Effect of medetomidine administration on bispectral index measurements in dogs during anesthesia with isoflurane

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The bispectral index (BIS) is a value derived from the electroencephalogram that has been extensively used to assess CNS depression in anesthetized people. Sedative and anesthetic depressant effects on the CNS have been correlated with the BIS in humans. The BIS is reported as a unitless value between 0 and 100, where 0 indicates an isoelectric electroencephalogram and 100 represents the normal, conscious state. In surgical practice, patients are typically maintained at a depth of anesthesia that yields a BIS between 40 and 60. The BIS has been helpful in fine tuning the titration of anesthetic agents in human patients, resulting in more rapid emergence from anesthesia and a decrease in costs associated with anesthetic use. Improved patient care and economic advantages from better titration of anesthetics provide incentive to apply BIS monitoring during anesthesia of animals as well.

There is a paucity of reports on the use of the BIS for monitoring the CNS during anesthesia in animals. In pigs undergoing surgery, BIS measurements during 1.0 times the minimum alveolar concentration (MAC) of halothane or xenon were comparable to those during total IV anesthesia with azaperone, atropine, and buprenorphine combined with continuous IV infusion of pentobarbital. In another study of pigs maintained at surgical depths of anesthesia with isoflurane, the BIS did not correlate with depth of anesthesia as assessed by use of a visual analogue scale. In goats, the BIS is inversely related to critical points in the continuum of isoflurane-anesthetic depth, including time of recumbency, tracheal intubation, and loss of corneal or withdrawal reflexes. An inverse relationship between the BIS and MAC multiples of sevoflurane in dogs has recently been reported.

Medetomidine is a potent α2-adrenoceptor agonist with sedative and analgesic properties that is commonly used as a preanesthetic agent in dogs. A MAC-reducing effect of medetomidine and the active racemate, dexmedetomidine, on inhaled anesthetics has been reported. Thus, relatively greater CNS depression is expected at a given MAC of inhaled anesthetic with coadministration of medetomidine, compared with the same MAC of inhaled anesthetic alone. The purpose of the study presented here was to determine the relationship between the BIS and MAC multiples of isoflurane after IM injection of medetomidine or saline (0.9% NaCl) solution in dogs. We hypothesized that the BIS would be inversely and linearly related to MAC multiples of isoflurane, and that administration of medetomidine during anesthesia at the same MAC multiples of isoflurane would yield lower BIS measurements.

Materials and Methods

Animals—Six Pointers (3 males, 3 females; mean [± SD] age and weight of 3.7 ± 2.0 years and 20.2 ± 4.8 kg, respectively) were studied. The university's Institutional Animal Care and Use Committee approved the study. It was con-
ducted in compliance with local and federal guidelines governing laboratory animal care and housing. Animals were housed in indoor-outdoor runs and fed a commercially prepared food. Food was withheld on the days of study. Dogs had ad libitum access to water. Dogs were examined, and blood and urine samples were collected prior to the study. Results of CBC determination, serum biochemical analysis (ie, total protein, albumin, electrolytes, urea nitrogen, creatinine, and total carbon dioxide concentrations, and alanine transaminase and glutamate dehydrogenase activities), and urinalysis were within reference range for each dog.

**Procedure**—Each dog was anesthetized 3 times. On the first occasion, each dog's MAC of isoflurane was determined by use of the tail clamp method. On the second occasion, dogs were instrumented for measurement of the BIS, ECG, direct arterial blood pressure, esophageal temperature, and end-tidal gas (CO₂ and isoflurane) concentrations and were randomly assigned to receive an IM injection of medetomidine hydrochloride (8 µg • kg⁻¹) or an equal volume of isotonic saline (0.9% NaCl) solution 30 minutes prior to beginning BIS measurements. On the third occasion, dogs were again instrumented and received the remaining treatment (medetomidine or isotonic saline solution). Dogs were anesthetized at each of 4 MAC multiples (ie, 0.8, 1.0, 1.5, and 2.0 MAC) of isoflurane on the basis of each dog's predetermined MAC value for isoflurane. The order of multiples of the MAC of isoflurane was randomized for each trial. After 20 minutes of equilibration at each MAC multiple of isoflurane, the BIS was recorded. All BIS measurements were completed by 120 minutes after medetomidine administration. The BIS was collected for 5 minutes and the median BIS determined for the recording period at each MAC multiple of isoflurane.

**Determination of MAC of isoflurane**—The technique for determination of the MAC of isoflurane for the dogs used by our laboratory has been previously described. Briefly, each dog was mask-induced, the trachea was intubated, and anesthesia was maintained for 20 minutes at 1.3% end-tidal isoflurane concentration. A padded sponge clamp was placed on the tail at a point in which the circumference of the tail was 9 cm. The clamp was closed to full ratchet and held in place for 60 seconds or until the dog responded with gross purposeful movement. If the dog did not respond, the end-tidal anesthetic concentration was reduced by 10%, a 20-minute equilibration period was allowed, and the clamp was reapplied. When the dog did respond to application of the clamp, end-tidal concentration was increased by 10%, a 20-minute equilibration period was allowed, and the clamp was reapplied to further categorize the MAC of isoflurane. The MAC of isoflurane was determined by averaging the highest end-tidal concentration when the dog responded and the lowest end-tidal concentration when the dog did not respond. After the MAC of isoflurane was identified, anesthesia was discontinued and dogs were allowed to recover.

**Physiologic monitoring**—On the day of BIS measurement, dogs were mask-induced with isoflurane and positioned in left lateral recumbency. Anesthesia was maintained with isoflurane in oxygen by use of a precision vaporizer and a rebreathing circuit on an anesthesia machine. Ventilation was controlled with a mechanical ventilator to maintain normocapnia (PaCO₂, 35 to 45 mm Hg). The cephalic vein and dorsal pedal artery were catheterized. Lactated Ringer's solution was administered IV at a rate of 5 mL/kg/h. The arterial catheter was connected to a mercury calibrated blood pressure transducer and physiologic monitor. Heart rate was determined by counting arterial pulse waves per minute. A 3-lead ECG and esophageal temperature were continuously monitored with a physiologic monitor. Arterial blood samples were collected at the end of bispectral recording periods for each MAC multiple of isoflurane. Arterial blood gases (PaO₂ and PaCO₂) and pH were measured within 5 minutes of collection by use of a calibrated blood gas machine. Bicarbonate concentration and base excess were calculated and reported by the blood gas machine. End-tidal CO₂ and isoflurane concentrations were measured from samples taken at the tracheal carina by use of a calibrated side-stream sampling anesthetic gas analyzer.

**Measurement of BIS**—The BIS was measured by use of a BIS monitor and software.” The BIS was recorded every 5 seconds for 5 minutes after equilibration at each MAC multiple of isoflurane, and data were stored on a computer. The BIS was reported as a unitless whole number between 0 and 100. Filters for elimination of electrical noise were set as follows: the low cutoff was set at 2 Hz, the 50/60 Hz filter was set to 60 Hz, and the high cutoff was set at 70 Hz. At startup, the monitor required a skin-electrode impedance of < 7.5 kΩ; thereafter, it provided for continuous impedance checking with impedance of < 2 kΩ at 16 Hz. High frequency activity (70 to 110 Hz) was identified as electromyographic activity measured in decibels with respect to 0.0001 µV² and was graphed in real time with the BIS. Increases in the BIS coincident with increases in electromyographic activity confirmed the interpretation of BIS measurements. Electromyographic activity was eliminated during BIS measurement in our study by providing neuromuscular blockade with IV administration of atracurium (0.2 mg/kg followed by 6 µg/kg/min as a continuous infusion). The monitor had automatic artifact detection and displayed a signal quality index as a function of good epochs and suppressed epochs in the previous 120 epochs (61.5 seconds) that were used for calculation of the BIS. The percentage of epochs in the past 63 seconds in which the electroencephalogram signal was suppressed was expressed as the suppression ratio. Burst suppression was identified as an isoelectric analog electroencephalogram for at least 1 second and detected by the monitor as indicated by an increase in the suppression ratio (ie, suppression ratio > 1). Presence of burst suppression at greater depths of isoflurane anesthesia was readily identified by spike activity followed by an isoelectric electroencephalogram and an increase in the suppression ratio. The BIS was recorded when the suppression ratio = 0. Measurements of the BIS in the presence of burst suppression were treated as missing values and not included in data analysis.

**Electrodes**—The primary lead was placed on the midline approximately a third of the distance from a line connecting the zygomatic processes of the frontal bone and the most caudal portion of the external frontal crest that was palpable. A secondary lead was placed 2 cm lateral and 1 cm caudal to the primary lead over the right temple. A ground electrode was placed rostral to the tragus of the right ear. A monopolar lead was placed 2 cm lateral and 1 cm caudal to the primary lead over the right temple. A monopolar lead was placed rostral to the tragus of the right ear. A modified ECG cable was connected to the BIS cable distal to the analog-to-digital converter. Three 29-gauge platinum needle electrodes were connected to the modified cable and placed subdermally in the locations as already described.

**Statistical analysis**—Data are reported as the mean ± SD. Data from each MAC multiple of isoflurane were compared by use of a general linear model for repeated measures with commercially available software. The level of significance was set at P < 0.05. When indicated by significant F values, treatment means were compared by use of the least-significant-difference method.

**Results**

The mean MAC of isoflurane was 1.3 ± 0.2% for this group of dogs. Bispectral index, esophageal temperature, end-tidal gas concentrations, and hemody-
indices during isoflurane-saline anesthesia were plotted against BIS measurements during isoflurane-medetomidine anesthesia (Fig 1).

During isoflurane-saline anesthesia, mean heart rate at 0.8 MAC was significantly decreased, compared with mean heart rate at 1.5 and 2.0 MAC. During isoflurane-medetomidine anesthesia, mean heart rate at 0.8 and 1.0 MAC was significantly decreased, compared with mean heart rate at 1.5 and 2.0 MAC. Heart rate at 0.8, 1.0, and 1.5 MAC was significantly higher during isoflurane-saline anesthesia, compared with isoflurane-medetomidine anesthesia.

Mean arterial blood pressure during isoflurane-saline anesthesia and isoflurane-medetomidine anesthesia was significantly higher at 0.8, 1.0, and 1.5 MAC, compared with at 2.0 MAC. No significant differences in mean arterial blood pressure were found between treatments. During isoflurane-medetomidine anesthesia, esophageal temperatures at 0.8, 1.5, and 2.0 MAC were significantly lower than at 1.0 MAC, and temperature at 1.5 MAC was significantly higher than at 2.0 MAC.

During isoflurane-saline anesthesia, end-tidal CO2 tension at 0.8, 1.0, and 1.5 MAC and PaO2 tension at 0.8 and 1.0 MAC was significantly greater than the respective values at 2.0 MAC. During isoflurane-saline anesthesia, the plasma bicarbonate concentration at 1.5 MAC was significantly greater than at 2.0 MAC, and the PaO2 tension at 2.0 MAC was significantly different from the respective value during isoflurane-medetomidine anesthesia. During isoflurane-medetomidine anesthesia, the PaO2 tension was significantly higher at 0.8, 1.0, and 1.5 MAC than at 2.0 MAC. No significant changes in arterial blood pH or base excess were found.

Discussion

In our study, the BIS during isoflurane anesthesia predictably decreased with increasing MAC multiples.

Table 1—Mean (± SD) values of physiologic variables from 6 dogs during collection of bispectral index (BIS) measurements at 4 minimum alveolar concentration (MAC) multiples of isoflurane following an IM injection of saline (0.9% NaCl) solution

<table>
<thead>
<tr>
<th>Variable</th>
<th>0.8 MAC</th>
<th>1.0 MAC</th>
<th>1.5 MAC</th>
<th>2.0 MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>91 ± 15*†‡</td>
<td>95 ± 11†</td>
<td>105 ± 16†</td>
<td>103 ± 13</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>73 ± 51</td>
<td>68 ± 51</td>
<td>64 ± 21†</td>
<td>47 ± 13</td>
</tr>
<tr>
<td>End-tidal CO2 (mm Hg)</td>
<td>37 ± 27</td>
<td>38 ± 11</td>
<td>37 ± 11</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.5 ± 0.3</td>
<td>37.5 ± 0.1</td>
<td>37.5 ± 0.3</td>
<td>37.5 ± 0.2</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 ± 0.05</td>
<td>7.35 ± 0.03</td>
<td>7.35 ± 0.03</td>
<td>7.37 ± 0.03</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>41 ± 41</td>
<td>40 ± 21</td>
<td>39 ± 5</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>652 ± 30</td>
<td>643 ± 29</td>
<td>638 ± 37</td>
<td>604 ± 49†</td>
</tr>
<tr>
<td>HCO3 (g/dL)</td>
<td>22.4 ± 1.3</td>
<td>22.2 ± 1.4</td>
<td>23.3 ± 5.9†</td>
<td>20.8 ± 1.8</td>
</tr>
</tbody>
</table>

BIS measurements at 0.8, 1.0, 1.5, and 2.0 MAC were significantly lower than at 1.5 MAC, compared with mean heart rate at 1.5 and 2.0 MAC. Heart rate at 0.8, 1.0, and 1.5 MAC was significantly higher during isoflurane-saline anesthesia, compared with isoflurane-medetomidine anesthesia.

Mean arterial blood pressure during isoflurane-saline anesthesia and isoflurane-medetomidine anesthesia was significantly higher at 0.8, 1.0, and 1.5 MAC, compared with at 2.0 MAC. No significant differences in mean arterial blood pressure were found between treatments. During isoflurane-medetomidine anesthesia, esophageal temperatures at 0.8, 1.5, and 2.0 MAC were significantly lower than at 1.0 MAC, and temperature at 1.5 MAC was significantly higher than at 2.0 MAC.

During isoflurane-saline anesthesia, end-tidal CO2 tension at 0.8, 1.0, and 1.5 MAC and PaO2 tension at 0.8 and 1.0 MAC was significantly greater than the respective values at 2.0 MAC. During isoflurane-saline anesthesia, the plasma bicarbonate concentration at 1.5 MAC was significantly greater than at 2.0 MAC, and the PaO2 tension at 2.0 MAC was significantly different from the respective value during isoflurane-medetomidine anesthesia. During isoflurane-medetomidine anesthesia, the PaO2 tension was significantly higher at 0.8, 1.0, and 1.5 MAC than at 2.0 MAC. No significant changes in arterial blood pH or base excess were found.

Discussion

In our study, the BIS during isoflurane anesthesia predictably decreased with increasing MAC multiples.

Table 2—Mean (± SD) values of physiologic variables from 6 dogs during collection of BIS measurements at 4 MAC multiples of isoflurane following an IM injection of medetomidine

<table>
<thead>
<tr>
<th>Variable</th>
<th>0.8 MAC</th>
<th>1.0 MAC</th>
<th>1.5 MAC</th>
<th>2.0 MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>66 ± 7*†‡</td>
<td>75 ± 11†</td>
<td>93 ± 13‡</td>
<td>94 ± 8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>74 ± 4*†</td>
<td>81 ± 11†</td>
<td>83 ± 4†</td>
<td>47 ± 13</td>
</tr>
<tr>
<td>End-tidal CO2 (mm Hg)</td>
<td>38 ± 3</td>
<td>38 ± 1</td>
<td>37 ± 2</td>
<td>36 ± 2</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.7 ± 1.05</td>
<td>38.3 ± 0.8*†</td>
<td>37.9 ± 1.01‡</td>
<td>37.3 ± 0.7</td>
</tr>
<tr>
<td>pH</td>
<td>7.35 ± 0.05</td>
<td>7.35 ± 0.04</td>
<td>7.35 ± 0.03</td>
<td>7.36 ± 0.04</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>42 ± 3</td>
<td>40 ± 2</td>
<td>39 ± 3</td>
<td>38 ± 4</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>621 ± 57†</td>
<td>617 ± 49†</td>
<td>606 ± 63†</td>
<td>497 ± 193‡</td>
</tr>
<tr>
<td>HCO3 (g/dL)</td>
<td>23.1 ± 2.5</td>
<td>21.7 ± 1.3</td>
<td>213 ± 0.7</td>
<td>213 ± 0.8</td>
</tr>
<tr>
<td>Base excess</td>
<td>−1.6 ± 2.3</td>
<td>−2.6 ± 1.5</td>
<td>−3.3 ± 0.9</td>
<td>−3.1 ± 0.8</td>
</tr>
</tbody>
</table>

*Significantly (P < 0.05) different from 1.5 MAC. †Significantly (P < 0.05) different from 2.0 MAC. §Significantly (P < 0.05) different from the same MAC multiple in dogs given medetomidine. MAP = Mean arterial pressure.
The mean BIS during isoflurane anesthesia at 1.0 MAC (60) was the targeted upper limit in surgical patients, which represents a degree of CNS depression that prevents recall of operative events. The mean BIS during isoflurane-saline anesthesia at 2.0 MAC (31) was less than the targeted value and may indicate the presence of excessive CNS depression when providing anesthesia with only an inhaled agent. However, we did not test the degree of CNS depression with surgical stimuli; therefore, these results must be interpreted cautiously.

Burst suppression in the electroencephalogram has been reported at deep anesthetic planes for most anesthetic agents. The effect of this electroencephalogram artifact during isoflurane anesthesia is a paradox in the BIS related to the monitor's interpretation of preburst electroencephalogram patterns as high-frequency activity (activation). This may lead to misinterpretation of the BIS when viewed independently from other monitoring variables during anesthesia. In our study, this confounding effect was minimized by omitting data from dogs that developed burst suppression in the electroencephalogram, as indicated by the BIS monitor via measurement of the suppression ratio.

The relationship between the BIS and MAC multiples of isoflurane was similar to that observed in dogs anesthetized with sevoflurane. One notable difference in BIS monitoring between these inhaled agents was observed at greater anesthetic depths. In the previous study, 6 of 8 dogs had burst suppression of the electroencephalogram that created artifact in measurement of the BIS during sevoflurane anesthesia at 2.0 MAC. By comparison in our study, only 1 of 6 dogs had this response during isoflurane anesthesia at 2.0 MAC. This finding may reflect a subtle difference in electroencephalogram activation and suppression that occurs with these 2 anesthetics.

Medetomidine is a commonly used preanesthetic agent for dogs undergoing inhalation anesthesia. In a previous study, on dogs, medetomidine (30 µg/kg, IV) administration decreased the MAC of isoflurane by 47%. In another study on dogs, medetomidine (5 µg/kg, IM) administration during isoflurane anesthesia resulted in a nonresponse to noxious stimulation of 2.6 ± 0.5 hours. Results of these studies support our finding of a sparing effect of medetomidine administration on the MAC of isoflurane during the 2-hour period in which BIS measurements were made. In our study, although the plasma concentrations of medetomidine were not measured and not held in steady-state with a continuous infusion of medetomidine, variability in medetomidine-induced CNS depression over time was attenuated by randomizing the order of each MAC multiple of isoflurane tested for BIS measurements. Addition of medetomidine (8 µg/kg, IM) to isoflurane anesthesia at 1.0 and 1.5 MAC was associated with a decrease in the BIS, compared with isoflurane-saline anesthesia alone. At 2.0 times the MAC of isoflurane, the variance in the BIS was high, and despite the observation that the measurement of the BIS during isoflurane-medetomidine anesthesia was 0 for 4 of 5 dogs, the mean BIS was not different from that during isoflurane-saline anesthesia. During isoflurane-medetomidine anesthesia, the BIS measurements at 0.8 and 1.0 MAC were significantly different from measurements at other MAC multiples.

During isoflurane-saline anesthesia, the mean (± SD) BIS for lightly anesthetized dogs (0.8 MAC) ranged from 73 to 57, whereas the BIS at a surgical depth of anesthesia (1.5 MAC) ranged from 55 to 49. In contrast, during isoflurane-medetomidine anesthesia, the BIS for lightly anesthetized dogs (0.8 MAC) ranged from 81 to 73, and the BIS at a surgical depth of anesthesia (1.5 MAC) ranged from 55 to 7. Thus, when monitoring the BIS, better discrimination among MAC multiples of isoflurane was observed with isoflurane-medetomidine anesthesia, compared with isoflurane-saline anesthesia.

In each treatment group, heart rate was generally higher during deep isoflurane anesthesia, compared with isoflurane anesthesia at 0.8 MAC, and was likely the result of reflex cardiac acceleration in response to vasodilation and hypotension associated with deep planes of anesthesia with isoflurane.

The decrease in mean arterial blood pressure observed with isoflurane anesthesia at 1.5 and 2.0 MAC is in agreement with previously published cardiovascular data on dogs. The decrease in heart rate associated with isoflurane-medetomidine anesthesia was likely the result of the well-documented medetomidine effect of induced bradycardia via sympatholytic or cholinomimetic mechanisms. These heart rate and arterial blood pressure changes were expected and represent clinically relevant scenarios during the use of these agents. The BIS has been used in 1 study to verify adequacy of cardiopulmonary resuscitation, but studies demonstrating a cause-effect relationship between cardiovascular physiologic changes and the BIS are lacking. Effects on CNS function or measurements of the BIS caused by changing cardiovascular variables remain speculative.

Significant differences in esophageal temperature, end-tidal CO2 concentration, PaO2, PaCO2, and plasma bicarbonate concentration were observed among MAC multiples of isoflurane in each group and between treatments. Differences between treatments for esophageal temperature and plasma bicarbonate concentration were small in magnitude (< 1°C and < 3 g/dl, respectively) and likely had minimal impact on BIS measurements. The decrease in end-tidal CO2 during isoflurane-saline anesthesia at 2.0 MAC was also small in magnitude. Large changes in CO2 tension (e.g., ± 20 mm Hg) have been shown to alter quantitative electroencephalographic data in dogs during halothane anesthesia. However, in our study, the values for end-tidal and arterial CO2 tension were within clinically acceptable limits for anesthetized patients, and the impact of these differences on BIS measurements is expected to be minimal.

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*aDomitor, Orion Corp, Espoo, Finland.
Isolto, Abbott Laboratories, North Chicago, Ill.
Narkovet 2, North American Drager, Telford, Pa.
Hallowell EMC, Pittsfield, Mass.
Angiocath, 20-gauge 48 mm, Becton-Dickinson, Sandy, Utah.
Lactated Ringer’s solution, Abbott Laboratories, North Chicago, Ill.
Datalogic 3000A, Datalogic Corp, Paramus, NJ.
References


