Background  Publications on the use of the bispectral index for sedation monitoring in the intensive care unit are increasing. However, few studies have involved correlation of bispectral index with serum drug concentrations.

Objectives  To assess the degree of correlation between bispectral index values, scores on the Sedation-Agitation Scale, and steady-state serum concentrations of lorazepam.

Methods  A prospective open-label study of patients in a surgical intensive care unit who were receiving mechanical ventilation and continuous infusions of lorazepam for more than 24 hours. Bispectral index was measured (BIS-XP, Aspect Medical, Norwood, Massachusetts) to assess patients’ sedation. Sensors were applied and values recorded before and after stimulation (endotracheal suctioning). Concomitant plasma samples were obtained to measure lorazepam concentration and scores on the Sedation-Agitation Scale were recorded.

Results  Sixteen patients were studied. Correlations between plasma concentrations of lorazepam and measurements of bispectral index for 1, 2, and 3 minutes before endotracheal stimulation were poor (0.21, 0.29, and 0.25, respectively). Correlation of peak values for bispectral index (after stimulation) with plasma concentrations of lorazepam was 0.29. Correlations of scores on the Sedation-Agitation Scale with the aforementioned values for bispectral index were similarly poor. Area under the curve for bispectral index values also correlated poorly with plasma concentration of lorazepam (0.19) and score on the Sedation-Agitation Scale (0.10).

Conclusions  The correlation between bispectral index and score on the Sedation-Agitation Scale was poor. Correlation between bispectral index and plasma concentration of lorazepam was modestly better, but insufficient for clinical utility. (American Journal of Critical Care. 2012;21:99-105)
The BIS monitor was first used to assess patients’ awareness during general anesthesia, and its use has broadened to include adult and pediatric patients in the ICU and the emergency department. With its expanded application, it has become clinically evident that BIS sensors detect not only electroencephalographic activity, but also electromyographic (EMG) activity. This EMG sensitivity has been the major limitation for BIS use outside of the operating room, where patients are usually not paralyzed. For this reason, Aspect Medical (Norwood, Massachusetts) had designed a newer device, BIS-xp, in an attempt to limit the contribution of EMG activity to BIS measurements.

Lorazepam is an agent that is commonly used in patients who require prolonged sedation in the ICU and is recommended in the 2002 SCCM sedation guidelines. To date, few data comparing sedation as measured by BIS and sedative drug concentration have been published, and the single study that includes lorazepam describes only 2 patients receiving the drug by continuous infusion. We thus postulated that BIS measurements in patients receiving continuous infusions of lorazepam might show better correlation with level of sedation than has previously been reported for patients receiving intermittent dosing. Further, few data on use of the newer BIS-XP device in critically ill patients have been published, and given the probable contribution of EMG activity to measurement, we sought to determine if BIS-XP measurements would show improved correlation with sedation scores. Finally, we hypothesized that lorazepam concentrations might provide a more objective representation of sedation level than sedation scores, and thus show better correlation with BIS values than previously reported.

**Methods**

This prospective open-label study used a convenience sample of surgical ICU patients undergoing mechanical ventilation who had been receiving continuous lorazepam infusions for 24 hours or longer. Patients may also have been receiving other sedatives and/or analgesics as required for clinical care. Patients with head trauma, cerebral edema, and facial burns were excluded from the study. Approval was obtained from the institutional review board and consent was acquired from the legal representative of each subject.

**Protocol**

The XP version of the BIS monitor and software (BIS-XP) was used in this study. Before the BIS sensor was used, a SAS score was obtained by one investigator to maximize consistency. The SAS score was obtained before BIS evaluation, to ensure that the investigator could not be influenced by the BIS results. If stimulation was needed to measure SAS, a light glabellar tap was performed. The patient’s forehead

**About the Authors**

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was then cleaned with alcohol and allowed to dry before the sensor was applied.

Patients were then allowed to reach a stable state, defined as all readings being within plus or minus 5 BIS values for 5 minutes. Subsequently, baseline BIS XP values were recorded continuously for 3 minutes before stimulation. Minimum, maximum, and mean BIS values were recorded each minute, with the output from the monitor printed at the end of the study session. Because of the variability of reported BIS values in the literature, BIS averages were reviewed for 3 minutes, 2 minutes, and 1 minute (1-min BIS) before BIS stimulation. BIS stimulation consisted of endotracheal suctioning as part of routine care by the bedside nurse. The peak BIS value achieved in the following 5 minutes was then recorded. Serum samples were concomitantly obtained to measure lorazepam concentration if the patient had been receiving the same dosage for 24 hours or longer, and SAS values were recorded.

To ensure quality of BIS data, we monitored signal quality index (BIS-SQI) and EMg activity (BIS-EMG) values, which were also provided in the output from the Aspect device. BIS-SQI gives an indication of adherence of forehead sensors and signal quality. BIS values with an SQI less than 80% were not used. BIS-EMG estimates potential electrical interference from muscle activity, and no cutoff value for EMG has been agreed upon. Sub-analysis was planned to include only BIS data that had less than 50 dB of EMG activity at baseline.

In addition to the BIS values recorded during the study, derived BIS variables were calculated for analysis. These variables included the Avg-BIS \[\frac{(\text{peak BIS}) + (1\text{-min BIS})}{2}\] and ΔBIS (peak BIS – 1-min BIS). Other data collected included whether or not the patient was receiving other sedatives, analgesics, or a neuromuscular blocking agent.

The area under the curve for 20 minutes (AUC0-20) of BIS data was calculated by the trapezoidal rule for monitoring periods. Because of technical difficulties, this was done in a subset of 8 patients where we were able to continuously capture the data electronically. When no data were available for a specified time point, the value for the preceding minute was used as a conservative estimate.

Monitoring was repeated daily for up to 7 days while patients were receiving continuous infusions of lorazepam. If the lorazepam dosage was adjusted, we waited 24 hours to allow approximation of a new steady state before subsequent evaluations. BIS values were not shared with patients’ health care providers so as to not influence any aspect of care.

### Data Analysis

All BIS data generated per the protocol just described were considered for inclusion. Descriptive statistics were used to describe demographics and lorazepam concentrations. Spearman rank correlation was performed to determine the correlation between BIS and SAS scores. Pearson correlation coefficients were generated between plasma concentrations of lorazepam and measured and derived BIS values. A Student t-test was used for post-hoc continuous data comparisons. A P value of .05 was set as statistically significant a priori.

### Results

Seventeen patients were enrolled, but lorazepam was discontinued in 1 patient before data acquisition, leaving 16 patients, of whom 12 were male; these patients underwent a total of 42 monitoring periods. The mean age of the patients was 48.8 (SD, 15.2) years and mean weight was 95.4 (SD, 28.9) kg. The mean score on the Acute Physiology and Chronic Health Evaluation II on admission to the ICU was 21.0 (SD, 8.6). The mean lorazepam dosage was 2.0 (SD, 1.7) mg/h, which resulted in mean lorazepam concentrations of 256.3 (SD, 147.9) ng/mL (multiply by 3.114 to convert to nanomoles per liter). The cumulative mean lorazepam dose was 118.86 (SD, 126.97) mg.

A total of 42 BIS–lorazepam concentration measurement pairs were obtained. Of these, 10 were from 3 patients also receiving cisatracurium, leaving 32 BIS-SAS measurements where no neuromuscular

### Table

<table>
<thead>
<tr>
<th>Variable</th>
<th>With lorazepam</th>
<th>With SASa</th>
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</thead>
<tbody>
<tr>
<td>1-Minute BIS</td>
<td>0.21</td>
<td>0.11</td>
</tr>
<tr>
<td>2-Minute BIS</td>
<td>0.29</td>
<td>0.10</td>
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<tr>
<td>3-Minute BIS</td>
<td>0.25</td>
<td>0.16</td>
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<tr>
<td>Peak</td>
<td>0.29</td>
<td>0.15</td>
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<tr>
<td>Avg-BIS</td>
<td>0.30</td>
<td>0.14</td>
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<tr>
<td>ΔBIS</td>
<td>0.03</td>
<td>0.006</td>
</tr>
<tr>
<td>AUC0-20b</td>
<td>0.19</td>
<td>0.10</td>
</tr>
</tbody>
</table>

a Data from 32 nonparalyzed patients who had a Sedation-Agitation Scale (SAS) measurement.
b Data from 21 patients for the lorazepam correlation and 20 patients for the SAS correlation. AUC, area under curve, was calculated in 8 patients.

Correlation between score on the Sedation-Agitation Scale and any of the measured or derived bispectral index values was poor.
blocker was administered. All patients received concurrent opioids, and all but 1 received them as a continuous infusion. One patient received fentanyl 150 µg/h, 4 received hydromorphone 0.79 (SD, 1.9) mg/hr, and 11 received morphine infusion 3.2 (SD, 2.3) mg/h. Correlation between SAS and any of the measured or derived BIS values (mean 1, 2, and 3 minute BIS; peak BIS; Avg-BIS; ∆BIS) was poor (see Table). The AUC0-20, calculated in 8 patients, also showed a poor correlation with SAS. Individual BIS value–SAS score pairs are shown in Figure 1. A Student t test was performed post hoc between BIS values in patients with an SAS score of 2 versus an SAS score of 3 because most of the SAS values were in the range of 2 to 3. The 2 groups did not differ significantly for the 1, 2, or 3 minutes before stimulation (P > .05 for all calculations).

Correlations between the lorazepam concentrations and BIS values are also shown in the Table. Correlation between 1-minute BIS and lorazepam dose was 0.13 in patients not receiving neuromuscular blocking agents. The 3 patients receiving neuromuscular blocking agents had similar correlations between BIS and lorazepam concentration, ranging from an r² of 0.19 to 0.29 for the 3 minutes before stimulation.

The impact of EMg activity was examined by correlating the peak BIS with the EMG value produced at that time, revealing a strong correlation (Figure 2). The correlation of baseline EMG values to the 1-minute BIS was similarly high (r² = 0.71). When monitoring periods with an EMG exceeding 45 dB were excluded, the correlation of BIS to lorazepam concentrations improved marginally to an r² of 0.236, 0.329, and 0.317 for the 1, 2, and 3 minutes before stimulation. As well, BIS and SAS correlation improved to 0.124, 0.192, and 0.187 for the 1, 2, and 3 minutes before stimulation, respectively.

No adverse events related to sensors were documented during or after the study period.

Discussion

This study shows poor and clinically insignificant correlations between recorded or derived BIS values and plasma concentrations of lorazepam. The correlations were similarly poor between BIS values and SAS scores. The most promising correlation was between the EMG values and peak BIS, suggesting that BIS values were influenced by EMG activity, despite the newer XP device algorithms.

The lorazepam concentrations found in our surgical ICU patients were lower than those reported in a study of medical ICU patients receiving a continuous infusion of lorazepam (mean 256.3 [SD, 147.9] ng/mL vs mean 629 [SD, 36] ng/mL). However, the cumulative lorazepam dosage was much higher in that study, and the study involved only 2 patients.

This study is the second one in which BIS has been compared with serum concentrations of lorazepam. A study by de Wit et al recently suggested that in medical ICU patients receiving mechanical ventilation, higher lorazepam concentrations were associated with deeper sedation as measured by a 2-minute averaged BIS calculated during sedation assessment (r² = 0.0625). We found a similarly low correlation in our study. Other studies have demonstrated that with increasing degrees of sedation, BIS values do trend lower. Overall, the poor correlation of BIS values with actual drug dosage in our study is consistent with the poor correlations previously reported for lorazepam, midazolam, propofol, morphine, and pentobarbital.

Since publication of the 2002 SCCM guidelines, various studies of BIS and sedation scales have been
completed. Specifically, correlations of BIS and scores on the SAS have demonstrated wide-ranging degrees of correlation. These studies have encompassed various methods, different versions of the BIS software, and divergent cutoff points for data collection, thus making comparisons of results difficult. Researchers evaluating BIS with other sedation scales have reported similarly poor correlations in ICU patients. Although some other studies have shown stronger correlations between BIS and SAS scores, the \( R^2 \) values have still been less than 0.5, suggesting that less than 50% of the variability in BIS is explained by the SAS score. Finally, 2 studies have shown correlations slightly greater than 0.5, but these included a subset of trauma patients from a larger study or they had BIS values associated with high EMG (>42 Hz) excluded. Interestingly, Karamchandani et al recently reported a positive correlation (\( r = 0.56 \)) between BIS values and scores on the Richmond Agitation Sedation Scale in critically ill patients, raising the question of whether this sedation scale more closely associates with BIS in ICU patients.

Because BIS is an objective measure being compared with more subjective SAS scales, it can be argued that statistical correlations between BIS values and SAS scores are not the most appropriate measure to determine whether these 2 variables concur in the clinical setting. If this were true, then BIS might be useful in concert with SAS to evaluate patients clinically and subsequently guide sedative therapy. However, the wide range of BIS values within a given SAS score is still of concern and may complicate its clinical application. In evaluating the clinical predictability of the BIS in this patient population, the BIS value was discordant with the SAS assessment in a number of cases. One patient had an SAS score of 5 and a BIS of 78 on study day 1, and then a SAS score of 3 and a BIS of 97 the subsequent day.

The impact of EMG interference has long been an impediment to the usefulness of BIS technology. Although the BIS-XP algorithms were designed to have less interference, we still found a very high correlation between peak-BIS and peak EMG values. Also of concern was the high association between baseline 1-minute BIS and EMG. Arbour et al previously reported positive association between the BIS-XP and EMG with an \( r^2 \) of 0.56, which was lower than the correlation found in our study. Several studies have demonstrated that elimination of data points associated with high EMG levels significantly improves correlation between BIS values and SAS scores, although the clinical applicability of this approach remains unknown. When BIS data with EMG levels greater than 45 dB were excluded in the present study, only marginal improvements in correlations of BIS values with SAS scores and with lorazepam concentrations were seen.

The AUC analysis was conducted to incorporate the magnitude and duration of BIS following stimulation and to assess this more global value with study variables. The correlations calculated with the AUC\(_{0-20}\) BIS with both the lorazepam concentrations and the SAS scores were also very low and did not improve patients’ assessment compared with other measured or derived BIS values. Ferreira et al evaluated the AUC for the BIS in anesthetized patients undergoing surgery and receiving boluses of remifentanil. They reported a significant decrease in the AUC for BIS between 90 and 120 seconds after the administration of the remifentanil bolus.

Limitations

This study had several limitations. We did not conduct a dose response range within each patient, as this would have been unethical in our critically ill patients. All of our patients were receiving opioids, and the sedative effects of opioids can affect the BIS reading. This influence may explain, in part, the poor correlation between lorazepam concentration and BIS value. However, opioids are routinely administered to critically ill surgical patients and those drugs could not be discontinued for the purposes of this study.

We chose to wait only 24 hours on a constant lorazepam infusion before sampling plasma concentrations. This time may not have been long enough for the concentration to reach a steady state in some patients. Before a steady state is reached, the ratio of serum to brain lorazepam concentrations would not be constant, but this time frame was practical and most likely approximated steady-state conditions, given lorazepam’s elimination half-life of 10 to 12 hours. However at 24 hours, patients would be at nearly 90% steady state if the half-life was 10 hours.
The small number of patients may also limit the validity of our results. Additionally, most patients studied were recorded as having an SAS score between 2 and 3, and it would have been beneficial to have more results with a greater range of SAS scores. With regards to the AUC for BIS values, only some of our patients had electronically captured data, so this analysis was conducted with fewer data than the other correlations. Finally, no clinical or pharmacoeconomic outcomes were assessed in this study.

Conclusion

Correlations between BIS values and SAS scores and serum concentrations of lorazepam were poor. BIS values appear to correlate better with EMG activity, so we suggest complying with the 2002 SCCM recommendation of not routinely using BIS in the ICU.

FINANCIAL DISCLOSURES

This work was supported in part by a grant from Aspect Medical Systems, Norwood, Massachusetts; the study sponsors had no involvement in any part of the study. At the time of the study, Professor Dasta was a consultant to Eisai, Hospira and a member of the continuing education speakers’ bureau, France Foundation (sponsored by Hospira).

REFERENCES


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1. Which of the following is the purpose of monitoring bispectral index values (BIS)?
   a. To measure hemoglobin levels during surgery
   b. To measure level of consciousness during surgery and in the intensive care unit (ICU)
   c. To measure sedative levels during surgery
   d. To measure brain function during surgery

2. What types of activity can a BIS monitor detect?
   a. A waves and electromyographic (EMG) activity
   b. B waves and intracranial pressure (ICP)
   c. ICP and electroencephalographic (EEG) activity
   d. EEG activity and EMG activity

3. Which of the following is the hypothesis of this study?
   a. Intermittent lorazepam dosing would show a greater correlation with BIS values.
   b. Steady lorazepam concentrations might provide a more objective representation of sedation levels than Sedation-Agitation Scale (SAS) scores and better correlation with BIS values.
   c. Continuous lorazepam infusions are less reliable in predicting a correlation between SAS scores and BIS values.
   d. Intermittent lorazepam concentrations might provide a better correlation with SAS scores.

4. Which of the following statements best describes the methodology of this study?
   a. Prospective, open label, randomized sample of surgical patients who require mechanical ventilation
   b. Retrospective, open label, convenience sample of all patients who require lorazepam infusions
   c. Prospective, open label, convenience sample of surgical patients receiving mechanical ventilation who require lorazepam infusions longer than 24 hours
   d. Retrospective, open label, randomized sample of surgical patients receiving mechanical ventilation who require lorazepam infusions longer than 24 hours

5. Which of the following study designs ensured that the BIS score did not influence the SAS score?
   a. The SAS score was obtained before the BIS value.
   b. The SAS score and BIS value were collected at the same time.
   c. The BIS value was obtained before the SAS score.
   d. The SAS score was obtained by multiple investigators.

6. Which of the following processes best describes how the 3 variables were collected (BIS value, SAS score, and lorazepam levels)?
   a. BIS values were recorded before stimulation, SAS scores were recorded after stimulation, lorazepam levels were checked hourly
   b. BIS values were recorded for 5 minutes after stimulation, concomitant serum lorazepam levels were drawn, SAS score was recorded
   c. SAS score and BIS value were collected 5 minutes after stimulation, concomitant serum lorazepam levels were drawn
   d. Morning daily lorazepam levels were drawn, BIS values were recorded for 5 minutes after stimulation, SAS score was recorded

7. Which of the following was the process for ongoing monitoring?
   a. The patient was assessed every 8 hours for 48 hours
   b. The patient was assessed daily for 3 days
   c. The patient was assessed daily for up to 7 days
   d. The patient was assessed every 2 hours for 24 hours

8. Which of the following sets of demographics best describes the patients used in this study?
   a. Mean age 48.8, mean weight 95.4 kg, 12 males and 4 females
   b. Mean age 57.9, mean weight 95.4 kg, 12 males and 4 females
   c. Mean age 48.8, mean weight 78.9 kg, 12 males and 4 females
   d. Mean age 48.8, mean weight 95.4 kg, 10 males and 6 females

9. How many paired BIS-lorazepam concentrations were obtained?
   a. 67
   b. 38
   c. 42
   d. 51

10. How many patients received a concurrent opioid?
    a. 16
    b. 12
    c. 8
    d. 4

11. Which of the following was a limitation of this study?
    a. A lorazepam dose response range was not collected for each patient, opioids were not given consistently to each patient, and small SAS score ranges of 2 to 3
    b. Sedative effects of opioids, small number of patients, and small SAS score ranges of 2 to 3 for most patients
    c. A lorazepam dose response range was not collected for each patient, sedative effects of opioids, small number of patients
    d. SAS score ranges of 1 to 4 for most patients, lorazepam dose response range was not collected for each patient, and small number of female patients

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Bispectral Index Values, Sedation-Agitation Scores, and Plasma Lorazepam Concentrations in Critically Ill Surgical Patients
Jaclyn M. LeBlanc, Joseph F. Dasta, Maria C. Pruchnicki, Anthony Gerlach and Charles Cook

Am J Crit Care 2012;21 99-105 10.4037/ajcc2012777
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