Spinal and Systemic Action of the $\alpha_2$ Receptor
Agonist Dexmedetomidine in Dogs

Antinociception and Carbon Dioxide Response

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Background: $\alpha_2$ Agonists are powerful analgesics after spinal delivery. The current work characterizes the dose-dependent antinociception and effects upon respiratory function of dexmedetomidine after intrathecal, epidural, intravenous, and intracisternal delivery in chronically prepared dogs.

Methods: Dogs were prepared with chronic tracheostomies and trained to perform rebreathing studies. These animals were then prepared with chronic lumbar intrathecal, epidural, or intracisternal catheters.

Results: A rapid dose-dependent increase in the thermal skin twitch response latency and paw withdrawal to mechanical pinch was observed after intrathecal, epidural, and intravenous dexmedetomidine (dose required to reach 50% of maximal effect for skin twitch = 1.8, 10, and 15 $\mu$g, respectively) but not after intracisternal dexmedetomidine (>15 $\mu$g), with the maximally effective dose lasting approximately 90 min. The spinal effect was unaccompanied by effects upon behavioral alertness, motor function, or changes in CO$_2$ response. In contrast, intravenous dexmedetomidine (1–10 $\mu$g/kg) resulted in a dose-dependent sedation and a significant reduction in heart rate and respiratory rate and a diminished response to increased CO$_2$; these effects lasting approximately 2 h. Intracisternal administration of up to 15 $\mu$g had no effect upon the nociceptive threshold, and CO$_2$ response, and failed to result in a significant reduction in alertness. All of the effects of dexmedetomidine were antagonized by the $\alpha_2$-antagonist atipamezole (30–300 $\mu$g/kg, intravenous), but not by the opioid antagonist naloxone (30 $\mu$g/kg, intravenous), while atipamezole did not reverse the antinociceptive or respiratory depressant actions of intravenous sufentanil (50 $\mu$g), effects which were reversible by naloxone.

Conclusions: Dexmedetomidine, acting through an $\alpha_2$-receptor, produces a powerful antinociceptive effect, mediated at the spinal level, while systemic redistribution of the drug leads to a hypnotic state with significant cardiorespiratory effects. (Key words: Anesthetic techniques: spinal. Lung(s), ventilation: carbon dioxide response. Pain: antinociception. Sympathetic nervous system, $\alpha_2$-adrenergic Agonists: dexmedetomidine.)

EARLY animal studies directed at defining the role of bulbospinal noradrenergic pathways in spinal nociceptive processing$^{1,2}$ demonstrated that the spinal administration of $\alpha_2$ agonists can produce a powerful effect upon nociceptive processing. This effect appears mediated by receptors which are pre- and postsynaptic to primary afferent terminals which project into the dorsal horn.$^3$ These spinal receptors are coupled, such that their occupancy results in depression of the release of small primary afferent neurotransmitters$^{1,5}$ and depression of the excitability of second-order projection neurons.$^6,7$ These joint actions are thought to account for the potent and selective antinociception observed after spinal delivery in a variety of species, including the mouse, rat, cat, and primate.$^8$ These analgesic effects of spinal $\alpha_2$ agonists have been confirmed in humans (see references 9–11 for examples). In addition to the spinal actions of these agents on nociception, the systemic administration of $\alpha_2$ adrenergic agonists will result in sedation and electroencephalographic synchronization$^{12,13}$ and a reduction in narcotic and volatile anesthetic requirements during surgery in animals$^{14,15}$ and in humans.$^{16,17}$

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While the ability of $\alpha_2$ agonists to produce analgesia and a reduced level of consciousness resembles that of opioids, the difference is important in two ways. First, systemic and spinally administered $\alpha_2$ agonists will result in significant bradycardia and hypotension, actions mediated by effects upon supraspinal as well as spinal sites. Second, unlike opiates, $\alpha_2$ agonists have been reported to have modest effects upon respiratory function at subesedative doses. These properties, in association with their analgesic actions, suggest the possible benefit of spinal $\alpha_2$ agonists.

An agent of current interest is Dexmedetomidine. This molecule is the pharmacologically active $\delta$-isomer of medetomidine, 4-{1-(2,3-dimethylphenyl)-methyl}-1H-imidazole. This $\alpha_2$ adrenergic agonist shows a very high $\alpha_2/\alpha_1$ selectivity ratio and a high efficacy, which makes this compound extremely interesting for spinal or systemic use. Recent studies in rodents have shown that this agent produces a powerful dose-dependent analgesia after spinal delivery mediated by an $\alpha_2$ receptor. These spinal actions are readily antagonized by agents such as yohimbine, idazoxan, and atipamezole (2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole), which are competitive $\alpha_2$ antagonists.

The aims of these studies were to investigate the antinociceptive actions and sedative and respiratory effects after spinal, intracisternal, and systemic administration of dexmedetomidine, and to examine the receptor selectivity of the observed drug effects by using the antagonists atipamezole ($\alpha_2$) and naloxone (opioid) in a chronically prepared and unanesthetized dog.

**Materials and Methods**

**Animals and Surgical Procedures**

The study was approved by the Institutional Animal Care Committee of the University of California, San Diego. The animals were adult laboratory-bred male beagles (15 ± 1 kg), obtained from Ridgelan Research Farms, Mount Horeb, Wisconsin. After an adaptation period of 3–5 days, the animals were prepared with a chronic tracheostomy, and trained to permit awake tracheal intubation and to rebreathe into a closed system (see below). The training period was followed by studies with intravenous drugs and a second surgical procedure to implant the intracisternal, intrathecal, and epidural catheters. A recovery interval of 3–5 days was allowed to elapse before the initiation of these studies. A period of 4–6 days was allowed to elapse between subsequent experiments.

For both surgical procedures, the animals received 1 mg/kg xylazine intramuscularly and 40 μg/kg atropine intramuscularly as premedication. At the same time, prophylaxis with 900,000 IU intramuscular procaine penicillin was administered. The animal was shaved at the sites of surgical incision, followed by cleansing with alcohol 70% and isobetadine. The animal was allowed to breathe 2–3% halothane in an O₂/N₂O mixture of 50/50% by mask. The animal was intubated and maintained with halothane (1–1.5%) in an O₂/N₂O mixture of 50/50%. A second time, isobetadine was spread over the surgical areas. Electrocardiogram, end-tidal CO₂, halothane, O₂, and N₂O were monitored intraoperatively. All procedures were carried out after rigid aseptic precautions. The implanted catheters and injection ports were sterilized in 70% ethanol for 24 h and flushed thoroughly with sterile saline before insertion. At the end of the operation, wounds were infiltrated with 0.5% bupivacaine and protected with a bacteriostatic ointment. Butorphanol (0.3 mg/kg, intramuscular) was used for postoperative analgesia. For the next 2 days the dogs received penicillin G intramuscularly (2 × 600,000 IU).

A tracheostomy was performed as described by Dueck and colleagues, consisting of an incision of the anterior third of two cartilaginous rings and an apposition of the tracheal mucosa to the skin.

The method for the intrathecal catheterization has been described previously by Archishon et al. The animal was positioned with its head in a stereotaxic head holder, a skin incision between the skull base and C1 was made, and the dura was exposed after blunt dissection between the posterior muscles of the neck. An incision in the dura was made on the midline, the dura and arachnoid retracted with a small hook and a polyethylene-50 catheter was passed caudally into the intrathecal space. The length of the intrathecal catheter was around 35 cm, but was measured for each animal to reach the L2-L3 spinal segment. Through the same intracisternal incision, a second polyethylene-50 catheter was passed caudally 2 cm into the intracisternal space. Both catheters were sheathed on the external portion with silastic tubing and fixed with a stainless steel suture to a stainless steel screw, placed in the occipital bone of the skull. The catheters were subcutaneously tunnelled to exit a few centimeters beside the incision and fixed to the skin with a suture. The catheters were closed at the exteriorized end with a stainless steel plug. The wound was closed in layers.
The implantation of the epidural catheter was performed following a modified technique, described originally by Durant and Yaksh. The catheter was surgically inserted between L7 and S1, and passed rostrally to the spinal segment level of L2–L3, a distance of approximately 10 cm. The catheter was fixed with a suture to the lumbar intraspinal muscles and connected with a subcutaneously installed injection port with a dead space volume of 0.1 ml (vascular-access-port model SLA, Access Technologies, Skokie, IL).

Catheter placement and patency were verified postoperatively by the appearance of clear flowing cerebrospinal fluid (CSF) from both the intracisternal and lumbar intrathecal catheter. The location of the epidural catheter was verified postoperatively by the anesthetic effects of lidocaine (2 ml, 1%). At sacrifice, the localization of the catheter was confirmed by localization of the tip and the distribution of dye delivered before exposure.

A schematic of the chronic model with the implanted catheters and the experimental setup is shown in figure 1.

**Drugs**

The test drugs used in these experiments were: dexmedetomidine hydrochloride (236.7 Da; Farnos Group, Turku, Finland), tritiated dexmedetomidine (25 mCi/ml), atipamezole hydrochloride (248.5 Da; Farnos Group), sufentanil citrate (578.7 Da; Janssen Research Foundation), naloxone hydrochloride (363.5 Da; DuPont, Wilmington, DE) and inulin [carboxyl-\(^{14}\)C] (3 mCi/g; 5,000–5,500 Da; DuPont).

The drugs were dissolved in sterile, preservative-free saline and administered in volumes of 5 ml for intravenous, 2 ml for epidural, 0.5 ml for intrathecal and 0.25 ml for intracisternal injection. After injection, the catheters were flushed with sterile saline using the same volume as the dead space of the catheter.

Different dose ranges were used after each route. The following agonist (dexmedetomidine) doses as a function of route were examined: intrathecal = 1, 3, or 10 μg; epidural = 3, 15, or 50 μg; intravenous = 1, 3, or 10 μg/kg; intracisternal 5 or 15 μg. All doses, unless specified otherwise, are presented as total doses. Because of the uniform body weights, for dose–response analysis, intravenous doses are given by total dose, based on a body mass of 15 kg. Table 1 presents a summary of the doses and routes for the antagonism studies. Intravenous administration of 300 μg/kg atipamezole and 30 μg/kg naloxone, together with saline administration given by the intrathecal, epidural, and intracisternal routes, were tested for their effects alone. Sufentanil (3 μg/kg, intravenous) was given to assess the selectivity of the antagonist effects of atipamezole.

**Table 1. Summary of Antagonist Dose Studies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route + Agonist Dose</th>
<th>Intravenous Antagonist + Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>iv (10 μg/kg)</td>
<td>Atipamezole (30, 100, or 300 μg/kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Naloxone (30 μg/kg)</td>
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<tr>
<td></td>
<td></td>
<td>atipamezole (300 μg/kg)</td>
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<tr>
<td>Sufentanil</td>
<td>iv (50 μg/kg)</td>
<td>Atipamezole (100 μg/kg)</td>
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<td></td>
<td></td>
<td>Naloxone (30 μg/kg)</td>
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</table>

iv = intravenous; it = intrathecal; epi = epidural.
minimum of five experiments were carried out for each drug dose combination.

For assessment of epidural kinetics, the radiolabeled solution for epidural injection consisted of 50 μg of dexamethasone to which was added 2 μCi of tritiated dexamethasone and 2 μCi of 14C-inulin in 2 ml.

**Functional Studies**

**Rebreathing.** The dogs were adapted in a sling adjusted such that the animal could stand or lie recumbent. For a rebreathing study, the endotracheal stoma was locally anesthetized with benzocaine—tetracaine topical spray (Cetacaine, Cetylite Industries, Pennsauken, NJ) and intubated with a size 10 cuffed endotracheal tube coated with a 5% lidocaine ointment. Dogs were extensively trained to undergo CO₂ rebreathing, using a modified Read rebreathing procedure.³⁰ ³¹ The system consisted of a breathing valve to open or close the rebreathing circuit to the animal, two one-way low resistance valves (inspiratory and expiratory), a flow cartridge and flow sensor immediately beyond the expiratory valve, two inlets behind the flow cartridge, one for the gas coming back from the capnograph after analysis and one to flush the system, before each measurement, with a fixed gas mixture of 5% CO₂/95% O₂. Both sides of the system were closed with an anesthesia breathing circuit consisting of two nonconductive breathing tubes, a Y elbow, and a 2 l breathing bag. Between the opening valve and the tracheal tube, the gas-collecting piece for the capnograph was placed. An Ohmeda 5250 respiratory gas monitor was used. This analyzer has an infrared CO₂ analyzer sampling 200 ml/min and a flow sensor to measure minute volumes. The data collected during the rebreathing cycle were sent every 10 s from the analyzer, through an analog-to-digital converter board, to an Apple IIx computer for analysis. To standardize data collection of the CO₂ response determinations, the data collection was started at an end-tidal CO₂ of 50 mmHg and was stopped when a CO₂ of 70 mmHg or a minute volume of 20 l was reached. Only in extreme cases of respiratory depression, measurements up to 85 mmHg CO₂ were performed. A CO₂ response was performed twice before each drug administration and typically at 10, 30, 60, 90, 120, 180, and 240 min after injection of the drug.

**Antinoceptive Testing.** Thermally evoked nociceptive reflexes were used to measure the magnitude of drug induced antinoception.³² The thermally evoked skin twitch response was examined using a probe with a contact area of 1 cm², maintained at 60 ± 1°C. Probe temperature was maintained by a proportional feedback current controller regulated by a temperature sensing thermistor built into the stimulus surface of the probe. The probe head is mounted to a spring loaded handle which allows the operator to press the probe head with a fixed pressure against the skin. Compression of the probe against the skin operates a switch controlling a timer for measurement of reflex latency. The probe was applied to shaven thoracic and lumbar areas of the back. Typically, this results in a brisk contraction of the local musculature within 1–2 s. The electrophysiology of this response is believed to reflect the activation of capsaicin sensitive C fibers in the dorsal cutaneous nerve evoking a nociceptive reflex contraction of the trunci cutaneous musculature,³³ causing a characteristic local contraction of the lower back. Upon the appearance of this response, the probe was immediately removed and the latency to respond recorded. Failure to respond within 10 s was cause to remove the probe and assign that value as the latency. The test was performed sequentially at four different places: thoracic (left to right) and lumbar (left to right). A skin twitch response was performed twice before each drug administration and typically once at 10, 30, 60, 90, 120, 180, and 240 min after drug delivery.

For computation of the agonist effect, the mean of the left and right response latencies was determined for each measurement time. The response latencies were converted to the percentage of the maximum possible effect (calculated as 100 × [postagonist latency − preagonist latency]/[10 s − preagonist latency]). In the antagonist studies, the antagonist was delivered after the agonist, and the reversal of the effect is expressed as the percentage of the maximum possible inhibition (calculated as 100 × [latency immediately before antagonist − latency after antagonist]/[latency immediately before antagonist − preagonist baseline]). Thus, no antagonism would be 0, and complete antagonism would be 100%.

After the assessment of the skin twitch latencies, the toes of the front and hind limbs were progressively compressed with Halsted forceps to observe the withdrawal response of the dog to a strong mechanical stimulus. Typically, in the absence of an analgesic, the initial, partial application of forceps would evoke a vigorous withdrawal response, and the stimulus was stopped immediately. The response was scored as present or absent (i.e., a full compression).

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Neurobehavioral Testing. At each time point, the ability of the dog to support its weight when elevated by its forepaws and walk (step) backward on its hind limbs when elevated by its forepaws was assessed. In addition, sedation was scored (0–5) according to the following criteria: 0 = normal alertness and responsiveness to the investigator; 1 = quiet repose, eyes closed, but readily alerted and retaining head tone continuously; 2 = quiet, drowsing, eyes transiently closed, minimal neck tone, but arousable; 3 = significant depression, eyes remain shut, loss of neck tone, difficult to arouse; 4 = eyes closed, persistent loss of neck tone, arousable with severe agitation; and 5 = not arousable, total loss of neck tone, no overt response to strong stimuli applied to paws.

Core Temperature. The rectal temperature was taken using a Yellow Springs Instruments (Yellow Springs, OH) 401 probe placed rectally 3–4 cm before each measurement.

Pharmacokinetic Analysis
Sampling and Sample Analysis. In separate studies, dogs were given epidural dexmedetomidine 50 μg/2 ml to which had been added tracer quantities of 3H dexmedetomidine and 14C-inulin (14C-inulin). In these studies, venous plasma and intracisternal and lumbar CSF were sampled at 0, 1, 3, 6, 10, 20, 30, 40, 60, 90, 120, 180, and 240 min after drug administration. The blood samples (2 ml) were drawn by a catheter placed in the brachiocephalic vein of the front limb which was flushed with heparinized saline (5000 U/l) after each sampling. The CSF samples (0.1–0.2 ml) were taken through the surgically implanted catheters as follows. The catheter dead space volume was drawn and discarded. The CSF sample was then taken and saved. The catheter was flushed with the catheter dead volume. Before taking the sample, a volume equal to the dead space of the catheter was drawn, and after each sample, the same volume of sterile saline was injected.

The CSF and plasma samples were diluted in 10 ml of Ecolite scintillation liquid (ICN Biomedicals, Irvine, CA) for analysis in a Tri-Carb liquid scintillation analyzer, model 19900 CA (Packard Instrument, Meriden, CT). Each sample was counted in the spectrum of the photoluminescence of 3H and 14C. To be able to distinguish and separate the photoluminescence of both molecules, a computerized automatic window tracking and gain restoration was used. The measured counts per minute values were converted to disintegrations per minute using transformed spectral index of external standard/automatic efficiency control as quench-indicating parameters for dual label measurements. Before the experiment, a dilution curve was made to verify the regression linearity, which was 0.98.

Pharmacokinetic Analysis. The pharmacokinetic noncompartmental analysis based on statistical moment theory was performed using a nonlinear least-squares regression fitting software program RSTRIP (MicroMath, Salt Lake City, UT). Time versus drug concentration points for each animal were fitted to an exponential function. Half-lives, peak concentrations and time to reach the peak concentrations were established in the chosen model. The area under the time versus concentration curve and the area under the moment curve were calculated with the same program and used to estimate the clearance (dose/area under the time versus concentration curve), mean residence time (area under the moment curve/area under the time versus concentration curve), and the distribution volume at a steady state (mean residence time X clearance). In separate computations, the sample drug/inulin ratios were determined with the measured values of disintegrations per minute, normalized to the drug/inulin ratio of the injected solution. This adjusted drug/inulin ratio makes it possible to compare the movement of the drug versus inulin, a molecule with no metabolism, protein binding or active transport mechanism.

Statistical Analysis
The CO2 and minute ventilation values collected every 10 s during one CO2 rebreathing challenge were used to perform a least squares linear regression, with a confidence interval of 95% for each animal. The correlation coefficient (r) and the value of t for the slope were calculated at the same time. Only in the case of an r value of < 0.97 was a second-order polynomial analysis performed to see if a polynomial analysis gave a better fit. Out of the linear regression, the slope and the intercept of the line with the CO2 axis were calculated.34 These values were subsequently used for further analysis. The slope of the CO2 rebreathing challenge at each given time after drug administration was compared with the baseline and expressed as percent change of baseline. Data are presented as mean values of percent change in slope (percentage) or intercept (millimeters mercury) (± SE). Changes in slope or intercept were evaluated for significance using the unpaired t test.

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The drug groups and drug plus antagonist groups were compared using one-way analysis of variance followed by a Dunnett's test. The comparison between front and hind limb withdrawal reflexes was performed using chi-square analysis; the comparison of the area under the time effect curve for lumbar and thoracic skin twitch responses was performed using the paired t test. Values reaching $P < 0.05$ level were considered to be statistically significant.

The relative potency, calculating the dose of dexmedetomidine required to reach 50% of the maximal effect, was obtained using the pharmacologic software of Tallarida and Murray. The dose of antagonist required to produce a 50% inhibition was calculated by the same approach. For assessment of the sedation scores, comparisons were made using a Kruskal–Wallace rank-order comparison.

Results

**Nociceptive Testing**

**Time Course.** The intravenous, epidural, and intrathecal injection of dexmedetomidine resulted in a significant increase in the skin twitch latencies (fig. 2) and a blockade of the withdrawal evoked by mechanical compression of the hind paw (fig. 3). Intracisternal injection of the highest dose employed was without effect. The maximal drug effect, as measured by increasing skin twitch depression (fig. 2, top) and a blockade of the paw withdrawal (time course not presented, but comparable to the skin twitch changes), was observed within 3 min after intravenous administration and 15 min after the epidural and intrathecal injections. As shown in figure 2, after the maximally effective dose, the duration of the drug action was approximately 90 min for the intrathecal and intravenous routes and 240 min for the epidural route.

**Dose Dependency.** Table 2 presents the calculated dose required to reach 50% of maximal effect for dexmedetomidine given by several routes. Based on these data, the rank ordering of potency on both the skin twitch and the paw withdrawal was intrathecal > EP ≥ intravenous.

**Somatotopy.** The antinociceptive effects after intrathecal administration appeared maximal in the vicinity of the dermatomes proximal to the tip of the catheter (i.e., lumbar). As shown in figure 3, after a fixed dose of intrathecal or epidural dexmedetomidine, the maximal blockade of the response to pinch occurred in the hind paw and not the forepaw. In contrast, high doses of intravenous dexmedetomidine produced an equivalent blockade of both fore- and hind paw responsiveness.

**Antagonism.** While intravenous atipamezole (at doses up to 300 μg/kg, intravenous) alone had no effect upon the skin twitch latency (data not shown), there was a clear, dose-dependent reversal of the effect of dexmedetomidine on antinociception. The calculated dose of antagonist required to produce a 50% inhibition (± 95% confidence intervals) required to produce a
50% reversal of the antinociceptive effects of dexametomidine (10 μg/kg intravenous) was 35 μg/kg (4–175 μg/kg). Though similar dose–response curves were not accomplished for the spinal routes of administration, as shown in figure 4, the administration of 100 μg/kg of atipamezole resulted in significant reductions in the effects of otherwise maximally active doses of intrathecally and epidurally administered dexametomidine. The decrease in withdrawal reflex due to compression of the digits of the hind paws after 50 μg of epidural and 10 μg of intrathecal dexametomidine was also significantly reversed by atipamezole (100 μg/kg, intravenous; P < 0.05; n = 5, both routes; data not shown).
Respiratory Parameters

Changes in Slope of the CO₂ Response Curve.
The injection of dexmedetomidine by the intravenous route resulted in a potent dose-dependent suppression in the slope of the CO₂ response curve, with the duration of the effect being approximately 1–2 h (see fig. 5). A significant reduction was also observed at the highest dose after epidural delivery but not after intrathecal or intracisternal doses of dexmedetomidine.

Saline (n = 5), naloxone (30 μg/kg, intravenous; n = 5) and atipamezole (300 μg/kg, intravenous; n = 7) had no effect upon the slope of the CO₂ response curve over a typical 4-h study period (P > 0.10; data not shown). Atipamezole, the selective α₂ antagonist, reversed the respiratory depressant effect of intravenous dexmedetomidine (fig. 6). Naloxone (30 μg/kg, intravenous) did not reverse the decrease in the CO₂ response induced by dexmedetomidine (n = 6; P > 0.10; data not shown).

Changes in Intercept of the CO₂ Response Curve.
Figure 7 represents the change over time of the x-intercept of the ventilation–CO₂ response curve. While the slope of the CO₂ response curve decreased significantly after intravenous administration of dexmedetomidine, the x-intercept shifted significantly to the left. The effect was not the same after dexmedetomidine administration by the intrathecal, epidural, or intracisternal routes. At the moment of the greatest change in x-intercept, we calculated the change in ventilatory response at a CO₂ tension of 60 mmHg. The ventilatory response remained decreased (10 μg/kg: 61.7 ± 5.2% of the baseline ventilatory response at a CO₂ tension of 60 mmHg).

The shift in the x-intercept evoked by dexmedetomidine (10 μg/kg, intravenous) was reversed in a dose-dependent fashion by atipamezole, but not naloxone (atipamezole 300 μg/kg > atipamezole 30 μg/kg > naloxone 30 μg/kg, intravenous = saline: P < 0.05).

Changes in Respiratory Rate and End-tidal CO₂.
As compared to preinjection values, the high intravenous (10 μg/kg, intravenous), epidural (50 μg) and intracisternal (15 μg) doses of dexmedetomidine induced a significant decrease in the resting respiratory rate (fig. 8, top). At these doses, there was no change in resting end-tidal CO₂, although a modest reduction in end-tidal CO₂ was observed early on in the experiments with a high dose of intravenous dexmedetomidine (10 μg/kg) (see fig. 8).

The reduction in resting respiratory rate evoked by dexmedetomidine (10 μg/kg, intravenous) was reversed in a dose-dependent fashion by atipamezole, but not naloxone (atipamezole 300 μg/kg > atipamezole 30 μg/kg > naloxone 30 μg/kg, intravenous = saline: P < 0.05).

Heart Rate. A significant dose-dependent decrease in heart rate was observed after intravenous administration (see fig. 9). After epidural administration, a significant reduction in heart rate was observed only after the highest dose of dexmedetomidine (50 μg). No statistically significant changes in heart rate were observed.
SPINAL AND SYSTEMIC DEXMEDETOMIDINE IN DOGS

**Antagonism: Δ CO2 Slope**

- POST-DEX 10 μg/kg, IV
- POST-ATIPAMEZOLE

Fig. 6. Percent change versus baseline of the slope the ventilation–CO2 response (% ΔVe/CO2) curve is presented 10 min after the injection of dexametomidine (IV POST-DEX, 10 μg/kg, black bar) and 10 later after the injection of one of three doses of atipamezole (30, 100, or 300 μg/kg, intravenous). Each pair of histograms present the mean and SEM of five dogs. *P < 0.05 compared to effect observed at 10 min, paired t test. # The magnitude of reversal induced by atipamezole was 100 = 300 > 30 μg/kg, one-way analysis of variance.

**Time Course: Respiratory Rate**

- 10 μg/kg IV
- 50 μg EP
- 10 μg/kg IT
- 15 μg IC

Fig. 8. (Top) Resting respiratory rate observed as a function of time after dexametomidine given by intrathecal (IT, 10 μg), epidural (EP, 50 μg), intravenous (IV, 10 μg/kg), or intracisternal (IC, 15 μg) administration. Each line presents the mean and SEM of five dogs. *P < 0.05, one-way repeated-measures analysis of variance. (Bottom) Resting end-tidal CO2 observed as a function of time after dexametomidine. Each line presents the mean and SEM of five dogs. No trend was significant: P < 0.10, one-way repeated-measures analysis of variance versus peak effect.

**CO2-Response: X-Intercept**

- 10 μg IT
- 50 μg EP
- 10 μg/kg IV
- 15 μg IC

Fig. 7. The x-intercept of the ventilation–CO2 curve is plotted versus time after dexametomidine given by intrathecal (IT, 10 μg), epidural (EP, 50 μg), intravenous (IV, 10 μg/kg), or intracisternal (IC, 15 μg) administration. Each line presents the mean and SEM of five dogs. *P < 0.05, one-way repeated-measures analysis of variance.

After the highest dose of intrathecal (10 μg) or intracisternal dexametomidine (15 μg), the effect on heart rate was dose-dependently reversed by atipamezole and not by naloxone: (atipamezole 300 μg/kg > atipamezole 30 μg/kg > naloxone 30 μg/kg, intravenous = saline: P < 0.05) (data not shown).

**Neurobehavioral Testing**

**Sedation.** Depression of spontaneous activity and a correlated loss of the ability to easily arouse the animal, and a reduction in the motor tone of the neck was observed after intravenous administration of dexametomidine (see fig. 10). Shaking the animal or placement of the rectal thermometer would serve to partially arouse the dog. In contrast, intrathecally, epidurally,
temperature was observed after intrathecal delivery (fig. 11).

**Pharmacokinetic Analysis**

Using a noncompartmental analysis, the concentration versus time of dexmedetomidine in the lumbar CSF after epidural administration could easily be fitted to a three-exponential function. The calculated pharmacokinetic parameters resulting from this function are presented in Table 3. The intracisternal levels could

and intracisternally injected animals showed only minor depression of behavior after the highest dosage.

**Core Temperature**

Saline treated animals demonstrated no statistically significant core temperature changes over time ($P > 0.10$; $n = 6$ data not shown). After intravenous, intracisternal, and, to a lesser extent, epidural dexmedetomidine administration, a dose-dependent reduction in core temperature was observed. No change in core

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not be fitted to any simple exponential function, but inspection of the data (fig. 12) demonstrates two possible peaks: the first one at 30 min and the second one at 90–120 min. This may indicate a fast vascular and slower CSF bulk flow redistribution. The $^3$H radioactivity measured in the plasma demonstrated an initial fast absorption and elimination phase, but over time, an accumulation of $^3$H radioactivity was observed, indicating an accumulation of the drug and/or its metabolites. The $^{14}$C-inulin disintegrations per minute versus time curve in the lumbar CSF could be fitted as well to a two- or three-exponential function. The resulting parameters for inulin out of a three-exponential function are presented in table 3. A three-exponential was best fitted on the plasma inulin counts, but no simple exponential function could be fitted to the intracisternal counted levels. The exponential function fitted to the plasma inulin counts resulted in an absorption, redistribution and elimination at 6.3 (± 1.5) min, 14.5 (± 3) min, and 56 (± 6.5) min, respectively. The time to reach the peak counts was 32.7 (± 5.3) min and a clearance of 84 (± 2.7) ml/min; mean residence time of 83.5 (± 2.8) min and distribution volume at a steady state of 7 (± 0.45) l were calculated.

The drug/inulin ratio versus time in the lumbar CSF presented in figure 12 (bottom) makes it possible to compare the drug movement versus an inert molecule from the lumbar epidural into the lumbar intrathecal space. Initially, as seen in the calculated parameters, dexmedetomidine moved twice as fast into the lumbar CSF as inulin, but the drug disappeared faster resulting in a ratio below 1. A shorter, calculated redistribution, elimination half-life and mean residence time for dexmedetomidine, together with a faster CSF clearance and larger distribution volume at a steady state for dexmedetomidine in the CSF (shown in table 3) confirm these findings.

**Discussion**

Dexmedetomidine is an $\alpha_2$ adrenergic agonist with a high $\alpha_2$ selectivity and efficacy. Consistent with

| Table 3. Pharmacokinetic Parameters in Lumbar CSF Following Epidural Injection of Dexmedetomidine and Inulin |
|--------------------------------------------------|--------------------------------------------------|
| **Dexmedetomidine** | **Inulin** |
| $T_{1/2}$ (min) | 6 ± 1.2 | 5.5 ± 1.1 |
| $T_r$ (min) | 7.7 ± 1.4 | 12.8 ± 4 |
| $T_{t}$ (min) | 66 ± 16 | 83 ± 15 |
| $C_{max}$ (ng) | 642 ± 56 |
| $T_{max}$ (min) | 12.2 ± 1 | 24.6 ± 3.6 |
| Cl (ml/min) | 1.8 ± 0.2 | 0.58 ± 0.08 |
| MRT (min) | 43 ± 2.4 | 53 ± 9.9 |
| $V_{ss}$ (ml) | 77 ± 6.6 | 31 ± 5.8 |

$T_{1/2}$ = time of appearance of $C_{max}$; $T_{max}$ = mean residence time; $V_{ss}$ = distribution volume at steady state.
previous rodent studies reviewed in the Introduction, after spinal administration, this agent was observed to produce a powerful and selective analgesic effect with minimal effects upon heart rate and respiratory function at doses required to produce a significant elevation in the nociceptive threshold, as measured either by thermal or mechanical nociceptive endpoints. Systemic injection of the agent was also observed to produce a significant elevation in the nociceptive response latencies, but these changes were typically observed at doses which led to bradycardia and a significant reduction in alertness and respiratory response to hypercarbia. Importantly, all of the effects observed were reversed by the a-selective atipamezole, but not the opioid antagonist naloxone. Given the affinity of dexametomidine for an a2 versus a1 site and the selective preference of atipamezole for the a2 receptor, these effects strongly support the role of an a2 receptor in all of these endpoints examined. Several points regarding these observations will be considered below.

**Antinociception**

Although it is clear that dexametomidine has the ability to redistribute after spinal delivery, several lines of evidence indicate that the analgesic effects observed after its intrathecal and epidural injections are mediated in these studies at the segmental level.

1. The dose–response curves for analgesia after several routes of delivery indicated a relative activity of: intrathecal > epidural ≥ systemic.
2. The injection of dexametomidine at a dose 50% greater than the maximally effective intrathecal dose into the cisterna was without effect, indicating that a simple rostral diffusion cannot account for the potent lumbar action.
3. After intrathecal and epidural injection, there was a preferential reduction in the response to pinching of the hind paws, as compared to the forepaws, after drug delivery through lumbar, epidural, or intrathecal catheters. In contrast, no such differences were noted after systemic delivery. Thus, after intrathecal administration at any given dose, the maximum degree of antinociception as defined by the ability to evoke a withdrawal of the paw was found in the skin dermatomes that were innervated by the segments of the spinal cord near the catheter tip.

This localization of effect is consistent with the likelihood that the highly soluble lipid agents are cleared rapidly from the CSF in the vicinity of the spinal injection site and the drug action is thereby anatomically limited. However, because of the rapid clearance, plasma levels are elevated. When the total dose required approaches that given systematically, the specificity of the effect is abolished (see below). Similar observations have been made for opiates such as sufentanil versus morphine in humans\(^{37,38}\) and in similar cat\(^{39}\) and dog models.\(^{39}\)

**Respiration**

Respiratory depression after the systemic administration of a2 agonists has been reported in animals\(^{19,20}\)

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![Graph showing CSF DEX CONCENTRATION vs TIME: 50 µg EP](image1)

![Graph showing CSF DEX/INULIN RATIO vs TIME: 50 µg EP](image2)

**Fig. 12.** The intracisternal and lumbar dexametomididine CSF concentrations (nanograms per milliliter) (top) and the respective dexametomididine/inulin ratios (bottom) are expressed versus time after epidural administration of the inulin–dexametomididine (50 µg) mixture at 0 min. Each line presents the mean and SEM of four dogs.
and humans.\textsuperscript{40} This depression is commonly manifested as a decrease in respiratory rate and a decreased respiratory response to hypercapnia. In the current study, systemic dexmedetomidine resulted in a dose-dependent depression in the rate and slope of the CO\textsubscript{2} response function. The magnitude of this depression corresponds closely to that which has been reported in lightly anesthetized dogs by similar doses of dexmedetomidine.\textsuperscript{41} Current data suggest that these actions are mediated by an action at a supraspinal site. Thus, after spinal delivery, little change in rate or the slope of the CO\textsubscript{2} response function was observed at intrathecal or epidural doses which produced a powerful segmental analgesia in the unanesthetized dog. Although higher spinal doses were not examined, examination of figure 5 suggests that there is a strong, correlative relationship between the degree of depression of the CO\textsubscript{2} response versus the total dexmedetomidine dose delivered, whether given spinally or systemically. This likely reflects upon the redistribution displayed by this agent after spinal delivery (see below). In humans, Penon and colleagues\textsuperscript{42} observed a mild decrease in the slope of the ventilatory response to CO\textsubscript{2} and incidences of apnea after the epidural administration of 300 μg of clonidine in postoperative patients. Filos and colleagues\textsuperscript{43} also observed moderate sedation, but no change in oxygen saturation after spinal clonidine.

The mechanisms underlying the respiratory depressive effects of the α\textsubscript{2} agonists are not understood. There is evidence that respiratory neurons located in the ventral brainstem\textsuperscript{44} are subject to an inhibitory modulation by a number of local receptor systems, such as those for the mu opioid and the α\textsubscript{2} receptor.\textsuperscript{45,46} It is tempting to speculate that the opioid and α\textsubscript{2} receptor systems may act similarly. However, in the current study, the failure of dexmedetomidine given intracisternally to produce either significant somnolence or respiratory depression argues against that hypothesis. In other studies using this dog model, we have shown that intracisternal mu agonists (sufentanil, morphine) will produce a significant depression of respiration and induce a prominent somnolence.\# These observations jointly suggest two points. First, that the site of respiratory depression must lie distal to the site of delivery in the cisterna, and second, that the modest depression observed after spinal α\textsubscript{2} agonists likely occurs by a systemic route rather than a spinal redistribution.

\textbf{Sedation}

The depressant action of α\textsubscript{2} adrenergic receptor agonists, in general, and dexmedetomidine, in particular, has been previously reported in a variety of species, including rats, rabbits, cats and dogs.\textsuperscript{18} As reviewed in the Introduction, in animals and humans, these agents, by a supraspinal action, have been shown to reduce anesthetic requirements, in part because of the reduced state of consciousness associated with their supraspinal action. Such effects after spinal administration must thus reflect upon supraspinal redistribution of the agent. The mechanisms underlying the changes in consciousness after activation of supraspinal α\textsubscript{2} receptors are not known. Considerable data has classically pointed to the role of supraspinal noradrenergic terminal systems in mediating states of arousal and sleep, and the pharmacology of the depressive actions of this system suggests the role of an α\textsubscript{2} site located in the brainstem.\textsuperscript{47,48}

\textbf{Motor Function}

With regard to motor function, in the current study, after spinal delivery of dexmedetomidine at doses which had potent analgesic actions, there was minimal effect on muscle tone and motor function. Agonists at the α\textsubscript{2} receptor have been shown to diminish exaggerated motor tone. Thus, after spinal injury, the associated spasticity can be reduced by α-adrenergic agonists.\textsuperscript{49,50}

\textbf{Core Temperature}

The observations of the changes in core temperature in these experiments with an α\textsubscript{2} agonist corresponds with earlier findings in the rat after subcutaneous administration.\textsuperscript{51} Significant decreases in core temperature were not observed in the intrathecal or epidural routes. Thus, a peripheral or supraspinal redistribution appears to account for the hypothermic action observed in these studies. The mechanism of this effect is not known. To the extent that these agents act to suppress sympathetic outflow, the decrease in temperature could reflect a peripheral vasodilatation. Conversely, adrenergic receptors in the hypothalamus have been shown to mediate a reduction in the set point for temperature regulation.\textsuperscript{52,53}

\textbf{Pharmacokinetic Analysis}

Dexmedetomidine is a highly lipid-soluble molecule.\textsuperscript{21} As such, the current results indicate that it is rapidly absorbed into the CSF, and circulation, after epidural injection, is consistent with previous work.


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with epidural drugs, such as morphine or sufentanil studied in humans.\cite{57,58} Comparison of its movement with the large inert marker molecule, inulin, revealed it to move twice as fast through the dura. Previous work has shown that low molecular weight and high lipid solubility serve to facilitate dural diffusion.\cite{54} Similarly, consistent with its lipid solubility, dexmedetomidine was rapidly eliminated from the intrathecal space. These kinetics obtained with spinal dexmedetomidine closely resembled those we have observed in this dog model with the lipid-soluble opioid, sufentanil.\# The concentrations of drug measured in the cisterna could not be fitted to a simple exponential function. This may indicate a complex process of drug movement into this space. Simple inspection of the data suggests the presence of two peaks, leading to the possible speculation of a vascular and CSF route of redistribution.

**Clinical Considerations**

The analgesic effects of spinally administered clonidine in humans confirms the observations in the preclinical literature regarding the selective effects of spinal $\alpha_2$ receptors on nociceptive processing.\cite{53-55} The potential advantages accruing from an $\alpha_2$ agonist relates to the distinct physiologic effects mediated by spinal $\alpha_2$ receptor systems. Both opioid and $\alpha_2$ receptors are able to regulate afferent processing. $\alpha_2$ agonists, however, are poorly influenced, if at all, by opioid antagonists\cite{55} and show minimal cross tolerance.\cite{56} Such a lack of pharmacologic overlap suggest that $\alpha_2$ agents may be of benefit to opioid-tolerant pain patients. Similarly, $\alpha_2$ agonists display a powerful functional synergism with other spinal analgesic agents, including opioids and nonsteroidal, antiinflammatory agents.\cite{57,58} This permits the use of relatively low doses of either family of agents to achieve analgesia. Such interactions have been posited to minimize the dose-dependent side effects associated with each receptor class. Some support for this approach has been obtained from clinical data.\cite{59}

The physiologic effects of spinal $\alpha_2$ receptors, other than their effects upon afferent processing, relate to the spinally mediated bradycardia and hypotension. These effects have been routinely observed with spinal clonidine in humans\cite{16} and appear to be characteristic of the $\alpha_2$ receptors acted upon by dexmedetomidine. The depressant effect of $\alpha_2$ agonists on CO$_2$ responsiveness has been similarly observed with clonidine in humans,\cite{60,61} although the effects may be mild at low doses in healthy volunteers.\cite{62} In contrast to the cardiovascular effects of spinal $\alpha_2$ agonists, this action appears mechanistically to reflect a supraspinal action of the agent. As such, the therapeutic index of the spinally administered $\alpha_2$ agonists will depend upon their respective redistribution properties. In this regard, for dexmedetomidine, we believe that the spinal therapeutic profile will have characteristics similar to the several lipid-soluble spinal opioids, such as sufentanil. Thus, the drug will have maximum efficacy when delivered at or near the spinal segments mediating the afferent input. In the animal studies, it is clear that doses necessary to alter the nociceptive threshold can have a significant effect upon respiratory responsiveness.\cite{63} Initial studies have suggested that the synergy demonstrated between $\alpha_2$ and opioid agonists with regard to analgesia does not apply to respiratory rate or to CO$_2$ accumulation in animals\cite{64} and humans.\cite{65} Further data on the interaction of these several receptors classes in dynamic models of respiratory function over a wide range of doses is clearly required.

In conclusion, the efficacy of dexmedetomidine and clonidine in preclinical models suggests that $\alpha_2$ agents may acquire an important role in pain management. The current emphasis upon subclasses of $\alpha_2$ receptors with apparent distinctions in their respective side effects profiles raise the possibility that a receptor-selective differentiation of analgesia from other physiologic effects may be achievable with $\alpha_2$ subtypes.\cite{66}

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