Bispectral EEG Index during Nitrous Oxide Administration

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Background: Nitrous oxide (N₂O) is a commonly used sedative for painful diagnostic procedures and dental work. The authors sought to characterize the effects of N₂O on quantitative electroencephalographic (EEG) variables including the bispectral index (BIS), a quantitative parameter developed to correlate with the level of sedation induced by a variety of agents.

Methods: Healthy young adult volunteers (n = 13) were given a randomized sequence of N₂O/O₂ combinations via face mask. Five concentrations of N₂O (10, 20, 30, 40, and 50% atm) were administered for 15 min (20 min for the first step). EEG was recorded from bilateral frontal poles continuously. At the end of each exposure, level of sedation was assessed using primarily the Observer Assessment of Alertness/Sedation (OAA/S) scale.

Results: One subject withdrew from the study because of emesis at 50% N₂O. N₂O (50%) increased theta, beta, 40–50 Hz, and 70–110 Hz band powers. BIS and spectral edge frequency at 50% N₂O/O₂ did not differ significantly from baseline values. Abrupt decreases from higher to lower concentrations frequently evoked a profound, transient slowing of activity. No significant change in OAA/S was detected during the study.

Conclusions: Although the spectral content of the EEG changed during N₂O administration, reflecting some pharmacologic effect, the subjects remained cooperative and responsive throughout, and therefore N₂O can only be considered a weak sedative at the tested concentrations. Despite changes in the lower and higher frequency ranges of EEG activity, the BIS did not change, which is consistent with its design objective as a specific measure of hypnosis. (Key words: Conscious sedation; monitoring.)

NITROUS OXIDE is among the most commonly used anesthetic and sedative agents. In addition to being an important adjuvant during general anesthesia, nitrous oxide combined with oxygen is widely administered for obstetrical analgesia and sedation in dental and medical procedures, such as endoscopy. Unlike currently available volatile anesthetic vapors, nitrous oxide is a potent analgesic at subanesthetic concentrations. The electrophysiologic effects reported during N₂O administration include acceleration of volatile anesthetic-induced fast activity, activation of high beta range frequencies, along with a shifting temporal pattern, which may represent acute tolerance. High-order spectral analysis in the form of the bispectral index (BIS; Aspect Medical Systems, Natick, MA) has been reported to correlate with or predict level of sedation in patients or volunteers receiving volatile agents or opioids. The effects of other general anesthetics in combination with nitrous oxide on BIS have been reported. However, the effects of N₂O alone on modern quantitative EEG parameters remain unknown despite the widespread use of N₂O as a sole agent. We therefore sought to determine the correlation of EEG with N₂O and to test the hypothesis that BIS correlates with sedation caused by nitrous oxide administration.

Methods

With approval of the Committee on Human Research at the University of California, we studied healthy volun-
teers (seven men and six women) aged 25 ± 3 yr (mean ± SD) and weighing 66 ± 12 kg. The protocol was randomized but unblinded. Subjects with neurologic or psychiatric disease were excluded, as were those with a recent history of prescription or illicit psychoactive drug use. They were instructed to take nothing by mouth for the 12 h before the study. Subjects were placed in the supine position and monitored with an oscilometric blood pressure monitor, electrocardiograph (ECG), and pulse oximeter. A self-adhesive face mask (AirCare, Apotheus Laboratories, Lubbock, TX) was applied, and oxygen was administered at 10 l/min via a circle breathing system with a carbon dioxide absorber. Concentrations of oxygen, nitrous oxide, and carbon dioxide were monitored continuously at the mask inlet with an airway gas analyzer (Capnomac Ultima, Datex, Finland) and recorded at 3-min intervals. Minute ventilation was recorded using an impeller spirometer in the exhalation limb of the breathing circuit.

We recorded two bipolar electroencephalographic (EEG) channels (FpZ-F7, FpZ-F8) as recommended for BIS monitoring by Aspect Medical Systems. ZipPrep electrodes (Aspect Medical Systems) were applied to the scalp after mild abrasion with a cotton sponge, resulting in contact impedance under 5 kΩ. The raw EEG waveform data was continuously recorded digitally at 256 Hz per channel. These signals were bandpass filtered to 0.5–50 Hz and processed in real time using version 3.22 of the BIS algorithm. Additional quantitative EEG (QEEG) variables, including absolute and relative band powers, median power frequency (MPF), 95th percentile spectral edge frequency (SEF95), and burst suppression ratio (BSR),23 were also calculated on-line. The QEEG variables were digitally recorded every 5 s for the duration of the study. Using the raw waveform data off-line, the spectral edge frequency (SEF) was calculated using the standard algorithm.24 A band power determination for the range 70–110 Hz ("EMGLow") was also determined before bandpass filtering. The mean of the two EEG channels was used for statistical analysis.

After instrumentation, subjects relaxed at least 10 min, followed by an awake baseline EEG recording, and then N2O was administered in a randomized sequence of concentration steps (10%, 20%, 30%, 40%) followed by 50% N2O, which was always given last because of the high incidence of nausea and emesis anticipated at this concentration (Unpublished data, Sessler DI, 1996). Each concentration was administered for 15 min, except for the first level, which was administered for 20 min. EEG was recorded and analyzed for at least 15 min after the termination of nitrous oxide administration. The EEG effects of decreasing the inspired concentration of N2O were quantified by examining the transition period from 50% to 0% N2O. The withdrawal response was measured at the point of maximal depression of BIS within 15 min after the N2O was discontinued and compared with the value 15 min after N2O termination ("recovery" state).

Level of sedation (LOS) was assessed using the Observer's Assessment of Alertness/Sedation Score25 (OAA/S) and a simple motor performance test at 10 min and 15 min of exposure at each concentration. The OAA/S test consists of four components (table 1). As described by Chernik,26 we chose to use the sum of the component scores. The motor performance test consisted of asking subjects to hold up a randomly specified number of fingers within 5 s. Subjects were also asked to respond verbally if they felt nauseated. In the case of the first (longer exposure) step, LOS was measured at 15 min and 20 min.

The QEEG values used for assessment of dose response were derived from 50-s averages immediately before LOS testing. The Aspect Medical Systems, Inc. signal quality index (SQI) was used to exclude EEG epochs contaminated with artifact from averaging. Before assessment of N2O-related changes, the EEG data were assessed to determine whether they were normally distributed. Quantitative EEG data for 5 min of non-roused, steady-state end-tidal N2O concentration was pooled for all subjects at each dose and for the awake baseline state. The closeness of fit to a normal probability curve was determined using the Shapiro-Wilk W test (JMP, SAS, Cary NC). Changes in quantitative EEG and LOS caused by an N2O dose response were compared using nonparametric analysis of variance with repeated measures (Friedman's test). A second Friedman's test was applied to compare the mean QEEG values during awake baseline, the "withdrawal" suppressive phase, and at the 15-min "recovery" point. P ≤ 0.025 was considered significant, given a correction for two sets of comparison.

Results

One subject did not complete the protocol because of nausea and emesis during 50% N2O; consequently the data from this male subject were excluded from statistical analysis.

Nitrous oxide did not alter any of the vital signs (table 2) or sedation scores (table 3). Even at 50% N2O this
study population did not evidence more than a trace of sedation as determined by our standard test instruments. Only one subject failed to perform the motor performance test with a lack of timely response at 20% and 50% N₂O, although a prompt, correct response occurred at all other concentrations. In the same subject the OAA/S score was 19 (completely awake score = 20) at 20% and 11 at 50% N₂O. The disparity between the motor performance and the OAA/S during 20% N₂O appeared to result from transient inattention. Another subject had an OAA/S score of 16 at 30%; all remaining OAA/S results were 17 or higher. Although it was no more sensitive, we separately report the OAA/S responsiveness subscore to allow comparison with previous reports comparing BIS and sedation (table 2).

All QEEG parameters calculated in this study were determined by the Shapiro-Wilks W test to not be normally distributed; therefore, the use of nonparametric statistics was justified. Nitrous oxide increased high beta (40–50 Hz) and EMGLo (70–110 Hz) range EEG activity as well as the BIS (fig. 1). However, analysis of the dose-response curve was complicated by the presence, in 7 of 11 volunteers, of an EEG-depressive phenomenon that occurred when the N₂O concentration was abruptly reduced from a higher concentration to a lower one (fig. 2). This change in EEG seen on withdrawal of N₂O was characterized by increased delta and theta range activity, decreased high frequency range activity, decreased BIS, and depressed spectral edge, particularly of the SEF_{65} variant. This depressive response substantially altered the EEG dose dependence that might have been expected from a simple set of monotonically increasing N₂O concentrations. One consequence was that the BIS value at 40% N₂O was different from the value at 10% but not the BIS value at baseline. Because the 10% dose level almost always followed a higher concentration, it was therefore likely to be subject to this suppressive phenomenon. It is therefore possible that the withdrawal

![Table 1. Observer's Assessment of Alertness/Sedation Scale (OAA/S) Scale]

<table>
<thead>
<tr>
<th>Subscore</th>
<th>Responsiveness</th>
<th>Speech</th>
<th>Facial Expression</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Responds readily to name spoken in normal tone</td>
<td>Normal</td>
<td>Normal</td>
<td>Clear, no ptosis</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to name spoken in normal tone</td>
<td>Mild slowing or thickening</td>
<td>Mild relaxation</td>
<td>Glazed or mild ptosis</td>
</tr>
<tr>
<td>3</td>
<td>Responds only after name is spoken loudly and/or repeatedly</td>
<td>Slurring or prominent slowing</td>
<td>Marked relaxation (slack jaw)</td>
<td>Glazed and marked ptosis</td>
</tr>
<tr>
<td>2</td>
<td>Responds only after mild prodding or shaking</td>
<td>Few recognized words</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Does not respond to mild prodding or shaking</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The final score is the sum of the responsiveness, speech, facial expression, and eyes component scores. Thus, a “wide awake” score = 20 and a “deeply sedated” score = 9 [(1(responsiveness) + 2(speech) + 3(facies) + 3(eyes)).

![Table 2. Hemodynamic and Respiratory Measurements during Nitrous Oxide Administration]

<table>
<thead>
<tr>
<th>Inspired Nitrous Oxide (% atm)</th>
<th>0 (baseline)</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>0 (withdrawal)</th>
<th>0 (recovery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>79.6 ± 11.4</td>
<td>78.8 ± 9.6</td>
<td>83.4 ± 9.5</td>
<td>80.4 ± 8.3</td>
<td>81.9 ± 10.3</td>
<td>84.2 ± 11.4</td>
<td>82.9 ± 13.6</td>
<td>84.8 ± 15.1</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>58.5 ± 10.4</td>
<td>57.7 ± 10.6</td>
<td>55.3 ± 10.0</td>
<td>57.2 ± 7.8</td>
<td>59.0 ± 12.8</td>
<td>58.8 ± 9.6</td>
<td>55.8 ± 8.0</td>
<td>56.9 ± 8.5</td>
</tr>
<tr>
<td>ET C0₂ (mmHg)</td>
<td>36.4 ± 5.2</td>
<td>38.0 ± 5.9</td>
<td>37.8 ± 4.9</td>
<td>35.7 ± 5.1</td>
<td>34.2 ± 5.1</td>
<td>37.6 ± 5.6</td>
<td>37.4 ± 5.2</td>
<td>38.3 ± 4.7</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>15.0 ± 2.5</td>
<td>16.7 ± 2.5</td>
<td>18.1 ± 3.1</td>
<td>16.5 ± 2.6</td>
<td>16.9 ± 3.4</td>
<td>15.8 ± 4.4</td>
<td>17.1 ± 1.7</td>
<td>16.3 ± 2.1</td>
</tr>
<tr>
<td>MV (L/min)</td>
<td>6.3 ± 1.9</td>
<td>6.7 ± 1.8</td>
<td>6.6 ± 1.9</td>
<td>7.1 ± 2.4</td>
<td>6.8 ± 3.0</td>
<td>6.6 ± 2.1</td>
<td>5.8 ± 1.5</td>
<td>6.6 ± 2.2</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>99.9 ± 0.3</td>
<td>99.6 ± 0.9</td>
<td>99.9 ± 0.3</td>
<td>99.7 ± 0.5</td>
<td>99.5 ± 0.7</td>
<td>99.4 ± 0.8</td>
<td>99.7 ± 0.5</td>
<td>99.6 ± 0.7</td>
</tr>
</tbody>
</table>

Values are mean ± SD. MAP = mean arterial pressure; HR = heart rate; ET C0₂ = end-tidal concentration of carbon dioxide; RR = respiratory rate; MV = minute volume; SpO₂ = hemoglobin saturation.

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Table 3. The Effect of Nitrous Oxide on Level of Sedation

<table>
<thead>
<tr>
<th>Nitrous Oxide Concentration (% atm)</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAA/S</td>
<td>20.0 ± 0.0</td>
<td>19.8 ± 0.6</td>
<td>19.7 ± 0.7</td>
<td>19.3 ± 1.0</td>
<td>19.8 ± 0.5</td>
<td>18.8 ± 2.8</td>
<td>0.16</td>
</tr>
<tr>
<td>RS</td>
<td>5.0 ± 0.0</td>
<td>5.0 ± 0.0</td>
<td>5.0 ± 0.0</td>
<td>4.9 ± 0.3</td>
<td>5.0 ± 0.0</td>
<td>4.7 ± 0.9</td>
<td>0.22</td>
</tr>
<tr>
<td>MP</td>
<td>2.0 ± 0.0</td>
<td>2.0 ± 0.0</td>
<td>1.8 ± 0.6</td>
<td>2.0 ± 0.0</td>
<td>2.0 ± 0.0</td>
<td>1.8 ± 0.6</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

OAA/S = Observer's Assessment of Alertness/Sedation score; RS = responsiveness subscore of the OAA/S; MP = motor performance score.

suppression, rather than a true dose–response, was responsible for the detected difference in mean values of BIS.

During exposure to 50% N₂O, the BIS values were 94.6 (median, 97.4; range, 75.3–98.1; interquartile range, 4.4). After withdrawal of N₂O, BIS declined transiently to 81.4 (median, 84.6; range, 45.6–97.2; interquartile range, 19.4) compared with 93.4 (median, 94.7; range, 86.1–97.9; interquartile range, 6.9) at awake baseline, and 95.5 (median, 93.3; range, 90.0–97.8; interquartile range, 2.7) at the 15-min recovery time (P = 0.001). In the subjects in whom EEG depression was noted, maximal suppression of BIS occurred on average at 6.1 ± 3.0 min after N₂O was terminated and lasted up to approximately 10 min. A separate comparison of the withdrawal phase EEG against awake baseline and "recovery" demonstrated differences in absolute theta, alpha, beta, high beta, and EMGLow range band powers as well as relative delta, theta, and alpha activity and BIS (fig. 1).

Two subjects developed notable high amplitude delta range activity during this period. Fifteen minutes after removal of N₂O, the EEG had incompletely returned to baseline values. EEG burst-suppression activity (i.e., a burst suppression ratio ≥ 0.0) was not seen at any point in this study.

Discussion

Concentrations of N₂O commonly used for "conscious sedation" produced little overt sedation in our volunteers as measured by the OAA/S. This observation is not inconsistent with the findings of Dwyer et al., who found that MAC-awake for N₂O was higher than the concentrations tested here at 0.64 MAC or about 67% atm.²⁰ Dwyer et al. also reported that recall was not completely suppressed even at 0.6 MAC. Galinkin et al.²⁷ recently reported a small reduction in OAA/S responsiveness score during 30% N₂O. Although a few of the present subjects reported some disorientation, this small degree of psychological effect was not reliably tested by the OAA/S or motor performance scales used. Henri²⁸ and Cook et al.²⁹ found that N₂O concentrations of 20–30% caused impairment of higher levels of functioning (i.e., explicit, immediate recall and visual reaction time, subjective sensory reporting).

Concentrations of N₂O exceeding 50% are rarely used in dental or office-based procedures and were not tested in this investigation because previous experience suggested a high probability of retching and emesis. We presume that sufficiently high concentrations of N₂O will produce behavioral sedation and more profound EEG changes than we observed. Glass has recently demonstrated a good correlation between the responsiveness component of the OAA/S and BIS at deeper levels of sedation. That correlation was independent of whether propofol, midazolam, isoflurane, or alfentanil were used.¹³ The full OAA/S scale²⁵ is presumably more sensitive than the isolated responsiveness subcomponent used by Glass.¹³ Nonetheless, our study is limited by the sensitivity of the behavioral scales we used. It is likely that more sensitive instruments would identify N₂O-induced changes in sensorium at concentrations below 50%. However, our data indicate that these concentrations alone do not produce clinically important sedation. Analgesia is a well-known consequence of N₂O administration.²⁴ It thus seems likely that N₂O's well-recognized efficacy in increasing a patient's tolerance to noxious stimulation may well be more related to higher level cognitive dysfunction²⁸,³⁰ and to analgesia than to a specific sedation or hypnotic effect.

A previously reported study of N₂O's effects on the EEG of healthy volunteers also identified an increase in the high beta range activity.¹¹ These investigators used higher N₂O concentrations (50–70%) and found that high frequency EEG activity was associated with significant sedation. They did not comment on changes in delta or theta range activity, but they did note a subjec-
EEG DURING NITROUS OXIDE SEDATION

Figure 1. Box plot summaries of the QEEG data. In panel 1A, absolute band powers are displayed in decibels (decibels = 10 log₁₀ [Power [µwatts]]). HiBeta was defined here as the range from 40–50 Hz. DR values are the P values resulting from the analysis of variance of the dose–response data, i.e., baseline, and 10%–50% N₂O. WP are P values resulting from the comparison of the awake state, the “withdrawal” phase, and the 15-min recovery time. Panel 1B illustrates the relative band powers, or power within a particular frequency range expressed as a percentage of the total EEG power during the measurement period. Panel 1C contains the results for the median power frequency (MPF), 95th percentile frequency (SEF₉₅), spectral edge frequency (SEF), very high frequency (70–110 Hz) range band power (EMG₉₅), and the bispectral index (BIS).

tive suppression of alpha band activity, whereas we observed only a small change at 50%.

Avramov et al. reported that initiation of 65% N₂O was associated in 12 of 13 patients with onset of continuous, high amplitude delta activity that persisted for an average 15 min, eventually being replaced by a beta pattern. We sought this shifting spectral pattern during the prolonged first concentration step but failed to detect it during our different study conditions. We observed the converse: removal of N₂O was associated with transient, high amplitude delta activity. This inconsistent result may be explained by the baseline 0.75–1.0 MAC halothane anesthetic, higher N₂O concentration, as well as concurrent surgery and mechanical ventilation in the earlier study.

In two subjects, abrupt reduction in inspired N₂O concentration was associated with prominent slow wave activity. Prominent delta range EEG activity is commonly associated with cerebral hypoxia or hypoperfusion caused by hypocapnia or hypotension, conditions not present in this study. A similar pattern of predominantly delta activity is also seen during anesthesia with high doses of halothane or opioids or after brain injury. With these etiologies, delta wave EEG activity is associated with altered mentation. Delta activity and depression of BIS occurred transiently during withdrawal of N₂O in these subjects while they remained awake and alert; therefore, slow EEG or depressed BIS activity may not be considered a specific indicator of deep anesthesia in all clinical circumstances. A similar phenomenon was described in 1961 by Henric. In that study, withdrawal of N₂O was associated with a transient, paroxysmal in-
crease in theta (4–7 Hz) activity not associated with drowsiness. In Henrie’s study, delta activity was not reported, possibly because it was outside the practical range of their EEG analyzer. Interestingly, prominent delta activity may also be seen in alert patients with hepatic or renal encephalopathy. Paroxysmal high amplitude delta activity has also been occasionally noted in surgical patients when the concentration of anesthetic is low relative to the degree of noxious stimulation. In the latter setting, this slow EEG activity has come to be known as paradoxical arousal. The mechanism(s) of EEG slowing during N2O withdrawal or during paradoxical arousal remain speculative as a putative mechanistic link between them. Nonetheless, based on our current results and previous reports of divergent pharmacologic effects, we propose that N2O possesses excitatory and inhibitory actions in the CNS. Furthermore, it appears that the effect leading to EEG acceleration is more potent but with a shorter pharmacodynamic profile than the depressive effect.

The algorithm that computes BIS evaluates predominantly three features of the EEG: the ratio of very high beta range activity to high alpha plus low beta activity (relative beta ratio), very high beta range phase relationships, and burst suppression phenomena. These features are used sequentially by the algorithm as sedation and anesthesia increase with the relative beta ratio being the most influential feature during light sedation. Although the exact computation used in the BIS calculation is not available externally, one might predict the relative beta ratio would change little during N2O because the beta and high beta band powers increased comparably, and the alpha power was essentially unaltered.

In summary, sharp reduction in administered N2O concentration often provoked a withdrawal-like phenomenon. In contrast, steady state N2O alone caused a slightly increased in high frequency and theta range activity EEG but did not alter BIS or create a significant degree of hypnosis. This is consistent with the empirically based development of the BIS as an indicator of level of consciousness. Additional data will be required to determine if the N2O withdrawal-linked EEG depression is a sufficiently confounding factor in clinical monitoring to justify an attempt to incorporate its occurrence in the BIS algorithm.

References

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