Nitrous oxide does not alter bispectral index: study with nitrous oxide as sole agent and as an adjunct to i.v. anaesthesia

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We have studied the effect of nitrous oxide on bispectral index (BIS), calculated from a bipolar encephalogram. Inhalation of 70% nitrous oxide resulted in loss of consciousness in all healthy volunteers ($n=10$) but no change in BIS. Brief inhalation up to 1.2% sevoflurane also resulted in loss of consciousness in volunteers ($n=5$), but with sevoflurane, BIS decreased. BIS and the haemodynamic effects of adding nitrous oxide were also measured during coronary artery bypass surgery in patients ($n=10$) receiving midazolam and fentanyl infusions. Measurements were made after 0%, 33%, 66% and 0% nitrous oxide, just before skin incision and after sternotomy. Nitrous oxide caused no change in BIS. BIS may indicate a sufficient hypnotic depth to prevent awareness during surgery, but our study demonstrated that pharmacological unconsciousness–hypnosis can also be reached by mechanisms to which BIS is not sensitive. Thus BIS is a sufficient but not a necessary criterion for adequate depth of anaesthesia or prevention of awareness.

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Nitrous oxide is used commonly both as an adjunct to balanced general anaesthesia and as the sole agent in dental and obstetric anaesthetic practice. When used as an adjunct, the resulting MAC reduction for the other anaesthetic agents is reliable and has been well described.[1 2]

The need to guarantee prevention of awareness during surgery has indicated the requirement for more reliable measures of an adequate hypnotic effect than the traditionally used clinical signs. Bispectral index (BIS) is a novel neurophysiological variable, calculated from a bipolar electroencephalogram (EEG), which has been shown to correlate reliably with drug concentration and depth of sedation produced by propofol, midazolam, isoflurane[3–5] and sevoflurane[6]. Nitrous oxide, in concentrations up to 50%, has been shown to have no effect on BIS in human volunteers.[7]

We have investigated the effect of nitrous oxide on BIS in human subjects. BIS was measured in a group of healthy volunteers sedated to loss of consciousness solely with nitrous oxide. In a group of patients, the added effect on BIS was also determined for nitrous oxide as an adjunct to i.v. midazolam–fentanyl anaesthesia during coronary artery bypass grafting (CABG) surgery.

Patients and methods

Volunteers and patients were examined after informed consent and approval from the Local Ethics Committee of Karolinska Hospital.

The effect of nitrous oxide on BIS was studied in two groups. We studied 10 healthy volunteers (mean age 40.9, range 27–52 yr) after a 6 h fast (group I). BIS (Aspect Medical Systems, Natick, MA, USA) was calculated continuously from two bipolar electroencephalographic channels (Fpz–F7, FpZ–F8) using four ZipPrep electrodes (Aspect Medical Systems) applied to the scalp after mild abrasion. Heart rate, oxygen saturation and inspired–expired gas concentrations (Capnomac Ultima; Datex, Helsinki, Finland) were recorded continuously. A Bain system with a fresh gas flow of 10 litre min^{-1} was used and volunteers breathed through a face mask held by an investigator (J. J.). Baseline measurements were made after resting for 5 min in the supine position. Nitrous oxide was introduced and slowly increased in increments of 10% to a maximal concentration of 70%. Measurements were made when end-tidal nitrous oxide concentrations stabilized at each 10% increment. Loss of consciousness was determined as loss of response to verbal commands.

Five individuals from the same volunteer group (mean age 45.4, range 40–47 yr) were investigated as above but with sevoflurane as the sole anaesthetic agent. Sevoflurane has been studied previously by others[6] and this group was included only as a validation of the study procedure. At least 1 week elapsed between the two study occasions. Sevoflurane was titrated in increments of 0.2% and measurements were made when end-tidal sevoflurane concentration was stable. The end-point was 0.6 MAC or 1.2% sevoflurane.

In group II, we studied 10 patients (mean age 65.8, range 53–79 yr) during elective CABG surgery. None had complicating diseases or a previous neurological history. Patients were premedicated with morphine 7.5–12.5 mg, and after induction of anaesthesia with midazolam 0.05 mg kg^{-1} and fentanyl 0.01 mg kg^{-1}, pancuronium 0.1 mg kg^{-1} was given to facilitate tracheal intubation The Servo 900D ventilator, using oxygen in air, was adjusted to ventilate the lungs so as to achieve normocapnia. Anaesthesia was maintained with a continuous infusion of midazolam 3 mg h^{-1} and fentanyl 0.3 mg h^{-1}. BIS (measured as for the volunteers described above), ECG, heart rate (HR), invasive arterial pressure and inspired–expired gas concentrations (TRAM Critical Care Monitor, Marquette Electronics, Milwaukee, WI, USA) were monitored continuously and arterial blood-gas values intermittently. Rate–pressure product (RPP) was calculated (HR×mean systemic arterial pressure).

BIS baseline values were recorded before and after intubation. The effect of nitrous oxide on BIS was recorded once after induction of anaesthesia but before the start of surgery and once during dissection of the left internal thoracic artery. Four measurements were made on each occasion: baseline measurement with no nitrous oxide, after stable end-tidal concentrations of 33% and 66% nitrous oxide were reached, and finally 15 min after nitrous oxide had been discontinued and end-tidal nitrous oxide had returned to zero.

Statistical analysis

Results are presented as mean (SD or range). BIS was shown to be normally distributed and therefore parametric statistics were used. Changes in BIS, HR, arterial pressure and RPP before and during nitrous oxide exposure in the CABG patients were analysed by ANOVA. The effect of increasing end-tidal concentration of nitrous oxide and sevoflurane on BIS in volunteers was studied by regression analysis. $P<0.05$ was considered statistically significant.

Results

In group I, all volunteers ($n=10$) reached loss of response to verbal command at or less than 70% nitrous oxide, but BIS did not change (Fig. 1). Slight excitement was noted in most volunteers at concentrations of 40–50%, as was increased ventilatory frequency. After cessation of nitrous oxide, all volunteers woke up within 1–3 min. All felt clearheaded and well but described various sensations experienced during exposure to nitrous oxide. Emesis did not occur but three subjects suffered nausea. All experienced a period of complete amnesia.

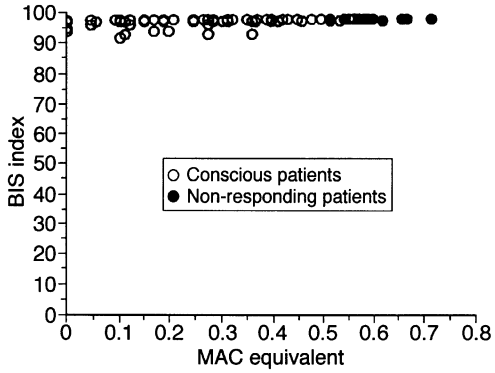

Fig 1 Effects of increasing concentrations of nitrous oxide on bispectral index (BIS) in healthy volunteers ($n=10$).

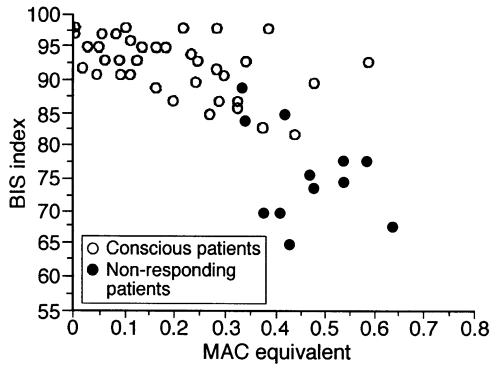

Fig 2 Effects of increasing concentrations of sevoflurane on bispectral index (BIS) in healthy volunteers ($n=5$).

Figure 2 shows the results for volunteers inhaling sevoflurane ($n=5$). Regression analysis showed a linear relationship between BIS and end-tidal sevoflurane concentration. All volunteers reached loss of response to verbal command by about the MAC-equivalent of 0.5. The clinical effect of sevoflurane inhalation in one volunteer is shown in Figure 3.

In group II, BIS decreased with induction of anaesthesia to a mean value of 45 (range 32–59; $n=10$). Nitrous oxide did not alter BIS either with or without surgical stimulation (Table 1). The haemodynamic effects of nitrous oxide were small and no significant changes were induced by addition of nitrous oxide. Increases in HR and RPP were seen after initiation of surgery (ANOVA, $P<0.05$) (Table 1).

Discussion

In this study, designed to investigate the effect of nitrous oxide on bispectral index (BIS) both as a sole anaesthetic and as an adjunct to general i.v. anaesthesia, we have demonstrated that loss of consciousness (defined as loss of response to verbal command) after nitrous oxide did not result in a change in BIS. Deepening of general i.v.

anaesthesia by adding nitrous oxide also did not alter BIS. In contrast, BIS decreased after brief inhalation of sevoflurane in a dose-dependent manner, and the BIS value at loss of response to verbal command was well below 90 in all subjects.

Recent investigations of awareness during surgery emphasized the distinction between analgesic and hypnotic components of general anaesthesia.[8] While haemodynamic and sympathetic indicators of pain seem to be adequate monitors of analgesia, guaranteeing a lack of awareness and not just amnesia has been more difficult.

BIS is a single numerical value (0–100) calculated from bipolar encephalography using an algorithm[9] which includes the frequencies and amplitudes of the raw EEG signals and is also sensitive to inter-relations between EEG components. It was developed to quantify hypnotic depth and has been shown to correlate well with the degree of sedation using several general anaesthetics.[3–5] One of the major goals for devices measuring depth of anaesthesia is to ascertain an adequate, but not excessive, depth of anaesthesia, regardless of drug combination or dose. Such devices make it possible to optimize the delivery of drug to each individual patient, to guarantee an adequate depth of anaesthesia, loss of awareness and recall. The clinical goal is to tailor drug delivery in order to minimize drug administration, to avoid inappropriately deep anaesthesia with undesirable respiratory and cardiovascular side effects, and to facilitate the recovery process.

Previous bispectral studies have shown that BIS decreased in a dose-dependent manner with isoflurane, propofol and midazolam. Clinically more important, however, BIS has also been correlated with increasing levels of sedation and has been shown to correlate even better with sedation scores than with hypnotic–anaesthetic drug concentrations.[3–6] For nitrous oxide we did not find any relationship between BIS and end-tidal concentration or loss of response to verbal command.

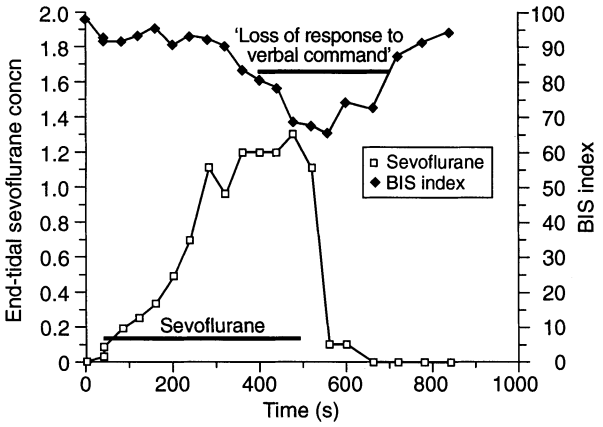

Fig 3 Effects of increasing concentrations of sevoflurane on bispectral index (BIS) in one volunteer.

Our results confirm earlier findings suggesting that loss of consciousness can occur through various mechanisms and with varying effects on the EEG. Rampil and colleagues[7] have recently demonstrated that in young volunteers, 50% nitrous oxide produced little sedation and no change in BIS. However, they observed activation in certain spectral regions of the EEG not detected by the BIS algorithm and therefore proposed that nitrous oxide has both excitatory and inhibitory CNS effects. Our findings agree with their hypothesis that nitrous oxide concentrations greater than 50% lead to sedation–hypnosis, but the EEG changes they predicted were not supported by our findings. At 70% nitrous oxide, all 10 volunteers had loss of reaction to verbal command and recall but with no alteration in BIS. Our results agree with those of Rampil and colleagues[7] that BIS is 'an indicator of level of consciousness', but that nitrous oxide exemplifies a mechanism of loss of consciousness to which BIS is not sensitive. However, this study cannot exclude the possibility that higher nitrous oxide partial pressures, such as in a pressure chamber, would produce changes in BIS during deeper sedation.

The mechanism of action of nitrous oxide is still not completely understood. At least part of the effect is believed to be mediated via release of endogenous neuromediators.[10] Both endorphin and norepinephrine release are stimulated by nitrous oxide.[10] For a given level of sedation or hypnosis, differences in EEG effects elicited by nitrous oxide and other potent anaesthetics may reflect differences in the mechanisms involved.

Other neurophysiological studies have shown varying effects of nitrous oxide. Only minor effects have been seen on auditory evoked potentials.[11] Effects on mid-latency auditory evoked responses have been shown to be less for nitrous oxide compared with isoflurane at MAC equivalent concentrations.[12 13] However, nitrous oxide had effects on the somato-evoked response (N20 wave) which were more pronounced than those of isoflurane.[13 14]

Table 1 Effects of addition of 33% and 66% end-tidal nitrous oxide (N_2O) during i.v. anaesthesia with fentanyl–midazolam before (prep.) and during surgical stimulation (mean (SD)). MAP=Mean arterial pressure; RPP=rate–pressure product; BIS=bispectral index

	0% N_2O postind.	**33% N_2O prep.**	**66% N_2O prep.**	**0% N_2O prep.**	**Baseline N_2O surgery**	**33% N_2O surgery**	**66% N_2O surgery**	**0% N_2O surgery**
Heart rate (beat min^{-1})	65.4 (13.5)	61.1 (11.9)	59.1 (11.8)	57.6 (10.6)	72.6 (15.1)	71.4 (15.0)	70.6 (17.4)	70.3 (15.7)
MAP (mm Hg)	74.9 (13.1)	72.9 (13.6)	68.3 (9.7)	72 (10.9)	88.3 (15.4)	82.7 (12.8)	77.6 (13.2)	75 (9.8)
RPP	4933 (1430)	4544 (1531)	4071 (1099)	4190 (1133)	6518 (2153)	6007 (1868)	5582 (2049)	5332 (1592)
BIS	45.7 (8.8)	47 (9.5)	45.6 (7.4)	44.1 (7.4)	51.2 (12.1)	43.8 (6.5)	45.4 (7.4)	42.2 (5.9)

In the clinical part of our study, we investigated the effect of nitrous oxide in patients undergoing CABG surgery in whom an adequate depth of anaesthesia had been achieved using i.v. agents. We studied the effect on BIS of adding 33% and 66% nitrous oxide both before and during surgical stimulation. BIS was not affected by addition of nitrous oxide.

Nitrous oxide in combination with more potent anaesthetics has been studied previously. Both Porkkala and colleagues and Yli-Hankala and colleagues have shown that nitrous oxide antagonized the depressant effects of isoflurane on the EEG.[14 15] In a study of the effects of nitrous oxide on the concentration of isoflurane required to achieve a constant median EEG frequency of 2–3 Hz, Rökcke and Schwilden found that increasing concentrations of nitrous oxide decreased isoflurane requirements in a linear manner but far less than was anticipated from clinical MAC studies.[16] The interaction between nitrous oxide and other anaesthetics on BIS has, however, not been studied systematically. Sebel and colleagues found that BIS values, when isoflurane was used in combination with nitrous oxide, were higher compared with isoflurane when used alone, without nitrous oxide.[17] Analogous effects were observed in a study by Kearse and colleagues[5] who showed that addition of nitrous oxide to propofol increased the BIS value at which patients did not respond to verbal command.

The lack of effect on BIS of adding nitrous oxide during anaesthesia may also be explained in part by a lower 'sensitivity' for effects beyond adequate sedation. In the study by Katoh, Suzuki and Ikdea, BIS correlated almost linearly with increasing sevoflurane concentration in sedative doses at which BIS values decreased.[6] However, at sevoflurane concentrations greater than 1.4%, BIS no longer decreased with increasing concentration.[6] This aspect may also limit the conclusions which can be drawn from the clinical portion of our study.

Whether or not our results are important for the general use of BIS is hard to determine. Nitrous oxide is not potent enough to be used as a sole anaesthetic at atmospheric pressure. It is therefore important to understand the effects of nitrous oxide when combined with potent inhaled or i.v. anaesthetics. Studies on the interaction of nitrous oxide and various anaesthetics used in clinical practice on BIS are needed. Earlier studies suggest that BIS can indicate a sufficient hypnotic depth to prevent awareness during surgery, but we have demonstrated that pharmacological unconsciousness–hypnosis can also be reached by mechanisms to which BIS is not sensitive. BIS is thus a sufficient but not a necessary criterion for adequate depth of anaesthesia or prevention of awareness.

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