

## CLINICAL INVESTIGATIONS

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# The Pharmacokinetics and Hemodynamic Effects of Intravenous and Intramuscular Dexmedetomidine Hydrochloride in Adult Human Volunteers

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**Background:** Dexmedetomidine is an  $\alpha_2$  agonist with potential utility in clinical anesthesia for both its sedative and sympatholytic properties.

**Methods:** The pharmacokinetics and hemodynamic changes that occurred in ten healthy male volunteers were determined after administration of dexmedetomidine 2  $\mu\text{g}/\text{kg}$  by intravenous or intramuscular route in separate study sessions.

**Results:** The intramuscular absorption profile of dexmedetomidine, as determined by deconvolution of the observed concentrations against the unit disposition function derived from the intravenous data, was biphasic. The percentage bioavailability of dexmedetomidine administered intramuscularly compared with the same dose administered intravenously was  $73 \pm 11\%$  (mean  $\pm$  SD). After intramuscular administration, the mean time to peak concentration was 12 min (range 2–60 min) and the mean peak concentration was  $0.81 \pm 0.27$  ng/ml. After intravenous administration of dexmedetomidine, there were biphasic changes in blood pressure. During the 5-min intravenous infusion of 2  $\mu\text{g}/\text{kg}$  dexmedetomidine, the mean arterial pressure (MAP) increased by 22% and heart rate (HR) declined by 27% from baseline values. Over the 4 h after the infusion, MAP declined by 20% from baseline and HR rose to 5% below baseline values. The hemodynamic profile did not show acute alterations after intramuscular administration. During the 4 h after intramuscular administration, MAP declined by 20% and HR declined by 10%.

**Conclusions:** The intramuscular administration of dexmedetomidine avoids the acute hemodynamic changes seen with intravenous administration, but results in similar hemodynamic alterations within 4 h. (Key words: Hemodynamics. Pharmacokinetics. Sympathetic nervous system,  $\alpha_2$  agonists: dexmedetomidine.)

THE  $\alpha_2$ -adrenergic agonists are a new class of potentially useful adjunctive anesthetic agents. Clonidine, the prototypic  $\alpha_2$ -adrenergic agonist, is the most widely used drug of this class of compounds and decreases anesthetic and analgesic requirements in surgical patients.<sup>1</sup> Furthermore, clonidine administered before anesthetic induction may also minimize intraoperative hemodynamic fluctuations and is an effective anxiolytic agent. Because clonidine has a long duration of action and is a partial agonist with only modest selectivity for the  $\alpha_2$  versus the  $\alpha_1$  adrenoceptor, a second generation of  $\alpha_2$  agonists is now being developed in an attempt to overcome the perceived shortcomings of clonidine in anesthetic settings. Dexmedetomidine (1,620:1 [ $\alpha_2$ : $\alpha_1$ ]) is more selective at the  $\alpha_2$  adrenoceptor than is clonidine (220:1) and is a full agonist.<sup>2</sup>

To administer dexmedetomidine accurately, it is necessary to characterize the pharmacokinetic profile using relevant doses *via* the intended routes of administration, and to correlate side effects, such as hemodynamic alterations, with the plasma concentrations of medication. Using a crossover study design, with dexmedetomidine administered intravenously and intramuscularly, we characterized dexmedetomidine pharmacokinetics and hemodynamic alterations in ten healthy adult volunteers.

## Materials and Methods

### Subjects

After approval by the Stanford University Investigational Review Board, ten healthy male volunteers were recruited for this study. The average age of the subjects was 35.5 yr (range 29–44 yr) and the average weight

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was 79 kg (range 60–98 kg). Male subjects between the ages of 18–50 yr, with weight less than 100 kg and ASA physical status 1–2, were eligible for study.

The volunteers were fasted from midnight before the study and were asked to abstain from any caffeine or alcohol consumption for the preceding 24 h. On arrival at the study site, an 18-G intravenous cannula was inserted, and 500 ml normal saline was rapidly infused, followed by an infusion at 125 ml/h. A 20-G catheter was inserted into the radial artery and used both to measure arterial blood pressure and to sample blood for analysis of plasma dexmedetomidine concentrations. After fluid loading, 2 µg/kg dexmedetomidine hydrochloride was administered intravenously with an infusion pump at a constant rate over 5 min. Subjects were kept in the supine position in a quiet room and disturbances were minimized until the initial 4 h of recording was completed. A minimum of 2 weeks after the intravenous study, the volunteer was given the same dose of dexmedetomidine as a single intramuscular injection into the deltoid muscle over 30 s during an otherwise similar study procedure.

#### *Blood Sampling*

Arterial blood was sampled at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5, 6, 8, 10, 12, 15, 20, 30, 45, 60, 90, 120, 180, and 240 min after the start of the intravenous infusion. The blood pressure transducer was exposed to valid arterial pressure waveform for at least 15 s between each of the blood samples obtained during the first 5 min of the intravenous infusion. During the intramuscular phase of the study, blood was sampled at 2, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 min after injection. Venous blood during both phases was sampled at 180, 240, 300, 450, 600, 900, 1,200, and 1,440 min. The 5-ml K<sub>2</sub>EDTA anticoagulated samples were centrifuged and the plasma frozen at –40° C until the dexmedetomidine concentration was assayed. Blood sampling changed from arterial to venous at 4 h to minimize the length of time the volunteers were subjected to the presence of an arterial line.

#### *Dexmedetomidine Assay*

The plasma was assayed for dexmedetomidine concentration using a gas chromatograph (GC) with mass spectroscopy (MS) detection.<sup>3</sup> The pentafluorobenzoyl derivatives of dexmedetomidine and the internal standard detomidine were produced during extraction of the plasma into n-hexane in the presence of Na<sub>2</sub>CO<sub>3</sub>

and pentafluorobenzoyl chloride. The organic phase was evaporated and the residue reconstituted in toluene. A 1-µl aliquot was injected onto a Hewlett-Packard fused silica capillary column cross linked with 5% phenyl methyl silicone (Part number 19091J-102, Hewlett-Packard Company, Little Falls, DE) of a Hewlett-Packard gas chromatograph (Model 5890A, Hewlett-Packard Company, USA) using helium as the carrier gas. The GC oven was programmed for 1 min at 90° C and 30° C/min up to 275° C with a 5.8-min hold at 275° C. The MS (Finnigan MAT TSQ 70, Finnigan MAT) using methane as the carrier gas was operated in negative ion chemical ionization and selected ion monitoring mode with 70 eV ionization energy at 200° C. The pentafluorobenzoyl derivatives of detomidine were detected at 380.1 (mass/charge ratio) and dexmedetomidine at 394.1. The lower limit of quantitation for this GC/MS technique was 50 pg/ml, recovery of tritiated dexmedetomidine was 81%, and the coefficient of variation for within-day assays at 75 pg/ml was 12%, at 350 pg/ml was 9%, and at 600 pg/ml was 17.1%. The coefficient of variation for between-day assays at 212 pg/ml was 12.8%, and at 537 pg/ml was 11.3%. When three extractions were injected into the GC/MS system ten times each, at 75, 350, and 600 pg/ml, respectively, the coefficient of variation was 9.7%, 7.5%, and 11.3%, respectively.

#### *Pharmacokinetic Analysis*

**Moment Analysis.** Moment analyses were performed on both the intravenous and intramuscular data to calculate the model independent parameters: area under the concentration *versus* time curve (AUC), area under the first moment of the concentration *versus* time curve (AUMC), clearance (Cl), volume of distribution (V<sub>d,ss</sub>), and mean residence time (MRT). Values for AUC and AUMC are intermediate steps in the calculations and are presented for the sake of continuity. The AUC was calculated using the trapezoidal method with linear interpolation when concentrations were increasing and log-linear interpolation when concentrations were decreasing.<sup>4</sup> At time points where both arterial and venous concentrations were obtained, the venous values were used in the trapezoidal integration. Extrapolation from the terminal data point to infinity was accomplished using log-linear regression of the terminal elimination phase and is presented as the terminal elimination half-life or ln(2) divided by the slope of the terminal phase. In similar fashion, the AUMC was calculated as the trapezoidal integration of the curve generated by mul-

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tipling each plasma concentration by its time. The volume of distribution at steady state was calculated as follows:<sup>5</sup>

$$Vd_{ss} = \frac{Dose \times AUMC}{(AUC)^2} - \frac{Dose \times T}{2 \times AUC},$$

where T was the duration of the infusion. Clearance was calculated as the ratio of dose to AUC:<sup>5</sup>

$$CL = \frac{Dose}{AUC},$$

and MRT as the ratio of  $Vd_{ss}$  to clearance:<sup>5</sup>

$$MRT = \frac{Vd_{ss}}{CL}.$$

The bioavailability of intramuscular dexmedetomidine was calculated as the ratio of the AUC after intramuscular *versus* intravenous administration of the same dose:

$$\% \text{ Bioavailability} = \frac{AUC_{IV}}{AUC_{IM}} \times 100.$$

**Deconvolution Analysis.** Based on the assumption that the pharmacokinetics of dexmedetomidine are linear and stationary, but making no assumptions about model structure, the absorption characteristics of intramuscular dexmedetomidine were determined through least-squares deconvolution of the intramuscular concentration *versus* time function with the intravenous unit disposition function (UDF)<sup>6,7</sup> for each individual patient. Knowing that:

$$C_p = I * D (* = \text{convolution operator}).$$

where  $C_p$  is the concentration in the plasma, I is the input function, and D is the unit disposition function, the known zero order intravenous infusion of dexmedetomidine can be deconvolved against the plasma *versus* time concentration profile to produce the intravenous-UDF. The deconvolution was constrained to be positive and unimodal.

#### Arterial Wave Form Recording and Analysis

The radial artery cannula was connected to a Deltran II transducer (Model 901-007, Utah Medical Products Inc., Midvale, Utah) on a Hewlett-Packard 78353A monitor. Analog output from the HP monitor was recorded by a TEAC R-71 recorder and simultaneously digitized on a DT2801 Data Translation A/D board at 128 Hz with 12-bit resolution to the hard disk of an

80386-based computer. Calibration signals were recorded from a Delta-Cal Transducer Simulator (Model 650-905, Midvale, Utah) at 0, 50, 100, 150, and 200 mmHg. The digitized binary file was read and analyzed with software that located the peak and trough of each wave, and calculated the MAP by integrating the area beneath the wave. The algorithm has specific criteria that define a wave, and rejected signals caused by opening the stopcock to draw a blood sample or flushing the arterial catheter. The heart rate was calculated as the reciprocal of the time interval between wave peaks. The systolic and diastolic blood pressure, MAP, and heart rate were recorded for each wave on the arterial pressure trace during the study. The hemodynamic data reported represents the median MAP and heart rate values for each 60-s period.

## Results

Figure 1 shows the dexmedetomidine plasma concentration *versus* time profiles for all ten volunteers during the 5-min intravenous infusion and for the following 24 h. At 3 and 4 h after the infusion, simultaneous arterial and venous blood samples were drawn. This allowed us to remove the arterial catheter from the subject while still sampling pharmacokinetic data. The venous concentrations were consistently higher than the arterial concentrations, as would be expected during the elimination phase of the pharmacokinetic profile.<sup>8</sup> The rise in plasma concentration was probably not elution from storage sites in skeletal muscle, because the subjects remained supine from the start of

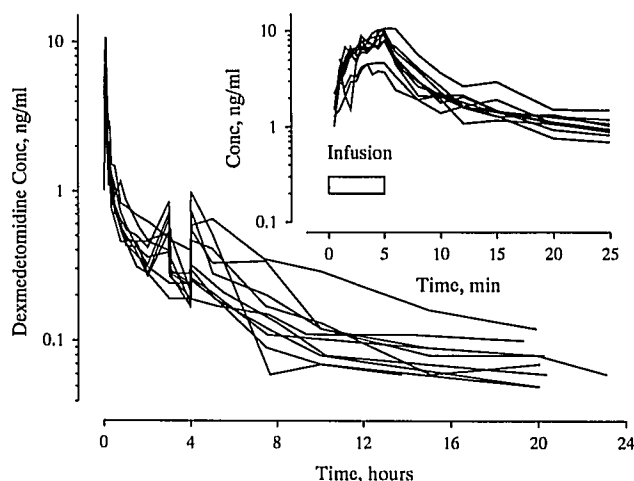


Fig. 1. Dexmedetomidine intravenous plasma concentration *versus* time.

**Table 1. Moment Analysis Intravenous (IV) Data**

Subject No.	AUC IV 0 to Infinity (ng · min · ml <sup>-1</sup> )	Terminal Half-life (min)	AUC (% under Data)	Clearance (L/min)	V <sub>ss</sub> (L)	AUMC (ng · min <sup>2</sup> )	AUMC (% under Data)	MRT (min)
1	361	963	62	0.403	486	437,000	19	1207
2	356	475	90	0.440	211	172,000	60	480
3	571	455	86	0.342	187	314,000	53	547
4	335	499	94	0.502	203	136,000	66	405
5	305	300	90	0.397	174	135,000	63	440
6	353	410	90	0.397	210	188,000	63	530
7	297	624	94	0.621	251	121,000	65	404
8	235	277	98	0.672	186	65,900	89	277
9	260	237	95	0.668	161	63,400	73	241
10	251	185	97	0.562	161	72,300	84	285
Mean*	329	385	90	0.511	194	141,000	68	401
SD	101	144	3.8	0.125	28.7	79,000	11	112

AUC = area under the curve; V<sub>ss</sub> = volume of distribution at steady state; AUMC = area under first moment curve; MRT = mean residence time.

\* Subject 1 excluded from summary statistics.

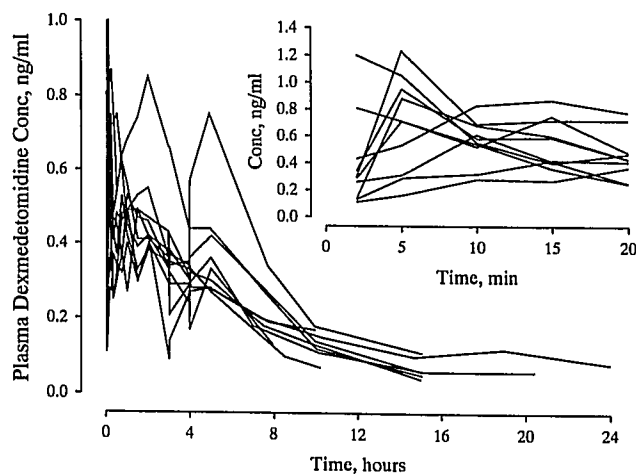
the study until the 240-min sample, and were only starting to ambulate by 300 min. The plasma dexmedetomidine concentrations after intravenous administration decreased to less than the limit of quantitation in six patients by 20 h after administration.

Moment analysis of the intravenous data for the ten subjects is presented in table 1. The MRT of subject 1 was so long that 24-h sampling did not adequately characterize the AUC. The AUC data for this subject encompassed only 62% of the total area and the AUMC 19%. The means of the moment analysis, therefore, do not include this subject. The mean clearance was  $0.511 \pm 0.125$  L/min, V<sub>d<sub>ss</sub></sub> was  $194 \pm 28.7$  L, and MRT was  $401 \pm 112$  min.

Figure 2 shows the plasma concentration *versus* time profile after intramuscular administration of 2 µg/kg dexmedetomidine. The time to peak plasma concentration was  $13 \pm 18$  min and the mean peak concentration was  $0.81 \pm 0.27$  ng/ml (table 2). The variability in peak and time to peak concentrations was high. This was due, in large part, to the first two subjects who showed slower absorption with longer time to peak concentrations and lower peak concentrations. If the mean values are recalculated to include only subjects 3–10, the time to maximum concentration was  $6.1 \pm 4.4$  min and the maximum concentration was  $0.91 \pm 0.22$  ng/ml. The average area under the concentration *versus* time curve for all subjects was  $243 \pm 78$  ng · min<sup>-1</sup> · ml<sup>-1</sup> and the average bioavailability was  $73 \pm 11\%$  (table 2).

The concentration *versus* time profile for the intravenous administrations was deconvolved against the

known zero order input function to arrive at the calculated unit disposition function (UDF) for each subject. Deconvolution was constrained to be positive and unimodal to restrict the output to physiologically meaningful results. Figure 3 shows average intravenous-UDF ( $\pm$  SD) of the ten subjects calculated through the deconvolution technique. The resulting UDF for dexmedetomidine after intravenous administration was deconvolved against the concentration *versus* time profile after intramuscular administration on a patient-by-patient basis to produce the rate of intramuscular absorption shown in figure 4. Integration of the absorption rate over time after intramuscular injection (figure 4) yields a total systemic dose of 133 µg and a



**Fig. 2. Dexmedetomidine intramuscular plasma concentration *versus* time.**

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Table 2. Moment Analysis Intramuscular (IM) Data

Subject No.	AUC IM 0 to Infinity (ng · min · ml <sup>-1</sup> )	Terminal Half-life (min)	AUC (% under Data)	Bioavailability (%)	Time to Peak Concentration (min)	Peak Concentration (ng/ml)
1	329	707	75	91	20	0.37
2	267	291	95	75	60	0.49
3	394	243	96	69	20	0.81
4	237	314	96	71	5	1.2
5	262	304	90	86	10	0.61
6	235	254	94	67	15	0.87
7	237	363	93	80	5	0.88
8	126	57	99	54	5	0.71
9	170	149	95	66	2	1.2
10	174	131	99	69	5	0.95
Mean	243	281	93	73	13	0.81
SD	78	177	6.9	11	18	0.27

AUC = area under the curve.

bioavailability of 84% (133  $\mu\text{g}$  systemically absorbed/158  $\mu\text{g}$  average intramuscular dose). Figure 5 shows the cumulative absorption over time, as a percent of total absorption. The mean intramuscular dose was 158  $\mu\text{g}$  resulting in a bioavailability of intramuscular-to-intravenous dosing of 84% using deconvolution analysis. The AUMC of figure 4 was 277  $\mu\text{g} \cdot \text{h}^2$ . The mean absorption time (MAT) calculated as AUMC/AUC was 2.08 h, and the mean first order rate constant ( $K_a$ ) for intramuscular absorption as the reciprocal of MAT was  $0.48 \text{ h}^{-1}$ .

Figures 6 and 7 show the mean MAP ( $\pm$ SD) of the ten volunteers during intravenous and intramuscular dexmedetomidine. The peak rise in MAP after intra-

venous dexmedetomidine occurred at 5 min and was 22% above baseline values. A much smaller increase in MAP occurred after intramuscular injection, but was even earlier in onset and was probably caused by the anxiety induced by the intramuscular injection. By 4 h, both intravenous and intramuscular dexmedetomidine resulted in a 20% decline in MAP from baseline. The blood pressure disturbance at 140–150 min was caused by subjects waking up abruptly, rather than by ambulation of the subjects. Figures 8 and 9 show the mean heart rate ( $\pm$ SD) for the ten volunteers after intravenous and intramuscular dexmedetomidine, respectively. The decline in HR after intravenous dexmedetomidine was 27% below baseline 4–5 min after

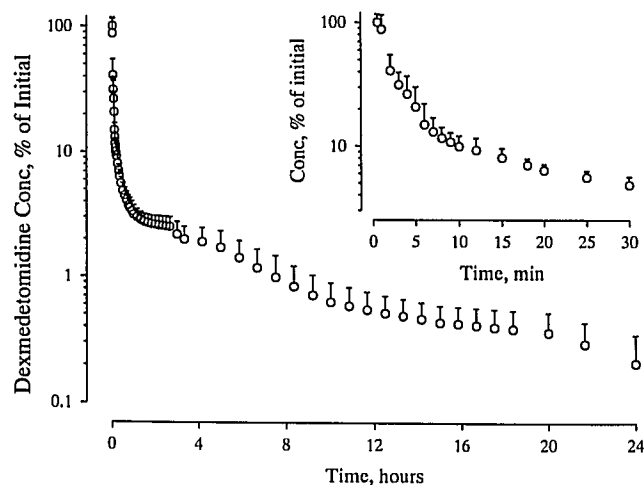


Fig. 3. Mean unit disposition function  $\pm$  SD of intravenous dexmedetomidine.

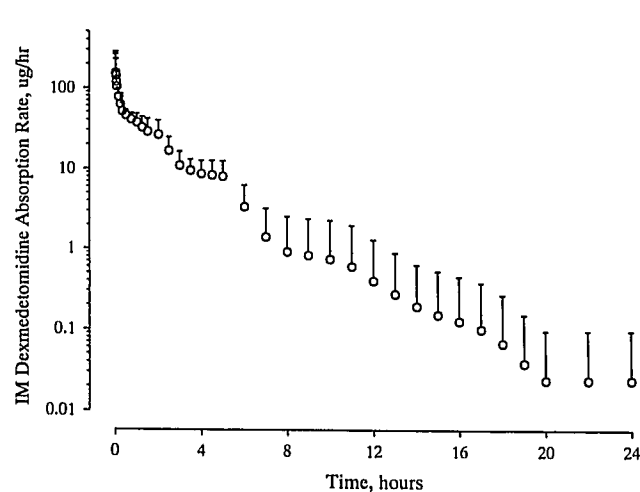


Fig. 4. Dexmedetomidine intramuscular rate of absorption ( $\pm$  SD) versus time.

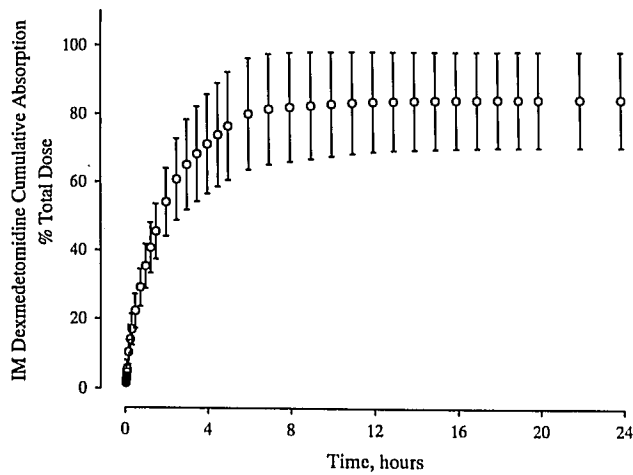


Fig. 5. Dexmedetomidine cumulative absorption ( $\pm$  SD) versus time.

starting the infusion. Again, this was not seen after intramuscular injection. Dexmedetomidine given by intramuscular and intravenous routes caused a 5% and 10% decline in HR, respectively, by the end of the 4-h recording period.

## Discussion

Hemodynamic alterations after intravenous administration preclude the use of dexmedetomidine as a rapid intravenous infusion or bolus. Compartmental pharmacokinetic analysis would be required to administer dexmedetomidine *via* a computer-controlled infusion pump, but dexmedetomidine would be more commonly administered by slow intravenous infusions

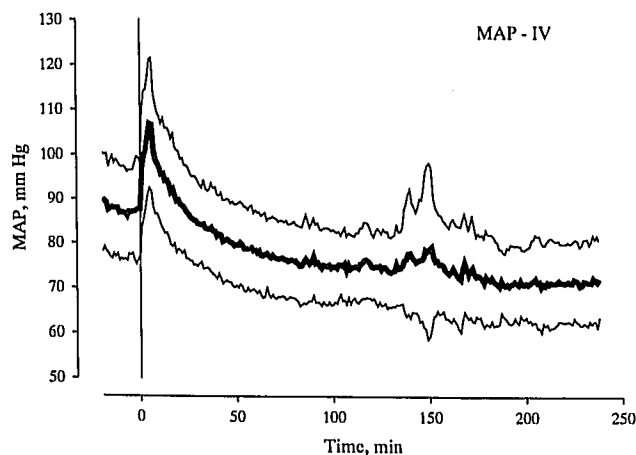


Fig. 6. Mean arterial pressure ( $\pm$  SD) of intravenous dexmedetomidine.

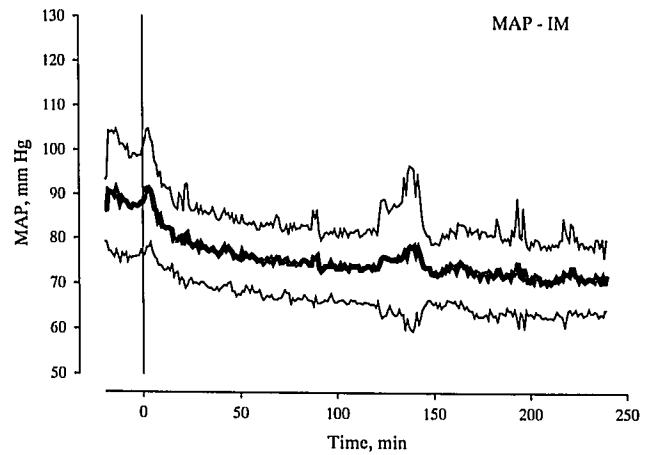


Fig. 7. Mean arterial pressure ( $\pm$  SD) of intramuscular dexmedetomidine.

to steady state or by intramuscular injections, for which moment analysis is adequate. Moment analysis is model independent and allows calculation of fundamental pharmacokinetic parameters, such as volume of distribution and clearance. Moment analysis cannot describe the multiple distribution phases, as are commonly modeled by compartmental pharmacokinetic analysis. The venous dexmedetomidine concentrations at 3 and 4 h were slightly greater than arterial concentrations and the calculated area under the curves may be slightly greater than an entirely arterial concentration profile.

Dexmedetomidine appears to have systemic clearance of approximately 0.5 L/min, approximately one-half of hepatic blood flow. Overall, the volume and clearance are fairly similar to those of fentanyl<sup>9</sup> with an ex-

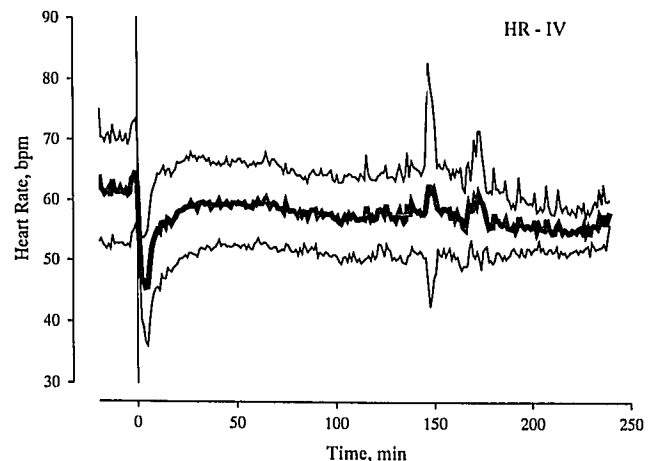


Fig. 8. Mean heart rate ( $\pm$  SD) of intravenous dexmedetomidine.

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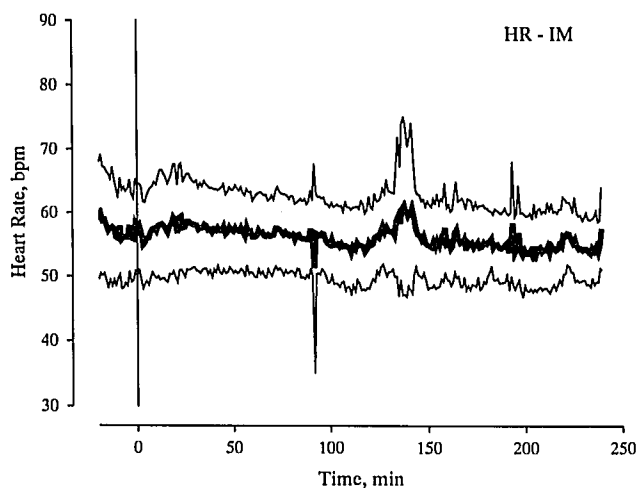


Fig. 9. Mean heart rate ( $\pm$  SD) of intramuscular dexmedetomidine.

tensive tissue distribution (fentanyl  $V_{d,ss}$  approximately 300 L) and a moderately large hepatic clearance (*i.e.*, large CL). The MRT is a term unfamiliar to many anesthesiologists, but one that might serve a useful purpose for comparison of medications given the misleading characteristics of the compartmental elimination half-life.<sup>10</sup> The MRT is the moment analysis equivalent of the half-life in compartmental analysis and represents the time required to eliminate 63.2% of an intravenous bolus dose. The effective half-life of a medication is 0.693 times the MRT.

The bioavailability of intramuscular dexmedetomidine was between 70% and 80%. On average, peak plasma concentrations of dexmedetomidine were obtained within 15 min after intramuscular injection, although the time to peak concentration after intramuscular injection varied widely. The intramuscular absorption profile was biphasic with early rapid absorption.

Intravenous dexmedetomidine as a rapid infusion caused biphasic changes in HR and MAP similar to those seen after administration of clonidine.<sup>11,12</sup> The clinical utility of intravenous dexmedetomidine will be limited by these hemodynamic alterations. Bolus intravenous administration of dexmedetomidine would be unwise in most circumstances. It is possible that dexmedetomidine pharmacokinetics are not linear secondary to the concentration-dependent hemodynamic alterations. Many of the drugs used in anesthesia practice (*i.e.*, propofol and thiopental) affect hemodynamics and probably have nonlinear pharmacokinetics. Thus, the as-

sumption of linearity is violated frequently in both compartmental pharmacokinetic analysis and moment analysis. As violation of linearity is part of model misspecification, the magnitude of such a violation can be roughly estimated from the size of the residual error when compartmental models are fit to the data. In practice, most pharmacokinetic studies simply ignore the issue of nonlinear pharmacokinetics because the extent of the violation is fairly small, and pharmacokinetics based on the assumption of linearity provide a succinct, easily estimated, and clinically useful description of pharmacokinetic behavior. The hypertension and bradycardia seen after intravenous dexmedetomidine were not seen after intramuscular administration.

The peak plasma concentrations were an order of magnitude lower after intramuscular administration. On the assumption that the differences in hemodynamic profiles may have been a result of concentration-dependent peripheral vasoconstriction, one might strive to maintain a plasma dexmedetomidine concentration of less than 1.0 ng/ml. From the presented moment analysis data, and knowing that clearance times targeted concentration will yield a corresponding infusion rate, the steady-state concentration of 1.0 ng/ml could be achieved through an infusion of dexmedetomidine at 0.511  $\mu\text{g}/\text{min}$ . The plasma concentration will asymptotically approach the targeted steady-state concentration of 1.0 ng/ml and would be very close to the steady-state concentration after three elimination half-lives or 1,155 min. If it is desirable to attain the target concentration before 19.25 h, a loading dose, calculated as targeted steady-state concentration times  $V_{d,ss}$  or 194  $\mu\text{g}$ , may be administered and followed by the maintenance infusion. The loading dose should not be administered as a bolus, but can be given as an infusion over 30–45 min with minimal increased risk of adverse hemodynamic alterations.

Two subjects lost consciousness when they assumed the upright posture, approximately 5 h after the intravenous infusion of dexmedetomidine. During these events, both subjects had bradycardia. The likely etiology for this loss of consciousness is the sympatholytic effect of the dexmedetomidine leaving unopposed vagal tone. Both subjects recovered from their vasovagal events spontaneously and uneventfully. No analogous events occurred after intramuscular administration, but increased caution on the part of both the investigators and the subjects during the second phase of the study may have prevented similar episodes.

We conclude that, although intramuscular absorption of dexmedetomidine is rapid, the peak plasma concentrations that result are less than those after a 5-min intravenous infusion with the same dose, and hemodynamic alterations are less severe.

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