Pharmacokinetics and pharmacodynamics of dexmedetomidine-induced vasoconstriction in healthy volunteers

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Running Title: Dexmedetomidine PK/PD

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Contribution of Authors

Pekka Talke: Designed the study, performed research and wrote the manuscript

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Abstract

AIMS

Alpha-2 agonists are direct peripheral vasoconstrictors by activation of vascular smooth muscle alpha-2 adrenoceptors. The impact of this response during dexmedetomidine infusion remains poorly quantified. Our goal was to investigate the pharmacokinetic (PK) and pharmacodynamic (PD, vasoconstriction) effects of a computer controlled dexmedetomidine infusion in healthy volunteers.

METHODS

After local ethics committee approval, we studied 10 healthy volunteers. To study the peripheral vasoconstrictive effect of dexmedetomidine without concurrent sympatholytic effects, sympathetic fibers were blocked with a brachial plexus block. Volunteers received dexmedetomidine target controlled infusion for 15 min to a target concentration of 0.3 ng/ml. Arterial blood samples were collected during and for 60 min after dexmedetomidine infusion for pharmacokinetic analysis. Peripheral vasoconstriction (PD) was assessed using finger photoelectric plethysmography. PK/PD analysis was done using nonlinear mixed effect models.

RESULTS

We found that the computer-controlled infusion pump delivered mean concentrations greater than 0.3 ng/ml over the 15 min infusion duration. The peripheral vasoconstrictive effect correlated with dexmedetomidine plasma concentrations during and after the infusion. This verifies that dexmedetomidine induced vasoconstriction is concentration dependent over time. A 3-compartment model provided a better fit to the data than a 2-compartment model.

CONCLUSIONS

We found that dexmedetomidine induced vasoconstriction is concentration dependent over time. Dexmedetomidine pharmacokinetics were best estimated by a 3-compartment model with allometric scaling. Our results will contribute to future modeling of dexmedetomidine induced hemodynamic effects.

Keywords: Dexmedetomidine, vasoconstriction, pharmacokinetics, pharmacodynamics

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What is already known about this subject

- Dexmedetomidine is a highly selective, non-subtype specific alpha-2 adrenergic agonist that is approved for clinical use for its sedative properties.
- Alpha-2 adrenergic agonists mediate hemodynamic effects by several different mechanisms. They mediate sympatholytic effects through activation of centrally and peripherally located alpha-2 adrenoceptors. They also activate vascular smooth muscle alpha-2 adrenoceptors which is responsible for direct peripheral vasoconstrictive effects.

What this study adds

- This manuscript demonstrates that dexmedetomidine induced peripheral vasoconstrictive effect correlates with dexmedetomidine plasma concentrations over time.
- This manuscript shows that the dexmedetomidine induced vasoconstrictive effect is more rapid ($T_{1/2}$ keo 2.16 min) than most other dexmedetomidine mediated effects, such as sedation and sympatholytic effects.
- The results of this manuscript contribute to future modeling of more complex dexmedetomidine induced hemodynamic effects.

Dexmedetomidine

http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=521

Alpha-a adrenoceptor

http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=4

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Introduction

Alpha-2 agonists, through activation of centrally located alpha-2 adrenoceptors, mediate sympatholytic and mild vagomimetic effects that are responsible for decreases in heart rate and blood pressure. Alpha-2 agonists are also direct peripheral vasoconstrictors. Activation of vascular smooth muscle alpha-2 adrenoceptors mediate a direct peripheral vasoconstrictive effect [1-3]. This can be observed clinically as an increase in blood pressure and a reflex decrease in heart rate when alpha-2 agonists are administered rapidly resulting in high alpha-2 agonist plasma concentrations.

In our previous studies, using computer controlled drug infusions that target specific drug plasma concentrations, we observed dose dependent peripheral vasoconstriction induced by two different alpha-2 agonists, clonidine and dexmedetomidine [4-6]. We also observed that with both alpha-2 agonists, the vasoconstriction was consistently more profound during the first 3-5 minutes of drug infusion and then reached a pseudo steady state during the next 10-15 minutes [4-6]. This direct vasoconstrictor response has been characterized in children after bolus dose administration [7]. The impact of this response in adults during infusion remains poorly quantified. Our goal was to investigate the pharmacokinetic and pharmacodynamic (vasoconstriction) effects of a 15-minute computer controlled infusion of a highly selective alpha-2 agonist, dexmedetomidine, in healthy volunteers.

Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. With approval of the institutional Review Board of the University of California, San Francisco, we enrolled 10 healthy volunteers. Informed consent was obtained from all individual participants included in the study. We excluded individuals who had a history of cardiac, pulmonary, hepatic or renal disease or of alcohol or drug abuse; those taking prescription medications; those older than 45 years and those weighing more than 130% of normal. Our drug/molecular target nomenclature conforms to BJP's Concise Guide to PHARMACOLOGY 2017/18 [8].

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Subjects rested in the supine position in a temperature controlled (22-23 ^{o}C) anesthesia study room. A catheter was inserted into a vein of the foot to permit administration of intravenous fluids and dexmedetomidine on the morning of study. Lactated Ringer's solution (5 ml/kg) was administered before drug administration, and 1.5 ml/kg/h was administered thereafter until the end of the study. After production of local anesthesia with lidocaine, a cannula was placed into the radial artery of the right arm to permit repeated blood sampling for pharmacokinetic analysis and measurement of arterial blood pressure. A pulse oximeter probe to measure finger blood volume (by photoplethysmography) was attached to the left hand as described below. To minimize locally mediated vasomotor activity in response to changes in body temperature, subjects were covered with blankets during the study.

In order to study the peripheral vasoconstrictive effect of dexmedetomidine without its concurrent sympatholytic effects, approximately 15 min after application of all monitors the sympathetic fibers of the left arm were blocked by administration of 30 mL of 1% mepivacaine for production of an axillary perivascular brachial plexus block. Successful block was confirmed approximately 25 min later by testing motor and sensory function of the left hand. Thirty minutes after production of axillary block baseline measurements of hemodynamics and finger blood volume were obtained and a baseline arterial blood sample was collected. We then determined finger blood volume (vasoconstriction) and dexmedetomidine plasma concentration responses during and after a 15 min dexmedetomidine infusion.

Dexmedetomidine infusion

A computer-controlled infusion pump (Harvard Apparatus 22; Harvard Apparatus, South Natick, MA) was used to infuse dexmedetomidine (4 μg/ml) (Precedex, 100 μg/mL dexmedetomidine HCl, Abbott Laboratories Inc.; North Chicago, IL) for 15 min to target plasma concentrations of 0.3 ng/ml. The pump was controlled by STANPUMP software (obtained from Steven Shafer, MD, Professor, Department of Anesthesia, Stanford University, Palo Alto, CA), which adjusted and recorded the rate of infusion every 10 s. We used the same dexmedetomidine pharmacokinetic parameters as we had used in our previous studies (i.e., a central volume of distribution of 0.427 l/kg and elimination and inter-compartment rate constants of k_{10} = 0.0212 min^{-1}, k_{12} = 0.0744 min^{-1}, and k_{21} = 0.0264 min^{-1}).

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Photoelectric Plethysmography

Blood volume in the finger was assessed using photoelectric plethysmography, which measures infrared light transmitted through a fingertip. The absolute level of transmitted light was determined by pulse oximeter (Nellcor N200; Nellcor Inc., Hayward, CA), for which we placed a sensor (Nellcor D25; Nellcor Inc., Pleasanton, CA) on the ring finger of the left hand.

The pulse oximeter consists of two parts, a sensor and a monitor. The sensor, which is applied to the tip of a finger, contains a low-voltage, low-intensity, light-emitting diode that is supplied with constant drive current and emits infrared light (approximately 920 nm). A detector photodiode in the sensor receives transmitted light and generates an electrical current proportional to the amount of light received. Data on electrical current thus generated were transmitted to a monitor, passed through an analog to digital converter (ADC), sampled every 10 s, and recorded by a computer. During vasoconstriction, blood volume in the finger decreases, and more light is transmitted through the finger. Thus, the ADC values increase in response to vasoconstriction. During vasodilation, blood volume in the finger increases, increasing tissue volume and decreasing the amount of light transmitted by the finger, resulting in a decrease in ADC values. During changes in blood vessel diameter (vasoconstriction or vasodilation) the change in light transmittance through the finger is rapid (seconds). This ADC measurement served as the qualitative measure of blood volume and, hence, vasoconstriction in the fingertip. ADC unit values were recorded for 3 min before and throughout the 15 min dexmedetomidine infusion and for 60 min after the end of the infusion.

Dexmedetomidine plasma concentrations

Five milliliter arterial blood samples were collected using the intra-arterial cannula at baseline, 1, 2, 3, 4, 5, 7.5, 10 and 15 minutes after the beginning of the dexmedetomidine infusion and 15, 30 and 60 minutes after the end of the dexmedetomidine infusion. Blood samples were immediately placed on ice and plasma was subsequently separated in a refrigerated centrifuge. Plasma samples were stored at -70 ^{0}C until analysis.

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Concentrations of dexmedetomidine (reference standard: dexmedetomidine hydrochloride, Fermion Oy, Oulu, Finland) in human EDTA plasma were determined with HPLC-MS/MS after solid phase extraction with Sep-Pak®tC18 96-well extraction plates (Waters Co., Milford, MA) with $^{2}H_{6}$-medetomidine (ORM-14385, Orion Pharma, Espoo, Finland) as an internal standard. After separation with a Gemini® column (2 x 150 mm, 5 µm, Phenomenex, Torrance, CA) and 0.1 % formic acid in water and a mixture of methanol and acetonitrile as solvents, quantitative detection was performed in multi-reaction monitoring mode (MRM) with a triple quadruple mass spectrometer (API 4000, MDS Sciex, Concord, Ontario, Canada). For dexmedetomidine and the internal standard, the precursor ions (m/z) were 201.2 and 208.2. The fragment ions (m/z) monitored and used for quantitation were 95.1 for dexmedetomidine and 97.1 for the internal standard. The chromatograms were processed using Applied Biosystems/MDS Sciex software (Analyst 1.4.1). Calibration standards with 8 non-zero concentrations and quality controls samples with three different concentration levels (low, medium and high) were included in all assays. The linear concentration range was from 0.02 ng/mL to 10.0 ng/ml. The inter-assay accuracies of the quality control samples (0.03, 0.9 and 8.0 ng/ml) were 89%, 89% and 101.5%, respectively. This assay has a lower limit of quantification of of 17 pg/mL and coefficient of variation of 5.7% in the relevant concentration range.

Hemodynamic Variables and Hemoglobin Oxygen Saturation

Systolic (SBP) and diastolic blood pressure were measured via the radial artery cannula and heart rate (HR) was measured noninvasively (Propaq 106; Protocol Systems, Beaverton, OR). Hemoglobin oxygen saturation (SpO_2) was measured continuously noninvasively by pulse oximeter (Nellcor N200; Nellcor Inc., Hayward, CA). Hemodynamic and SpO_2 data were recorded at baseline 5, 10 and 15 min after the beginning of the dexmedetomidine infusion and 15, 30 and 60 min after the end of the dexmedetomidine infusion.

PKPD Analysis

The pharmacokinetic (PK) and pharmacodynamic (PD) data were initially analysed simultaneously using nonlinear mixed effects models (NONMEM 7.3, ICON Development Solutions, USA). This method can distort PK model parameter estimates when pharmacodynamic or effect compartment model misspecification is present [8, 9]. Consequently, a second modelling process was undertaken whereby the PK parameters were estimated separately and then fixed in the PKPD model (known as the Population PK Parameters and Data, PPPD method) [9, 10]. A three-compartment (central and two peripheral) disposition linear model was used for the PK data.

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The model was parameterised in terms of elimination clearance (CL), two inter-compartment clearances (Q2, Q3), a central volume (V1) and two peripheral volumes (V2, V3). The parameter values were standardized for a body weight of 70 kg using the allometric model [11, 12].

$$P_i = P_{STD} \times \left(W_i / W_{STD} \right)^{PWR}$$

where P_i is the parameter in the ith individual, W_i is the weight in the ith individual and P_{STD} is the parameter in an individual with a weight W_{STD} of 70 kg. The *PWR* exponent was 0.75 for clearance, 0.25 for half-times and 1 for distribution volumes [12].

An additional effect compartment was incorporated into the model in order to describe the delayed peripheral vasoconstrictor response quantified by photoplethysmography data. An equilibration rate constant (*keo*) characterising the temporal relationship between effect compartment and plasma was parameterised as an equilibration half-time ($T_{1/2}$keo):

$$T_{1/2}keo = \frac{Ln(2)}{keo}.$$

The relationship between vasoconstriction and concentration was described using a sigmoid E_{MAX} model:

$$Effect = E_0 + \frac{E_{MAX}\, x\, Ce^N}{C_{50}^N + Ce^N}$$

Where E_0 is the baseline effect, Ce is the concentration in the vasoconstrictor effect compartment, E_{MAX} is the maximum response for vasoconstriction, C_{50} is the concentration in the effect compartment producing 50% of E_{MAX}, N is the Hill coefficient defining the steepness of the concentration-response curve.

The population parameter variability in model parameters was modelled by a proportional variance model. An additive (ERR_{ADD}) and a proportional term (ERR_{PROP}) characterised the residual unknown variability. The variances of the residual unidentified variability ($\eta_{RUV,i}$) were estimated. The population mean parameters, between subject variance and residual variance were estimated using the first order conditional interaction estimate method using ADVAN13 TOL9 (differential equation solver) of NONMEM VII. Convergence criterion was three significant digits. A Compaq Digital FORTRAN Version 6.6A compiler with Intel Celeron 333 MHz CPU (Intel Corp., Santa Clara, CA, USA) under MS WINDOWS XP was used to compile NONMEM.

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The population parameter variability is modelled in terms of random effect (η) variables. Each of these variables was assumed to have mean 0 and a variance denoted by ω^2, which is estimated. The covariance between two elements of η (e.g. C_{50} and E_{MAX}) is a measure of statistical association between these two variables. Their covariance is related to their correlation (R) i.e.

$$R = \frac{covariance}{\sqrt{\omega^2_{C_{50}} x \omega^2_{E_{max}}}}$$

The covariance of E_{MAX} and C_{50} variability was incorporated into the model.

Quality of Fit

Models were nested and an improvement in the objective function was referred to the Chi-squared distribution to assess significance, e.g. an objective function change (ΔOBJ) of 3.84 is significant at α=0.05. The quality of fit of the pharmacokinetic model to the data was sought by NONMEM's objective function and by visual examination of plots of observed vs. predicted concentrations. Non-parametric bootstrap methods provided a means to evaluate parameter uncertainty [13]. A total of 1000 simulations were used to estimate confidence intervals. A visual predicted check [14], a modelling tool that estimates the prediction intervals and graphically superimposes these intervals on observed data after a standardised dose, was used to evaluate how well the model predicted the distribution of observed mean arterial pressures.

In any model, the quality of the individual parameter estimate will depend heavily on the observed data available. For example, sparse data can result in reduced variance (ω^2) of parameter estimates and distortions of the distribution shape. If no data are available on a particular individual, the individual's estimate will be equal to the population value; the variance is shrinking towards zero as the quantity of information at the individual level diminishes, a phenomenon defined as η-shrinkage (sh_ε). This was calculated:

$$sh_\epsilon\% = 100\, x \left\{1 - {SD(\eta)}/{\omega}\right\}$$

where SD approximates the standard deviation. When there is no shrinkage the model is correct and individual data are sufficiently abundant for individual parameter estimation. Data contain virtually no information about these parameters when shrinkage is 100% and the individual parameter values approach the typical parameter value.

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [15], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [8].

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Results

Table 1 shows dexmedetomidine plasma concentrations, ADC unit, and hemodynamic values during and after dexmedetomidine infusion. Figure 1 illustrates the association between plasma dexmedetomidine concentrations and % change in ADC unit values. Figure 2 shows the changes in ADC unit values during and for 60 minutes after dexmedetomidine infusion. Pharmacokinetic data were available for 10 adult volunteers with 120 concentrations. The mean age of the volunteers was 29 (SD 4, range 21-36) years, mean weight of 72 (SD 13, range 52-89) kg, mean height 174 (SD 9, range 160-183) cm and mean BMI was 23 (SD 2, range 20-27). Five of the volunteers were female and five were male. The cumulative dose of dexmedetomidine administered was 0.28 µg/kg. There were no adverse effects during the study.

Nested models revealed that a 3-compartment model (Table 2A) provided a better fit to the data than a 2-compartment model (2 extra parameters, ΔOBJ 12.919, $p<0.005$). The correlation of between subject variability is provided in Table 2B. There were 4560 observations available for the PD analysis and the final consequent parameter estimates are shown in Table 3A. The correlation of between subject variability for PD parameters are provided in Table 3B. A visual predictive check (VPC) comparing the distribution of simulated PK data with observed data are shown in Figure 2; those for simulated PD data are shown in Figure 3. Shrinkage was acceptable for all model parameters. The effect site concentrations and its nonlinear relationship to vasoconstriction is shown in Figure 4.

Discussion

We investigated the dynamic vasoconstrictive effects of computer controlled dexmedetomidine infusions. We found that the computer-controlled infusion pump delivered mean concentrations greater than 0.3 ng/ml over the 15 min infusion duration; a peak concentration of 0.5 ng/ml at 2 min decreased to 0.4 ng/ml at 15 min The alpha-2 agonist induced peripheral vasoconstrictive effect correlates with dexmedetomidine plasma concentrations during and after the infusion. This verifies that dexmedetomidine induced vasoconstriction is dose dependent over time. The estimated 3-compartment model PK parameters are consistent with several of those published previously [16, 17].

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Several of our previous studies that investigated alpha-2 agonist induced peripheral vasoconstriction used computer controlled alpha-2 agonist infusions targeting a wide range of clonidine and dexmedetomidine plasma concentrations [4, 5, 6, 18]. In these studies, we consistently observed an initial short-term peak in alpha-2 agonist induced vasoconstriction followed by pseudo steady state of vasoconstriction [4, 5, 6, 18]. These vasoconstrictive effects were associated with concomitant increases in intra-arterial blood pressure and decreases in heart rate [4, 5, 6, 18]. In our studies that used multistep infusions targeting increasing clonidine or dexmedetomidine plasma concentrations, we observed similar dynamic vasoconstrictive effects at the beginning of each infusion step [4, 5, 6, 18]. Since these dynamic vasoconstrictive effects were identical with two different alpha-2 agonists (clonidine and dexmedetomidine) with independently derived PK models, we hypothesized that the initial 3-5 min peak in vasoconstriction may be due to PD effects. Theoretically it seemed feasible that the alpha-2 agonist induced vasoconstriction may have been rapidly attenuated either by alpha-2 agonist mediated release of NO from endothelial cells or by release of other compensatory vasodilators. We had previously shown that dexmedetomidine-induced NO release attenuates dexmedetomidine induced vasoconstriction by 19% in healthy volunteers, further supporting the theory of compensatory vasodilation [19]. Since there was no available high frequency data on the performance of the clonidine and dexmedetomidine PK models during the beginning of the computer controlled infusion we also considered a possibility that our observations of dynamic vasoconstrictive effects in the beginning of the infusion could be due to plasma concentration changes. The results of this current study suggest that the observed dynamic peripheral vasoconstriction is attributable to rapid onset concentration dependent direct effects on the vasculature.

Our study is unique in performing pharmacodynamic modeling of dexmedetomidine using a continuously measured observation (vasoconstriction). Dexmedetomidine induced vasoconstriction is mediated by vascular smooth muscle alpha-2B receptors [3]. This vasoconstrictive effect is rapid ($T_{1/2}$ keo 2.16 min). Most other alpha-2 agonist mediated effects, such as sedation and sympatholytic effects, may take 10-15 min to approach their maximum [20, 21]. Blood pressure, is complicated to model as it is a sum of several PD effects such as peripheral vasoconstriction and centrally and peripherally mediated sympatholytic effects and central vagomimetic effects all of which may have varying time courses. Our study adds to the understanding of dexmedetomidine-induced vasoconstriction, and may further help in modeling other more complex hemodynamic effects such as arterial blood pressure, which is a product of complex interactions of

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dexmedetomidine induced central sympatholytic, vagomimetic and imidazoline receptor mediated effects and peripherally mediated vasoconstrictive effects. The use of PKPD modelling in volunteers with sympathectomised limbs helps our understanding of the vasoconstrictor response. The use of target controlled infusions without assay of plasma dexmedetomidine concentrations can result in incorrect assumptions of plasma drug concentrations and introduce inaccuracies to PK and PD analysis. Dexmedetomidine PK parameter estimates from one population, when used in a different cohort, may not be applicable. Predicted concentrations used in any analysis may not be true. Front end kinetics at the beginning of an infusion can also result in misinterpretation. Arterial sampling for early drug assay (0-2 min) may be falsely high (Figure 5); PK analysis relies on a "well stirred" model and that is not achievable in the first few minutes within blood. This false assumption of "instantaneous mixing" in PK analysis could contribute to the initial peak in peripheral vasoconstriction observed in the present study; this artifact is particularly true of drugs with a rapid distributional half-life. Others have modeled the pulse like changes in concentration reflected in early arterial assay samples using models of greater complexity (e.g., semiparametric approaches, physiological based models, more input compartments, sinusoidal models) [22, 23]. Slower infusions, the use of sampling times that avoid this initial "unmixed' phase or censoring of early assays has also been employed to reduce this artifact [24]. Despite this impediment, modeling shows consistently raised concentrations above 0.3 ng/ml that decrease over the subsequent 15 min. The cohort studied was small and healthy. Covariates such as sex, age or preexisting disease processes (e.g., hypertension) could not be investigated.

In patients dexmedetomidine causes a biphasic response after intravenous administration; there is an initial vasoconstriction followed by delayed vasodilation. The initial vasoconstriction is mediated by activation of vascular smooth muscle alpha-2 adrenoceptrors and is associated with increase in blood pressure and baroreflex mediated bradycardia. This vasoconstrictor effect is why dexmedetomidine loading dose should be administered over 10 minutes (to avoid high plasma drug concentrations and to allow time for central vasodilator effects). Once dexmedetomidine reaches the central nervous system, it mediates a slowly evolving (10-15 minutes) sympatholytic effect that is associated with reduction of blood pressure and heart rate. We have quantified the initial vasoconstrictor concentration-effect in vivo. At increasing dexmedetomidine concentrations the central sympatholytic effect will be maximized, whereas the vasoconstrictive effects will continue increasing resulting in increase in systemic vascular resistance and potentially reduced organ blood flow [25].

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In conclusion, we found that dexmedetomidine induced vasoconstriction is dose dependent over time and that our earlier findings of stronger than expected peripheral vasoconstriction in the beginning of dexmedetomidine infusion can be explained by dexmedetomidine pharmacokinetics. We also found that dexmedetomidine pharmacokinetics were best described by a three compartment model. Our results will contribute to future modeling of dexmedetomidine induced hemodynamic effects.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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Table 1 Demographics of the 10 study subjects

Variable	
Age (years)	29 ± 4 (21-36)
Height (cm)	174 ± 9 (160-183)
Weight (kg)	72 ± 13 (52-89)
BMI	23 ± 2 (20-27)
Male/Female	5/5

BMI= Body Mass Index. Data are mean ± SD (range).

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Table 2. Dexmedetomidine plasma concentration, ADC unit, and hemodynamic values during and after dexmedetomidine infusion. Data are mean (Standard deviation).

Dexmedetomidine infusion									Post infusion		
0 min	**1 min**	**2 min**	**3 min**	**4 min**	**5 min**	**7.5 min**	**10 min**	**15 min**	**15 min**	**30 min**	**60 min**
Dexmedetomidine plasma concentration (ng/ml)											
0	.39 (.26)	1.11 (.37)	.63 (.17)	.52 (.12)	.48 (.13)	.44 (.11)	.41 (.09)	.43 (.13)	.16 (.04)	.12 (.02)	.09 (.02)
ADC units (% change from baseline)											
0	0 (3)	22 (13)	31 (15)	29 (15)	27 (15)	25 (14)	23 (14)	23 (14)	12 (9)	9 (8)	8 (6)
SBP (mmHg)											
125 (10)					118 (10)		114 (12)	109 (12) *	103 (14) *	105 (13) *	108 (13) *
DBP (mmHg)											
65 (9)					59 (11)		61 (9)	57 (10)	55 (10)	55 (10)	58 (10)
HR (bpm)											
67 (11)					64 (8)		67 (13)	64 (11)	65 (10)	64 (11)	63 (12)

SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, HR=Heart rate. * = Hemodynamic values that are significantly different from baseline (0 min) values (ANOVA with Dunnett's post hoc test)

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Table 3A Pharmacokinetic parameter estimates for the 3-compartment mammillary disposition model

Parameter	**Estimate**	**PPV**	**SE%**	**Shrinkage%**	Bootstrap estimate	**95% CI**
CL (L/min/70 kg)	0.751	0.158	4.6	5.7	0.712	0.107, 0.872
Q2 (L/min/70kg)	1.01	0.590	11.2	9.4	0.96	0.531, 1.816
Q3 (L/min/70kg)	1.03	-	3.7	-	1.06	0.674, 1.39
V1 (L/70kg)	12	0.339	6.3	4.6	12.8	9.570, 16.9
V2 (L/70kg)	11.7	0.868	13.1	5.9	13.1	6.369, 35.61
V3 (L/70kg)	47.2	-	11.2	-	48.4	35.295, 217.025
ERR_{ADD} ($mcg.L^{-1}$)	0.011	η_{RUV} 0.66		5.4	0.010	0.001, 0.132
ERR_{PROP} (%)	10.4				11.8	7.02, 19.36

ERR_{ADD}=additive residual error; ERR_{PROP}=proportional residual error, PPV = Apparent co-efficient of variation of between subject variability estimated with a an exponential random effect (sqrt(NONMEM Omega)), SE is the standard error of the structural parameter estimate, CI is the confidence interval

Table 3B Correlation of between subject variability for PK parameters

	CL	**V1**	**Q2**	**V2**
CL	1			
V1	0.420	1		
Q2	0.685	-0.367	1	
V2	0.971	0.210	0.833	1

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Table 3A Parameter estimates for an effect compartment concentration response relationship using an Emax model (BSV is the between subject parameter variability, CI is the confidence interval presented as 5^{th}, 95^{th})

Parameter	Estimate	PPV	Shrinkage%	Bootstrap estimate	95% CI
E_0 (ADC units)	5860	0.462	11.3	5666	4549, 7527
Emax (ADC units)	3090	1.349	13	3160	1540, 7777
C_{50} (mcg.L^{-1})	0.233	1.628	28.6	0.211	0.098, 0.390
Hill	2.83	-	-	3.28	1.70, 4.35
$T_{1/2}$keo (min)	2.16	0.841	18.2	2.01	1.37, 2.90
Err additive (unit?)	113	η_{RUV} 0.442	29.2	103	72, 138
Err proportional (%)	61.8			61.8	36.4, 326

PPV = Apparent co-efficient of variation of between subject variability estimated with a an exponential random effect (sqrt(NONMEM Omega)

Table 3B The correlation of between subject variability for PD parameters

	E_0	**E_{MAX}**	**C_{50}**	**$T_{1/2}$ keo**
E_0	1			
E_{MAX}	0.116	1		
C_{50}	0.374	0.897	1	
$T_{1/2}$ keo	-0.458	-0.716	-0.913	1

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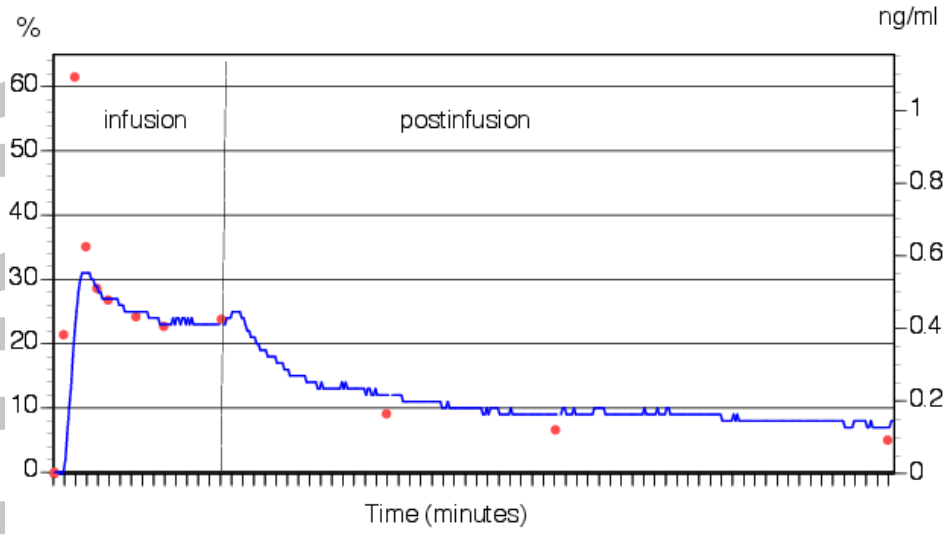

Fig. 1 Mean dexmedetomidine plasma concentrations (red dots, right axis) and mean percent change in ADC units (blue line, left axis) during dexmedetomidine infusion and for 60 minutes after the infusion

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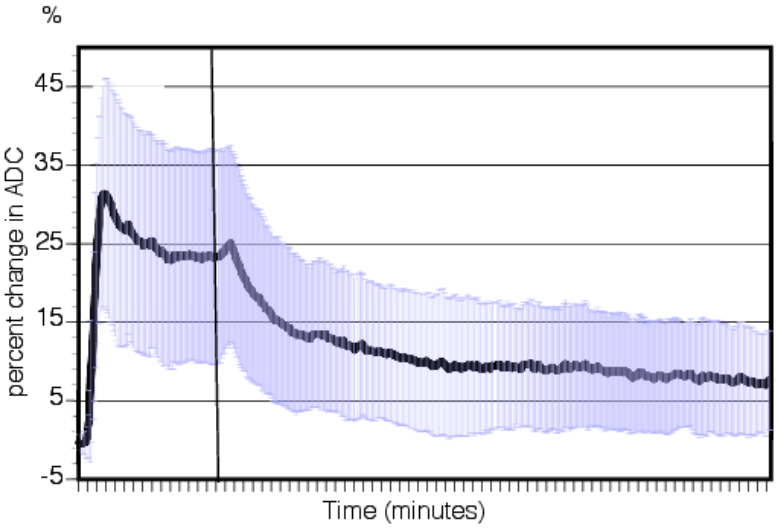

Fig. 2 Mean and standard deviation of percent change in ADC units during dexmedetomidine infusion and for 60 minutes after the infusion.

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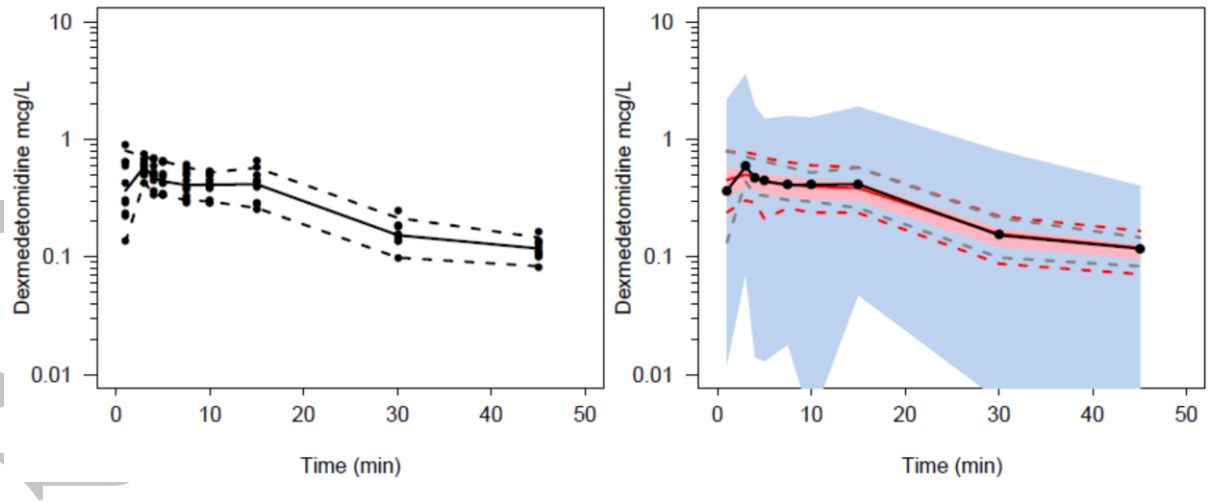

Fig. 3 Visual predictive check for the PK model. All plots show median (solid) and 90% intervals (dashed lines). Left hand plot shows all prediction corrected observed concentrations. Right hand plot shows prediction corrected percentiles (10%, 50%, and 90%) for observations (black dashed lines) and predictions (pink dashed lines) with 95% confidence intervals for prediction percentiles (median, pink shading; 5^{th} and 95^{th} blue shading). There is a mismatch between observed and predicted concentrations in the first 2 min

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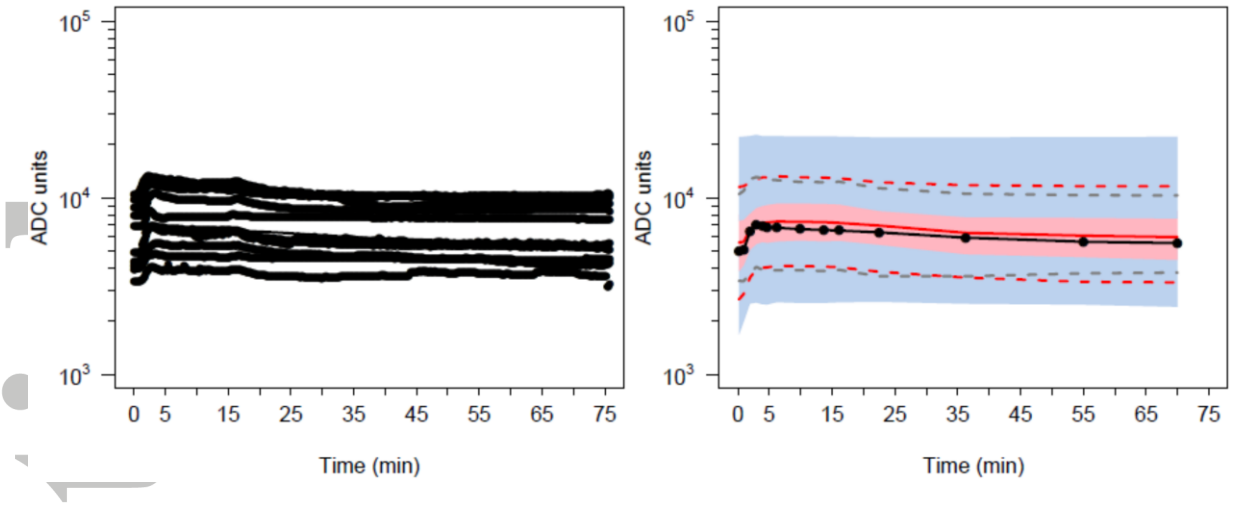

Fig. 4 Visual predictive check for the PK model. All plots show median and 90% intervals (solid and dashed lines). Left hand plot shows all prediction corrected observed concentrations. Right hand plot shows prediction corrected percentiles (10%, 50%, and 90%) for observations (black dashed lines) and predictions (pink dashed lines) and predictions (lines) with 95% confidence intervals for prediction percentiles (median, pink shading; 5^{th} and 95^{th} blue shading)

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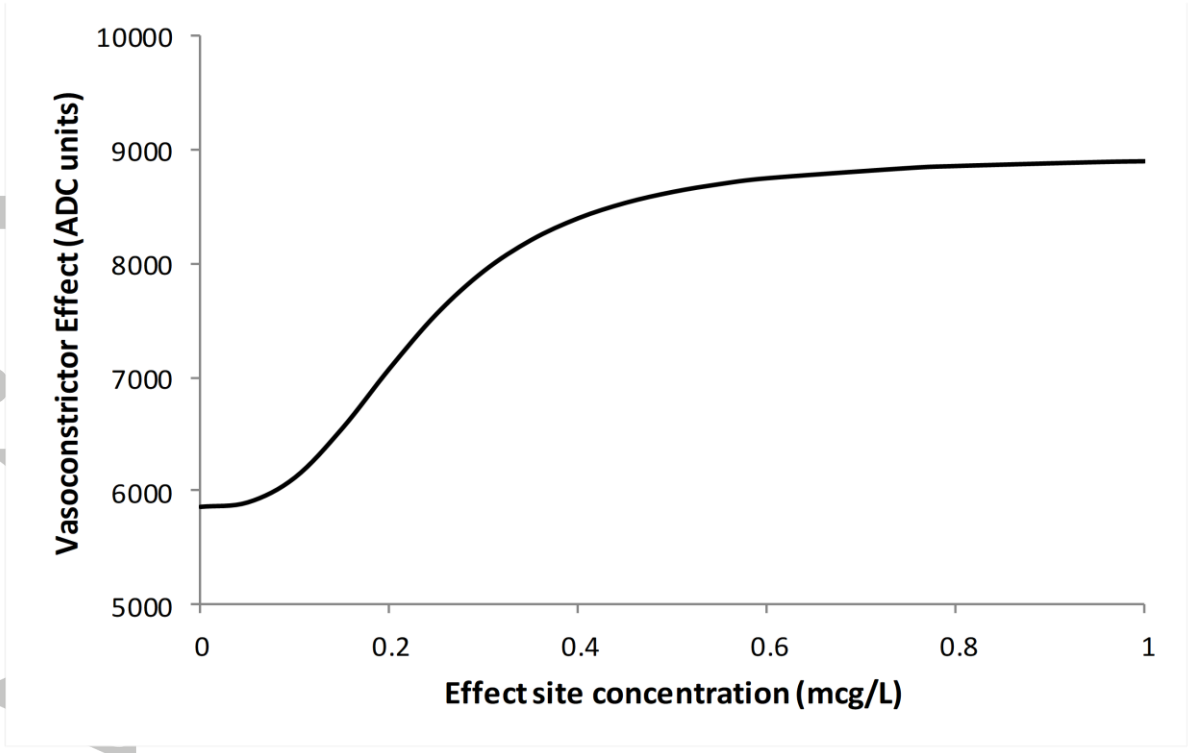

Fig. 5. A final model of absolute ADC units vs. dexmedetomidine plasma concentration illustrating a nonlinear relationship between effect site concentrations and vasoconstriction response.

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