Evaluation of the bispectral index as an indicator of degree of central nervous system depression in isoflurane-anesthetized horses

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Objective—To determine whether the bispectral index (BIS) can be used as an indicator of degree of CNS depression in isoflurane-anesthetized horses.

Animals—10 Standardbred and 6 Norwegian coldblooded trotter stallions admitted for routine castration.

Procedure—A 2-channel referential electrode configuration was used to record EEG for calculation of BIS by the EEG monitor. The BIS was calculated before (awake) and after (sedated) administration of detomidine (0.01 mg/kg of body weight, IV) and butorphanol (0.01 mg/kg, IV). Anesthesia was induced with ketamine hydrochloride (2.5 mg/kg, IV) and diazepam (0.04 mg/kg, IV) and maintained with isoflurane delivered in oxygen. The BIS was calculated after 30 minutes of equilibration at an end-tidal isoflurane concentration of 1.4% (n = 8) or 1.9% (8) and recorded continuously during surgery.

Results—Bispectral index was significantly less in sedated and anesthetized horses, compared with awake horses. However, BIS was not significantly different between sedated and anesthetized horses. Mean BIS in horses anesthetized at 1.9% isoflurane was significantly greater, compared with horses anesthetized at an end-tidal concentration of 1.4%. Four horses in the 1.4% group moved during surgery, and BIS increased immediately prior to movement in 2 of these horses.

Conclusions and Clinical Relevance—BIS is not a precise indicator of degree of CNS depression in isoflurane-anesthetized horses. Thus, determination of BIS may not be a useful technique for monitoring anesthetic depth in isoflurane-anesthetized horses. (*Am J Vet Res* 2002;63:438–442)

It is obviously important to be able to monitor the degree of CNS depression in anesthetized horses. An inadequate plane of anesthesia may be associated with movement that may injure the horse or personnel or harm the equipment. However, an excessive level of anesthesia increases the risk of complications from cardiovascular depression and other adverse effects. Evaluation of eye reflexes, degree of cardiovascular depression, and movement may all be used to evaluate the degree of CNS depression in isoflurane-anesthetized horses.[1] Despite these techniques, additional methods for evaluating CNS depression would be useful. It has long been known that anesthesia alters the EEG.[2] Some authors have advocated the use of EEG power spectrum analysis to indicate anesthetic depth in horses,[3] but this technique has not gained widespread acceptance.

An algorithm has been empirically derived to evaluate the depressive effect of anesthesia in humans.[4] This algorithm uses data obtained from EEG recorded from humans at various anesthetic depths. The algorithm takes into account power spectrum analysis variables, burst suppression, and the degree of phase coupling assessed through use of bispectral analysis. From this information, the algorithm calculates a number between 0 and 100, called the **bispectral index (BIS)**. A high BIS indicates an awake patient, and a low value indicates a patient with severe CNS depression. The BIS incorporates more information from the original EEG than does traditional power spectrum analysis.[4] Results of human studies indicate that the BIS correctly predicts degree of CNS depression associated with isoflurane-induced anesthesia.[5,6] The purpose of the study reported here was to determine whether the BIS can be used as an indicator of CNS depression in isoflurane-anesthetized horses.

Materials and Methods

Animals—Ten client-owned Standardbred stallions and 6 Norwegian coldblooded trotter stallions were used in this study. These horses were between 2 and 9 years old and weighed between 345 and 548 kg. All were healthy, and all were admitted to the hospital for routine castration. The trainer or owner provided informed consent prior to inclusion of each horse in the study. Horses were randomized into a 1.4 and 1.9% end-tidal isoflurane concentration group. To ensure 2 groups of equal size but not biased with regard to breed, horses were block randomized and stratified with respect to breed. Each block consisted of 2 horses. Final groups consisted of 5 Standardbreds and 3 Norwegian coldblooded trotters.

Electroencephalography and calculation of BIS—The day before surgery, a physical examination was performed. Each horse was weighed, detomidine[a] (0.01 mg/kg of body weight, IV) was administered, and a catheter was placed in the left jugular vein. Hair was clipped over the locations for placement of EEG electrodes, and the skin was defatted with diethyl ether.

On the day of surgery, sodium penicillin (10×10^6 units, IV) was administered. Skin at electrode placement sites was again defatted with diethyl ether, and self-adhesive EEG silver chloride electrodes[b] were applied. Recording electrodes were placed bilaterally over the frontal bones 1 cm medial to the temporal line and 2 cm caudal to the lateral canthus of the eyes. The reference electrode was placed on the midline of the head rostral to the medial canthus of the eyes, and the ground electrode was placed within the atlanto-occipital

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region on the left side. The EEG was recorded continuously, using an EEG monitor,[c] and every 5 seconds data were automatically calculated by the BIS algorithm software[d] and stored in a computer. Before each EEG recording, impedance was checked and maintained at < 2,000 ohms at 16 Hz. The filters were set as follows: high-frequency filter, 70 Hz; 50/60-Hz filter, 50 Hz; and low-frequency filter, 2 Hz. The monitor also provided electromyography data recorded through the EEG electrodes, which were calculated in the frequency range of 70 to 110 Hz and expressed in decibels with respect to 0.0001 μV.[2] Data calculated from a combination of both recording electrodes were used in the BIS algorithm. The EEG monitor had an inbuilt artifact detection system and calculated a signal quality index indicating the percentage of epochs for the last 60 seconds that could be used to calculate BIS. Data were stored from 5-minute EEG recordings obtained before premedication (awake), 5 minutes after premedication (sedated), and before castration but after 30 minutes of equilibration at an end-tidal isoflurane concentration of either 1.4 or 1.9%. Electroencephalograms, **electromyograms (EMG)**, and BIS were recorded continuously throughout surgery.

Anesthesia and surgery—After placement of EEG electrodes and recording the 5-minute EEG for determination of BIS in the awake state, detomidine (0.01 mg/kg, IV) and butorphanol[e] (0.01 mg/kg, IV) were administered. Five minutes later, a 5-minute EEG was again recorded for determination of BIS in the sedated state. Ten minutes after administration of the premedicants, horses were led to the induction area, where a second dose of detomidine (0.004 mg/kg, IV) was administered. When the detomidine had taken effect, anesthesia was induced with ketamine hydrochloride[f] (2.5 mg/kg, IV) and diazepam[g] (0.04 mg/kg, IV). Horses were intubated and positioned in dorsal recumbency on the operating table. The orotracheal tube was connected to a circle anesthetic system, and intermittent positive-pressure ventilation was started. Anesthesia was maintained with isoflurane[h] delivered in oxygen, and to avoid parasympathetic activation during castration, glycopyrrolate (0.005 mg/kg, IV) was administered. A balanced isotonic electrolyte solution was also administered intravenously at an approximate rate of 5 L/h. Horses were maintained for 30 minutes at an end-tidal isoflurane concentration of either 1.4 or 1.9% before 5-minute EEG were recorded for calculation of BIS in the anesthetized state. Surgeries began once these recordings were completed.

The same surgeon performed all surgeries. Skin over the testes was incised with a scalpel, and the common vaginal tunic was isolated, using blunt dissection. Each testis was held with a towel clamp, and the cremaster muscle and funiculus were clamped, then ligated, using absorbable suture. The common vaginal tunic with its contents was cut with scissors, and the subcutaneous tissue and skin were sutured. After surgery but before recovery, flunixin meglumine (1.1 mg/kg, IV) was administered to reduce postoperative discomfort.

Monitoring—Gas was continuously drawn from the rostral end of the endotracheal tube to an anesthesia monitor[i] that measured inspiratory and expiratory isoflurane, O_2, and CO_2 concentrations. Mean blood pressure and pulse rate were measured via a catheter placed in a facial artery and connected to a pressure transducer zeroed at the level of the thoracic aperture. A base-apex ECG was recorded, and body temperature was measured via a sensor placed nasally. Arterial oxygen saturation was monitored by use of a pulse oximeter sensor placed on the tongue or the nasal septum. Dobutamine was infused at a rate required to maintain mean blood pressure > 60 mm Hg. End-tidal CO_2 concentration was maintained between 4.5 and 5.5%, and oxygen saturation was maintained at > 90%.

Statistical analyses—Electroencephalograms with a signal quality index < 50% or containing an error message were excluded from further analysis. Mean values for each 5-minute BIS recording (ie, awake, sedated, anesthetized at 1.4%, and anesthetized at 1.9%) were calculated for every horse. Differences between these means were calculated for the awake and sedated recordings (awake – sedated), awake and anesthetized recordings (awake – anesthetized), and sedated and anesthetized recordings (sedated – anesthetized). These differences and BIS recorded at an end-tidal isoflurane concentration of 1.4 or 1.9% were found to be normally distributed by use of a Shapiro-Wilkes test (α = 5%). Differences were tested to determine whether they were significantly different from 0 by use of a Student *t*-test (α = 5%). The difference between means in the 1.4 and 1.9% groups was evaluated by use of a Student *t*-test for 2 independent groups(α = 5%). Mean (± SD) values were also calculated for EMG power recorded during awake, sedated, and each anesthetized state.

Results

In 14 of the 16 horses, we were able to record EEG in the awake state; 2 Standardbreds in the 1.9% isoflurane group were too restless to enable recording of an EEG of sufficient quality. Mean BIS was significantly (P < 0.001) less in sedated horses, compared with awake horses **(Fig 1)**. In addition, BIS obtained at end-tidal isoflurane concentrations of 1.4 or 1.9% were significantly (P < 0.001) less than the awake values. Values obtained from sedated horses were not significantly different from values obtained from anesthetized horses, regardless of the end-tidal isoflurane concentration (sedated vs 1.4% isoflurane, P = 0.109; sedated vs 1.9% isoflurane, P = 0.230). However, mean BIS of horses anesthetized at 1.4% isoflurane was significantly (P = 0.022) less than that of horses anesthetized at 1.9% isoflurane.

Electroencephalograms, EMG, and BIS were recorded throughout surgery; however, these values were not statistically analyzed. Mean (± SD) time from administration of detomidine and butorphanol to the start of surgery was 88.4 ± 9.3 minutes in the 1.4% isoflurane group and 100.6 ± 13.6 minutes in the 1.9%

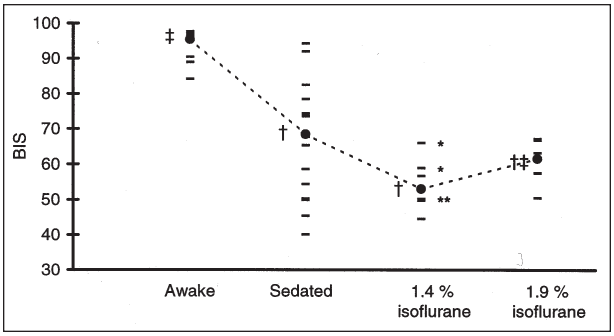

Figure 1—Bispectral indices (BIS) determined from EEG of healthy horses before (awake; n = 14) and 5 minutes after (sedated; 16) premedication with detomidine and butorphanol and after 30 minutes of equilibration at an end-tidal isoflurane concentration of 1.4 or 1.9% (n = 8 and 8, respectively). Horizontal lines indicate values for individual horses; filled-in circles represent the mean value for each state. *Values for horses that moved during subsequent surgery (castration). †Significantly (P < 0.05) different from mean value for awake horses. ‡Significantly (P < 0.05) different from mean value for the 1.4% isoflurane group.

group. In the 1.4% isoflurane group, 4 horses moved at least once during surgery. An obvious increase in BIS immediately prior to movement was detected in 2 of these 4 horses. Moreover, total power determined from the EMG appeared to increase concomitantly in these 2 horses (**Fig 2**). However, no clear change in BIS or EMG was detected in the other 2 horses (**Fig 3**).

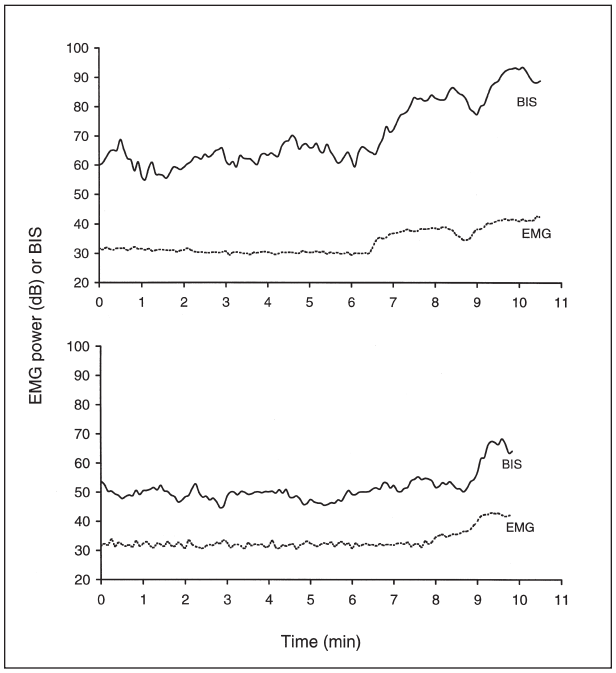

Figure 2—Absolute power (in dB; dotted line), determined from electromyograms (EMG), and BIS (solid line), determined from EEG, of 2 horses (top, Norwegian coldblooded trotter; bottom, Standardbred) that moved during surgery while anesthetized at an end-tidal isoflurane concentration of 1.4%. Movement was detected at 10 minutes. Notice that both BIS and EMG power increased immediately prior to movement.

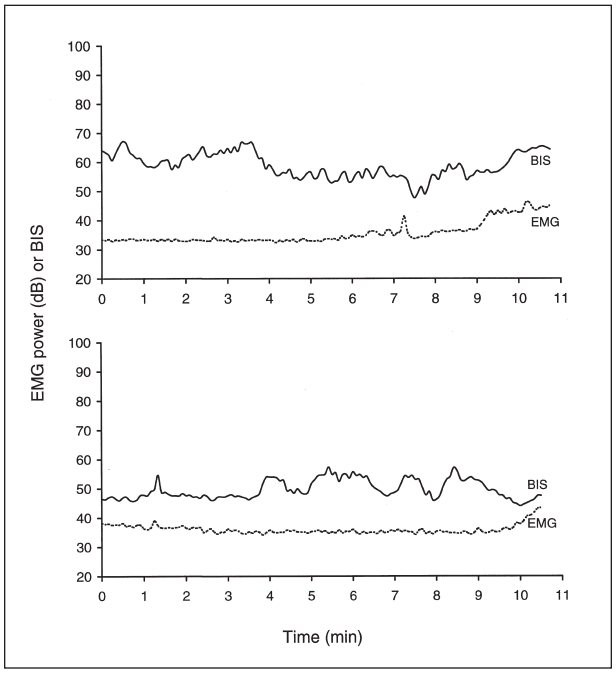

Figure 3—Absolute power (in dB; dotted line), determined from EMG, and BIS (solid line), determined from EEG, of 2 horses (top, Norwegian coldblooded trotter; bottom, Standardbred) that moved during surgery while anesthetized at an end-tidal isoflurane concentration of 1.4%. Movement was detected at 10 minutes in these horses, but there is no clear increase in BIS or EMG power prior to movement.

Electromyograms were recorded and EMG power calculated at each state. Mean (± SD) power in awake horses was 54.7 ± 3.6 dB (n = 14); in the sedated state, 41.3 ± 3.7 dB (16); during 1.4% isoflurane-anesthesia, 32.1 ± 2.1 dB (8); and during 1.9% isoflurane-anesthesia, 33.6 ± 2.6 (8). Only 1 horse in the 1.4% isoflurane group did not require dobutamine to maintain mean blood pressure > 60 mm Hg. Mean infusion rates of dobutamine were 18.6 ± 13.5 µg/kg/h and 29.2 ± 10.4 µg/kg/h in the 1.4 and 1.9% isoflurane groups, respectively. All horses recovered without complications, and postoperative complications were not observed.

Discussion

In humans, BIS appears to be a good indicator of degree of CNS depression.[5] In an unmedicated awake person, BIS is typically > 90; a BIS < 60 is a strong indication of unconsciousness.[5] In 1 study, mean BIS after an infusion of dexmedetomidine was 60.[7] It is reasonable to believe that degree of alertness is greatest when awake, less when sedated, low when anesthetized at 1.4% isoflurane, and lowest when anesthetized at 1.9% isoflurane. If BIS is to be used as an ideal indicator of degree of CNS depression in horses, it should be significantly different between each of these states. However, our data indicated that this is not the case. Although there were significant differences in BIS between the awake and sedated states and the awake and anesthetized states, BIS did not differ between the sedated and either anesthetized state. In addition, mean BIS in the 1.9% isoflurane group was significantly greater than in the 1.4% group. In horses, the **minimum alveolar concentration (MAC)** of isoflurane has been defined as an end-tidal concentration of 1.31%.[8] Thus, horses in the 1.4% isoflurane group were anesthetized at 1.08 MAC and those in the 1.9% group, at 1.45 MAC. These concentrations correspond to light and surgical planes of anesthesia, which are within the range of anesthesia used clinically. It is precisely within this range that an indicator of degree of CNS depression would be most valuable to help control the amount of anesthetic agent administered.

All horses were given the same dose of detomidine and butorphanol. This dose is associated with induction of clinically profound sedation. Mean BIS in horses sedated with detomidine (an α_2-adrenoceptor) and butorphanol (an opioid) was 68 (range, 39 to 95). This value was close to that calculated for humans sedated with dexmedetomidine.[7] We calculated BIS in sedated horses to determine whether this index could be used as an absolute indicator of the level of consciousness in horses. Although mean BIS in sedated horses was greater than in horses anesthetized with 1.4 or 1.9% isoflurane, this difference was not significant. The range of BIS in sedated horses included the mean for anesthetized horses. These results indicate that it is unlikely that BIS is an absolute indicator of degree of consciousness in horses. We did not see any clinical

need for evaluating sedation by use of EEG, so we did not record response to sedation and cannot conclude whether BIS is correlated with degree of sedation.

Degree of CNS depression is probably greater in horses anesthetized at an end-tidal isoflurane concentration of 1.9%, compared with 1.4%. However, we found that BIS was significantly higher in horses anesthetized at 1.9% isoflurane. In a previous study in pigs, BIS increased, but not significantly, as end-tidal isoflurane concentration increased.[9] In humans, a paradoxical increase in BIS has also been detected with increasing isoflurane concentration.[10] It is hypothesized that this increase in BIS may be caused by a continuous preburst pattern in the EEG. **Spectral edge frequency 95% (SEF)** is a power spectrum variable indicating the upper frequency limit encompassing 95% of the power.[11] An increase in SEF is associated with a change in EEG toward higher frequencies, and a decrease suggests a change toward lower frequencies. In a previous study,[12] EEG were recorded for horses anesthetized with halothane, isoflurane, or methoxyflurane. Results of that study indicated that increasing the end-tidal isoflurane concentration from 1.25 MAC (1.5%) to 1.5 MAC (1.8%) is associated with an increase in SEF, whereas increasing halothane or methoxyflurane concentrations is associated with a decrease in SEF.[12] The increase in BIS that we observed in horses anesthetized at 1.9% isoflurane, compared with 1.4%, could be a general effect of isoflurane that develops prior to a high degree of burst suppression.

Four horses in the 1.4% isoflurane group moved during surgery, and in 2 of these, we observed an obvious increase in BIS prior to movement. During surgery in horses, an increase in BIS may be an early warning that the plane of anesthesia is too low. The increase in BIS may be related to an increase in EMG power. In humans, increasing EMG power is known to increase BIS.[13] Bispectral indices calculated after anesthesia but before surgery for these 4 horses were not apparently different from BIS calculated for the other horses in this group. This could indicate that the absolute BIS calculated prior to stimulation has little value for predicting movement during surgery in isoflurane-anesthetized horses.

Time from sedation to calculation of BIS in the anesthetized state was greater for those horses anesthetized at an end-tidal isoflurane concentration of 1.9%. This was attributable to the time required to achieve the higher end-tidal isoflurane concentration. Because BIS in the anesthetized state was measured 12.2 minutes later in the 1.9% isoflurane group, the effect of premedication and induction agents on BIS in the anesthetized state was probably less in this group, compared with the 1.4% isoflurane group. Any influence of ketamine would probably result in an increase in BIS, because in humans under propofol-fentanyl anesthesia[14] or isoflurane anesthesia,[15] ketamine induces an increase in BIS. In our study, however, ketamine was probably no longer influencing BIS when anesthetized indices were recorded, because mean duration of action of ketamine administered at a dose of 2 mg/kg after promazine administered at a dose of 1 mg/kg is 23.8 minutes.[16] We believe that it is unlikely that the slight difference in effect of premedication and induction agents would override the effect of a 0.5% difference in end-tidal isoflurane concentration. Thus, we believe that the higher BIS in the 1.9% isoflurane group was an effect of isoflurane.

In horses under general anesthesia it is essential to monitor the cardiovascular system and to keep blood pressure at an adequate level. Fifteen of the 16 horses required dobutamine infusion to support the cardiovascular system, and the infusion rate was greater in the 1.9% isoflurane group than in the 1.4% group. However, because dobutamine does not penetrate the blood-brain barrier,[17] it is unlikely to have any direct effect on BIS. Mean EMG power recorded in the 2 anesthetized groups were almost equal, making it unlikely that differences in EMG were the reason for the higher mean BIS in the 1.9% isoflurane group.

The design used during anesthesia was a comparison of 2 groups. A Latin-square design would have given a higher power and avoided any problems with unequal groups. We did not use this experimental design because these were client-owned horses admitted for routine castration, and we could not justify either anesthetizing each horse twice or prolonging the anesthesia time to the extent required by use of a Latin-square design. The main aim of the present study was to evaluate BIS in isoflurane-anesthetized horses, and we did find a significant difference in BIS between the 1.4 and 1.9% isoflurane groups. Uniformity between groups was achieved by stratifying with regard to breed; this was the single factor we believed may influence BIS. Thus, the study design used was adequate for answering the aims of the study.

Bispectral indices are recorded in humans, using a bifrontal referential montage electrode configuration.[18] Data from both channels are included in calculations of BIS. Equine anatomy hampers a duplication of this electrode configuration. The configuration we used has been used previously in horses[19] and is an approximation of the electrode configuration used in humans. We cannot exclude that differences in electrode configuration may have interfered with the calculation of BIS. Quality of EEG was indicated by the artifact detection system within the monitor. A 50% quality index level was chosen, because as indicted by the manufacturer of the monitor, recordings at this level are of sufficient quality to calculate BIS. For a monitoring system to function in a clinical setting, data provided in real time must be reliable, so quality control was performed by use of the artifact detection system. Although EEG recorded in the present study were of sufficient quality and recorded BIS were within the range determined for humans, our results suggest that the BIS is not a reliable indicator of degree of CNS depression in isoflurane-anesthetized horses. In addition, although an increase in BIS may be an early warning of movement, this change may be mainly related to an increase in EMG power.

[a]Domosedan, Orion Corp, Turku, Finland.
[b]Zipprep, Aspect Medical Systems, Natick, Mass.
[c]Model A-1000, Aspect Medical Systems, Natick, Mass.
[d]BIS algorithim, version 3.1u, Aspect Medical Systems, Natick, Mass.
[e]Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa.

[f]Narketan, Chassot AG, Berne, Switzerland.
[g]Stesolid, Dumex-Alpharma A/S, Copenhagen, Denmark.
[h]Forene, Abbott Scandinavia AB, Kista, Sweden.
[i]Model AS/3, Datex-Engstrom, Helsinki, Finland.

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