5 (25-135)	60 (30-75)	<0.001
Sedation duration (min)	202.5 (105–225)	147.5 (65-220)	170 (155–180)	0.88

Table 3 Parameter estimates of the final pharmacodynamic model

Parameter	Estimates	
	Fixed Effects (RSE)	Inter-individual variability (RSE)[shrinkage]
$B_{1,pre=2}$	-3.44 (17%)	
$B_{2,pre=2}$	-1.51 (19%)	
$B_{3,pre=2}$	-0.838 (40%)	
$B_{4,pre=2}$	-0.758 (58%)	
$E_{max,pre=2}$	6.34 (58%)	
$B_{1,pre=3}$	-0.724 (127%)	
$B_{2,pre=3}$	-3.79 (12%)	
$B_{3,pre=3}$	-2.22 (27%)	
$B_{4,pre=3}$	-1.12 (71%)	
$E_{max,pre=3}$	9.07 (58%)	
$B_{1,pre=4}$	0.414 (200%)	
$B_{2,pre=4}$	-0.682 (32%)	
$B_{3,pre=4}$	-2.49 (12%)	
$B_{4,pre=4}$	-1.44 (22%)	
$E_{max,pre=4}$	4.99 (76%)	
$B_{1,pre=5}$	2.05 (43%)	
$B_{2,pre=5}$	-0.192 (103%)	
$B_{3,pre=5}$	-1.71 (22%)	
$B_{4,pre=5}$	-3.69 (10%)	
$E_{max,pre=5}$	3.85 (83%)	
$B_{1,pre=6}$	20 FIXED	
$B_{2,pre=6}$	-18.6 (9%)	
$B_{3,pre=6}$	-1.69 (38%)	
$B_{4,pre=6}$	-1.17 (24%)	
$E_{max,pre=6}$	9.15 (79%)	
$EC50$ $(pg{\cdot}ml^{-1})$	903 (85%)	36.6% (31%) [2%]
γ	1.2 (60%)	0
k_{eo} (h^{-1})	12.6 (35%)	0

E_{max}: maximum drug effect on the logit scale
$EC50$: concentration in effect compartment causing half $E_{max.}$
γ: steepness coefficient of concentration effect
k_{eo}:first-order distribution constant of drug into and out of effect compartment
$B_{k,pre=m}$: baseline fixed-effects parameters of the logit transformation of probabilities given a previous observation of sedation score equals to m. As there was no transition from sedation score 6 to 2, $B_{1,pre=6}$ was fixed to 20.

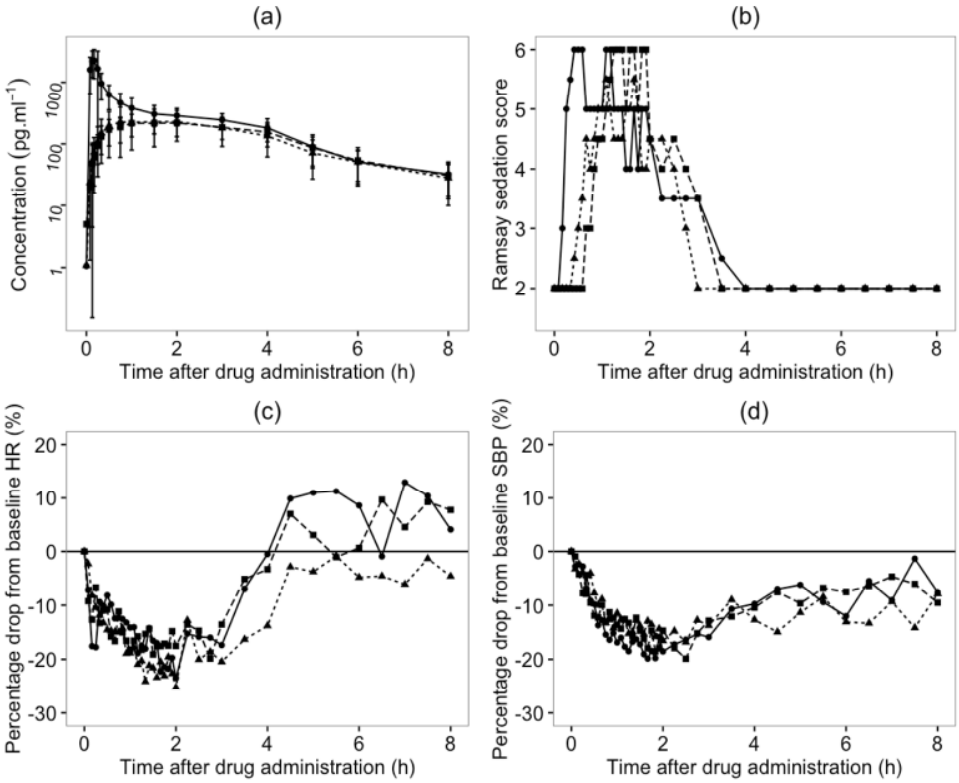

Figure 1 Raw data of (a) mean dexmedetomidine plasma concentration, (b) median sedation score, (c) median percentage in heart rate from baseline, and (d) median percentage change in SBP from baseline. Dexmedetomidine administered by intravenous infusion is shown as circle with solid line, intranasal by atomiser as rectangle with long dash line, and intranasal by drops as triangle with dash line.

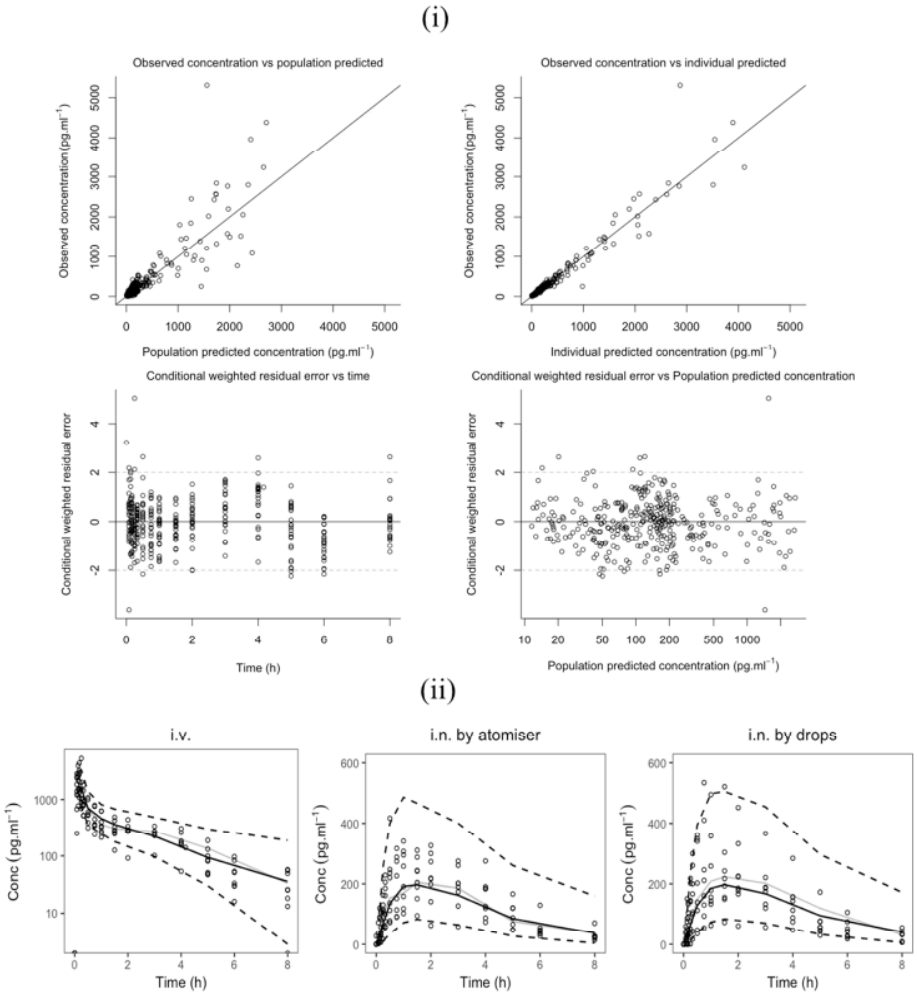

Figure 2 (i) Basic goodness-of- fit plots for the final pharmacokinetic model and (ii) Visual predictive checks for dexmedetomidine pharmacokinetic profile after (a) intravenous, (b) intranasal by atomiser, (c) intranasal by drops administration. Observed data is shown as circles, the median of observed data as gray solid line, the 50th, 5th, and 95th percentile of simulated data as black solid line and dashlines, respectively.

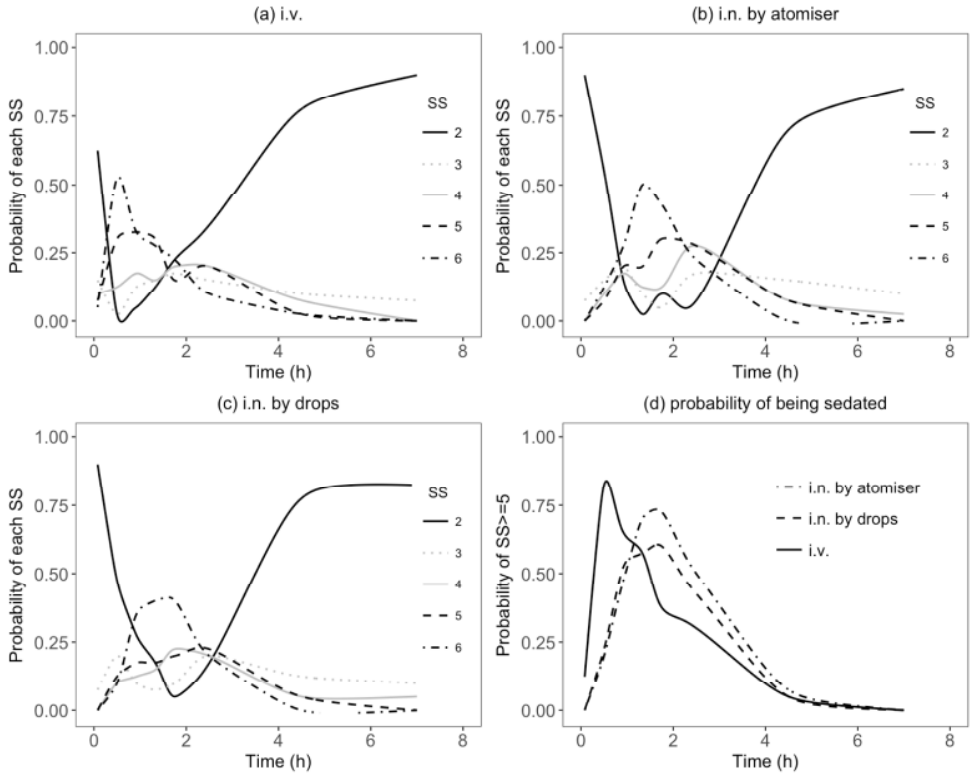

Figure 3 Simulated mean probability of each sedation score over time following administration of 1μg kg^{-1} dexmedetomidine via (a) intravenous infusion, (b) intranasal by atomiser, and (c) intranasal by drops. And (d) probability of being sedated (sedation score 5 or 6) following each administration mode. Simulated for 1000 times.

Table S1 Ramsay sedation score

Score	Response
1	Anxious or restless or both
2	Cooperative, orientated and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

Table S2 Pharmacokinetic parameters after 1μg·kg^{-1} of dexmedetomidine administered intravenously, intranasal by atomizer and intranasal by drops. Values are expressed in mean ± SD (range)

	Intravenous (n=8)	Atomiser (n=8)	Drops (n=8)
T_{max} *(h)*	0.17 ± 0.04 (0.13 – 0.25)	1.25 ± 0.69 (0.5 – 2.0)	1.34 ± 0.48 (0.75-2.0)
C_{max} *(pg·ml^{-1})*	2712 ± 1452 (1089 – 5303)	276 ± 145 (74 – 534)	250 ± 102 (103 – 417)
$AUC_{0\text{-}480}$ *(pg·h^{-1}·ml^{-1})*	1968 ± 790 (881 – 3211)	984 ± 540 (310 – 2100)	1011 ± 382 (459 – 1390)
$t_{1/2}$ *(h)*	1.88 ± 0.27 (1.61 – 2.36)	2.34 ± 0.96 (1.30 – 3.86)	1.97 ± 0.47 (1.63 – 2.75)
Cl (l/hr)	33.9 ± 10.97 (22.6 – 45.00)	-	-
Vd (l)	91.1 ± 27.2 (64.8 – 133.64)	-	-
F (%)	-	53.0 ± 23.1 (17.7 – 81.8)	60.9 ± 42.0 (26.2 – 157.8)

Table S3 Key modelling steps

Description	ΔOFV* (compare to base model)	p-value
Pharmacokinetic model-deposition		
Two-compartment (base model)		
one-compartment	+196.7	
three-compartment	-2.9	P>0.05
well-stirred model	-10.8	P<0.05
Pharmacokinetic model-absorption		
single first-order with lag time (base model)		
parallel first-order with lag time	-30.9	P<0.05
transit compartment model	-55.3	P<0.05
Pharmacodynamic model		
Sigmoid Emax model (base model)		
hypothetical effect compartment	-233.3	P<0.05
hypothetical effect compartment + first-order Markov	-818.5	P<0.05

*ΔOFV: change of objective function value comparing to the base model. P≤0.05 if ΔOFV ≤ -3.84 given degrees of freedom equals to 1.

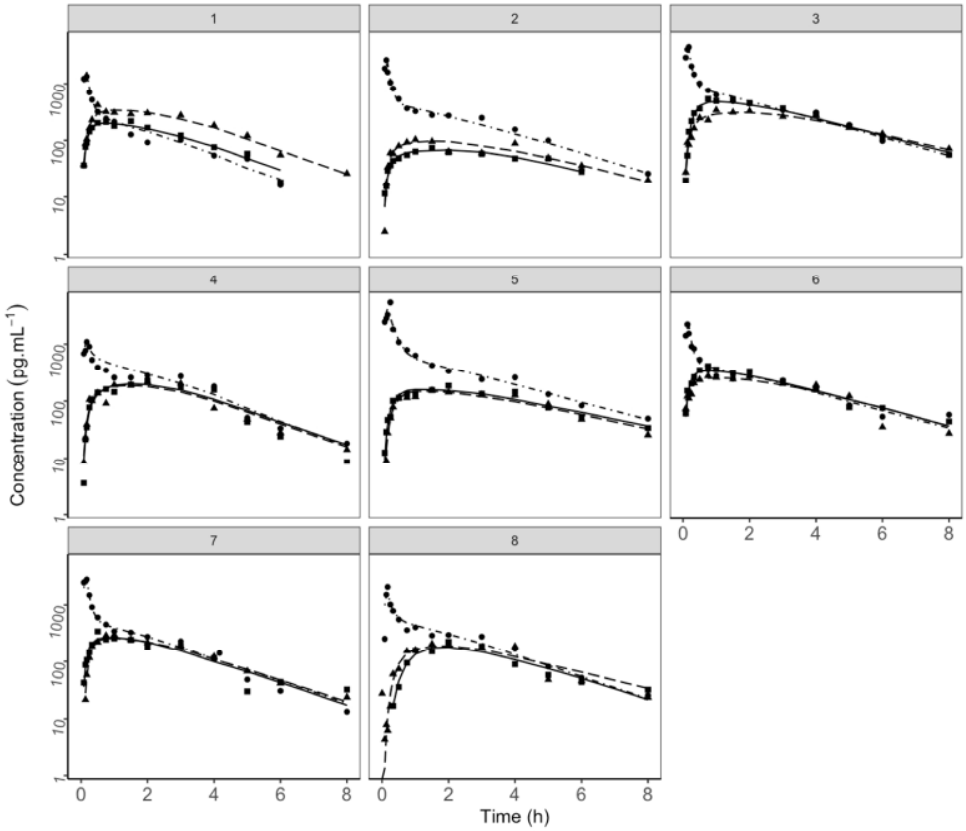

Figure S1 Measured and predicted dexmedetomidine concentration of each subject. The lines represent model predicted values and dots are measured plasma concentrations. Circle, rectangle, and triangle dots represents intravenous infusion, intranasal by atomiser, and intranasal by drops, respectively.

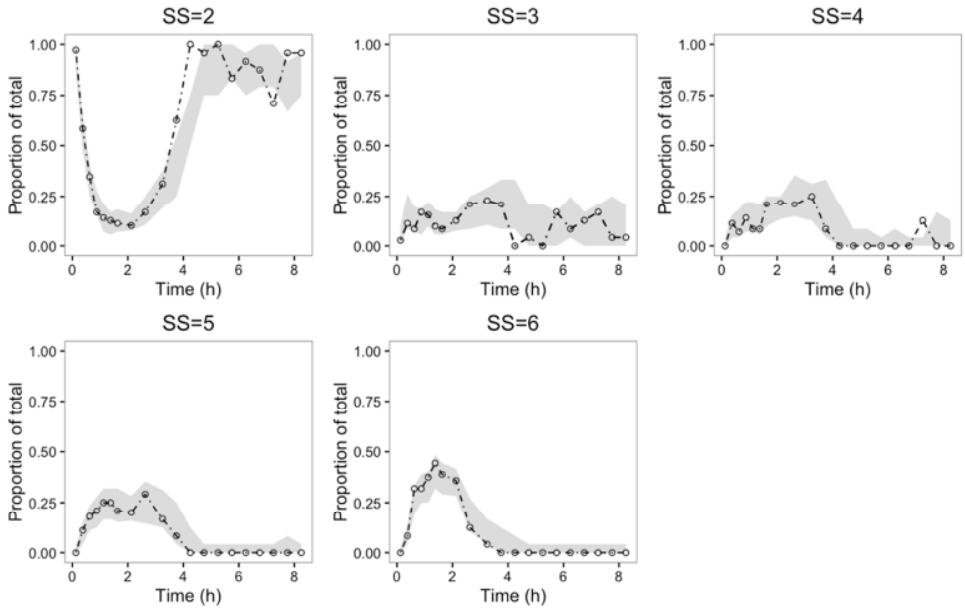

Figure S2 Categorical Visual Predictive Checks (VPC) for simulated and measured probability of each sedation score level over time after dosing. The dot-line represents the observed probability, and the shaded area is the 95% confidence interval of the simulated proportion of each score level.

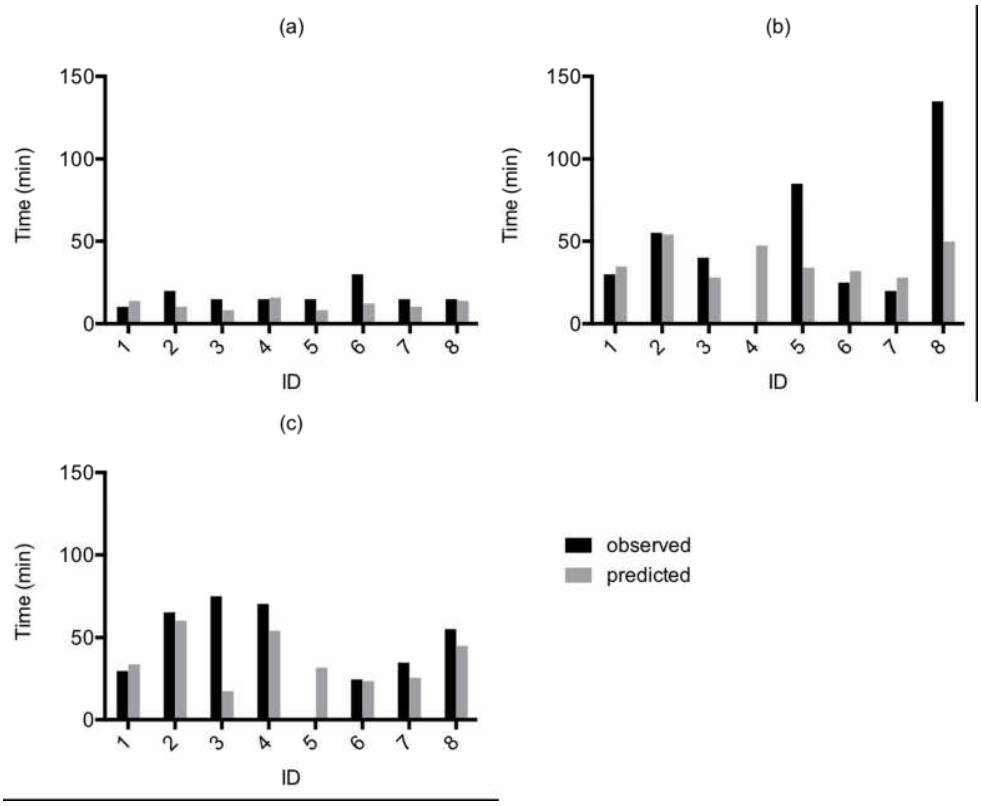

Figure S3 Observed and model predicted onset time of each subject after (a) intravenous, (b) intranasal by atomiser, and (c) intranasal by drops administration. The model predicted value is the median value obtained in 1000 simulations using the final PD model.

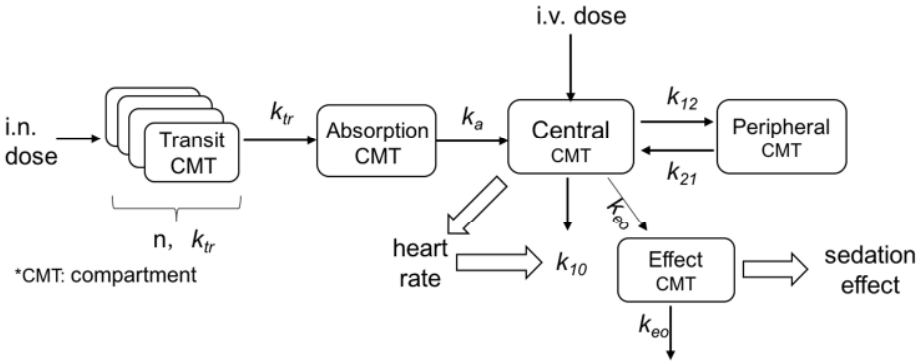

Figure S4 Scheme of the final PK/PD model. k_{10} is the elimination rate constant from central compartment, k_{12} and k_{21} are first-order rate constant for drug transfer between central and peripheral compartment. k_{tr} represents the rate constant of drug compound transport across transit compartment. n is the number of transit compartment. k_a is the absorption rate constant. k_{eo} is the distribution rate constant of drug compound into and out of hypothetical effect compartment.