Anesthesiology
80:1349–1359, 1994

Pharmacokinetics and Pharmacodynamics of Intraspinal Dexmedetomidine in Sheep

James C. Eisenach, M.D., Steven L. Shafer, M.D.,† Brenda A. Bucklin, M.D.,‡ Carswell Jackson, M.D.,§ Antero Kallio, M.D.,#*

Introduction: **Epidural and spinal injection of α_2-adrenergic agonists causes analgesia and hypotension. For opioids, relative analgesic potency of epidural to intravenous administration decreases with increasing lipophilicity, but such pharmacodynamic studies have been performed with only one α_2-adrenergic agonist, clonidine, of moderate lipophilicity. This study examines antinociception, transfer to cerebrospinal fluid (CSF), and CSF pharmacokinetics in sheep of the selective α_2-adrenergic agonist dexmedetomidine, with lipophilicity 3.5 times greater than clonidine, and correlates CSF concentrations to hemodynamic effects.**

Methods: **Six sheep with chronically implanted epidural, intrathecal, and vascular catheters received, on separate days, 100 μg dexmedetomidine intravenously, epidurally, or intrathecally. Cerebrospinal fluid and blood were sampled at specified intervals for dexmedetomidine assay. Pharmacokinetics of dexmedetomidine in CSF were determined using a NONMEM approach. Hemodynamic effects were measured and correlated to CSF concentrations. A second group of four sheep received intrathecal dexmedetomidine to define its time course for antinociception.**

Results: **Intrathecal dexmedetomidine decreased blood pressure within 1 min, with a maximum reduction of −22 ± 3%. Epidural injection decreased blood pressure with a slower onset (11 min) and to a lesser degree (−14 ± 4%), whereas intravenous injection did not affect blood pressure (−8 ± 6%). Dexmedetomidine absorption in CSF after epidural injection was rapid (T_{max} = 5–20 min), although pharmacokinetic modeling suggested a biphasic absorption process. Only 22% of the injected dose was identified in the CSF. There was a delay of at least 30 min between peak CSF concentrations and time of maximal reduction in blood pressure. At times of identical CSF dexmedetomidine concentrations, blood pressure decreased more after epidural than after intrathecal administration. Intrathecal dexmedetomidine injection produced maximum antinociception within 20–30 min of injection.**

Conclusions: **These data support a primary spinal site of action for decreased blood pressure after intraspinal dexmedetomidine injection. Dexmedetomidine appears rapidly in CSF after epidural administration and decreases blood pressure. The relationship between CSF dexmedetomidine concentrations and drug effect may require more complex modeling tools than those used to relate plasma drug concentrations to effects of systemically administered opioids or neuromuscular blockers. (Key words: Analgesia. Anesthetic techniques: epidural; spinal. Pharmacokinetics. Sympathetic nervous system, α-adrenergic agonists: dexmedetomidine.)**

CLONIDINE, an α_2-adrenergic agonist, produces effective analgesia when injected epidurally[1] or intrathecally[2] in patients with postoperative pain but also causes hypotension and sedation. In sheep, epidurally administered clonidine appears rapidly in cerebral spinal fluid (CSF),[3] with a concentration time course in CSF closely approximating its time course for antinociception. These observations were confirmed recently in humans.[4] Clonidine decreases blood pressure more after intrathecal than after epidural injection in sheep and humans,[3–5] likely because of higher concentrations of clonidine near preganglionic sympathetic neurons after intrathecal injection.

Dexmedetomidine is another α_2-adrenergic agonist under clinical development for use in anesthesia. Dexmedetomidine is three- to fourfold more selective than clonidine for α_2-adrenoceptors, and, in some animal models in which clonidine is a partial agonist, dexmedetomidine is a full agonist.[6] For these reasons, dex-

* Associate Professor, Department of Anesthesia, The Bowman Gray School of Medicine of Wake Forest University.

† Staff Anesthesiologist, Palo Alto Veterans Administration Medical Center; Assistant Professor, Department of Anesthesia, Stanford University.

‡ Assistant Professor, Department of Anesthesia, University of Nebraska.

§ Research Fellow, Department of Anesthesia, The Bowman Gray School of Medicine of Wake Forest University.

#Clinical Research Manager, Orion Farmos Pharmaceuticals.

Received from the Department of Anesthesia, The Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina. Accepted for publication February 25, 1994. Supported in part by a grant from Orion Farmos Pharmaceuticals, Turku, Finland, and grant GM35523 from the National Institutes of Health. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 1991.

Address reprint requests to Dr. Eisenach: Department of Anesthesia, The Bowman Gray School of Medicine, Wake Forest University Medical Center, Medical Center Boulevard, Winston-Salem, North Carolina 27157-1009.

medetomidine may be preferable to clonidine for intraspinal analgesia. On the other hand, dexmedetomidine is more lipophilic than clonidine (octanol:buffer partition coefficient of 2.8 for dexmedetomidine *vs.* 0.8 for clonidine).[7] Increasing lipophilicity is associated with decreased potency of intrathecal compared with intravenous administration for opioids[8] and cannabinoids,[9] and dexmedetomidine's greater lipophilicity, compared with that of clonidine, may reduce its potency by this route of injection. The purpose of this study was to examine antinociception and CSF pharmacokinetics of dexmedetomidine in sheep and to correlate CSF dexmedetomidine concentrations with hemodynamic effects. A second aim was to describe differences in hemodynamic action between intrathecal, epidural, and intravenous administration of dexmedetomidine.

Materials and Methods

After approval by the Animal Care and Use Committee, seven ewes of mixed Western breeds, weighing 36–42 kg, were studied. After a 48-h fast, ewes were anesthetized with ketamine (10–15 mg/kg, intramuscular), and anesthesia was maintained with 1–2% halothane in oxygen *via* controlled tracheal ventilation. Polyvinyl catheters were inserted under direct vision into a femoral artery and vein and advanced 10 cm centrally. Polyvinyl or polyamide catheters were inserted under direct vision *via* a lumbar laminectomy into the epidural space and, through a small nick in the dura, into the lumbar intrathecal space. Both epidural and intrathecal catheters were advanced 25 cm cephalad. In previous studies,[10,11] this resulted in catheter tips at upper thoracic dermatomes, but this was not verified in the current study. A thoracic site was chosen to maximize hemodynamic depression from neuraxially administered α_2-adrenergic agonists in sheep.[10] Catheters were tunneled subcutaneously and maintained in a canvas pouch at the flank. All incisions were closed, anesthesia was discontinued, and the animal was returned to a portable metabolic cart. Behavioral signs of pain or distress were to be treated with 0.1–0.2 mg/kg intramuscular xylazine postoperatively. In no case was this necessary, and all animals were standing and eating normally within 3 h of surgery. Animals received prophylactic antibiotic therapy with 900,000 μ intramuscular procaine penicillin each day for 3 days following surgery. Experiments began a minimum of 72 h from the time of surgery.

On the day of the experiment, the arterial catheters was connected to a Viggo-Spectromed (Oxnard, CA) transducer connected to a Grass (Quincy, MA) SD7 polygraph and computer data acquisition system for continuous measurement of blood pressure and heart rate. Average heart rate and systolic, diastolic, and mean arterial pressure were recorded at 1-min intervals *via* the computer data acquisition system throughout the experiment.

After 15 min of baseline recording, 100 μg dexmedetomidine (Orion Farmos Pharmaceuticals, Turku, Finland) was injected in a 1.0-ml volume through the intravenous, epidural, or intrathecal catheter, followed immediately by saline flush (5 ml for intravenous, 0.4 ml for epidural or intrathecal catheter). Baricity of the dexmedetomidine solution was not measured; however, because the dexmedetomidine was dissolved in a low concentration in normal saline, it was most likely isobaric or slightly hyperbaric. Animals were standing during injection and throughout the study. Animals received dexmedetomidine once by each route, with injections separated by a minimum of 48 h. One animal did not receive intravenous dexmedetomidine, because the arterial catheter was not functioning at the time of the planned experiment.

Arterial blood was sampled before and 1, 5, 10, 20, 40, 60, 90, 120, 240, and 360 min after dexmedetomidine injection and analyzed for arterial blood gas tensions and *p*H using a Radiometer (Copenhagen, Denmark) microanalyzer and for dexmedetomidine. Cerebral spinal fluid was sampled (0.5 ml) at identical times, except for the 1-min period, for dexmedetomidine analysis. Dexmedetomidine was analyzed by Orion Farmos Pharmaceuticals using a gas chromatography-mass spectrometry method.[12] The method has a detection limit of 50 pg/ml and an intra-assay coefficient of variability of 10% in the relevant concentration range.

Pharmacokinetic Analysis

Three pharmacokinetic analyses were performed: characterization of the intrathecal disposition function of dexmedetomidine, characterization of the intrathecal absorption of epidurally administered dexmedetomidine, and characterization of the hysteresis between the CSF and the hypothetical site of drug effect for intrathecally and epidurally administered dexmedetomidine.

Intrathecal Disposition Function

The parameters of a polyexponential disposition function of the form

$$\sum_{i=1}^{n} A_i e^{-\lambda_i t},$$

where A_i and λ_i are the parameters, were fit to the observed concentrations after intrathecal injection using the program NONMEM. The intra- and interindividual errors were modeled as log-normally distributed. Both biexponential (n = 2) and triexponential (n = 3) disposition curves were investigated. Model selection was based on both examination of the extended least squares objective function determined by NONMEM and by examination of the residual curves and quality of the individual fits.

Intrathecal Absorption after Epidural Administration

The intrathecal absorption after epidural administration was considered to be the convolution of an input function with the intrathecal disposition function. This analysis was performed in two steps. Because we had intrathecal measurements after intrathecal administration, these observations were used to determine the individual intrathecal disposition curve in each animal. The analysis of the absorption after epidural administration then incorporated the individual intrathecal disposition function in that same animal, limiting the parameter estimation after epidural administration to the absorption parameters.

The intrathecal disposition function was estimated for each animal by fitting the parameters of a biexponential disposition equation as shown above to the observed intrathecal concentrations for that animal. The individual fits were performed using the solver function of Excel (Microsoft, Redmond, WA), programmed to minimize the extended least squares objective function.[13]

Two different absorption functions were investigated: a simple absorption model,

$$\text{Input rate} = DFke^{-kt},$$

where D is the dose, F is the fraction absorbed, and k is the absorption rate constant, and a biexponential absorption model,

$$\text{Input rate} = DF\frac{Pe^{-K_1 t} + (1-P)e^{-k_2 t}}{\frac{P}{k_1} + \frac{(1-P)}{k_2}},$$

where k_1 and k_2 are absorption rate constants, and P is the relative contribution of the first rate constant (k_1).

The convolution of these input functions against the individual biexponential disposition function yielded two models to describe the intrathecal concentrations over time after epidural injection:

$$C_{\text{intrathecal}} = DFk\sum_{i=1}^{2}\frac{A_i}{k-\lambda_i}(e^{-\lambda_i t} - e^{-kt})$$

for the monoexponential absorption model as described by Aarons *et al.*[14] and

$$C_{\text{intrathecal}} = DF\frac{\sum_{i=1}^{2}\frac{PA_i}{k_1-\lambda_i}(e^{-\lambda_i t} - e^{-k_1 t}) + \frac{(1-P)A_i}{k_2-\lambda_i}(e^{-\lambda_i t} - e^{-k_2 t})}{\frac{P}{k_1} + \frac{(1-P)}{k_2}}$$

for the biexponential absorption model. In each case, the parameters A_i and λ_i were not estimated but were assumed to be the same as that after intrathecal administration. For the monoexponential absorption model, only the parameters F and k were estimated. For the biexponential absorption model, the parameters F, k_1, k_2, and P were estimated. Analysis of the area under the curve of the biexponential absorption input reveals that the relative absorption from the rapid component was therefore

$$\frac{\frac{P}{k_1}}{\frac{P}{k_1} + \frac{(1-P)}{k_2}},$$

and the relative absorption from the slower component was

$$\frac{\frac{(1-P)}{k_1}}{\frac{P}{k_1} + \frac{(1-P)}{k_2}},$$

the sum of these being 1.

The parameter estimation was performed using NONMEM. Interindividual variability was characterized only around the parameter F because the limited size of the data set did not permit estimation of additional interindividual variability. Both interindividual variability and intraindividual variability were assumed to be log-normal.

Characterization of Hysteresis

The time course of concentration and drug effect was analyzed by plotting CSF dexmedetomidine concentration and blood pressure as functions of time after injection into either the epidural or intrathecal space. These graphs permitted visual assessment of the variability in the time course of both concentration and drug effect. The peak concentration, the time of peak concentration, and the ranges were summarized after both routes of administration. Also, the minimum blood pressure in each animal, the time of the minimum blood pressure, and the ranges were summarized for both routes of administration.

In each animal, the blood pressure was plotted as a function of the observed CSF dexmedetomidine concentration, creating a "hysteresis loop." The hysteresis between dexmedetomidine concentration in the intrathecal space and the dexmedetomidine concentration at the site of drug effect then was modeled as an effect site using the method of Verotta and Sheiner.[15] The rate constant for CSF-effect site equilibration, k_{e0}, was estimated for each animal. Additionally, an average loop was constructed based on the average CSF dexmedetomidine concentration and the average blood pressure response after intrathecal and epidural injections.

Antinociception

A separate group of four animals were prepared in a similar manner, except that no epidural catheter was inserted, and an intrathecal catheter was inserted under direct vision at C2–C3 and advanced 5 cm caudad. At least 72 h later, these animals received a single injection of 100 μg dexmedetomidine through the intrathecal catheter. Noxious stimulation was performed as previously described[16] with a mechanical device attached to a foreleg through which increasing pressure was applied. The stimulus was increased until a withdrawal response, consisting of lifting the leg, occurred, and the pressure at the time of this response was recorded. A cutoff value of 13N was used to avoid tissue damage during periods of intense analgesia. Mechanical stimulation was performed before and 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 min after dexmedetomidine injection. Data were converted to percent maximum possible effect, where

$$\%MPE = \frac{Observed - Cutoff}{Baseline - Cutoff} \times 100.$$

Data Analysis

Unless indicated otherwise, data are presented as mean ± SEM. Effects of dexmedetomidine on blood pressure, heart rate, arterial blood gas tensions, and *p*H were tested by one-way analysis of variance for repeated measures followed by Dunnett's test for comparison with baseline values. Differences in these variables among injection routes were compared by two-way analysis of variance. $P < 0.05$ was considered significant.

Results

CSF Pharmacokinetics

After intrathecal injection, dexmedetomidine declined in a biexponential manner (fig. 1, top), with distribution and elimination half-lives of 10 and 259 min, respectively (table 1). Figure 2 shows the best, median, and worst fits of the model to the observed concentrations after intrathecal injection. The coefficient of variation estimated by NONMEM was 0.48% for the initial coefficient and 1.1% for the most rapid half-life. The remaining intraindividual variability was estimated by NONMEM at 55%.

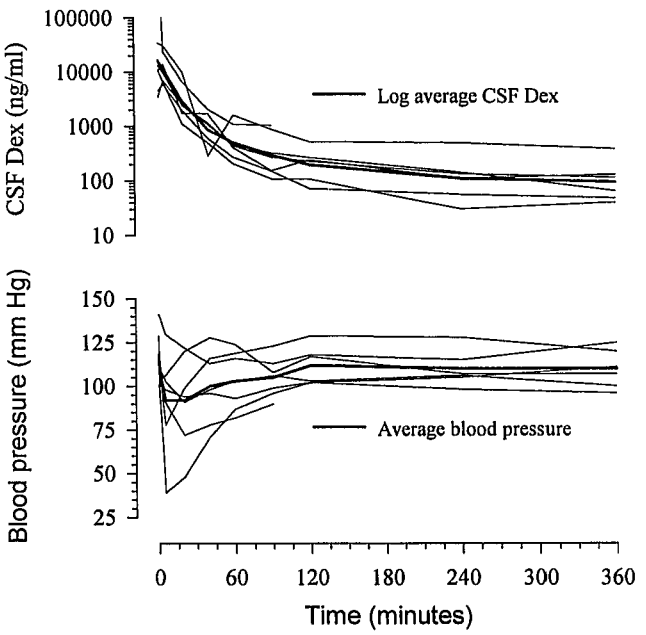

Fig. 1. Cerebrospinal fluid (CSF) dexmedetomidine concentrations (*top*) and mean arterial blood pressure (*bottom*) over time after intrathecal injection of 100 μg at time 0. Individual animal data represented by fine lines and average data by the heavy line.

Table 1. Intrathecal Disposition Parameters

Coefficients (ng/ml)	
A_1	1.59
A_2	1.49
Rate constants (min^{-1})	
λ_1	0.069
λ_2	0.0027
Half-lives (min^{-1})	
$t_{1/2}\lambda_1$	10
$t_{1/2}\lambda_2$	259

After epidural injection, dexmedetomidine appeared rapidly in CSF, with maximum concentrations occurring within 5 min after injection in five of seven animals (fig. 3, top). Both monoexponential and biexponential

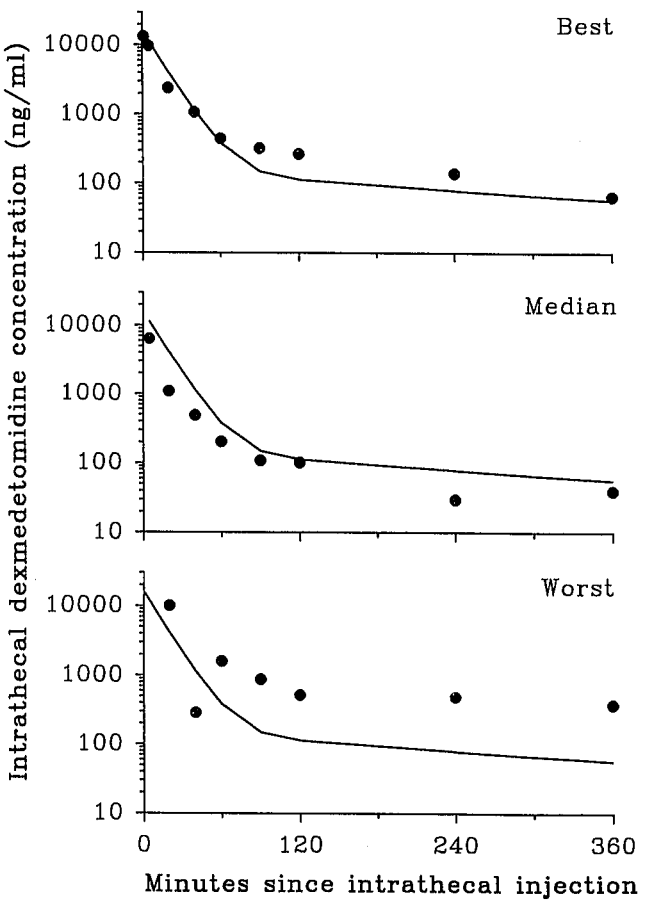

Fig. 2. Best (*top*), median (*center*), and worst (*bottom*) fits of individual cerebrospinal fluid (CSF) dexmedetomidine concentrations after intrathecal injection using NONMEM analysis.

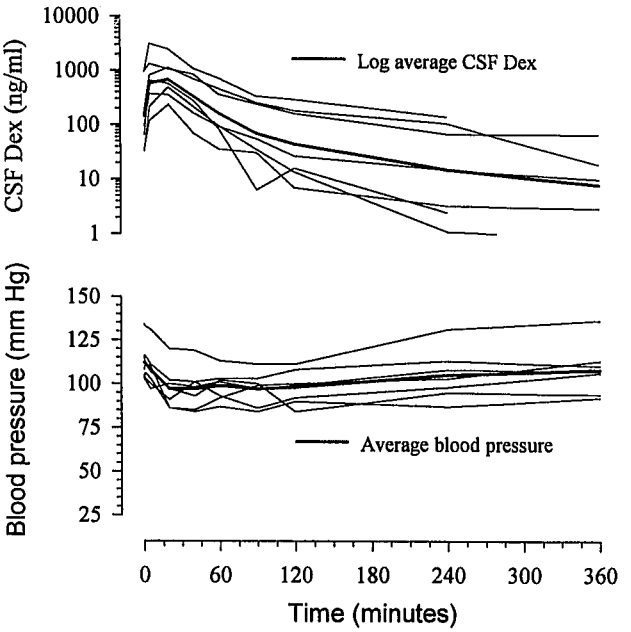

Fig. 3. Cerebrospinal fluid (CSF) dexmedetomidine concentrations (*top*) and mean arterial blood pressure (*bottom*) over time after epidural injection of 100 μg at time 0. Individual animal data represented by fine lines and average data by the heavy line.

absorption models were used to characterize CSF dexmedetomidine concentrations after epidural injection. Figure 4 shows the best, median, and worst fits for the monoexponential absorption model. As suggested by all three fits, there was a consistent pattern of overpredicting the concentrations in the 1st hour with the monoexponential absorption function. Figure 5 shows the best, median, and worst fits with the biexponential absorption model. With this model, the data were described more accurately, particularly the initial observations and the terminal slope. The biexponential absorption model resulted in a 40-point improvement in the NONMEM objective function, suggesting significantly better characterization of the data. The parameters of the biexponential absorption model are shown in table 2. There was a rapid initial absorption phase with a half-life of less than 1 min followed by a slower phase with a half-life of 25 min. The partition of 0.95 distributed the absorption between the two values, resulting in 34% of the total absorption from the more rapid component and 66% of the total absorption from the slower component. The total amount of the epidurally administered dexmedetomidine absorbed into the intrathecal space was 22%, but the interindividual

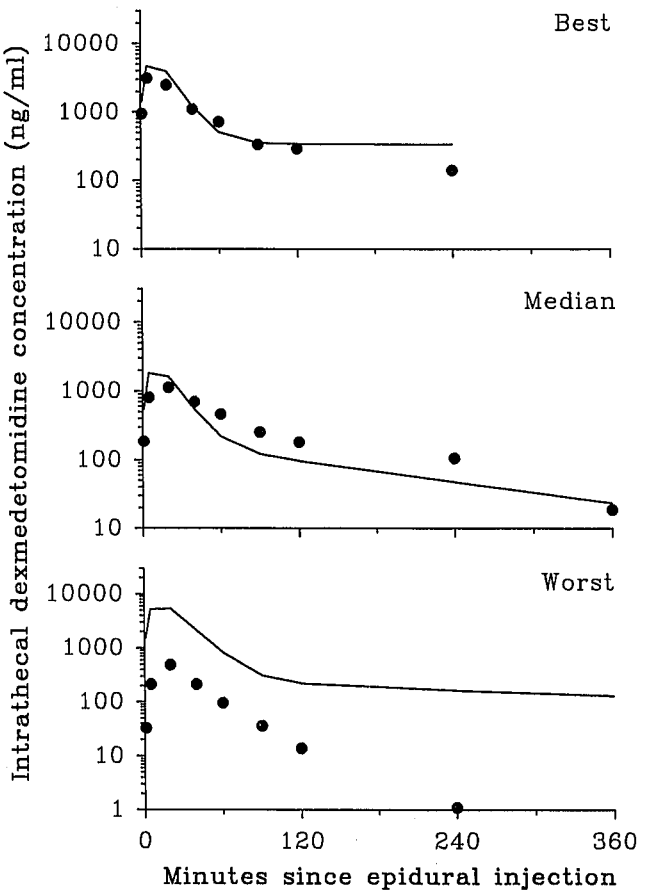

Fig. 4. Best (*top*), median (*center*), and worst (*bottom*) fits of individual cerebrospinal fluid (CSF) dexmedetomidine concentrations after epidural injection, using a monoexponential absorption analysis.

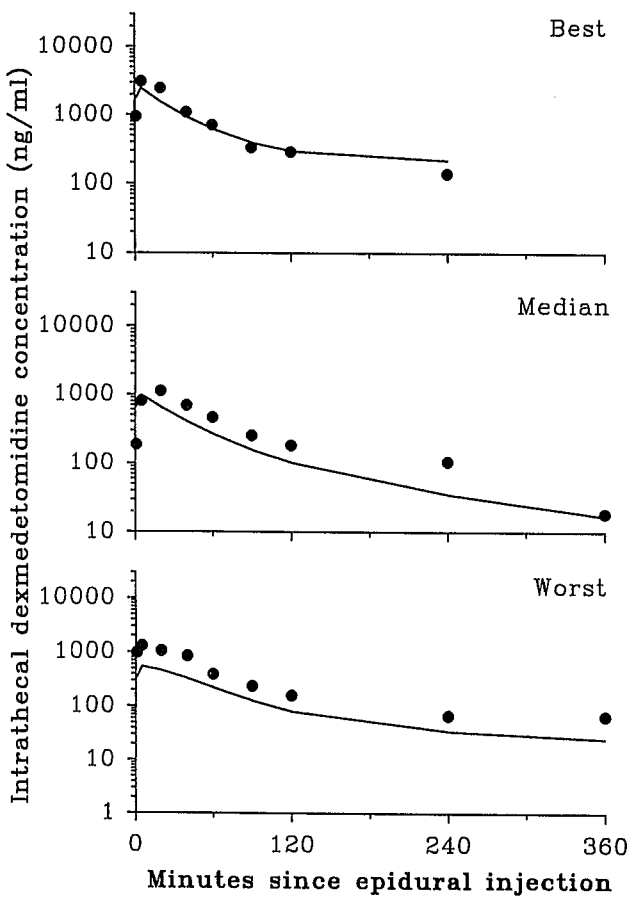

Fig. 5. Best (*top*), median (*center*), and worst (*bottom*) fits of individual cerebrospinal fluid (CSF) dexmedetomidine concentrations after epidural injection, using a biexponential absorption analysis.

variability in fraction absorbed was high (coefficient of variation 54%). The residual intraindividual variability of the NONMEM estimates was 17%.

Dexmedetomidine concentrations in CSF after intravenous injection were near or below the limit of detection of the assay (50 pg/ml).

Plasma Pharmacokinetics

After intravenous injection, dexmedetomidine was present in low concentrations in plasma at or near the limits of detection of the assay. In only one animal did dexmedetomidine concentrations remain above detection limit for more than 20 min. Dexmedetomidine concentrations in plasma after epidural and intrathecal injection were near or below the limit of detection of the assay.

Hemodynamic Effects

Dexmedetomidine decreased blood pressure after intrathecal and epidural but not after intravenous injection (fig. 6). Blood pressure first decreased signifi-

Table 2. Epidural Absorption Parameters

Fraction absorbed	0.22
Rate constants (min^{-1})	
λ_1	0.967
λ_2	0.028
Half-lives (min^{-1})	
$t_{1/2}\lambda_1$	0.7
$t_{1/2}\lambda_2$	25
Partition	0.95

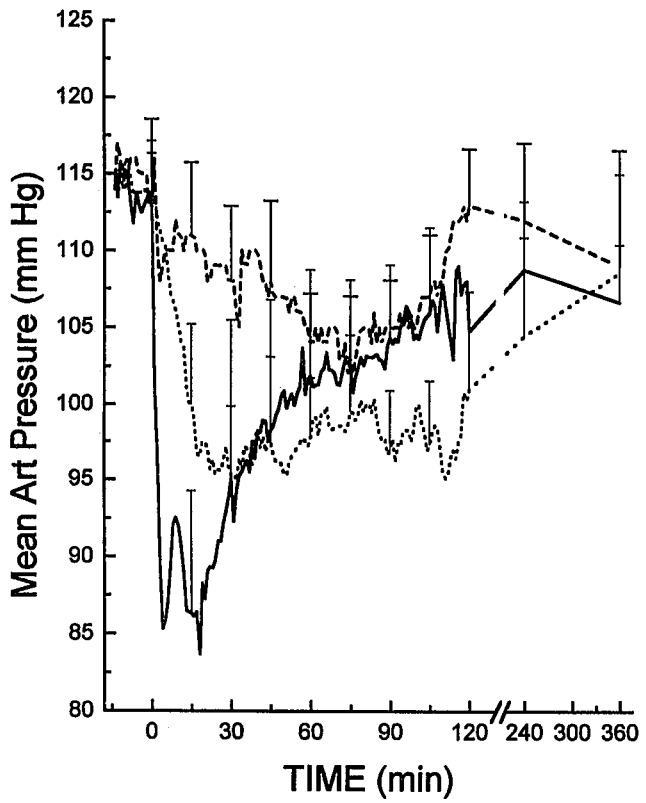

Fig. 6. Effects of intrathecal (solid line), epidural (dotted line), and intravenous (dashed line) injection of 100 μg dexmedetomidine at time 0. Each line represents the mean ± SEM of six or seven animals.

cantly below baseline 2 min after intrathecal injection *versus* 11 min after epidural injection.

Figures 1 and 3 show the CSF and blood pressure response to intrathecal and epidural injection, respectively, and are summarized in table 3. After intrathecal injection, the average minimum mean arterial blood pressure observed was 84 mmHg, and that minimum was observed, on average, 29 min after injection. After epidural injection, the average minimum blood pressure was 92 mmHg, and that minimum was observed, on average, 73 min after injection. Thus, there was a tendency toward a larger and more rapid decrease after intrathecal than after epidural injection.

Although there was considerable variability, the minimum blood pressure trailed the peak concentration with both routes of administration. After intrathecal administration, the peak concentration was almost instantaneous, whereas the peak effect (minimum blood pressure) was not observed until 29 min after administration. After epidural administration, the CSF dexmedetomidine concentration peaked within 12 min, whereas the peak effect was not observed until 73 min after injection. This delay between the peak concentration and peak effect suggests a long equilibration between dexmedetomidine CSF concentration and dexmedetomidine concentration at the site of drug effect.

Two animals did not have the expected decrease in blood pressure after intraspinal dexmedetomidine. The effect-site modeling in the remaining animals produced estimates of the CSF-effect equilibration half-time ranging 2–231 min after intrathecal administration and 13–123 min after epidural administration. This wide range in equilibration rates suggests that the assumptions of the model were violated by the experimental design, as explained in the discussion. Therefore, the results were not further considered.

Figure 7 shows the average blood pressure response plotted as a function of the average CSF dexmedetomidine concentration after epidural and intrathecal injection. Intrathecal injection results in a higher dexmedetomidine concentration for any given response compared with epidural injection (fig. 7). Also, figure 7 suggests that the apparent decrease in potency of intrathecal dexmedetomidine is approximately 1 order of magnitude.

Heart rate was unaffected by dexmedetomidine injection, remaining within 6% of baseline values, despite a reduction in blood pressure after epidural and intrathecal injection. Dexmedetomidine did not affect arterial blood gas tensions or *p*H, except for a transient decrease in arterial partial pressure of oxygen after intravenous administration (106 ± 2 mmHg before, 83 ± 5 mmHg 5 min after injection; $P < 0.05$).

Antinociception

Intrathecal dexmedetomidine injection produced its maximal antinociceptive effect within 20–30 min of injection, lasting 1.5 h (fig. 8). Cerebral spinal fluid was not sampled for dexmedetomidine assay in these animals; therefore, correlation of antinociception with CSF concentrations was not possible.

Discussion

Dexmedetomidine produces antinociception and hypotension after intrathecal injection, consistent with activation of spinal α_2-adrenoceptors. These data are

Table 3. CSF Dexmedetomidine/Blood Pressure Summary

	Intrathecal		Epidural	
	Log Average	Range	Log Average	Range
CSF concentrations				
Max (ng/ml)	19,400	5,900–336,000	1,050	236–3,120
T Max (min)	2	1–5	12	5–20
Blood pressure response				
Min (mmHg)	84	39–113	92	84–111
T Min (min)	29	1–90	73	40–120

CSF = cerebrospinal fluid; Max = maximum; T Max = time of maximum; Min = minimum; T Min = time of minimum.

in agreement with previous studies in sheep that demonstrate high density of α_2-adrenergic binding sites in the superficial dorsal horn and surrounding preganglionic sympathetic neurons.[17] Other studies in sheep demonstrate antinociception and hypotension from intrathecal injection of α_2-adrenergic agonists that are reversed specifically with α_2-adrenergic antagonists.[10,18,19] This study is the first to describe the detailed CSF pharmacokinetics and pharmacodynamics of intraspinally administered dexmedetomidine.

We chose a dose of 100 μg dexmedetomidine for several reasons. First, this is within the dose range used intravenously in humans during and after anesthesia.[20–22] Because we wished to compare the effects of the current study to one of similar design in sheep,[3] we chose a dose of similar analgesic potency (300 μg clonidine and 100 μg dexmedetomidine yield near-maximum effective doses after intrathecal administration, using the mechanical stimulation test). The same dose of dexmedetomidine was injected by all three routes to contrast potency at producing hemodynamic effects, although, in clinical practice, different doses might be administered by each of these routes.

The NONMEM analysis of the intrathecal disposition of dexmedetomidine described the observations reasonably well. NONMEM was used because of the in-

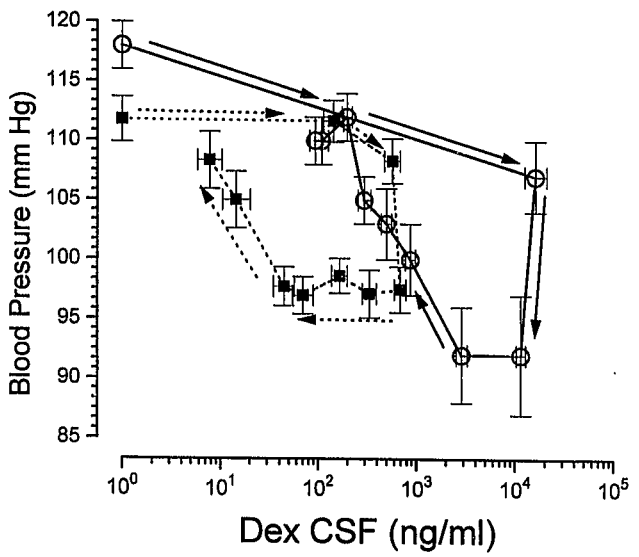

Fig. 7. Observed mean arterial pressure *versus* observed cerebrospinal fluid (CSF) dexmedetomidine concentration after epidural (■, dotted line) or intrathecal (○, solid line) administration. Each point represents the mean ± SEM of arterial pressure and log mean ± SEM of CSF dexmedetomidine of seven animals. The direction of time is indicated by the arrows.

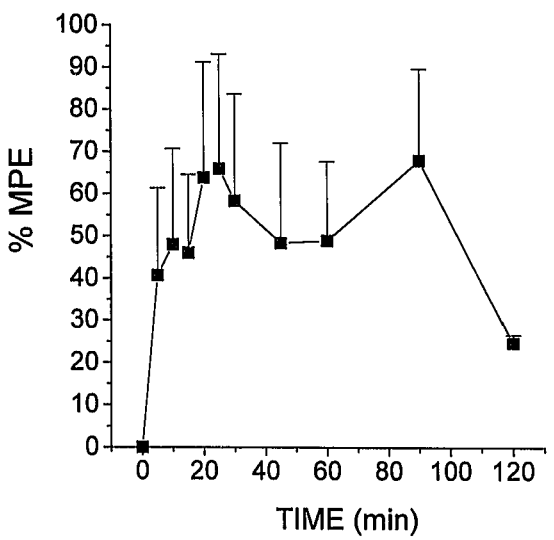

Fig. 8. Antinociception, expressed as percent maximum possible effect (%MPE) over time after intrathecal injection of 100 μg dexmedetomidine at time 0. Each symbol represents the mean + SEM of four animals.

ability of the mean results from the traditional two-stage analysis to accurately describe our observed concentrations.

The need for a biphasic absorption model for epidurally administered dexmedetomidine was unexpected. There are several possible explanations. Dexmedetomidine is more lipophilic than clonidine.[7] This may cause local distribution into epidural fat, with subsequent return to the epidural space, which could produce a biphasic absorption profile for dexmedetomidine that is not present with clonidine. However, biphasic absorption models have not been examined previously for epidurally administered α_2-agonists; thus it is possible that a biphasic absorption profile is not unique to dexmedetomidine.

The effect of lipophilicity on transfer of drug from the epidural to the intrathecal space is controversial. Some argue that drug transfer is more rapid and extensive as lipophilicity increases, whereas others describe a biphasic relationship between drug transfer and lipophilicity. Bernards and Hill[23] and Bernards[24] examined transfer across monkey meninges *in vitro* and transfer across rabbit arteries *in vivo*. In both cases, there was an increase in permeability with increasing lipophilicity up to an octanol:buffer partition coefficient of 129, and permeability decreasing and lipid solubility increasing thereafter. In comparison with a study of similar design with clonidine in sheep,[3] the current study demonstrates that the more lipophilic agent, dexmedetomidine, has a greater CSF bioavailability than clonidine after epidural administration. Whether this difference is due to differences in transfer into the CSF space or in rates of elimination from the CSF by both vascular uptake and specific as well as nonspecific binding in the cord and nerve roots is not known. Nonetheless, based on these results in sheep, one would predict that, clinically, dexmedetomidine would be efficiently administered epidurally.

Lipophilicity also may affect analgesic potency of intrathecally administered agents. In rats, there is an inverse relationship between lipophilicity and potency of intrathecally administered opioids[8] and cannabinoids[9] such that the poorly lipophilic agents are more potent compared with intravenous administration than highly lipophilic agents. A similar relationship has been observed clinically,[25,26] perhaps because of nonspecific binding of highly lipophilic drugs to spinal cord white matter. We did not measure antinociceptive potencies of systemically administered dexmedetomidine in sheep in this study. Nevertheless, the 3:1 potency ratio for dexmedetomidine to clonidine after intrathecal injection in sheep is less than their potency ratios (8–10:1) after intravenous injection in other species. This comparison supports studies in rodents and preliminary observation in humans that relative potency of highly lipophilic to poorly lipophilic analgesic declines from systemic to intrathecal administration.

Hemodynamic effects of dexmedetomidine after intraspinal administration can be predicted from its pharmacokinetics. Intrathecal administration rapidly decreases blood pressure, as expected by actions in the spinal cord to diminish sympathetic nervous system outflow.[27] The hypotensive effect differs between intrathecal and epidural administration only in the first 30 min. Thereafter, the rapid transfer of dexmedetomidine yields similar CSF concentrations and similar hemodynamic effects after either epidural or intrathecal administration. Lack of significant effect of intravenous dexmedetomidine in this small dose on blood pressure in the current study demonstrates the local action of 100 μg dexmedetomidine in the spinal cord.

The relationship between CSF dexmedetomidine concentration and blood pressure is complex, and we have not satisfactorily explained our observations in the current analysis. The common method to establish the relationship between concentration and response in a non-steady-state experiment, such as this, is to use the effect-site model proposed by Hull *et al.*[28] and Sheiner *et al.*[29] The primary assumption of this model is that the drug effect is an instantaneous manifestation of the drug concentration at the site of drug effect. Often, this is a reasonable assumption. However, many physiologic mechanisms influence blood pressure, and many reflex mechanisms work to maintain blood pressure. As a result, the time course of blood pressure may be an imprecise (although clinically important) measure of drug effect. In the current study, some of the animals became anxious during measurement of the blood pressure, which likely increased the blood pressure recorded. Thus, using effect-site models for hemodynamic effects can be expected to violate the assumption that the drug effect is an instantaneous reflection of effect-site concentration, which may have contributed to the variability in the drug-effect measurement.

A second assumption of the model, as usually implemented, is that the relationship between the observed concentration and the concentration at the site of drug effect can be described by simple diffusion, *i.e.*, a 1st-

order rate constant (k_{c0}). When this assumption is true, the potency of a drug is unaffected by the route of delivery. However, in this study, the potency of dexmedetomidine administered into the epidural space was at least 10-fold greater than the potency of dexmedetomidine administered into the intrathecal space. This suggests that the intrathecally administered dexmedetomidine was not well mixed within the CSF and hence was sampled from a smaller dilution volume than the epidurally administered dexmedetomidine. Whereas a slowly mixing (*e.g.*, catenary) model of the intrathecal space might unify the potency of epidurally and intrathecally administered dexmedetomidine, the resolution of our measurement of drug effect (blood pressure) probably is not precise enough to support estimation of additional parameters. Alternative explanations for the large variability in the CSF concentration-effect relationship include variable positioning of epidural and intrathecal catheter tips, differing effect of intrathecal *versus* epidural dexmedetomidine injection on spinal cord blood flow and clearance of drug by this process, and effects of mild hyperbaricity and horizontal position of the intrathecal space in this species.

We observed a low CSF bioavailability of epidurally administered dexmedetomidine (22%). The bioavailability was modeled on the common assumption that the disposition of dexmedetomidine was uniform once it reached the intrathecal space, regardless of the initial site of injection. If the intrathecal space is not well mixed, as suggested by the differing potencies observed after epidural and intrathecal administration, it is possible that the disposition function after intrathecal injection is proportionally higher, reflecting a smaller dilution volume. This, in turn, would lead to an apparently reduced bioavailability and may be one reason that our CSF bioavailability was much less than 100%.

In summary, 100 μg dexmedetomidine decreases blood pressure after intrathecal and epidural but not intravenous administration in sheep. Cerebral spinal fluid concentrations are similar after epidural and intrathecal administration beyond the first 10 min, and bioavailability of dexmedetomidine in CSF after epidural injection is greater than that of clonidine or previously examined opioids. These data provide a pharmacokinetic basis for initial studies in humans and suggest that dexmedetomidine may produce both hypotension and analgesia after epidural administration.

The authors acknowledge L. Vuorilehto, M.Sc., who performed the dexmedetomidine analyses.

References

1. Bonnet F, Boico O, Rostaing S, Saada M, Loriferne J, Touboul C, Abhay K, Ghignone M: Postoperative analgesia with extradural clonidine. Br J Anaesth 63:465–469, 1989

2. Filos KS, Goudas LC, Patroni O, Polyzou V: Intrathecal clonidine as a sole analgesic for pain relief after cesarean section. ANESTHESIOLOGY 77:267–274, 1992

3. Castro MI, Eisenach JC: Pharmacokinetics and dynamics of intravenous, intrathecal, and epidural clonidine in sheep. ANESTHESIOLOGY 71:418–425, 1989

4. Eisenach J, Detweiler D, Hood D: Hemodynamic and analgesic actions of epidurally administered clonidine. ANESTHESIOLOGY 78:277–287, 1993

5. Coombs DW, Saunders RL, LaChance D, Savage S, Ragnarsson TS, Jensen LE: Intrathecal morphine tolerance: Use of intrathecal clonidine, DADLE, and intraventricular morphine. ANESTHESIOLOGY 62:357–363, 1985

6. Kendig JJ, Savola MKT, Woodley SJ, Maze M: α_2-Adrenoceptors inhibit a nociceptive response in neonatal rat spinal cord. Eur J Pharmacol 192:293–300, 1991

7. Savola J, Ruskoaho H, Puurunen J, Salonen JS, Karki NT: Evidence for medetomidine as a selective and potent agonist at α_2-adrenoreceptors. J Auton Pharmacol 5:275–284, 1986

8. Dickenson AH, Sullivan AF, McQuay HJ: Intrathecal etorphine, fentanyl and buprenorphine on spinal nociceptive neurones in the rat. Pain 42:227–234, 1990

9. Lichtman AH, Smith PB, Martin BR: The antinociceptive effects of intrathecally administered cannabinoids are influenced by lipophilicity. Pain 51:19–26, 1992

10. Eisenach JC, Tong C: Site of hemodynamic effects of intrathecal α_2-adrenergic agonists. ANESTHESIOLOGY 74:766–771, 1991

11. Williams JS, Tong C, Eisenach JC: Neostigmine counteracts spinal clonidine-induced hypotension in sheep. ANESTHESIOLOGY 78: 301–307, 1993

12. Vuorilehto L, Salonen JS, Anttila M: Picogram level determination of medetomidine in dog serum by capillary gas chromatography with negative ion chemical ionization mass spectrometry. J Chromatogr 497:282–287, 1989

13. Sheiner LB, Beal SL: Pharmacokinetic parameter estimates from several least squares procedures: Superiority of extended least squares. J Pharmacokinet Biopharm 13:185–201, 1985

14. Aarons L, Mandema JW, Danhof M: A population analysis of the pharmacokinetics and pharmacodynamics of midazolam in the rat. J Pharmacokinet Biopharm 19:485–496, 1991

15. Verotta D, Sheiner LB: Simultaneous modeling of pharmacokinetics and pharmacodynamics: an improved algorithm. Comput Appl Biosci 3:345–349, 1987

16. Nolan A, Livingston A, Morris R, Waterman A: Techniques for comparison of thermal and mechanical nociceptive stimuli in the sheep. J Pharmacol Methods 17:39–49, 1987

17. Bouchenafa O, Livingston A: Autoradiographic localisation of α_2 adrenoceptor binding sites in the spinal cord of the sheep. Res Vet Sci 42:382–385, 1987

18. Waterman A, Livingston A, Bouchenafa O: Analgesic effects of intrathecally-applied α2-adrenoceptor agonists in conscious, unrestrained sheep. Neuropharmacology 27:213–216, 1988

19. Detweiler DJ, Eisenach JC, Tong C, Jackson C: A cholinergic interaction in *alpha*$_2$ adrenoceptor-mediated antinociception in sheep. J Pharmacol Exp Ther 265:536–542, 1993

20. Aantaa RE, Kanto JH, Scheinin M, Kallio AMI, Scheinin H: Dexmedetomidine premedication for minor gynecologic surgery. Anesth Analg 70:407–413, 1990

21. Aho M, Lehtinen A, Erkola O, Kallio A, Korttila K: The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. ANESTHESIOLOGY 74:997–1002, 1991

22. Jaakola M, Ali-Melkkilä T, Kanto J, Kallio A, Scheinin H, Scheinin M: Dexmedetomidine reduces intraocular pressure, intubation responses and anaesthetic requirements in patients undergoing ophthalmic surgery. Br J Anaesth 68:570–575, 1992

23. Bernards CM, Hill HF: Physical and chemical properties of drug molecules governing their diffusion through the spinal meninges. ANESTHESIOLOGY 77:750–756, 1992

24. Bernards CM: Flux of morphine, fentanyl, and alfentanil through rabbit arteries *in vivo*: Evidence supporting a vascular route for redistribution of opioids between the epidural space and the spinal cord. ANESTHESIOLOGY 78:1126–1131, 1993

25. Glass PSA, Estok P, Ginsberg B, Goldberg JS, Sladen RN: Use of patient-controlled analgesia to compare the efficacy of epidural to intravenous fentanyl administration. Anesth Analg 74:345–351, 1992

26. Camann WR, Denney RA, Holby ED, Datta S: A comparison of intrathecal, epidural, and intravenous sufentanil for labor analgesia. ANESTHESIOLOGY 77:884–887, 1992

27. Coote JH: The organisation of cardiovascular neurons in the spinal cord. Rev Physiol Biochem Pharmacol 110:148–277, 1988

28. Hull CJ, Van Beem HB, McLeod K, Sibbald A, Watson MJ: A pharmacodynamic model for pancuronium. Br J Anaesth 50:1113–1123, 1978

29. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. Clin Pharmacol Ther 25:358–371, 1979