J Anesth (2005) 19:102–105
DOI 10.1007/s00540-004-0295-8

Journal of
Anesthesia

The bispectral index predicts responsiveness to verbal commands in patients emerging from nitrous oxide anesthesia supplemented with a subhypnotic concentration of isoflurane

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Abstract
Purpose. Nitrous oxide (N_2O) administered alone has minimal effects on the bispectral index (BIS), an electroencephalogram-derived parameter of hypnosis. However, because this gas is commonly supplemented with a volatile anesthetic, we sought to determine how it would affect the BIS when coadministered with a low concentration of isoflurane.
Methods. Twelve patients were anesthetized with 70% N_2O + 0.2% isoflurane (all concentrations are end-tidal). Following the end of surgery, the concentration of N_2O was decreased in decrements of 10% while isoflurane was continued at 0.2%, and each new concentration of N_2O was maintained for 15 min. This procedure was repeated until the patients first opened their eyes or squeezed the investigator's hand on command.
Results. N_2O 70% + isoflurane 0.2% reduced the BIS to 68 ± 9 (mean ± SD). When the concentration of N_2O was decreased toward awakening (which occurred at the N_2O concentration of 36% ± 8%), the BIS progressively increased until it reached 93 ± 5 on awakening.
Conclusion. The BIS reflects the level of hypnosis during N_2O anesthesia supplemented with a low concentration of isoflurane.

Key words Nitrous oxide · Electroencephalography · Bispectral index · Spectral analysis

Introduction

It has been demonstrated that nitrous oxide (N_2O) administered alone has minimal effects on the bispectral index (BIS) [1–3], an electroencephalogram (EEG)-derived univariate parameter specifically reflecting the level of hypnosis [4]. Extrapolation of this finding to clinical practice requires caution, however, because clinicians commonly supplement N_2O with another potent hypnotic to compensate for its weak hypnotic properties. Because such supplemental agents are rarely completely washed out from the brain at the time of emergence, it would be clinically relevant to investigate the effects of N_2O on the BIS in the presence of a low concentration of a hypnotic agent.

The aim of this study was to characterize how decreasing concentrations of N_2O would affect the BIS during emergence from anesthesia when isoflurane was co-administered at a fixed concentration of 0.2%. This isoflurane concentration was chosen as 0.5 times the minimum alveolar concentration (MAC)-awake [5–7], where MAC-awake is the concentration preventing voluntary response to simple verbal command in 50% of the population.

Patients and methods

Patient selection, anesthetic management, and data acquisition were similar to those described in our previous investigation [8] with slight modifications. Briefly, following institutional approval and written informed consent, 12 ASA Physical Status I or II women who were aged 38–56 years and were scheduled to have general and epidural anesthesia for elective total abdominal or vaginal hysterectomy were studied. In addition to routine monitoring devices, the EEG signal was acquired using four electrodes (Zipprep; Aspect Medical Systems, Natick, MA, USA). The BIS (version 3.22) and the 95% spectral edge frequency (SEF_{95}) were obtained using an Aspect EEG monitor (model A-1050; Aspect Medical Systems). The concentrations of N_2O, isoflurane, and CO_2 were measured using an infrared analyzer (Capnomac Ultima, Datex, Helsinki, Finland).

After obtaining the stable baseline EEG with the patient's eyes closed, anesthesia was induced using propofol 2.5 mg · kg^{-1} intravenously (i.v.) and the

Address correspondence to: T. Goto
Received: May 24, 2004 / Accepted: December 10, 2004

trachea was intubated with the aid of vecuronium 10 mg i.v. Anesthesia was then maintained using 70% N_2O and 0.2% isoflurane (all concentrations of inhalational anesthetics are end-tidal unless specified). The patients also received a continuous epidural infusion of 1.5% mepivacaine containing 1:200 000 epinephrine to maintain the mean arterial pressure and heart rate within 20% of the preoperative values.

Shortly before the end of surgery, residual neuromuscular blockade was antagonized with neostigmine 2.5 mg and atropine 1.0 mg i.v. When surgery was completed, a designated investigator blinded to the EEG data asked the patient in a normal tone to open her eyes and to squeeze and release the investigator's hand. If the patient failed to follow both these commands, the end-tidal concentration of N_2O was reduced by 10% while that of isoflurane was maintained at 0.2% until the patient awoke. The new concentration of N_2O was maintained for 15 min. During this period, the patient's ability to respond to verbal commands was checked every 5 min and whenever clinical signs of imminent awakening such as coughing, bucking, or frowning were noted. If no response was observed for the entire 15-min period, the concentration of N_2O was reduced again. This process was repeated until an alveolar concentration was reached at which the patient first appropriately responded to either one of the commands. This concentration was termed the awakening concentration (C_{awake}).

The BIS and SEF_{95} values at each concentration where no response to verbal command was observed during the entire 15-min equilibration period were calculated by averaging the values obtained over the last 3 min of that period. The values at the C_{awake} were those obtained immediately before the patient responded to a verbal command. The data from the right- and left-sided electrodes were averaged.

Fifteen minutes after extubation, the epidural block level to pinpricks was examined, and the patient was asked to rate her incisional pain using a 0–10 verbal rating scale, with 0 and 10 being no pain and the worst pain imaginable, respectively.

The results were reported as mean ± standard deviation (SD) and/or median (range). One-way repeated-measures analyses of variance (ANOVA) were used to compare the BIS values and the SEF_{95} across five different N_2O concentrations: preinduction, 70%, 20% + C_{awake}, 10% + C_{awake}, and C_{awake}. Note that the C_{awake} used here is the concentration for each individual patient. The data at the N_2O concentration of 30% + C_{awake} were not included in the analysis because one patient awoke at the N_2O concentration of 50% and therefore the highest N_2O concentration studied (70%) corresponded to only 20% + C_{awake}. For post hoc comparisons, paired *t* tests with Bonferroni's correction were used. All the statistical analyses were performed using StatView 5 (SAS Institute, Cary, NC, USA). A *P* value less than 0.05 was considered statistically significant.

Results

The patients' demographic and postoperative data are summarized in Table 1. One, 4, 6, and 1 patient(s) awoke at N_2O concentrations of 20%, 30%, 40%, and 50%, respectively. Therefore, the mean C_{awake} was 36% ± 8%.

One-way repeated measures ANOVAs revealed highly significant changes in both the BIS and the SEF_{95} with varying concentrations of N_2O (both $P < 0.001$; Fig. 1). The BIS decreased from 96 ± 3 before induction of anesthesia to 68 ± 9 during administration of N_2O 70% + isoflurane 0.2% ($P < 0.01$; post hoc paired *t* test). As the concentration of N_2O was decreased, the BIS increased progressively to the preinduction level. Compared with the value at C_{awake} (93 ± 5), even the BIS at the N_2O concentration 10% higher than the C_{awake} (88 ± 6) was significantly smaller ($P < 0.01$). The SEF_{95} also increased progressively with decreasing concentrations of N_2O. However, the SEF_{95} during the anesthetic maintenance with N_2O 70% + isoflurane 0.2% was not different from the preinduction value (21 ± 5 versus 22 ± 4 Hz), and the SEF_{95} at C_{awake} (27 ± 3 Hz) was only modestly greater than that during maintenance.

All the 12 patients completed the study uneventfully. No patient had recall of intraoperative events when interviewed postoperatively.

Discussion

We have demonstrated that (1) 70% N_2O administered together with the 0.5 MAC-awake concentration of isoflurane (0.2%) decreases the BIS to the level indica-

Table 1. Patient demographics and postoperative data

Age (years)	48 ± 6
Height (cm)	157 ± 6
Weight (kg)	61 ± 11
Duration of anesthesia (min)	167 ± 60
Esophageal temperature (°C)	36.0 ± 0.1
Epidural dose (ml)	29 ± 8
Epidural level	T8 [T4–T10]
Pain rating	2 [0–5]

The epidural dose is the total volume of 1.5% mepivacaine with 1:200 000 epinephrine administered epidurally until 15 min after extubation. The pain rating was the numerical quantification of incisional pain by the patient using a 0–10 verbal rating scale, with 0 and 10 being no pain and the worst pain imaginable, respectively. Data are mean ± SD or median [range]

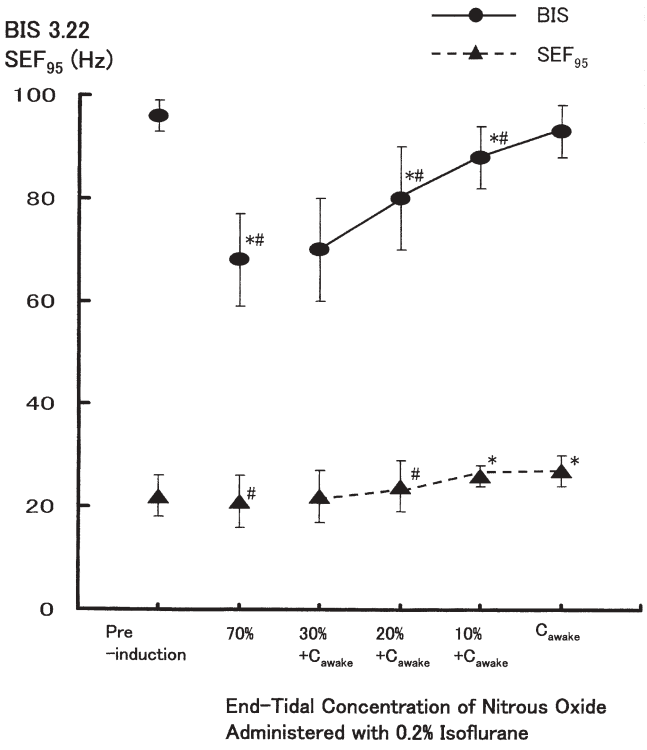

Fig. 1. The changes in the bispectral index (*BIS*) and 95% spectral edge frequency (SEF_{95}) with decreasing concentrations of nitrous oxide in the presence of 0.2% isoflurane. Data represent means ± SD. C_{awake} is the concentration at which each individual patient first responded to the verbal command. * $P < 0.05$ versus preinduction; # $P < 0.05$ versus C_{awake}. The data at 30% + C_{awake} were not included in the statistical analyses (see text)

tive of light hypnosis; and that (2) decreasing the N_2O concentration from that level toward awakening is associated with a progressive increase in the BIS.

The first finding is consistent with that of Nakayama et al. [9], who demonstrated that the BIS value was lower when 67% N_2O was administered with 0.5%–2% sevoflurane than when the same concentration of sevoflurane was used alone. On the other hand, our results may appear contradictory to the previous reports where N_2O administered alone minimally affected the BIS [1–3]. Several mechanisms may account for this discrepancy. First, the level of anesthesia we examined was deeper than those tested by the previous investigators. In our study, the subjects were always unresponsive to verbal commands except at the lightest stage of anesthesia (i.e., C_{awake}). Furthermore, because the average C_{awake} of N_2O in the presence of 0.2% isoflurane was 36%, the maximum anesthetic level we studied (70% N_2O + 0.2% isoflurane) exceeded the C_{awake} by 34% in terms of the absolute N_2O concentration. In contrast, the maximum concentrations of N_2O used in the previous studies where N_2O was the sole anesthetic were only marginally higher (70%) [2,3] or even lower (50%) [1] than the MAC-awake of N_2O (66%) [5]. In fact, in the study where up to 50% N_2O was administered [1], all the subjects remained cooperative and responsive all the time. This finding suggests that the degree of hypnosis was simply insufficient to produce any decrease in the BIS in that study [1].

Second, N_2O may differently affect the EEG when administered as a sole agent or in combination with another volatile anesthetic. When administered alone, N_2O tends to activate the EEG: it increases the EEG spectral power in the high-beta (40–50 Hz) frequency range [1] and produces fast (~35 Hz) oscillatory activity [10]. In contrast, N_2O slows the EEG when added to halothane or isoflurane [11] and decreases the concentration of isoflurane required to suppress the median EEG frequency to 2.5 Hz [12]. Such differential effects of N_2O would naturally result in the different alterations in the BIS because the BIS heavily depends on the high-frequency (30 or 40–47 Hz) component of EEG [4]. However, this remains speculative because the exact algorithm for the BIS computation has not been published in detail.

The third mechanism may be related to the possible development of acute tolerance to the EEG-activating effects of N_2O [13]. All the previous studies [1–3] measured the N_2O effects shortly after the start of its administration. On the other hand, the mean time from the start of N_2O administration until the measurement in our study was more than 2 h, a sufficient time for acute tolerance to develop [13].

The SEF_{95} changed much less markedly than did the BIS with decreasing concentrations of N_2O. In fact, although the BIS at 70% N_2O + 0.2% isoflurane was lower than the awake preinduction value, the SEF_{95} did not differ between these two levels. This result implies that the BIS may be more useful than SEF_{95} in measuring the depth of anesthesia during N_2O-isoflurane anesthesia.

This study has several limitations. First, we used only one concentration (0.2%) of isoflurane. It remains unclear whether N_2O has the same effects on the BIS when combined with different concentrations of isoflurane. Second, we used epidural analgesia, which may affect the sensitivity of the brain to general anesthetics [14]. However, it has recently been shown that epidural analgesia does not disturb the relationship between the BIS and the desflurane concentration [15]. Third, we studied only females, although the relationship between the dose of anesthetics and the BIS may be sex dependent [16].

In summary, N_2O reduced the BIS when combined with a low (0.2% or 0.5 times MAC-awake) concentration of isoflurane. Decreasing the concentration of N_2O toward awakening permitted the BIS to increase

progressively, although the SEF_{95} changed little. These results suggest that the BIS may be a useful index of the level of hypnosis during N_2O-isoflurane anesthesia.

Acknowledgment. Supported in part by the Japanese Ministry of Education Grant #09877310 to TG. The authors do not consult for, accept honoraria from, or own stock or stock options in any company related to this research.

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