Effects of epidural administration of dexmedetomidine on the minimum alveolar concentration of isoflurane in dogs

Daniela Campagnol, MV, MSc; Francisco J. Teixeira Neto, MV, PhD; Tatiana Giordano, MV; Tatiana H. Ferreira, MV; Eduardo R. Monteiro, MV, MSc

Objective—To evaluate the effects of epidural administration of 3 doses of dexmedetomidine on isoflurane minimum alveolar concentration (MAC) and characterize changes in bispectral index (BIS) induced by noxious stimulation used for MAC determination in dogs.

Animals—6 adult dogs.

Procedures—Isoflurane-anesthetized dogs received physiologic saline (0.9% NaCl) solution (control treatment) or dexmedetomidine (1.5 [DEX1.5], 3.0 [DEX3], or 6.0 [DEX6] µg/kg) epidurally in a crossover study. Isoflurane MAC (determined by use of electrical noxious stimulation of the hind limb) was targeted to be accomplished at 2 and 4.5 hours. Changes in BIS attributable to noxious stimulation and cardiopulmonary data were recorded at each MAC determination.

Results—With the control treatment, mean ± SD MAC values did not change over time (1.57 ± 0.23% and 1.55 ± 0.25% at 2 and 4.5 hours, respectively). Compared with the control treatment, MAC was significantly lower at 2 hours (13% reduction) but not at 4.5 hours (7% reduction) in DEX1.5-treated dogs and significantly lower at 2 hours (29% reduction) and 4.5 hours (13% reduction) in DEX3-treated dogs. The DEX6 treatment yielded the greatest MAC reduction (31% and 22% at 2 and 4.5 hours, respectively). During all treatments, noxious stimulation increased BIS; but changes in BIS were correlated with increases in electromyographic activity.

Conclusions and Clinical Relevance—In dogs, epidural administration of dexmedetomidine resulted in dose-dependent decreases in isoflurane MAC and that effect decreased over time. Changes in BIS during MAC determinations may not represent increased awareness because of the possible interference of electromyographic activity. (Am J Vet Res 2007;68:1308–1318)

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From the Department of Veterinary Surgery and Anesthesiology, Faculdade de Medicina Veterinária e Zootecnia, Universidade Estadual Paulista (UNESP), Botucatu, São Paulo, Brazil. This manuscript represents a portion of the dissertation submitted by the first author to the Faculdade de Medicina, Universidade Estadual Paulista, for the MSc degree.

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Address correspondence to Dr. Teixeira Neto.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>MAC</td>
<td>Minimum alveolar concentration</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<td>BIS</td>
<td>Bispectral index</td>
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<tr>
<td>SAP</td>
<td>Systolic arterial blood pressure</td>
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<tr>
<td>DAP</td>
<td>Diastolic arterial blood pressure</td>
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<tr>
<td>MAP</td>
<td>Mean arterial blood pressure</td>
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<tr>
<td>ETISO</td>
<td>End-tidal isoflurane</td>
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<tr>
<td>ETCO₂</td>
<td>End-tidal carbon dioxide</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>SQI</td>
<td>Signal quality index</td>
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As with other α₂-adrenergic receptor agonists, higher doses of dexmedetomidine (20 µg/kg) may induce profound hypnosis, resulting in substantial reductions in injectable and inhalant anesthetic requirements. In dogs that are not premedicated, the standard IV dose of propofol is approximately 6 to 7 mg/kg; however, when high doses of dexmedetomidine (20 µg/kg) are administered as premedication, propofol requirements to achieve induction of anesthesia are decreased to approximately 1 mg/kg. Dexmedetomidine also decreases inhalant anesthetic requirements (ie, MAC) in a dose-related fashion. A high dose of dexmedetomidine (20
μg/kg, IV) reduced the isoflurane MAC in dogs by 89% and 50% at 30 minutes and 4 hours after administration of the α2-adrenergic receptor agonist, respectively.3

Interest in epidural administration of α2-adrenergic receptor agonists such as dexmedetomidine has increased because α2-adrenergic receptors that play a functional role in the modulation of pain have been identified in the spinal cord of rats.5,7 Results of a study in dogs have provided evidence that in comparison to effects achieved via IV administration, epidural administration of dexmedetomidine potentiated and prolonged the analgesic effect of the α2-adrenergic receptor agonist. This characteristic may have important clinical implications because the use of reduced doses of dexmedetomidine given epidurally, in addition to prolonging the beneficial analgesic effects, might be associated with a reduction in severity of the adverse effects that develop after IV administration of relatively high doses (eg, bradycardia and decreases in cardiac output).3,9

The MAC is the end-tidal concentration of an inhalant anesthetic that prevents arousal from anesthesia in response to supramaximal noxious stimulation in 50% of a population, and this variable is the standard method used to evaluate the effects of drugs and other physiologic conditions on the potency of inhalant anesthetics.9-11 Classically, motor responses (defined as gross purposeful movement of the head, trunk, or limbs) to noxious stimulation are used as a measure of arousal from anesthesia during MAC studies.9,10 In laboratory settings, the MAC value for each individual from a population is calculated as the arithmetic mean of the highest end-tidal inhalant concentration that allows arousal from anesthesia and lowest end-tidal inhalant concentration that prevents such response.10,12 Although reflex motor responses (eg, limb withdrawal in response to nociceptive stimulation of the foot) and autonomic responses (eg, increases in arterial blood pressure and heart and respiratory rates) are often detected at the end-tidal anesthetic concentrations that originated the MAC value, these responses are not considered a measure of corticocerebral arousal.13-15 Nociceptive stimulation may induce EEG changes that are suggestive of arousal from anesthesia.9,10 In a variety of species, increases in the EEG median frequency following noxious stimulation may be suggestive of cortical perception of pain during anesthesia (corticocerebral arousal).17-19 The BIS is a numeric scale calculated on the basis of EEG-derived variables that has been used to assess the level of hypnosis and anesthetic requirements in humans.13,20 The BIS value may range from 0 to 100, where 0 represents electrocortic silence of the CNS and 100 represents a fully conscious, alert individual. The lack of significant changes in BIS after nociceptive stimulation is suggestive of adequate depth of anesthesia.21,22

The main purpose of the study reported here was to evaluate the effects of epidural administration of 3 doses of dexmedetomidine on isoflurane MAC in dogs. The hypothesis of the study was that epidural administration of dexmedetomidine in dogs would decrease the MAC of isoflurane in a dose-related fashion and that this effect would decrease over time. The potential advantages of administering α2-adrenergic receptor agonists via the epidural route include increases in the duration and intensity of analgesia (compared with that achieved via other routes of administration) and a reduction in the intensity of the adverse effects because of the lower doses used. To our knowledge, there are no published studies in which BIS changes during MAC determinations in dogs were assessed. Therefore, our intent was also to characterize the changes in BIS induced by nociceptive stimulation used for isoflurane MAC determinations and assess the effects of epidural administration of dexmedetomidine on these changes in dogs.

Materials and Methods

The study was performed following the guidelines of the Brazilian College of Animal Experimentation, and the experimental procedure was approved by an institutional animal care committee (protocol No. 435/2004 CEEA).

Animals—Six clinically normal mixed-breed dogs (4 females and 2 males) were used in the study; mean ± SD weight of the dogs was 18.8 ± 4 kg. Health status was assessed by means of physical examination, a CBC, and serum biochemical analyses; all findings were within reference ranges.

Instrumentation and study design—The experiments were always started at the same time in the morning. Dogs were allowed free access to water until just prior to the start of each experiment. Food was withheld for 12 hours and then anesthesia was induced with isoflurane administered through a face mask by use of a circle breathing circuit. The precision vaporizer was adjusted to deliver 5% isoflurane with an oxygen flow rate of 4 to 5 L/min until the laryngeal reflexes were abolished. After orotracheal intubation, oxygen flow rate was decreased to approximately 1 to 2 L/min and the vaporizer was adjusted to maintain a moderate depth of anesthesia (determined on the basis of clinical assessments).

Each dog was positioned in lateral recumbency for catheterization of a cephalic vein and a dorsal pedal artery with 20-gauge catheters.4 The venous access was used for administration of lactated Ringer’s solution (3 mL/kg/h) by use of a peristaltic infusion pump throughout the anesthetic episode. The arterial catheter was connected to a fluid-filled pressure transducer system for measurement of SAP, DAP, and MAP on the screen of a monitor; the accuracy of this system was previously checked with a mercury column. The zero reference value of the pressure transducer was set at the manubrium in each laterally recumbent dog and at the level of the scapulohumeral joints after the dog was positioned in dorsal recumbency. Blood samples were collected from the arterial catheter in syringes containing heparin; pH, PaCO2, PaO2, and bicarbonate concentration were immediately analyzed by use of an automated blood gas system.6 Blood gas variables were corrected on the basis of body temperature; temperature was determined by use of an esophageal probe that was positioned with its tip at the level of the thoracic inlet. During MAC determinations, esophageal temperature was maintained at 37.5° to 38.5°C by means of a forced warm air blanket and an electric heating pad. To moni-
tor heart rate and rhythm, adhesive lead II ECG electrodes were attached to the skin; the ECG tracing was downloaded to a computer for subsequent analysis.

Samples of airway gases were collected continuously from the distal end of the endotracheal tube at a constant rate (200 mL/min) into an infrared gas analyzer to monitor ETCO$_2$ and ETCO$_3$ concentrations. The gas analyzer was calibrated with a standard gas mixture supplied by the manufacturer before and during each experiment. Pressure-controlled mechanical ventilation was instituted to maintain eucapnia (PacO$_2$, at 35 to 45 mm Hg) throughout the study. The arterial-to-ETCO$_2$ gradient was determined, and ETCO$_3$ concentration was used as an estimate of PacO$_2$ to guide ventilator adjustments. To maintain PacO$_2$ within the expected range, peak inspiratory pressure and respiratory rate were adjusted from 9 to 15 cm H$_2$O and from 8 to 18 breaths/min, respectively, while the inspiration-to-expiration ratio was held constant (1:2). During MAC determinations in mechanically ventilated dogs, spontaneous respiratory efforts are often caused by the nociceptive stimulation or may be evident in some dogs during light anesthesia. Therefore, to avoid undesirable changes in pulmonary mechanics, the inspiratory flow sensitivity of the ventilator was adjusted to allow the spontaneous respiratory efforts to trigger assisted ventilatory cycles.

The manufacturer-designed BIS surface adhesive sensors were placed along the median sagittal plane of the head, as previously described in dogs. Electrode 1 was placed 1 cm dorsal to an imaginary line connecting the medial canthi of the eyelids, and electrode 3 was placed on the occipital crest. Impedance of the electrodes was automatically verified by the BIS monitor, and the signal was rejected if impedance was > 7.5 kΩ. The EEG and EMG activities were continuously recorded by the BIS monitor (low- and high-frequency filters were set at 2 and 70 Hz, respectively). The SQI was continuously averaged by the monitor on a minute-to-minute basis. The SQI is a numeric value that indicates the degree of artifact signal captured by the BIS sensors; SQI of 100 represents the lowest artifact signal possible. The monitor automatically rejected BIS values associated with SQI < 50, but for the purposes of the present study, BIS values associated with SQI values < 70 were rejected.

After each dog was positioned in sternal recumbency, the skin over the lumbosacral area was surgically prepared and an 18-gauge Tuohy needle was aseptically introduced at an angle of approximately 45° to 60° into the lumbosacral epidural space. Correct needle placement was confirmed by the lack of CSF or blood obtained during aspiration of the needle and by a lack of resistance to the injection of 2 to 3 mL of air from a glass syringe. Approximately 10 cm of an epidural catheter was positioned into the epidural canal (determined from the markings along the catheter and by the length of the Tuohy needle introduced until the epidural space was reached).

At the end of the instrumentation period, Et$_{SO_2}$ concentration was measured for 50 cycles/s (10 milliseconds) administered to one of the hind limbs. The hind limb that underwent electrical stimulation during the first experiment was chosen at random, and the other hind limb was used on the following experimental day, so that the same limb did not undergo nociceptive stimulation during 2 subsequent experiments. For this purpose, an electrical stimulator was connected to 2 subcutaneous 23-gauge stainless-steel needle electrodes placed at 5 cm from each other on the medial aspect of the middle third portion of the tibia. The stimulation protocol consisted of 2 single stimuli and 2 continuous stimuli of 3 seconds’ duration each, with 5-second intervals between each of the 4 stimuli. The electrical stimulation was interrupted if gross purposeful movement was observed. The motor response to nociceptive stimulation was classified as positive (detection of gross purposeful movement) or negative (no noticeable gross purposeful movement) by an observer (DC) who was unaware of the treatment. The criteria used for classification of motor response were based on those used in a previous study (Appendix).

Fifteen minutes after the epidural injection, each dog was placed in dorsal recumbency. To assess temporal changes in MAC, 2 isoflurane MAC determinations were performed for each treatment. Minimum alveolar concentration measurements were to be determined at 2 and 4.5 hours after the epidural injection. The MAC for each time point was accepted if the measurement was determined within a tolerance interval of ± 30 minutes of the targeted time. If MAC determination could not be achieved within the preestablished time interval, the experiment was terminated; 1 week later, the experiment involving the same treatment and the same dog was repeated until the predefined time criterion for MAC determinations could be met.

Fifteen minutes after epidural injection, Et$_{SO_2}$ concentration was initially adjusted to maintain moderate depth of anesthesia on the basis of clinical evidence (ie, lack of palpebral reflexes, jaw tone, and spontaneous respiratory efforts during mechanical ventilation). The Et$_{SO_2}$ concentration was maintained constant for 15 minutes before the supramaximal nociceptive stimulation for MAC determination was applied. If a negative motor response was initially detected, the Et$_{SO_2}$ concentration was reduced by 0.2% and the nociceptive concentration was maintained at 1.8% for 15 minutes, and each dog was randomly assigned to receive 4 epidural treatments in a double-blinded, randomized crossover study design. An interval of ≥ 1 week was allowed to elapse between each treatment. As a control treatment, physiologic saline (0.9% NaCl) solution (0.25 mL/kg) was administered into the epidural space. For the remaining treatments, dexmedetomidine was administered either at 1.3, 3.0, or 6.0 μg/kg. The final volume of the dexmedetomidine solution injected into the epidural space was adjusted to 0.25 mL/kg with physiologic saline solution. All treatments were administered during a 1-minute period by an individual (DC) who was unaware of the drug being administered. At the end of each epidural injection, the epidural catheter was flushed with 1 mL of physiologic saline solution and then removed.

**MAC determination**—The supramaximal nociceptive stimulation used for isoflurane MAC determination in each dog consisted of an electrical current (50 V at 50 cycles/s for 10 milliseconds) administered to one of the hind limbs. The hind limb that underwent electrical stimulation during the first experiment was chosen at random, and the other hind limb was used on the following experimental day, so that the same limb did not undergo nociceptive stimulation during 2 subsequent experiments. For this purpose, an electrical stimulator was connected to 2 subcutaneous 23-gauge stainless-steel needle electrodes placed at 5 cm from each other on the medial aspect of the middle third portion of the tibia. The stimulation protocol consisted of 2 single stimuli and 2 continuous stimuli of 3 seconds’ duration each, with 5-second intervals between each of the 4 stimuli. The electrical stimulation was interrupted if gross purposeful movement was observed. The motor response to nociceptive stimulation was classified as positive (detection of gross purposeful movement) or negative (no noticeable gross purposeful movement) by an observer (DC) who was unaware of the treatment. The criteria used for classification of motor response were based on those used in a previous study (Appendix).
stimulation was repeated after a new equilibration period of 15 minutes. This procedure was repeated until a positive motor response was evident. After this, ETISO concentration was altered by 0.1% increments until the motor response to nociceptive stimulation could be inhibited. If dogs that had an initial positive response, the ETISO concentration adjustments were performed in a reverse order. The MAC of isoflurane was calculated as the arithmetic mean of the highest ETISO concentration that allowed gross purposeful movement in response to nociceptive stimulation and the lowest ETISO concentration that inhibited such response.9,10,12

Assessments—Esophageal temperature, cardiovascular data (heart rate, SAP, DAP, and MAP), arterial blood pH and bicarbonate concentration, PaCO2, and Pao2 were recorded immediately before nociceptive stimulations. The aforementioned variables corresponding to each MAC were calculated as the arithmetic mean of the values determined at the ETISO concentrations used for determination of MAC.

To assess the changes in BIS induced by the nociceptive stimulation used for isoflurane MAC determinations and the effects of dexmedetomidine administrations on these changes, BIS values were recorded at the highest ETISO concentration that allowed a positive response (gross purposeful movement) to nociceptive stimulation and at the lowest ETISO concentration that prevented such response. Simultaneous EMG recordings were also registered at the same time of BIS recordings to assess the possible interference of EMG activity on BIS values.26–28 The BIS and EMG values were recorded 1 minute before and 2 minutes after commencing the nociceptive stimulation protocol.

After the end of the experiment, administration of the inhaled anesthetic was discontinued. The intervals from the cessation of isoflurane administration to orotracheal tube removal (ie, return of swallowing reflex), attainment of sternal recumbency, and attainment of standing position were recorded.

Data analysis—Data are presented as mean ± SD. Statistical analysis was performed by use of a commercial software program.9 For the analysis of the effects of the epidural treatments on isoflurane MAC, BIS, and physiologic variables, a split-plot design (considering time as a plot and epidural treatment as a subplot) was used. The F test of the ANOVA was used for evaluation of the effects of time and dexmedetomidine dose and the time-dose interaction, followed by a multiple comparison test to assess the effect of dose and time on the continuous variables. A simple linear regression analysis (involving BIS and EMG as dependent and independent variables, respectively) was used to assess the correlation between BIS and EMG values during both MAC measurements for each treatment. An ANOVA followed by a Tukey test was used to compare the times for extubation and attainment of sternal recumbency and standing position among treatments. The significance was set at a value of P < 0.05.

Results

Isoflurane MAC—The actual times for isoflurane MAC determination did not differ among treatments (Table 1). In 1 dog treated with 1.5 µg of dexmedetomidine/kg, isoflurane MAC could not be determined within the predefined time intervals (ie, 2 ± 0.5 hours and 4.5 ± 0.5 hours after epidural injection). After this treatment was repeated in the same dog 1 week later, MAC determinations were successfully completed within the targeted periods.

The MAC of isoflurane in dogs that were administered the control treatment did not change over time (1.57 ± 0.23% and 1.55 ± 0.25% at 2 and 4.5 hours, respectively; Table 1). Two hours after epidural injection, all doses of dexmedetomidine significantly reduced isoflurane MAC, compared with the value for the control treatment; at that time, the percentage reduction in MAC was 13 ± 10%, 29 ± 5%, and 31 ± 6% for the dexmedetomidine doses of 1.5, 3.0, and 6.0 µg/kg, respectively. At 4.5 hours after the epidural injection, the 3.0 and 6.0 µg/kg doses significantly decreased isoflurane MAC, compared with the value for the control treatment (percentage reduction in MAC was 13 ± 9% and 22 ± 7%, respectively); however, the MAC value after the lowest dexmedetomidine dose (1.5 µg/kg) did not differ from the control treatment value (percentage reduction in MAC was 7 ± 11%).

Comparisons among the 2-hour data for each dexmedetomidine dose revealed that the MAC reductions associated with the 2 highest doses (3.0 and 6.0 µg/kg) were similar, and both were significantly greater than

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>DEX1.5</th>
<th>DEX3</th>
<th>DEX6</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC at 2 hours (%)</td>
<td>1.57 ± 0.23a</td>
<td>1.35 ± 0.11a</td>
<td>1.12 ± 0.18b</td>
<td>1.08 ± 0.20c</td>
</tr>
<tr>
<td>Actual time (h)</td>
<td>2.15 ± 0.27a</td>
<td>2.11 ± 0.27a</td>
<td>1.97 ± 0.31b</td>
<td>2.05 ± 0.24c</td>
</tr>
<tr>
<td>MAC at 4.5 hours (%)</td>
<td>1.55 ± 0.25a</td>
<td>1.43 ± 0.23a</td>
<td>1.33 ± 0.16b</td>
<td>1.20 ± 0.20c</td>
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<tr>
<td>Actual time (h)</td>
<td>4.38 ± 0.25a</td>
<td>4.39 ± 0.14a</td>
<td>4.59 ± 0.32b</td>
<td>4.38 ± 0.13b</td>
</tr>
</tbody>
</table>

*For a given treatment, mean MAC value at 4.5 hours is significantly (P < 0.05) different from the value at 2 hours.

**For a given variable, mean values with different superscript letters are significantly (P < 0.05) different.
the MAC reduction detected after administration of the 1.5 µg/kg dose. At 4.5 hours, the reduction in the MAC value determined for the highest dexmedetomidine dose (6.0 µg/kg) was significantly greater than the previously recorded MAC value determined at 2 hours. The MAC values determined after dogs were treated with 6.0 µg of dexmedetomidine/kg did not change significantly during the experimental period.

In dogs that were treated with 3.0 µg of dexmedetomidine/kg, the MAC value at 4.5 hours was significantly greater than the previously recorded MAC value (determined at 2 hours). The MAC values determined after dogs were treated with 6.0 µg of dexmedetomidine/kg did not change significantly during the experimental period.

Table 2—Mean ± SD values of physiologic variables obtained at equipotent isoflurane concentrations (1 × MAC) at 2 and 4.5 hours after epidural administration of physiologic saline (0.9% NaCl) solution (control treatment) or dexmedetomidine (1.5, 3.0, and 6.0 µg/kg [DEX1.5, DEX3, and DEX6, respectively]) in 6 dogs in a crossover study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time point (h)</th>
<th>Control</th>
<th>DEX1.5</th>
<th>DEX3</th>
<th>DEX6</th>
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</thead>
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<tr>
<td>Heart rate (beats/min)</td>
<td>2</td>
<td>102 ± 8a</td>
<td>74 ± 17b</td>
<td>60 ± 11b</td>
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<td>4.5</td>
<td>99 ± 20a</td>
<td>79 ± 19b</td>
<td>78 ± 10b</td>
<td>64 ± 17b</td>
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<tr>
<td>SAP (mm Hg)</td>
<td>2</td>
<td>104 ± 22a</td>
<td>107 ± 24a</td>
<td>123 ± 14a</td>
<td>125 ± 24b</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>123 ± 22bb</td>
<td>109 ± 23a</td>
<td>116 ± 13b</td>
<td>125 ± 21b</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>2</td>
<td>65 ± 11b</td>
<td>64 ± 13a</td>
<td>76 ± 11b</td>
<td>79 ± 10b</td>
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<td></td>
<td>4.5</td>
<td>77 ± 11bb</td>
<td>68 ± 16a</td>
<td>72 ± 9b</td>
<td>80 ± 9b</td>
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<tr>
<td>DAP (mm Hg)</td>
<td>2</td>
<td>54 ± 10a</td>
<td>54 ± 13a</td>
<td>62 ± 10a</td>
<td>65 ± 9b</td>
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<td></td>
<td>4.5</td>
<td>61 ± 8a</td>
<td>57 ± 16a</td>
<td>59 ± 8a</td>
<td>66 ± 7b</td>
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<td>Arterial blood pH</td>
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<td>7.39 ± 0.02a</td>
<td>7.40 ± 0.04a</td>
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<td>4.5</td>
<td>7.40 ± 0.03a</td>
<td>7.42 ± 0.05a</td>
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<td>7.41 ± 0.02a</td>
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<td>Paco2 (mm Hg)</td>
<td>2</td>
<td>40 ± 3a</td>
<td>37 ± 5a</td>
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<td>36 ± 4b</td>
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<td></td>
<td>4.5</td>
<td>38 ± 3a</td>
<td>36 ± 6a</td>
<td>35 ± 3b</td>
<td>34 ± 4b</td>
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<td>Pao2 (mm Hg)</td>
<td>2</td>
<td>507 ± 25a</td>
<td>513 ± 64a</td>
<td>499 ± 41a</td>
<td>506 ± 34a</td>
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<td>4.5</td>
<td>514 ± 40a</td>
<td>502 ± 50a</td>
<td>499 ± 49a</td>
<td>463 ± 54a</td>
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<td>Bicarbonate (mEq/L)</td>
<td>2</td>
<td>24 ± 1a</td>
<td>22 ± 3a</td>
<td>23 ± 3a</td>
<td>22 ± 3a</td>
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<td></td>
<td>4.5</td>
<td>23 ± 1a</td>
<td>22 ± 3a</td>
<td>20 ± 2b</td>
<td>21 ± 3a</td>
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<td>Esophageal temperature (°C)</td>
<td>2</td>
<td>37.9 ± 0.2a</td>
<td>38.0 ± 0.2a</td>
<td>37.9 ± 0.3a</td>
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<td></td>
<td>4.5</td>
<td>38.1 ± 0.1a</td>
<td>38.1 ± 0.2a</td>
<td>38.2 ± 0.3a</td>
<td>38.3 ± 0.3a</td>
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</table>

*For a given treatment, mean value at 4.5 hours is significantly (P < 0.05) different from the value at 2 hours.
**For a given variable at 1 time point, mean values with different superscript letters are significantly (P < 0.05) different.

Table 3—Mean ± SD BIS values obtained before and after nociceptive stimulation during isoflurane MAC determinations at 2 and 4.5 hours after epidural administration of physiologic saline (0.9% NaCl) solution (control treatment) or dexmedetomidine (1.5, 3.0, and 6.0 µg/kg [DEX1.5, DEX3, and DEX6, respectively]) in 6 dogs in a crossover study.

<table>
<thead>
<tr>
<th>Motor response of dogs*</th>
<th>Time point relative to nociceptive stimulation†</th>
<th>Control</th>
<th>DEX1.5</th>
<th>DEX3</th>
<th>DEX6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive response</td>
<td>Before (MAC determined at 2 hours)</td>
<td>64 ± 5</td>
<td>69 ± 7</td>
<td>72 ± 41</td>
<td>69 ± 41</td>
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<tr>
<td></td>
<td>After</td>
<td>76 ± 48</td>
<td>76 ± 29</td>
<td>77 ± 33</td>
<td>75 ± 33</td>
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<tr>
<td>Negative response</td>
<td>Before (MAC determined at 2 hours)</td>
<td>63 ± 5</td>
<td>65 ± 5</td>
<td>70 ± 41</td>
<td>66 ± 6</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>75 ± 38</td>
<td>76 ± 23</td>
<td>75 ± 45</td>
<td>74 ± 45</td>
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<tr>
<td>Positive response</td>
<td>Before (MAC determined at 4.5 hours)</td>
<td>67 ± 7</td>
<td>74 ± 5</td>
<td>71 ± 4</td>
<td>71 ± 2</td>
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<tr>
<td></td>
<td>After</td>
<td>78 ± 76</td>
<td>78 ± 38</td>
<td>78 ± 38</td>
<td>77 ± 48</td>
</tr>
<tr>
<td>Negative response</td>
<td>Before (MAC determined at 4.5 hours)</td>
<td>62 ± 2</td>
<td>67 ± 5</td>
<td>69 ± 31</td>
<td>71 ± 51</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>74 ± 55</td>
<td>74 ± 45</td>
<td>78 ± 28</td>
<td>76 ± 28</td>
</tr>
</tbody>
</table>

*Positive and negative responses corresponded to the ET<sub>50</sub> concentration used for MAC calculation that allowed and prevented gross purposeful movement in response to nociceptive stimulation, respectively.
†Before and after stimulation corresponded to the BIS value recorded 1 minute before and 2 minutes after nociceptive stimulation, respectively.
‡For a given variable, value is significantly (P < 0.05) different from the BIS value for the control treatment. §Within a given treatment within a response subgroup, value is significantly (P < 0.05) different from value before nociceptive stimulation.
Physiologic variables—After the control treatment was administered, the dogs’ heart rate did not change over time; however, arterial blood pressure (SAP and MAP) increased at 4.5 hours after epidural injection (Table 2). All dexmedetomidine doses significantly decreased heart rate at 2 and 4.5 hours after epidural injection, compared with the values for the control treatment. In dogs treated with 3.0 µg of dexmedetomidine/kg, heart rate at 2 hours was significantly lower than the heart rate at 4.5 hours. Although no significant difference in heart rate among dexmedetomidine doses was identified, 2, 5, and 6 dogs that were administered 1.5, 3.0, and 6.0 µg of dexmedetomidine/kg, respectively, developed bradycardia (defined as heart rate < 60 beats/min) during MAC determinations; second-degree atrioventricular blockade was detected in 2 dogs that received the 6.0 µg/kg dose of dexmedetomidine.

Among the study dogs, the 3.0 and 6.0 µg/kg doses of dexmedetomidine resulted in significantly higher SAP and MAP values than the control treatment at 2 hours. At that time, the 6.0 µg/kg dose was also associated with an increase in DAP. Prior to noxious stimulation during MAC determinations, arterial hypotension (defined as MAP < 60 mm Hg) was detected in 2 dogs that were treated with 1.5 µg of dexmedetomidine/kg (MAP was approx 50 mm Hg at 2 and 4.5 hours). In one of those dogs, MAP immediately prior to epidural dexmedetomidine was already low (50 mm Hg) and the other dog had low MAP after administration of saline solution (MAP was 49 mm Hg at 2 hours after that injection). No dogs that received 3.0 or 6.0 µg/kg doses of dexmedetomidine developed arterial hypotension during MAC measurements. Arterial hypertension (defined as MAP > 100 mm Hg) was not detected prior to noxious stimulation for MAC measurements in any dog throughout the study.

We did not detect significant differences in arterial pH, PaO₂, and body temperature (Table 2). A significant difference between some treatments was recorded for PaCO₂ and for bicarbonate concentration, but mean values of PaCO₂ and bicarbonate concentration for all treatments ranged from 34 to 40 mm Hg and from 20 to 24 mEq/L, respectively, which are close to physiologic ranges for dogs (PaCO₂, 35 to 45 mm Hg; bicarbonate concentration, 20 to 26 mEq/L).

BIS changes—Electroencephalographic burst suppression was not detected during MAC measurements throughout the study. For all treatments, nociceptive stimulation significantly increased BIS from prestimul-

![Figure 1](https://example.com/image1.png)

**Figure 1**—Scatterplots of BIS and EMG activity recorded during isoflurane MAC determinations at 2 (A, C, E, and G) and 4.5 (B, D, F, and H) hours after epidural administration of physiologic saline (0.9% NaCl) solution (control treatment [A and B]) or dexmedetomidine (1.5 [C and D], 3.0 [E and F], and 6.0 [G and H] µg/kg) in 6 dogs in a crossover study. The regression line and the equation of the line are included in each graph.

Regression analysis revealed a positive linear correlation between BIS and EMG changes (Figure 1).
During the first MAC determination, the correlation coefficients ($r$ values) between BIS and EMG changes were 0.88, 0.77, 0.87, and 0.76 for the control treatment and 1.5, 3.0, and 6.0 µg/kg doses of dexmedetomidine, respectively. During the second MAC determination, $r$ values were 0.84, 0.59, 0.78, and 0.56 for the control treatment and 1.5, 3.0, and 6.0 µg/kg doses of dexmedetomidine, respectively. Although there were some weaker correlations between BIS and EMG over time and the correlation between these variables was smaller in dogs receiving dexmedetomidine, the slope of all equations was significantly greater than zero regardless of the epidural treatment.

Anesthetic recovery characteristics—No difference was detected in any of the continuous variables recorded during recovery from anesthesia among the treatment groups. Pooled data from all 4 treatment groups for time until orotracheal tube removal, time until attainment of sternal recumbency, and time until attainment of a standing position were 5 ± 2 minutes, 6 ± 3 minutes, and 11 ± 6 minutes, respectively. All dogs recovered from anesthesia without complications, except for episodes of emesis during the recovery phase in 1 and 3 dogs that were treated with 1.5 and 6.0 µg of dexmedetomidine/kg, respectively.

**Discussion**

Supramaximal nociceptive stimulation is the most potent stimulus used to assess the level of unconsciousness during anesthesia.\(^9\)\(^12\)\(^14\) During deep anesthesia, arousal from a hypnogentic state through noxious stimulation is prevented by inhibition of both corticocerebral activity and ascending nociceptive pathways.\(^14\)\(^15\) In clinical practice, presence of muscle relaxation and lack of movement and autonomic responses to surgical stimuli are used to determine whether depth of anesthesia is adequate. Although the criteria of autonomic responses (increases in heart rate, arterial blood pressure, and respiratory rate) have been used to define arousal from anesthesia in some MAC studies\(^20\)\(^31\) in cats and humans, these autonomic changes may be primarily of subcortical origin and may not reflect conscious perception of the nociceptive stimulus.\(^9\)\(^10\)\(^13\)\(^15\) In the present study, the concept of gross purposeful movement was used to define arousal from anesthesia during isoflurane MAC determinations because it allows comparison of these data with findings of other studies involving similar criteria.

Mean isoflurane MAC values in the dogs that received the control treatment did not change over time (1.57% and 1.55% at 2 and 4.5 hours after administration of physiologic saline solution, respectively) and were within the range reported in the literature (range of mean MAC values from 1.16% to 1.8% for various populations of dogs).\(^9\)\(^13\)\(^24\)\(^25\)\(^32\)\(^33\) Factors that may influence differences in mean isoflurane MAC values reported by different laboratories include hypocapnia, body temperature, circadian rhythm, age, and the methods used for MAC assessment.\(^5\)\(^12\)\(^24\)\(^25\) In the present study, $\text{Paco}_2$ was maintained close to physiologic limits (35 to 45 mm Hg), esophageal temperature was maintained within a narrow range (37.5° to 38.5°C), and the experiments were started at a similar time in the morning in an attempt to minimize the influence of these variables on MAC values. Although the age of the dogs could not be reliably determined, all dogs included in the study were adults and were deemed clinically normal on the basis of detailed physical and laboratory evaluations.

Three conditions are required to avoid bias during MAC determinations: stable anesthetic inhalant concentration in the CNS, supramaximal nociceptive stimulation, and a clearly defined criterion of arousal from anesthesia in response to noxious stimulation.\(^10\) A proper equilibration time is important to achieve equilibration of an inhalant anesthetic agent between the alveoli and the CNS. The equilibration time between these compartments is expected to be shorter for inhalant anesthetics with relatively lower brain-blood partition coefficients.\(^9\)\(^10\) In the present study, 15-minute periods of steady $\text{ET}_{\text{ISO}}$ concentrations were allowed before nociceptive stimulation. This period was likely sufficient for adequate equilibration between compartments because a similar equilibration time has been proposed for halothane, which is an inhalant anesthetic with a higher brain-blood partition coefficient than isoflurane.\(^9\)\(^10\)

Nociceptive stimulation is considered supramaximal if increases in its intensity do not result in changes in the observed response for the studied population.\(^9\)\(^12\)\(^24\) The intensity of the electrical current administered to the dogs of the present study (50 V at 50 cycles/s for 10 milliseconds) has been characterized as supramaximal, resulting in MAC values that were similar to the MAC values obtained by the tail clamping method.\(^9\)\(^24\)

Another methodologic problem that may account for some variability in MAC values reported in the literature is the characterization of the gross motor response to noxious stimulation. For MAC determinations, arousal from anesthesia involves the observation of a gross purposeful movement of the head, trunk, or limbs.\(^9\)\(^10\) Autonomic responses (eg, increased heart rate and blood pressure; swallowing; coughing; and other motor responses that could be reflex in nature, such as limb withdrawal in response to electrical stimulation of the foot and discrete, repetitive limb movements) were not considered as signs of arousal from anesthesia because these responses do not necessarily require corticocerebral participation.\(^9\)\(^10\)\(^13\)\(^15\) Given that the criterion of gross purposeful movement appears somewhat subjective and may represent a source of bias, the individual assessing the motor response of the dogs to noxious stimulation was unaware of the drug administered epidurally to avoid any bias in results of our study.

On the basis of the data obtained in the present study, it is evident that epidural administration of relatively low doses of dexmedetomidine reduced isoflurane MAC in a dose-dependent fashion in dogs. The doses of 3.0 and 6.0 µg of dexmedetomidine/kg administered epidurally caused clinically relevant decreases (defined as a reduction > 20%) in mean isoflurane MAC values for approximately 2 and 4.5 hours, respectively, compared with values achieved with administration of saline solution. However, the MAC reduction achieved by the smaller dose (1.5 µg/kg) may not be considered relevant
A dose of approximately 10 µg/kg of dexmedetomidine/kg administered IV was necessary to achieve maximum analgesia in dogs, but a dose that was a third as much (3.3 µg/kg) given epidurally resulted in a similar but longer-lasting analgesic effect (duration of analgesia was 90 minutes via the IV route and 240 minutes via the epidural route). On the basis of these observations, one may hypothesize that the prolonged analgesic effect induced by epidural administration of dexmedetomidine is in part responsible for the reduction in isoflurane MAC (compared with control treatment values) identified in the present study. Nevertheless, it is not possible to state that the reduction in isoflurane MAC was solely attributed to the drug's spinal analgesic effect. Because of its high lipid solubility, dexmedetomidine administered epidurally may be absorbed into the circulation, resulting in systemic effects such as sedation. The sedative CNS effects induced by α2-adrenergic receptor agonists contribute to the reported reduction in inhalant anesthetic requirements. Possible central mechanisms that explain the reduction in MACs of inhalant anesthetics induced by α2-adrenergic receptor agonists include a decrease in norepinephrine release in the CNS that is caused by presynaptic α2-adrenergic receptor stimulation and neuronal hyperpolarization that is induced by activation of postsynaptic α2-adrenergic receptors.

The MAC-reducing effects of IV administration of dexmedetomidine are dose dependent. In dogs, isoflurane MAC was decreased by approximately 90% (compared with a mean isoflurane MAC of 1.16% before dexmedetomidine administration) at 30 minutes after IV administration of a high dose (20 µg/kg). However, despite the major inhalant anesthetic-sparing effect, significant hemodynamic changes (persistent bradycardia, 75% reduction in cardiac output, and prolonged increases in systemic vascular resistance and arterial blood pressure) were also detected. Those findings indicate that although high doses of dexmedetomidine administered IV cause a marked reduction in the MAC of inhalant anesthetic agents, the cardiovascular depression (ie, decrease in cardiac output) can obtund the expected improvement in hemodynamic function associated with decreased inhalant requirements.

In the present study, heart rate was decreased regardless of the dose of dexmedetomidine administered and remained lower than the values in saline solution–treated dogs throughout the experimental period (approx 4.5 hours after epidural injection). However, the changes in arterial blood pressure were not clinically relevant. Although hypertension (MAP > 100 mm Hg) was not detected immediately prior to the noxious stimulation in either MAC determination for all treatments, only 2 dogs that received 1.5 µg of dexmedetomidine/kg developed hypotension (MAP, 50 mm Hg). At the equipotent isoflurane concentrations measured 2 hours after epidural injection, the use of 3.0 and 6.0 µg of dexmedetomidine/kg in the dogs of our study (MAC decreased by 29% and 31%, respectively)

The benefits of epidural administration of analgesic drugs include increases in the intensity and duration of the analgesic effects and reduced hemodynamic adverse effects because of the use of lower doses. The spinal analgesic effect induced by α2-adrenergic receptor agonists has been attributed to the activation of α2-adrenergic receptors located in the dorsal horn of the spinal cord. Antinociception appears to be attributable to presynaptic inhibition of the release of excitatory neurotransmitters (glutamate, substance P, and other neuropeptides) by the afferent nociceptive fibers.

In dogs, there is evidence that the epidural administration of dexmedetomidine potentiates and prolongs the analgesic effect of the α2-adrenergic receptor agonists. In 1 study, a dose of approximately 10 µg/kg of dexmedetomidine/kg administered IV was necessary to achieve maximum analgesia in dogs, but a dose that was a third as much (3.3 µg/kg) given epidurally resulted in a similar but longer-lasting analgesic effect (duration of analgesia was 90 minutes via the IV route and 240 minutes via the epidural route). On the basis of these observations, one may hypothesize that the prolonged analgesic effect induced by epidural administration of dexmedetomidine is in part responsible for the reduction in isoflurane MAC (compared with control treatment values) identified in the present study. Nevertheless, it is not possible to state that the reduction in isoflurane MAC was solely attributed to the drug's spinal analgesic effect. Because of its high lipid solubility, dexmedetomidine administered epidurally may be absorbed into the circulation, resulting in systemic effects such as sedation. The sedative CNS effects induced by α2-adrenergic receptor agonists contribute to the reported reduction in inhalant anesthetic requirements. Possible central mechanisms that explain the reduction in MACs of inhalant anesthetics induced by α2-adrenergic receptor agonists include a decrease in norepinephrine release in the CNS that is caused by presynaptic α2-adrenergic receptor stimulation and neuronal hyperpolarization that is induced by activation of postsynaptic α2-adrenergic receptors.

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However, given the limited cardiovascular monitoring of dogs in the present study, the mechanism responsible for this phenomenon cannot be provided.

Recent studies have attempted to validate changes in the level of hypnosis as determined by BIS evaluation as a criterion for determining the MAC of isoflurane in cats and dogs. Minimum alveolar concentration values based on BIS are calculated as the arithmetic mean of the highest end-tidal anesthetic concentration that allows an increase in BIS over a preestablished threshold and the lowest end-tidal anesthetic concentration that prevents BIS from exceeding that threshold. In the present study, arousal from anesthesia was not based on increases in BIS in excess of a predefined
value but was based on motor responses. Our intention was to characterize changes in BIS attributable to noxious stimulation at the ET_{iso} concentration used for MAC determinations and assess the influence of epidural administration of dexmedetomidine on those changes. Regardless of dexmedetomidine administration, noxious stimulation significantly increased the BIS values recorded during MAC determinations. The increase in BIS from prestimulation values was also not dependent on whether the noxious stimulus was administered at the lowest ET_{iso} concentration that allowed the motor response or the highest ET_{iso} concentration that prevented such response. These results might suggest that, similar to the noticeable autonomic changes (increases in heart and respiratory rates and blood pressure), corticocerebral activation denoted by increases in BIS is in response to noxious stimulation during classic MAC determinations. However, these assumptions may be limited by the fact that the increase in BIS was correlated with an increase in EMG activity.

The BIS is calculated on the basis of 3 variables derived from an EEG: the bicoherence of EEG waveforms (the degree to which waveforms are in phase), the power spectrum (the amount of EEG that is in the delta vs beta range), and the proportion of the EEG that is isoelectric (burst suppression).

Because of the possible overlap between EEG and EMG power spectra in the 30- to 50-Hz range and the fact that the BIS monitor was reported to filter only frequencies > 70 Hz, artifact generated by increased EMG activity may not be completely removed, thereby contaminating BIS calculations. There is evidence that EMG activity may artificially increase BIS values in humans during consciousness or light sedation, conditions in which power spectrum of the EEG and EMG may overlap.

In the present study, the positive correlation between BIS and EMG changes suggested that increased EMG activity after noxious stimulation could have contributed to the increases in BIS. However, to confirm this hypothesis, BIS changes attributable to noxious stimulation should have been determined in dogs in which EMG activity was eliminated or reduced via administration of a neuromuscular blocking agent and in nonparalyzed animals. In our study, we used a newer version of the BIS monitor (algorithm version 4.1), and the BIS algorithm has not been disclosed by the manufacturer to date. In previous versions of the BIS algorithm, filtering of EMG activity could not be efficiently achieved.

High levels of cortical activity (awareness) can contribute directly to EMG activity because the motor cortexes project to motor neurons that are responsible for EMG noise. In conscious, lightly sedated, or anesthetized humans, reduction of EMG activity induced by neuromuscular blocking agents results in an obvious decrease in BIS values, corroborating the hypothesis there is EMG contamination of BIS values when cortical activity level is high. However, the influence of EMG activity on BIS values does not appear to be clinically relevant in deeply sedated or anesthetized individuals because the use of neuromuscular blocking agents in these circumstances does not cause significant changes in BIS.

In the present study, all dogs were lightly anesthetized at the ET_{iso} concentrations that were used for MAC determination. This observation reinforces the possibility of a significant influence of EMG changes on BIS values in our experimental setting.

Needle-type electrodes or sensors developed for use in humans have been used to capture the EEG signal during BIS-measurements in animal species.

In the present study, we placed the manufacturer-designed BIS sensor on the frontal-occipital region of each dog's head. In a previous study, the frontal-occipital positioning of the sensor yielded BIS values that were similar to the values obtained via 2 other sensor positions in isoflurane-anesthetized dogs. Findings of that study indicated that the frontal-occipital placement of the BIS sensor may result in more artifact signal (as denoted by low SQI values) in some dogs during deep isoflurane anesthesia (ET_{iso} concentration of 3.0%). However, it is unlikely that artifact signals influenced BIS measurements in the present study because SQI values were > 70 throughout the study.

The indices used to assess the rapidity of the recovery from anesthesia were similar among treatments. However, the development of emesis in some dogs receiving dexmedetomidine epidurally provided evidence for a persisting CNS effect of that drug at the end of anesthesia. Emesis after parenteral and epidural administration of α₂-adrenergic receptor agonists in dogs and cats has been reported. The mechanism of α₂-adrenergic receptor agonist-induced emesis is apparently related to the activation of α₂-adrenergic receptors that are located in the area postrema of the chemoreceptor trigger zone. Incidence of this adverse effect in dogs after IM administration of the α₂-adrenergic receptor agonists xylazine and clonidine may exceed 80%. In conscious cats, incidence of emesis after epidural administration of medetomidine (10 μg/kg) was also reported to be high (80% at 6 minutes after epidural administration).

The results of the present study have suggested that epidural administration of dexmedetomidine has potential for clinical use in dogs because of its isoflurane MAC–reducing effect. Reduction of inhalant anesthetic requirements via epidural administration of dexmedetomidine is dose related, and this effect is inversely proportional to the time of injection. Changes in BIS during MAC determinations might not be indicative of increases in awareness level because of possible interference of EMG activity.

a. Isoforine, Cristália, Itapira, Brazil.
b. Inter VPZ ISO, Intermed, São Paulo, Brazil.
c. BD Insyte, Becton Dickinson, São Paulo, Brazil.
d. LF2001, Lifemed, São Paulo, Brazil.
f. A/S 3 monitor, Datex-Engstrom, Helsinki, Finland.
g. pH/Blood gas analyzer model 348, Chiron Diagnostics, Halstead, England.
h. Warmtouch, Mallinkrodt Medical, Pleasanton, Calif.
i. ECGPC, Tecnologia Eletrônica Brasileira, São Paulo, Brazil.
j. Gas analyzer module G-AO, Datex-Engstrom, Helsinki, Finland.
k. Quick Cal Calibration Gas, Datex-Engstrom, Helsinki, Finland.
l. Inter Linea C, Intermed, São Paulo, Brazil.
m. BIS Quatro sensor, Aspect Medical Systems, Newton, Mass.
o. Tuohy needle, Becton Dickinson, Jujuf de Fora, Brazil.
p. 18-gauge epidural catheter, Portex, Keene, NH.
References


Appendix
Criteria used to classify the motor response to nociceptive stimulation during isoflurane MAC determinations in dogs (modified from Ewing et al(25)).

<table>
<thead>
<tr>
<th>Negative motor response</th>
<th>Positive motor response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single or sustained flexion or extension of the limbs</td>
<td>2 consecutive and evident flexions of the limbs</td>
</tr>
<tr>
<td>Repeated and discrete flexions of limb extremities (metacarpophalangeal or metatarsophalangeal joints)</td>
<td>2 consecutive and evident flexions of the neck</td>
</tr>
<tr>
<td>Single neck flexion</td>
<td>2 consecutive and evident twisting movements of the head</td>
</tr>
<tr>
<td>Single head-twisting movement</td>
<td>Evident movements of the trunk</td>
</tr>
<tr>
<td>Chewing and coughing</td>
<td></td>
</tr>
<tr>
<td>Spontaneous respiratory movements; increased respiratory effort and rate</td>
<td></td>
</tr>
<tr>
<td>Movements not coincident with the nociceptive stimulation</td>
<td></td>
</tr>
</tbody>
</table>