

ANESTHESIOLOGY

A Pharmacokinetic and Pharmacodynamic Study of Oral Dexmedetomidine

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Dexmedetomidine is an alpha-2 adrenergic agonist sedative that is approved for intravenous use
- Plasma dexmedetomidine concentrations between 0.2 ng/ml and 0.3 ng/ml result in rousable sedation
- Low plasma dexmedetomidine concentrations are associated with decreased mean arterial pressure and heart rate

What This Article Tells Us That Is New

- The hypotheses that oral dexmedetomidine would be associated with hemodynamic stability and plasma concentrations consistent with rousable sedation were tested in a phase I dose-escalation study in 15 normal volunteers
- Oral dexmedetomidine bioavailability was low (7.2% [95% CI, 4.7 to 14%])
- Oral dexmedetomidine (300 µg, 500 µg, and 700 µg) was associated with plasma concentration-dependent decreases in mean arterial pressure and heart rate
- Only the 700-µg oral dose produced plasma concentrations associated with sedation

Dexmedetomidine is an alpha-2 adrenergic agonist sedative that promotes sleep neurophysiology.^{1–10} It is widely administered to patients in intensive care units as a pharmacologic aid to reduce the incidence and duration of delirium.^{11–15} Dexmedetomidine is only approved for use in humans as an intravenous medication. An oral

ABSTRACT

Background: Dexmedetomidine is only approved for use in humans as an intravenous medication. An oral formulation may broaden the use and benefits of dexmedetomidine to numerous care settings. The authors hypothesized that oral dexmedetomidine (300 mcg to 700 mcg) would result in plasma concentrations consistent with sedation while maintaining hemodynamic stability.

Methods: The authors performed a single-site, open-label, phase I dose-escalation study of a solid oral dosage formulation of dexmedetomidine in healthy volunteers (n = 5, 300 mcg; followed by n = 5, 500 mcg; followed by n = 5, 700 mcg). The primary study outcome was hemodynamic stability defined as lack of hypertension, hypotension, or bradycardia. The authors assessed this outcome by analyzing raw hemodynamic data. Plasma dexmedetomidine concentrations were determined by liquid chromatograph–tandem mass spectrometry. Nonlinear mixed effect models were used for pharmacokinetic and pharmacodynamic analyses.

Results: Oral dexmedetomidine was associated with plasma concentration-dependent decreases in heart rate and mean arterial pressure. All but one subject in the 500-mcg group met our criteria for hemodynamic stability. The plasma concentration profile was adequately described by a 2-compartment, weight allometric, first-order absorption, first-order elimination pharmacokinetic model. The standardized estimated parameters for an individual of 70 kg was $V_1 = 35.6$ [95% CI, 23.8 to 52.8] l; $V_2 = 54.7$ [34.2 to 81.7] l; $CL = 0.56$ [0.49 to 0.64] l/min; and $F = 7.2$ [4.7 to 14.4]%. Linear models with effect sites adequately described the decreases in mean arterial pressure and heart rate associated with oral dexmedetomidine administration. However, only the 700-mcg group reached plasma concentrations that have previously been associated with sedation (>0.2 ng/ml).

Conclusions: Oral administration of dexmedetomidine in doses between 300 and 700 mcg was associated with decreases in heart rate and mean arterial pressure. Despite low oral absorption, the 700-mcg dose scheme reached clinically relevant concentrations for possible use as a sleep-enhancing medication.

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formulation of dexmedetomidine is expected to broaden its sedation and delirium-sparing benefits to numerous care settings (e.g., general medical and surgical units). We recently reported that a single nighttime loading dose of intravenous dexmedetomidine promoted non-rapid eye movement stage 3 sleep, preserved regular sleep cycling, and may confer the cognitive benefits of sleep to healthy subjects.⁶ This result suggests that continuous infusions of dexmedetomidine may not be necessary for sleep promotion

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and that dexmedetomidine could be developed as an oral sleep-enhancing medication.

Whether a solid oral formulation of dexmedetomidine will reach plasma concentrations, and by proxy, brain concentrations necessary to promote sleep neurophysiology, is unclear. In humans, plasma concentrations of dexmedetomidine between 0.2 ng/mg and 0.3 ng/ml result in rousable sedation,¹⁶ whereas plasma concentrations above 1.9 ng/ml may be necessary for unarousable sedation.¹⁷ Also, intravenous dexmedetomidine has been associated with a biphasic mean arterial blood pressure (MAP) response.^{16–18} Low dexmedetomidine plasma concentrations (less than ~1.9 ng/ml) are associated with decreased MAP and heart rate (HR),¹⁷ whereas high plasma concentrations (greater than ~1.9 ng/ml) are associated with increased MAP.¹⁷ These MAP and HR findings are likely mediated through drug activity on peripheral vascular endothelium and in the central nervous system, respectively.^{16,19,20} However, MAP and HR changes associated with oral dexmedetomidine have not been characterized.

Therefore, we performed a phase I dose-escalation study (n = 5, 300 mcg; followed by n = 5, 500 mcg; followed by n = 5, 700 mcg) of oral dexmedetomidine. We hypothesized that oral dexmedetomidine would be associated with hemodynamic stability (see the Materials and Methods section for definition) and plasma concentrations that are consistent with rousable sedation. We constructed a pharmacokinetic–pharmacodynamic model to characterize the relationship between plasma concentrations of dexmedetomidine, MAP, and HR data.

Materials and Methods

The Partners Human Research Committee approved this study, which was conducted at the Massachusetts General Hospital, Boston, Massachusetts, and was registered on clinicaltrials.gov (NCT02818569) on June 29, 2016 (Principal Investigator: Oluwaseun Akeju). This study was conducted under a Food and Drug Administration Investigator–Initiated Investigational New Drug Application (IND129461). A data and safety monitoring board was charged with the safety of study subjects and to ensure that the scientific goals of the study were met.

Recruitment for this study occurred between October 2016 and April 2017. A study flyer was disseminated through the Partners Public Affairs distribution list. Potential study participants contacted a clinical research coordinator who administered a questionnaire to confirm that the study inclusion and exclusion criteria were met. The primary inclusion criterion was meeting the American Society of Anesthesiology Physical Status I. The following information was also verified by self-report: regular sleep–wake cycles, absence of naps or consumption of alcohol or caffeinated beverages before sleep, drug-free, and nonsmoking status. Before potential enrollment, subjects underwent a complete medical history and standard preanesthesia assessment.

Other procedures included a toxicology screen to rule out prohibited drug use, a pregnancy test for females, and an electrocardiogram to rule out cardiac conduction abnormalities. None of the subjects had any known history of sleep disorders or any physical or psychiatric illness. Written informed consent was obtained from all subjects before any study-related procedures. There was no evidence of abnormal liver or renal function blood tests at baseline screening.

This was a single-site, open-label, phase I dose-escalation study (n = 5, male = 2, 300 mcg; followed by n = 5, male = 4, 500 mcg; followed by n = 5, male = 1, 700 mcg) of a solid oral dosage formulation of dexmedetomidine in 15 healthy subjects. The primary outcome of the study was hemodynamic stability. We defined hemodynamic instability as (1) hypotension: systolic blood pressure (SBP) less than 60 mmHg, diastolic blood pressure (DBP) less than 40 mmHg, or decrease of SBP by greater than or equal to 50% from baseline which was sustained over two consecutive minutes; (2) hypertension: SBP greater than 180 mmHg, DBP greater than 100 mmHg, or increase of SBP by greater than 50% from baseline which was sustained over two minutes; or (3) bradycardia: HR less than 40 bpm or decrease by more than 50% from baseline sustained over two consecutive minutes.

Study subjects were instructed to arrive at 7:30 AM to prepare for study-related procedures. A urine toxicology screen was performed to rule out the use of prohibited substances, and a urine pregnancy test was also performed to rule out pregnancy in all female subjects. An anesthesiologist placed arterial and intravenous lines, and blood samples were obtained at the following intervals from the arterial line: baseline, 10, 20, 30, 45 min, and 1, 2, 3, 4, 5, 6, 7 h after the oral administration of dexmedetomidine. Blood samples were centrifuged within 2 h of collection at 3,000 revolutions per minute for 30 min at 24°C, stored in a –20°C freezer for 24 h and then transferred to a –80°C freezer for long-term storage (9 to 15 months) before transfer to an outside laboratory for plasma concentration analysis. The arterial line was also used to monitor blood pressure. Physiologic measurements included 5-lead electrocardiogram, pulse oximetry, end-tidal carbon dioxide, and 32-channel electroencephalogram data. Dexmedetomidine hydrochloride, USP, purchased from Jiangsu Hengrui Medicine Company Limited (China) was weighed in a laminar flow hood and packaged in oral capsules with lactose powder. The capsules were stored according to recommendations in airtight containers at room temperature and for less than 6 months. All capsules were administered before the drug retest date on the certificate of analysis. A board-certified anesthesiologist monitored all subjects throughout the study.

Plasma dexmedetomidine concentrations were determined by liquid chromatograph–tandem mass spectrometry. To each (0.1 ml) plasma sample and appropriate calibration standards, dexmedetomidine-D4 was added as an internal standard. Samples were extracted by protein precipitation

by the addition of 0.5 ml of acetonitrile. The samples were centrifuged and the supernatant transferred to autosampling vials. The analytic instrument was an AB Sciex API Qtrap 5500 quadrupole mass spectrometer equipped with QJet ion guide and accelerated by a LINAC collision cell (AB Sciex, USA) with an atmospheric pressure chemical ionization probe in a Turbo Vion source, interfaced with a Waters Corporation (USA) Acquity ultra pressure liquid chromatograph. Analyst software 1.6.2 (AB Sciex, USA) was used for system control and data processing. The liquid chromatography system was equipped with an Acquity UPLC HSS T3 1.8- μ m, 2.1 \times 50 mm HPLC column, and an Acquity UPLC HSS T3 1.84- μ m VanGuard precolumn (USA). The mobile phase consisted of a mixture of 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B) with a flow rate of 0.5 ml/min and run time of 2 min. Solvents A and B were combined in a gradient: 0 to 1 min: 85% A; 1 to 1.5 min: 50% A; 1.6 to 2 min: return to initial conditions and hold for 3 min. The electrospray source was operated in the positive ionization mode, using collision gas 12, curtain gas 20, ion source gas 40, and ion spray voltage 5,500 V with temperature 500°C. The instrument was operated in the multiple reaction monitoring mode. The following multiple reaction monitoring transitions of precursor ions to product ions were selected: dexmedetomidine, m/z 337.2 \rightarrow 188.2 (collision energy, 24 V); dexmedetomidine-D4, m/z 342.2 \rightarrow 188.2 (collision energy, 35 V). The scan time was 100 ms for all analyses. The concentration range in calibration standards was 0.05 to 5 ng/ml of dexmedetomidine. Thus, the lower limit of sensitivity was 0.05 ng/ml of plasma using a 0.1-ml sample. The within- and between-day variability did not exceed 10%.

The hemodynamic dataset contained SBP, DBP, and HR measurements collected every 5 s per session for all subjects. MAP was calculated based on SBP and DBP, as previously described.²¹ We assessed our primary study endpoint by analyzing the raw hemodynamic data in MATLAB (MathWorks, USA). Briefly, to detect episodes of hemodynamic instability, we first defined baseline as the mean of the first 5 min (60 data points). We assessed for hemodynamic instability (as defined above) by iteratively scanning the data over 24 data points using a sliding window of 1 data point (*i.e.*, 0 to 2 min, 5 s to 2 min 5 s, *etc.*).

We recorded electroencephalogram data using a standard 32-channel electroencephalogram cap (ANT Neuro, The Netherlands) with average referencing. We downsampled the electroencephalogram data to 256 Hz and analyzed data from C3–C4 and P3–P4 bipolar electrodes. We used the Chronux toolbox in MATLAB (MathWorks) to compute the multitaper spectral estimates. The spectral parameters were: TW or time-bandwidth product = 3, K or number of tapers = 5, and T or window size = 4 s with 3 s of overlapping windows.

For pharmacokinetic–pharmacodynamic modeling, we performed data reduction by retaining raw hemodynamic records 10 min apart. After data reduction, we checked the data to reduce the influence of artifacts associated with arterial line handling (*e.g.*, blood sample draws, saline flushes). For missing values or outlying values, we replaced the data using a 60-second median filter. For illustrative purposes, we calculated the mean MAP and mean HR and fitted a smooth function to the data ('rloess' method) in MATLAB (MathWorks).

One- and two-compartment, first-order absorption, and first-order elimination pharmacokinetic models were used to fit the dexmedetomidine plasma concentration (Cp) data. Population parameter estimates (V1, central volume of distribution [l]; V2, peripheral volume of distribution [l]; CL, elimination clearance [l/min]; Q, distribution clearance [l/min]; T_{abs} , absorption rate half-time [min]; and F_i bioavailability) were obtained using nonlinear mixed effects modeling performed in NONMEM v7.4 (ICON Development Solutions, USA). Population and individual parameters were estimated using the first-order conditional estimation method that included interaction options.²² The convergence criterion was 3 significant digits. Between-individual variability in model parameters was assumed to be log-normal. Residual variability was characterized by a proportional error model. Because our study subjects did not receive intravenous dexmedetomidine, we did not have a reference to estimate the fraction of the administered dose that reached the systemic circulation (F_i bioavailability). Thus, to estimate bioavailability, we pooled our study data with the data from a previous study of intravenous dexmedetomidine with 13 healthy normal-weight adults.²³ Data were selected from 13 nonobese healthy patients, aged 29 to 58 yr old, and weighing 47 to 91 kg, who received a loading dose of dexmedetomidine of 0.5 mcg/kg over 10 min followed by a continuous infusion of 0.5 mcg \cdot kg⁻¹ \cdot h⁻¹ during general anesthesia. Venous blood samples of 6 ml were drawn at 0, 5, 10, 20, 30, 45, 60, 90, 120, 240, and 360 to 480 min after the onset of dexmedetomidine administration. Dexmedetomidine serum concentrations were measured by high-performance liquid chromatography coupled with tandem mass spectrometric. The lower limit of quantification in this study was 0.01 ng/ml.

Parameter values were standardized to 70-kg total body weight, as expressed in equation 1:

$$P_i = P_{TVSi} \cdot \left(\frac{W_i}{70} \right)^{PWR} \quad (1)$$

where P_i is the parameter in the i^{th} subject, P_{TVSi} is the population parameter estimate standardized for a 70 kg subject, W_i is the weight of the i^{th} subject, and PWR is the exponent for the allometric model, accounting for a value of 1 for volume of distribution, 0.25 for absorption rate half-time, and 0.75 for clearance.

Individual pharmacokinetic model predictions were directly linked to HR and MAP data. Additionally, an effect compartment model was used to characterize the time delay between dexmedetomidine C_p and measured hemodynamic responses. This model was parameterized with a single parameter keo , the plasma effect-site equilibration rate constant, as expressed in equation 2:

$$\frac{dCe}{dt} = keo \times (C_p - Ce) \quad (2)$$

where Ce is the predicted dexmedetomidine effect-site concentration.

A linear model (Equation 3) and a sigmoidal E_{max} model (Equation 4) were used to fit hemodynamic response data.

$$Effect = E_0 + SLOPE \cdot Ce \quad (3)$$

$$Effect = E_0 + (E_{max} - E_0) \cdot \frac{Ce^\gamma}{Ce^\gamma + Ce_{50}^\gamma} \quad (4)$$

where E_0 is the heart rate value or mean arterial blood pressure value before dexmedetomidine administration. SLOPE describes the steepness of the linear concentration-response curve. E_{max} is the response value at the maximum drug effect. Ce_{50} is the effect-site concentration at half of E_{max} . γ is the coefficient describing the steepness of the concentration-response curve in the E_{max} model.

Pharmacokinetic parameters estimated for each individual (*post hoc* Bayesian estimates) in the previous pharmacokinetic step were used as input for the pharmacodynamic part of the analysis (sequential approach). Between-individual variability in model parameters was assumed to be log-normal. Residual variability for hemodynamic response data was characterized by an additive error model.

Model selection was based on the inspection of goodness-of-fit plots, visual predictive check plots, precision, plausibility of the estimated parameters, and minimum value of the objective function ($-2 \cdot \log[\text{likelihood}]$) estimated by NONMEM. For 2 nested models, a decrease in $-2 \cdot \log(\text{likelihood})$ of 3.84, or 6.63 points for an added parameter, is considered significant at 0.05 or 0.01, respectively (χ^2 distribution). Likelihood profiles, implemented in PLT Tools version 6 (a graphical interface for the NONMEM system),²⁴ provided a means to evaluate parameter uncertainty. Visual predictive check plots were simulated in R with the 'vpc' package. Visual predictive check plots are modeling tools that estimate the concentration prediction intervals and graphically superimpose these intervals on observed concentrations after a standardized dose.

We did not perform a formal sample size calculation. However, our sample size is consistent with a previous dexmedetomidine pharmacokinetic-pharmacodynamic study in 10 healthy volunteers.²⁵

Results

The mean \pm SD ages and weights were: 31.0 ± 11.0 yr and 71.2 ± 9.4 kg for the 300-mcg group; 25.0 ± 6.0 yr and 82.0 ± 7.6 kg for the 500-mcg group; and 24.0 ± 5.0 yr and 74 ± 17.9 kg for the 700-mcg group.

The maximum mean plasma concentrations of dexmedetomidine were 0.18 ± 0.18 ng/mL, 300-mcg group; 0.12 ± 0.09 ng/mL, 500-mcg group; and 0.38 ± 0.44 ng/mL, 700-mcg group. These data are summarized in figure 1A. MAP and mean HR data are presented in figure 1, B and C. We found that the maximum plasma concentration in the 500-mcg group was lower than the 300-mcg group. However, measured plasma concentrations were consistent with hemodynamic changes. Dexmedetomidine plasma concentration, electroencephalogram, and HR data of an illustrative subject from each dose group (300 mcg, 500 mcg, and 700 mcg) are presented in Supplemental Digital Content 1 through 3 (<http://links.lww.com/ALN/C480>, <http://links.lww.com/ALN/C481>, <http://links.lww.com/ALN/C482>).

One subject in the 500-mcg group did not satisfy our criteria for hemodynamic stability. This subject, with a baseline HR in the 50s, exhibited HRs less than 40 bpm that lasted 2.5 min. This event began 295 min after the administration of dexmedetomidine when the subject was sleeping (electroencephalogram slow-delta and spindle oscillations were observed; Supplemental Digital Content 2, <http://links.lww.com/ALN/C481>) and resolved spontaneously. No other periods in this, nor other subjects, met our definition of hemodynamic instability. No other adverse events were reported during this study.

We observed that the measured plasma concentrations were not consistent with the increase in dexmedetomidine dose (*i.e.*, the maximum plasma concentration in the 500-mcg group was lower than the 300-mcg group; fig. 1A). Therefore, to estimate the pharmacokinetic-pharmacodynamic parameters reliably, we excluded the 500-mcg group data from our modeling analysis.

Dexmedetomidine plasma concentration data were better described by a 2-compartment than a 1-compartment, first-order absorption, and first-order elimination, pharmacokinetic model (ΔOBI 215.128, $P < 0.001$). The body weight in our study ranged between 63 and 103 kg. Considering the sample size and observed inconsistencies in dose-concentration relationships, we decided to use a weight scaled allometric model as our base structural model. This model assumes robust previous knowledge regarding the effect of size in model parameters.²⁶ An additional parameter to represent elapsed time between drug intake and the beginning of the absorption process (time lag) elicited an improvement in model fit (ΔOBI 93.347, $P < 0.001$). No other covariates were tested. The 2-compartment model with time lag was selected as our final pharmacokinetic model. Final population parameter estimates, coefficient of variation, standard errors, and

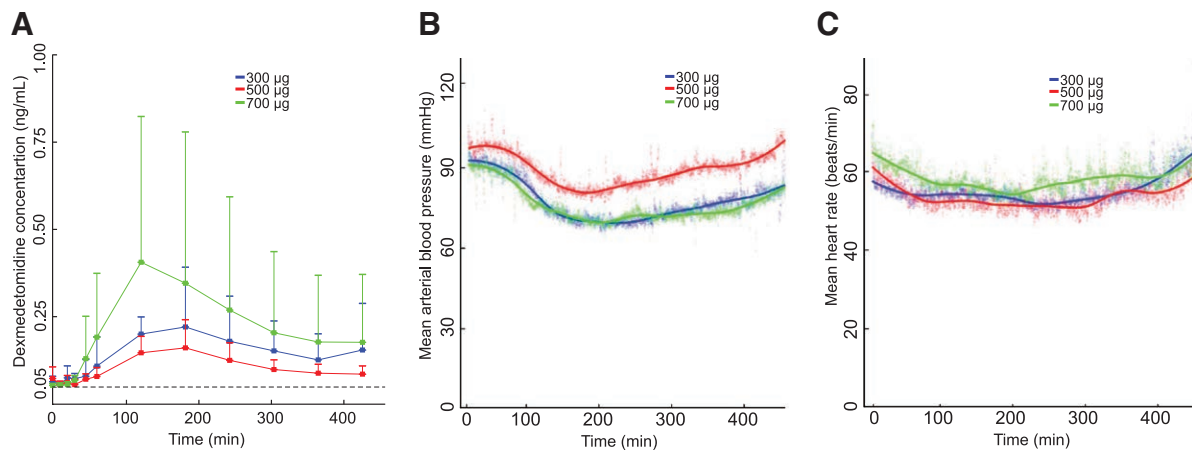


Fig. 1. Dexmedetomidine plasma concentration, mean arterial blood pressure, and mean heart rate. (A) Dexmedetomidine plasma concentration measured by liquid chromatograph–tandem mass spectrometry. The mean plasma concentration for the 500-mcg group was lower than the 300-mcg and 700-mcg groups at all time points beginning 30 min after drug administration. Vertical error bars represent the SD. Dotted black line at 0.05 ng/ml represents the lower limit of sensitivity. (B) Group mean arterial blood pressure. The line represents a smoothed best-fit line to the data. Shaded colored bubbles represent the mean of arterial pressure over each group. (C) Group mean heart rate. The line represents a smoothed best-fit line to the data. Shaded colored bubbles represent the mean of heart rate over each group. Blue color represents the 300-mcg group ($n = 5$), red color represents the 500-mcg group ($n = 5$), and the green color represents the 700-mcg group ($n = 5$). Mcg, micrograms.

95% CI are presented in table 1. Diagnostic plots confirmed the adequacy of model fit in the oral study data (fig. 2A, Supplemental Digital Content 4, parts A and C [http://links.lww.com/ALN/C483], Supplemental Digital Content 5, parts A, C, E [http://links.lww.com/ALN/C484], and Supplemental Digital Content 6, Part A [http://links.lww.com/ALN/C485]), and the pooled intravenous study data (fig. 2B, Supplemental Digital Content 4, Parts B, D [http://links.lww.com/ALN/C483], Supplemental Digital Content 5, Parts B, D, F [http://links.lww.com/ALN/C484], and Supplemental Digital Content 6, Part B [http://links.lww.com/ALN/C485]).²⁷

The observed decreases in MAP and HR after the administration of oral dexmedetomidine were adequately described by linear models. We also tested the sigmoidal inhibitory Emax model. However, with both responses, the Emax and C50 parameters were estimated with poor precision. The linear model was selected as our final structural model for MAP and HR. In our modeling approach, we first directly related dexmedetomidine plasma concentrations and response data. Then, we incorporated an effect site model. The effect-site model improved the fit of the MAP data ($\Delta\text{OBJ } 159, P < 0.001$) and the HR data ($\Delta\text{OBJ } 71.332, P < 0.001$). The likelihood profile analysis confirmed that E_0 , slope, and keo parameters were estimated with good precision for both responses. Final population parameter mean (coefficients of variation %), standard error, and 95% CI are presented in table 2 and table 3 for MAP and HR, respectively. Diagnostic plots (visual predictive

Table 1. Summary of Dexmedetomidine Individual Pharmacokinetic Parameter Estimates

Parameters	Typical Value of the Population (Coefficient of Variation, %)	Standard Error	95% CI
Central volume of distribution, V_1 (l)	35.6 (19.4)	6.92	23.8, 52.8
Peripheral volume of distribution, V_2 (l)	54.7 (17.9)	9.83	34.2, 81.7
Elimination clearance, CL (l/min)	0.56 (6.3)	0.03	0.49, 0.64
Distribution clearance, Q (l/min)	2.18 (11.4)	0.24	1.76, 2.69
Absorption rate half-time, T_{abs} (min)	54.7 (17.9)	11.6	26.1, 96.5
Lag time (min)	41.6 (2.4)	0.99	39.3, 47.6
Bioavailability, F (%)	7.2 (26.1)	0.02	4.7, 14.4
Additive residual error (ng/ml)	0.02	—	—
Proportional residual error (%)	27	—	—

Between-subject variability expressed as an apparent coefficient of variation. CI, CI of the parameter estimated by likelihood profile.

check and goodness of fit plots) confirmed the model adequately, describing the median observed MAP (fig. 3A, Supplemental Digital Content 7, parts A, C, E [http://links.lww.com/ALN/C486], and Supplemental Digital Content 8, parts A, C [http://links.lww.com/ALN/C487])²⁷ and HR (fig. 3B, Supplemental Digital Content 7, parts B, D, F [http://links.lww.com/ALN/C486] and Supplemental Digital Content 8, parts B, D [http://links.lww.com/ALN/C487])²⁷ in the dataset. For MAP model, variability in the dataset is overpredicted.

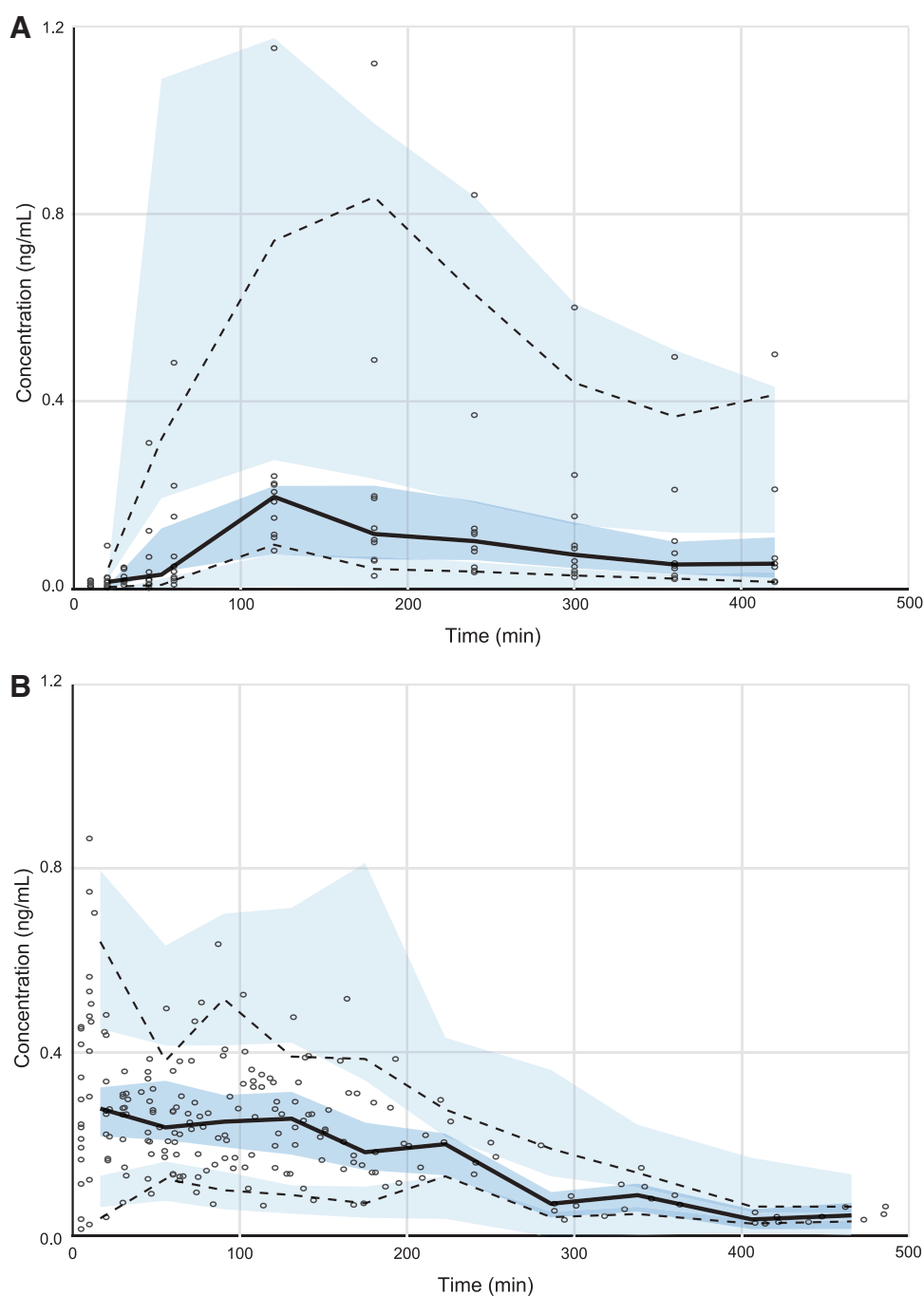


Fig. 2. Visual predictive check (VPC) plots. Dexmedetomidine plasma concentration of (A) our oral study group ($n = 10$) and (B) pooled intravenous study group ($n = 13$). Solid black line indicates 50 percentiles and dashed black lines indicate 2.5 and 97.5 percentiles of observation. Shaded area indicates 95% prediction interval. The VPC plot confirms the adequacy of model predictions, showing no apparent deviations between model and data. The 95% CI and median for observed data lies within the predicted intervals obtained by simulation.

Discussion

In this phase I study, we administered a solid oral formulation of dexmedetomidine to healthy human subjects and assessed for hemodynamic stability. Oral dexmedetomidine (300

mcg, 500 mcg, and 700 mcg) resulted in maximum mean plasma concentrations (0.12 to 0.38 ng/ml) that occurred 2 to 3 h after drug administration. These doses were associated with low plasma concentration-dependent decreases in MAP and HR that were adequately described by linear

Table 2. Dexmedetomidine Population Pharmacodynamic Parameter Estimates for the Effect in Mean Arterial Blood Pressure

Parameters	Mean (Coefficient of Variation, %)	Standard Error	95% CI
Effect at zero concentration, E_0 (mmHg)	90 (10)	3.1	84, 96
Slope	-704 (70)	159	-1,168, -426
Rate constant for elimination from the effect compartment, K_{20} (min^{-1})	0.005 (20)	0.0007	0.0007, 0.006
Additive Error (mmHg)	5.44	—	—

CI, CI of the parameter estimated by likelihood profile analysis.

effect-site models. However, only the 700-mcg group was associated with plasma concentrations that have previously been associated with sedation (greater than 0.2 ng/ml).¹⁶

The primary outcome of this study was hemodynamic stability. We did not intervene with vasoactive medications to maintain hemodynamic stability in any study subject because the MAP and HR decreases associated with oral dexmedetomidine were not deemed clinically significant. We did not observe the known biphasic effect of dexmedetomidine on the MAP (decrease followed by increase) in our study. This is likely because plasma concentrations in our study were much lower than those associated with the hypertensive effect of dexmedetomidine (onset of hypertension ranges from 1.9 ng/ml¹⁷ to 2.4 ng/ml¹⁶).

One subject in the 500-mcg group experienced an episode of bradycardia with HR less than 40 bpm that lasted for 2.5 min before spontaneous resolution (Supplemental Digital Content 2, <http://links.lww.com/ALN/C481>). This episode occurred approximately 5 h after the administration of dexmedetomidine, at a relatively low plasma concentration (0.05 to 0.08 ng/ml), and approximately 3 h after we measured the peak plasma concentration of 0.15 ng/ml. During this episode, delta (0.1 to 4 Hz) and spindle (13 to 16 Hz) oscillations, which were consistent with rapid eye movement stage 2 sleep, were visible on the electroencephalogram. Thus, it is likely that this HR finding was normotypical of sleep in this subject.

We previously found that a nighttime 1-mcg/kg loading dose of intravenous dexmedetomidine biased the sleep architecture during the first half of the night to non-rapid eye movement stage 3 sleep,⁶ which is also known as restorative sleep. The plasma concentration profile of oral dexmedetomidine in our study did not approximate those previously reported for a 1-mcg/kg loading dose of intravenous dexmedetomidine.^{16,28} Thus, it is unlikely that oral dexmedetomidine will bias the sleep architecture to restorative sleep. However, in humans, relatively low doses of dexmedetomidine have been associated with non-rapid eye movement stage 2 sleep

Table 3. Dexmedetomidine Population Pharmacodynamic Parameter Estimates for the Effect in Mean Arterial Heart Rate

Parameters	Mean (Coefficient of Variation, %)	Standard Error	95% CI
Effect at zero concentration, E_0 (mmHg)	60 (11)	2.3	56, 65
Slope	-160 (56)	48	-273, -89
Rate constant for elimination from the effect compartment, K_{20} (min^{-1})	0.011 (69)	0.005	0.008, 0.029
Additive error (mmHg)	5.7	—	—

CI, CI of the parameter estimated by likelihood profile analysis.

in numerous studies.^{29–31} Thus, although the bioavailability of oral dexmedetomidine reported in this study was low, a clinical implication of our finding is that 700 mcg of oral dexmedetomidine is likely to promote non-rapid eye movement stage 2 sleep. Further, the nocturnal administration of low-dose dexmedetomidine has been associated with decreased incidence and duration of delirium.^{15,32} Thus, another clinical implication of our finding is that the nocturnal administration of oral dexmedetomidine may generalize its delirium sparing benefits to non-intensive care unit settings.

The plasma concentration time profile of oral and intravenous dexmedetomidine was adequately described by a 2-compartment, first-order absorption, and first-order elimination, pharmacokinetic model. The elimination clearances and volume of distribution in our study are largely consistent with previous studies.^{16,33} A relevant finding from the current pharmacokinetic analysis is that overall bioavailability after oral administration was low (7.2% [95% CI, 4.7 to 14]). To allow estimation of bioavailability, we pooled the current data with a subset of data from a previous study that administered dexmedetomidine intravenously. We note that our estimate could be biased because intravenous data were based on venous rather than arterial sampling, and drug concentrations were measured using a different assay. However, our findings are consistent with a previous study that reported a 16% oral bioavailability of dexmedetomidine compared with an 82% buccal bioavailability, suggesting an extensive first-pass effect.³⁴

The major limitation of our study is that the measured plasma concentrations of the 500-mcg group were lower than concentrations observed in the 300-mcg group. We reviewed study records with the trial pharmacist and confirmed that this finding was not secondary to dispensing errors and might be attributable to poor dexmedetomidine content uniformity in capsules. To eliminate the inconsistencies observed in the dose-concentration relationship between the 300-mcg and 500-mcg doses, we decided to exclude the 500-mcg group from our modeling analysis. The fact that current pharmacokinetic estimates are

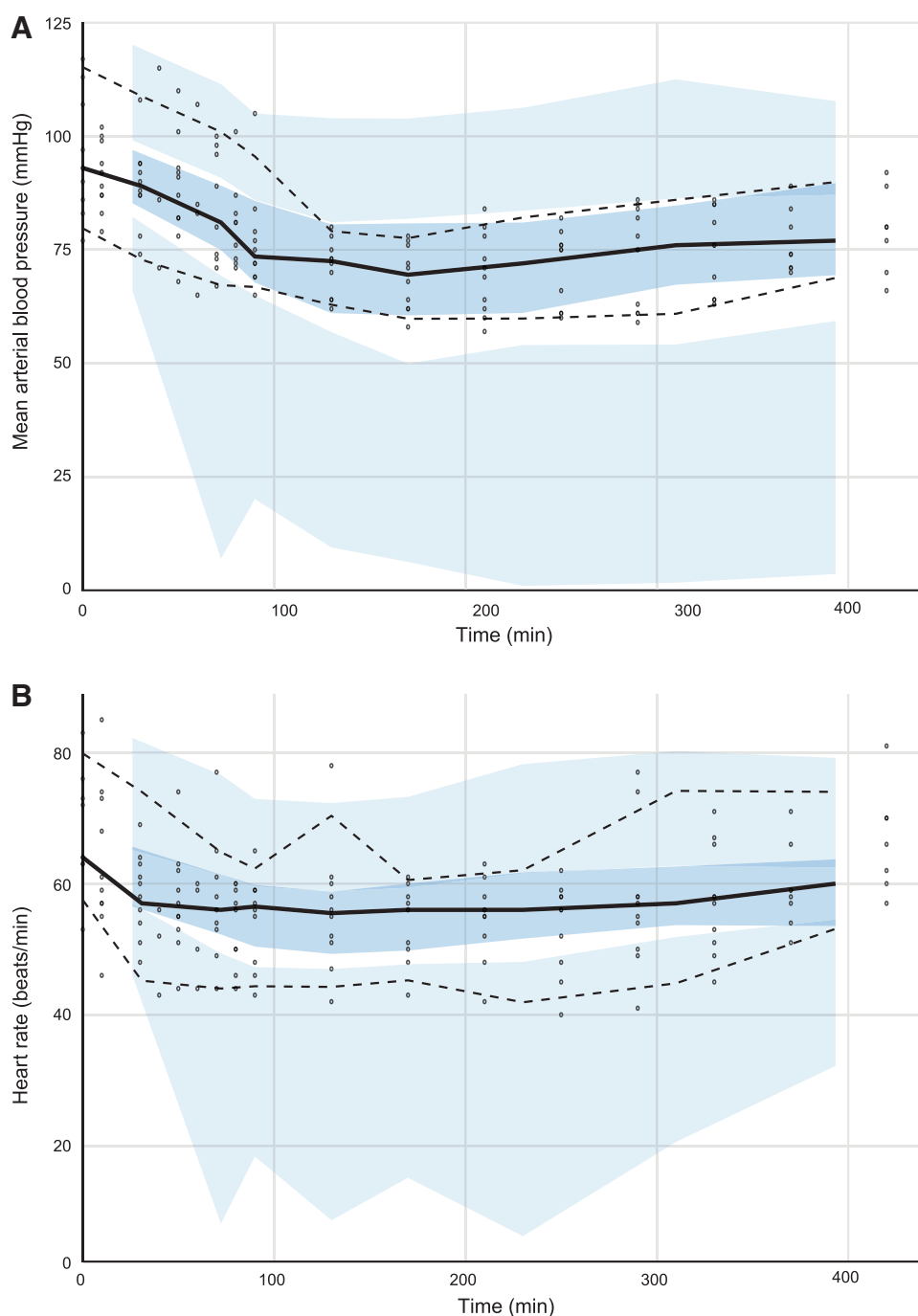


Fig. 3. Visual predictive check (VPC) plots. (A) Mean arterial blood pressure and (B) heart rate *versus* time. Solid black line indicates 50 percentiles, and dashed black lines indicate 2.5 and 97.5 percentiles of observation. Shaded area indicates 95% prediction interval. The VPC plot confirms the adequacy of model predictions, showing no apparent deviations between model and data. The 95% CI and median for observed data lies within the predicted intervals obtained by simulation.

consistent with those of previous studies supports our modeling approach.^{16,33,34} Other limitations are that we studied only healthy subjects between 20 to 47 yr of age, lacked a placebo group, and had a relatively low sample size.

The overprediction of the variability in our MAP model is a likely consequence of the limited sample size used to develop the model. Further, we did not study hemodynamic stability after the administration of anesthetic drugs

that are known to significantly affect physiology.^{35–40} Thus, future studies in various populations are necessary.

We conclude that oral administration of dexmedetomidine in doses between 300 and 700 mcg was associated with decreases in heart rate and mean arterial pressure. Despite low oral absorption, the 700-mcg dose scheme reached clinically relevant concentrations for possible use as a sleep-enhancing medication.

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Competing Interests

Dr. Akeju has received speaker's honoraria from Masimo Corporation (Irvine, California) and is listed as an inventor on a patent on brain monitoring during general anesthesia and sedation that is assigned to Massachusetts General Hospital (Boston, Massachusetts). Dr. Akeju has received institutionally distributed royalty from this licensed patent. Drs. Pedemonte and Cortinez have received funds from the Department of Anesthesiology, School of Medicine, Pontificia Universidad Católica de Chile (Santiago, Chile). The remaining authors declare no competing interests.

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McKennan's Local Anesthetic Branded Maxine—Utilitarian or Uxorial?



At 11 yr of age, Roy Clinton McKennan (1880 to 1958) moved with his Hoosier parents from his native Illinois back to their Connersville home in east central Indiana. Roy spent his college years 130 miles to the northwest at Purdue University, where he earned his graduate pharmacy degree, his Ph.G., in 1900. He returned home to Connersville to partner with his pharmacist father in the firm of S.O. McKennan & Son. In 1905 young McKennan had prospered well enough to marry his high school sweetheart. By 1912 he had compounded his “Maxine” local anesthetic, his proprietary brand for dental extractions and “All Other Minor Surgical Operations.” He advertised his original Maxine as comprised of 1.1% cocaine and his Maxine Special as 2% procaine (Novocain) compounded with “Adrenaline 1:30000, Phenol 1:500, and Glycerin” (right). Derived from Latin *via* French, “Maxine” means “greatest,” perhaps an appropriate branding for what McKennan advertised as the “ideal local anesthetic.” On the other hand, “Maxine” may have been named after or by his wife, Madge M. Kensler McKennan. So, regarding Maxine local anesthetic, was Roy McKennan’s branding utilitarian...or uxorial? (Copyright © the American Society of Anesthesiologists’ Wood Library-Museum of Anesthesiology.)

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