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Bispectral EEG Index during Nitrous Oxide Administration

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Background: **Nitrous oxide (N_2O) is a commonly used sedative for painful diagnostic procedures and dental work. The authors sought to characterize the effects of N_2O 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 N_2O/O_2 combinations *via* face mask. Five concentrations of N_2O (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% N_2O. N_2O (50%) increased theta, beta, 40–50 Hz, and 70–110 Hz band powers. BIS and spectral edge frequency during 50% N_2O/O_2 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 N_2O administration, reflecting some pharmacologic effect, the subjects remained cooperative and responsive throughout, and therefore N_2O 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[1] and medical procedures, such as endoscopy.[2] Unlike currently available volatile anesthetic vapors, nitrous oxide is a potent analgesic at subanesthetic concentrations,[3–6] induces sympathetic nervous system activation,[7–9] and increases muscle tone at high anesthetic (>1 MAC) concentrations.[10] The electrophysiologic effects reported during N_2O administration include acceleration of volatile anesthetic-induced fast activity,§ activation of high beta range frequencies,[11] along with a shifting temporal pattern, which may represent acute tolerance.[12] 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,[13,14] propofol,[15–19] midazolam,[13,17,20] or opioids.[13,17] The effects of other general anesthetics in combination with nitrous oxide on BIS have been reported.[21,22] However, the effects of N_2O alone on modern quantitative EEG parameters remain unknown despite the widespread use of N_2O as a sole agent. We therefore sought to determine the correlation of EEG with N_2O 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-

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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 oscillometric 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/m *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 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 (SEF_{95}), 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 N_2O was administered in a randomized sequence of concentration steps (10%, 20%, 30%, 40%) followed by 50% N_2O, 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 N_2O were quantified by examining the transition period from 50% to 0% N_2O. The withdrawal response was measured at the point of maximal depression of BIS within 15 min after the N_2O was discontinued and compared with the value 15 min after N_2O termination ("recovery" state).

Level of sedation (LOS) was assessed using the Observer's Assessment of Alertness/Sedation Score[25] (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,[25] 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 N_2O-related changes, the EEG data were assessed to determine whether they were normally distributed. Quantitative EEG data for 5 min of non-aroused, steady-state end-tidal N_2O 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 N_2O 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. $P \leq 0.025$ 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% N_2O; 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% N_2O this

Table 1. Observer's Assessment of Alertness/Sedation Scale (OAA/S) Scale[16]

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

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)].

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% N_2O, 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% N_2O. The disparity between the motor performance and the OAA/S during 20% N_2O 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).[13,18]

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 EMGLow (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 N_2O concentration was abruptly reduced from a higher concentration to a lower one (fig. 2). This change in EEG seen on withdrawal of N_2O was characterized by increased delta and theta range activity, decreased high frequency range activity, decreased BIS, and depressed spectral edge, particularly of the SEF_{95} variant. This depressive response substantially altered the EEG dose dependence that might have been expected from a simple set of monotonically increasing N_2O concentrations. One consequence was that the BIS value at 40% N_2O 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 2. Hemodynamic and Respiratory Measurements during Nitrous Oxide Administration

	Inspired Nitrous Oxide (% atm)							
	0 (baseline)	10	20	30	40	50	0 (withdrawal)	0 (recovery)
MAP (mmHg)	79.6 ± 11.4	78.8 ± 9.6	83.4 ± 9.5	80.4 ± 8.3	81.9 ± 10.3	84.2 ± 11.4	82.9 ± 13.6	84.8 ± 15.1
HR (bpm)	58.5 ± 10.4	57.7 ± 10.6	55.3 ± 10.0	57.2 ± 7.8	59.0 ± 12.8	58.8 ± 9.6	55.8 ± 8.0	56.9 ± 85
ET_{CO_2} (mmHg)	36.4 ± 5.2	38.0 ± 5.9	37.8 ± 4.9	35.7 ± 5.1	34.2 ± 5.1	37.6 ± 5.6	37.4 ± 5.2	38.3 ± 4.7
RR (breaths/min)	15.0 ± 2.5	16.7 ± 2.5	18.1 ± 3.1	16.5 ± 2.6	16.9 ± 3.4	15.8 ± 4.4	17.1 ± 1.7	16.3 ± 2.1
MV (L/m)	6.3 ± 1.9	6.7 ± 1.8	6.6 ± 1.9	7.1 ± 2.4	6.8 ± 3.0	6.6 ± 2.1	5.8 ± 1.5	6.6 ± 2.2
SP_{O_2} (%)	99.9 ± 0.3	99.6 ± 0.9	99.9 ± 0.3	99.7 ± 0.5	99.5 ± 0.7	99.4 ± 0.8	99.7 ± 0.5	99.6 ± 0.7

Values are mean ± SD.

MAP = mean arterial pressure; HR = heart rate; ET_{CO_2} = end-tidal concentration of carbon dioxide; RR = respiratory rate; MV = minute volume; Sp_{O_2} = hemoglobin saturation.

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

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

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% N_2O, the BIS values were 94.6 (median, 97.4; range, 75.3-98.1; interquartile range, 4.4). After withdrawal of N_2O, 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 N_2O 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 N_2O, the EEG had incompletely returned to baseline values. EEG burst-suppression activity (*i.e.*, a burst suppression ratio[23] > 0.0) was not seen at any point in this study.

Discussion

Concentrations of N_2O 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 N_2O was higher than the concentrations tested here at 0.64 MAC or about 67% atm.[26] 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% N_2O. 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. Henrie[28] and Cook *et al.*[29] found that N_2O 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 N_2O 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 N_2O 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 scale[25] 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 N_2O-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 N_2O administration.[4] It thus seems likely that N_2O's well-recognized efficacy in increasing a patient's tolerance to noxious stimulation may well be more related to higher level cognitive dysfunction[28,30] and to analgesia than to a specific sedation or hypnotic effect.

A previously reported study of N_2O's effects on the EEG of healthy volunteers also identified an increase in the high beta range activity.[11] These investigators used higher N_2O 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-

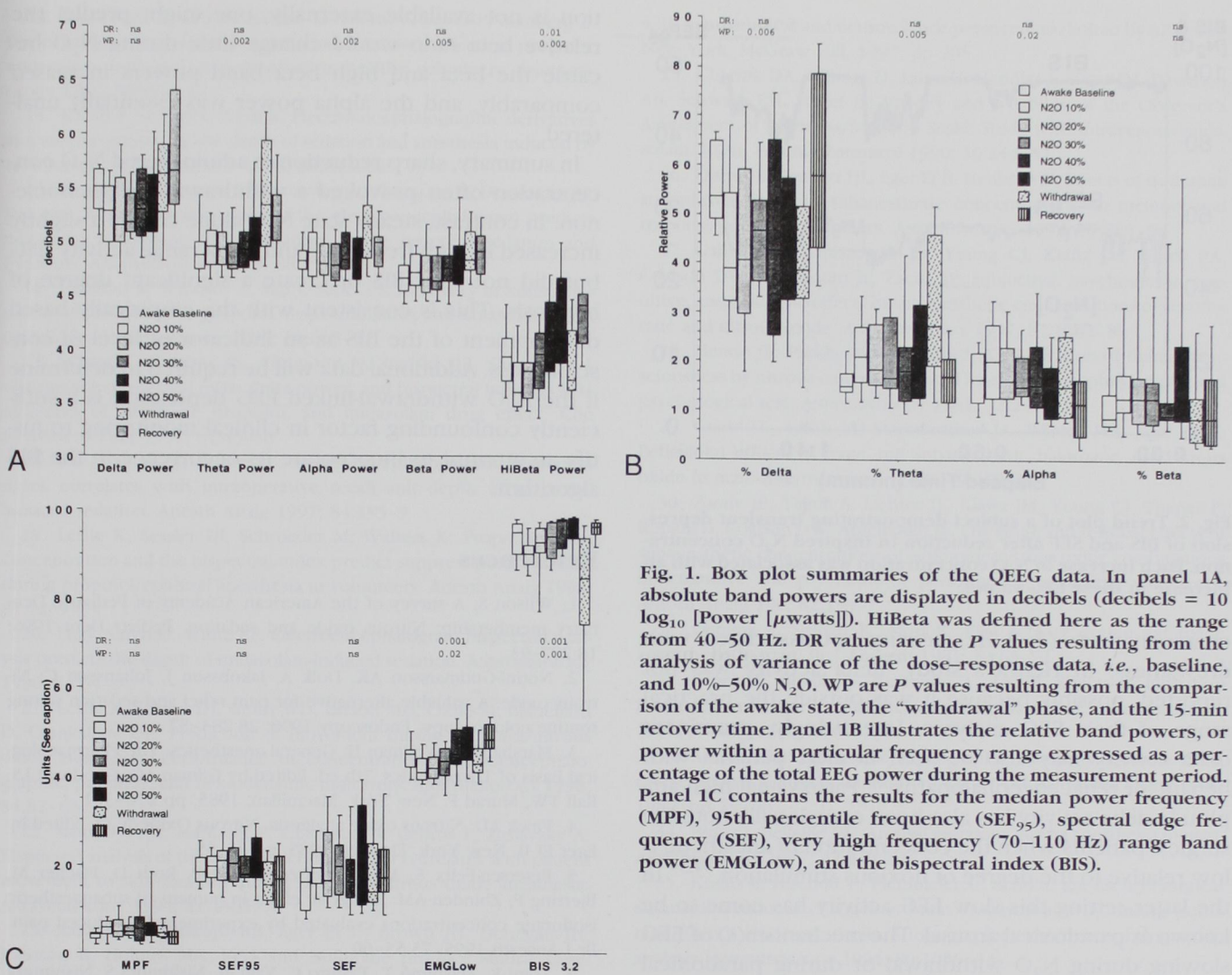

Fig. 1. Box plot summaries of the QEEG data. In panel 1A, absolute band powers are displayed in decibels (decibels = 10 $\log_{10}$ [Power [μwatts]]). HiBeta was defined here as the range from 40–50 Hz. DR values are the *P* values resulting from the analysis of variance of the dose–response data, *i.e.*, baseline, and 10%–50% N_2O. 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 (SEF_{95}), spectral edge frequency (SEF), very high frequency (70–110 Hz) range band power (EMGLow), and the bispectral index (BIS).

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

Avramov *et al.*[12] reported that initiation of 65% N_2O was associated in 12 of 13 patients with onset of continuous, high amplitude delta activity that persisted for an average 13 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 N_2O 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 N_2O concentration, as well as concurrent surgery and mechanical ventilation in the earlier study.

In two subjects, abrupt reduction in inspired N_2O 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[31] or opioids[32] or after brain injury.[33] With these etiologies, delta wave EEG activity is associated with altered mentation. Delta activity and depression of BIS occurred transiently during withdrawal of N_2O 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 Henrie.[28] In that study, withdrawal of N_2O was associated with a transient, paroxysmal in-

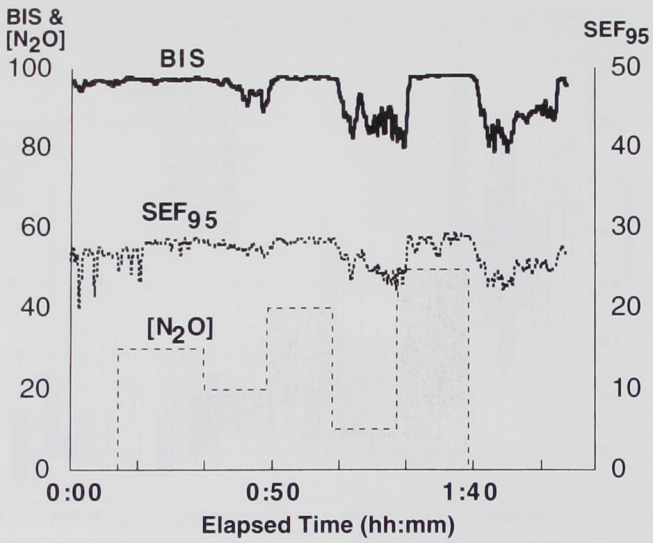

Fig. 2. Trend plot of a subject demonstrating transient depression of BIS and SEF after reduction in inspired N_2O concentration. Each increase in N_2O concentration was associated with an increase in these EEG values.

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.[33] 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.[34,35] In the latter setting this slow EEG activity has come to be known as paradoxical arousal. The mechanism(s) of EEG slowing during N_2O withdrawal or during paradoxical arousal remain speculative as is a putative mechanistic link between them. Nonetheless, based on our current results and previous reports of divergent pharmacologic effects, we propose that N_2O 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.[36] 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 N_2O because the beta and high beta band powers increased comparably, and the alpha power was essentially unaltered.

In summary, sharp reduction in administered N_2O concentration often provoked a withdrawal-like phenomenon. In contrast, steady state N_2O 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 N_2O 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

1. Wilson S: A survey of the American Academy of Pediatric Dentistry membership: Nitrous oxide and sedation. Pediatr Dent 1996; 18:287–93

2. Notini-Gudmarsson AK, Dolk A, Jakobsson J, Johansson C: Nitrous oxide: A valuable alternative for pain relief and sedation during routine colonoscopy. Endoscopy 1996; 28:283–87

3. Marshall BE, Wollman H: General anesthetics, The Pharmacological Basis of Therapeutics, 7th ed. Edited by Gilman AG, Goodman LS, Rall TW, Murad F. New York, Macmillan, 1985, pp 276–301

4. Finck AD: Nitrous oxide analgesia, Nitrous Oxide/N_2O. Edited by Eger EI II. New York, Elsevier, 1985, pp 41–55

5. Petersen-Felix S, Arendt-Nielsen L, Bak P, Roth D, Fischer M, Bjerring P, Zbinden AM: Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by experimentally induced pain. Br J Anaesth 1995; 75:55–60

6. Tomi K, Mashimo T, Tashiro C, Yagi M, Nishimura S, Nishimura M, Yoshiya I: Alterations in pain threshold and psychomotor response associated with subanesthetic concentrations of inhaled anaesthetics in humans. Br J Anaesth 1993; 70:684–6

7. Ebert TJ: Differential effects of nitrous oxide on baroreflex control of heart rate and peripheral sympathetic nerve activity in humans. ANESTHESIOLOGY 1990; 72:16–22

8. Fukunaga AF, Epstein RM: Sympathetic excitation during nitrous oxide-halothane anesthesia in the cat. ANESTHESIOLOGY 1973; 39:23–36

9. Ebert TJ, Kampine JP: Nitrous oxide augments sympathetic outflow: direct evidence from human peroneal nerve recordings. Anesth Analg 1989; 69:444–9

10. Hornbein TF, Eger EI II, Winter PM, Smith G, Wetstone D, Smith KH: The minimum alveolar concentration of nitrous oxide in man. Anesth Analg 1982; 61:553–6

11. Yamamura T, Fukuda M, Takeya H, Goto Y, Furukawa K: Fast oscillatory EEG activity induced by analgesic concentrations of nitrous oxide in man. Anesth Analg 1981; 60:283–8

12. Avramov MN, Shingu K, Mori K: Progressive changes in electroencephalographic responses to nitrous oxide in humans: A possible acute drug tolerance. Anesth Analg 1990; 70:369–74

13. Glass PSA, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane and alfentanil in healthy volunteers. ANESTHESIOLOGY 1997; 86:836–47

14. Katoh T, Suzuki A, Ikeda K: Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. ANESTHESIOLOGY 1998; 88:642–50

15. Kearse LAJ, Rosow C, Zaslavsky A, Connors P, Dershwitz M, Denman W: Bispectral analysis of the electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. ANESTHESIOLOGY 1998; 88:25–34

16. Flaishon R, Windsor A, Sigl J, Sebel PS: Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique. ANESTHESIOLOGY 1997; 86:613–9

17. Billard V, Gambus PL, Chamoun N, Stanski DR, Shafer SL: A comparison of spectral edge, delta power, and bispectral index as EEG measures of alfentanil, propofol, and midazolam drug effect. Clin Pharmacol Ther 1997; 61:45–58

18. Liu J, Singh H, White PF: Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. Anesth Analg 1997; 84:185–9

19. Leslie K, Sessler DI, Schroeder M, Walters K: Propofol blood concentration and the bispectral index predict suppression of learning during propofol/epidural anesthesia in volunteers. Anesth Analg 1995; 81:1269–74

20. Liu J, Singh H, White PF: Electroencephalogram bispectral analysis predicts the depth of midazolam-induced sedation. ANESTHESIOLOGY 1996; 84:64–9

21. Leslie K, Sessler DI, Smith WD, Larson MD, Ozaki M, Blanchard D, Crankshaw DP: Prediction of movement during propofol/nitrous oxide anesthesia. Performance of concentration, electroencephalographic, pupillary, and hemodynamic indicators. ANESTHESIOLOGY 1996; 84:52–63

22. Kearse LA Jr, Manberg P, Chamoun N, deBros F, Zaslavsky A: Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia. ANESTHESIOLOGY 1994; 81:1365–70

23. Rampil IJ, Weiskopf RB, Eger EI II, Brown JH, Donegan JH, Johnson B, Holmes MA: I653 and isoflurane produce similar dose-related depression of the EEG. ANESTHESIOLOGY 1988; 69:298–302

24. Rampil IJ: Electroencephalogram, Textbook of Neuroanesthesia with neurosurgical and neuroscience perspectives. Edited by Albin MS. New York, McGraw Hill, 1997, pp 205

25. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51

26. Dwyer R, Bennett HL, Eger EI II, Heilbron D: Effects of isoflurane and nitrous oxide in subanesthetic concentrations on memory and responsiveness in volunteers. ANESTHESIOLOGY 1992; 77:888–98

27. Galinkin JL, Janiszewski D, Young CJ, Klafta JM, Klock PA, Coalson DW, Apfelbaum JL, Zacny JP: Subjective, psychomotor, cognitive, and analgesic effects of subanesthetic concentrations of sevoflurane and nitrous oxide. ANESTHESIOLOGY 1997; 87:1082–8

28. Henrie JR, Parkhouse J, Bickford RG: Alteration of human consciousness by nitrous oxide as assessed by electroencephalography and psychological test. ANESTHESIOLOGY 1961; 22:247–59

29. Cook TL, Smith M, Starkweather JA, Winter PM, Eger EI II: Behavioral effects of trace and subanesthetic halothane and nitrous oxide in man. ANESTHESIOLOGY 1978; 49:419–24

30. Zacny JP, Yajnik S, Lichtor JL, Klafta JM, Young CJ, Thapar P, Rupani G, Coalson DW, Apfelbaum JL: The acute and residual effects of subanesthetic concentrations of isoflurane/nitrous oxide combinations on cognitive and psychomotor performance in healthy volunteers. Anesth Analg 196; 82:153–7

31. Oshima E, Shingu K, Mori K: EEG activity during halothane anaesthesia in man. Br J Anaesth 1981; 53:65–72

32. Sebel PS, Bovill JG, Wauquier A, Rog P: Effects of high-dose fentanyl anesthesia on the electroencephalogram. ANESTHESIOLOGY 1981; 55:203–11

33. Aminoff MJ: Electroencephalography, Electrodiagnosis in Clinical Neurology. Edited by Aminoff MJ. New York, Churchill Livingstone, 1980, pp 23–66

34. Bimar J, Bellville JW: Arousal reactions during anesthesia in man. ANESTHESIOLOGY 1977; 47:449–54

35. Kochs E, Bischoff P, Pichlmeier U, Schulte am Esch J: Surgical stimulation induces changes in brain electrical activity during isoflurane/nitrous oxide anesthesia. A topographic electroencephalographic analysis. ANESTHESIOLOGY 1994; 80:1026–34

36. Rampil IJ: A primer for EEG signal processing in anesthesia. ANESTHESIOLOGY 1998; 89:(In press)