NITROUS OXIDE-MEDIATED ACTIVATION OF THE EEG DURING ISOFLURANE ANAESTHESIA IN PATIENTS

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SUMMARY

We have studied the effects of nitrous oxide on EEG burst suppression patterns during stable isoflurane anaesthesia in 13 ASA I patients. After induction of anaesthesia with propofol, the concentration of isoflurane was increased with continuous EEG monitoring to burst suppression level (mean end-tidal concentration of isoflurane, 1.7 (SD 0.2) %), and kept constant during the study. During surgery, isoflurane in air and oxygen (FIO₂ 0.35), or isoflurane in 65% nitrous oxide in oxygen were given to each patient for 30 min, in random order. EEG was recorded and digitized off-line. The proportion of EEG suppression time was measured after a washin or washout period of at least 15 min for nitrous oxide. There was a significant decrease in the proportion of EEG suppression time (from 69.5 to 43.7%) when air was replaced by nitrous oxide. We conclude that the EEG effects of isoflurane and nitrous oxide are not additive and that nitrous oxide opposes the depression of isoflurane on the central nervous system. (Br. J. Anaesth. 1993; 70: 54-57)

KEY WORDS


The effects of nitrous oxide on the electroencephalogram (EEG) during inhalation anaesthesia have been studied extensively. In a study using spectral analysis [1], there were no changes in the EEG from nitrous oxide when it was used in combination with other anaesthetics. Other studies, however, have reported a reduction of total EEG spectral power [2], or an increase in fast frequency EEG power bands [3] when inhalation anaesthesia was supplemented with nitrous oxide.

At 1.5–2.0 minimal alveolar concentration (MAC) of isoflurane anaesthesia, the EEG shows a burst suppression pattern—relatively silent EEG periods interrupted by high amplitude bursts [4]—which appear synchronously in the whole cortex [5]. When anaesthesia is deepened further, duration of suppressions increases and, finally, an isoelectric EEG results [4]. We have demonstrated that nitrous oxide slows the rhythm of EEG activity during isoflurane anaesthesia in man, without appearance of an EEG burst suppression pattern, when 1.5% end-tidal isoflurane anaesthesia is deepened with 65% nitrous oxide [6]. Recent animal studies have demonstrated the activation of EEG by nitrous oxide during burst suppression isoflurane anaesthesia [7, 8]. Rampil and colleagues have reported that nitrous oxide activates EEG during desflurane burst suppression anaesthesia in volunteers [9]. The effect of nitrous oxide on isoflurane burst suppression has not, however, been studied in humans. Therefore, we studied the effect of nitrous oxide on the EEG burst suppression pattern during isoflurane anaesthesia and surgery in healthy patients.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of Helsinki University Central Hospital. Thirteen healthy ASA I patients (table I) gave informed consent.

Anaesthesia

Patients were premedicated with oral diazepam 0.2 mg kg⁻¹ 90 min before induction of anaesthesia with propofol (mean) 1.8 (SD 0.2) mg kg⁻¹ i.v. Vecuronium was given for neuromuscular block and no anticholinergic agent was used. Positive pressure ventilation was performed via a tracheal tube, using a Servo respirator (Siemens–Elema, Sweden). Tidal volume was adjusted to maintain normocapnia (end-tidal carbon dioxide 5.0 kPa), measured with a Datex Capnomac monitor (Instrumentarium Ltd, Fin-

| Table I. Patient characteristics and operations (mean (SD) or range). Data for 13 patients |
|---------------------------------|-----------------|-----------------|
| Sex (M/F) | 9/4 |
| Age (yr) | 36.8 (26-49) |
| Weight (kg) | 72 (19) |
| Height (cm) | 164 (15) |
| Operation | |
| Breast surgery | 4 |
| Abdominal surgery | 9 |

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FIG. 1. Definition of the beginning of EEG burst and suppression. Burst onset at the short, down-pointing arrow. Suppression onset at the long, up-pointing arrow. Note the EEG notch at the beginning of suppression.

land). Arterial pressures were measured non-invasively with a Datex Normocap monitor at intervals of 3 min. Temperature was measured from the nasopharynx and normothermia was maintained using warming blankets. All patients were horizontal and supine during the study.

At first, isoflurane was delivered with oxygen in air (FIO2 0.35). Isoflurane concentrations were monitored on-line (Datex Capnomac). For each patient, the analyser was calibrated with a known concentration of isoflurane and carbon dioxide, and at 0%.

All the recordings were performed during the surgical procedure. After induction of anaesthesia, we waited 45 min to allow the effect of propofol to disappear. EEG was monitored continuously. Anaesthesia was deepened gradually to a point at which burst suppression occurred on the EEG (1.7 (0.2)% end-tidal isoflurane), and then kept constant during the study.

During two 30-min periods, isoflurane in air and oxygen (FIO2 0.35), and isoflurane and 65% nitrous oxide in oxygen (FIO2 0.35) was delivered to each patient. The initial gas mixture was selected at random. In seven patients, air and oxygen were given before challenge with nitrous oxide and oxygen, while the other patients received nitrous oxide and oxygen first. Analyses were performed on EEG data recorded after a washin or washout period of 15 min for nitrous oxide.

Signal recording and analysis

Silver-silver chloride dome EEG electrodes were placed in C2 and F3 positions (International 10–20 System). EEG was amplified and monitored with Datex ABM monitor (Instrumentarium, Finland, bandwidth 1.5–25 Hz (−3 dB)) and recorded on tape (Rascal FM tape recorder, Rascal, England). Event marks, such as turning on/off nitrous oxide, also were recorded on tape.

EEG and event mark signals were digitized offline at 200 samples s−1 per channel to a PC-compatible microcomputer. EEG burst–onset points and suppression-onset points were selected manually with a cursor on the computer screen. This selection was always performed by one of the authors (T.P.) unaware of the order of randomization. End-point of the burst was defined as the EEG notch, which is seen at the beginning of suppression (fig. 1).

As the recordings were made during routine surgical procedures, artefacts occurred randomly in the signal. Only bursts and suppressions completely devoid of artefact were included in the analysis. Recordings were analysed for duration of suppression, which was expressed as percentage of the sum of artefact-free bursts and suppressions in a 15-min period.

Statistics

Data were analysed using the computer software program BMDP (University of California, Berkeley, U.S.A.). The comparisons were tested with Wilcoxon’s matched-pairs signed-ranks test. The data are given as mean (SD). P < 0.05 was considered statistically significant.

RESULTS

The duration of EEG bursts and suppressions occurring in one patient is presented in figure 2. In the study group, the proportion of EEG suppression

Fig. 2. Duration of EEG bursts and suppressions in one patient. Both horizontal and vertical scales present time. Horizontal line = baseline. Bursts are presented as lines upwards, suppressions as down-pointing lines from the baseline. The long dotted vertical lines delimit the two EEG analysis periods. N2O = EEG analysis period during isoflurane–nitrous oxide–oxygen anaesthesia. Air = EEG analysis period during isoflurane–air–oxygen anaesthesia. The proportion of EEG suppression time was evaluated during nitrous oxide inhalation and after a wash-out period of 20 min for nitrous oxide. Note the rapid reduction in the duration of EEG bursts, when nitrous oxide exposure was replaced by air at the end of the first analysis period.
time was 69.5 (15.1)% during isoflurane–air–oxygen anaesthesia. This proportion decreased to 43.7 (33.1)% during isoflurane–nitrous oxide–oxygen anaesthesia ($P < 0.05$) (fig. 3). Mean length of EEG bursts changed from 10 (7) s to 24.8 (28) s ($P < 0.01$), and that of EEG suppressions from 22.7 (13) s to 20.8 (23) s (ns), when air was replaced by nitrous oxide.

The course of surgery was uneventful and without major bleeding in all patients. Mean arterial pressure and heart rate at the end of isoflurane–air–oxygen recording period were 73 (18) mm Hg and 82 (13) beat min⁻¹, respectively. The same figures at the end of nitrous oxide inhalation were 70 (16) mm Hg and 76 (13) beat min⁻¹, respectively (ns).

DISCUSSION

The present study shows that, when burst suppression isoflurane anaesthesia was supplemented by 65% nitrous oxide, the duration of EEG suppression decreased and the duration of bursts increased—that is, nitrous oxide activated the EEG during burst suppression.

The activation of isoflurane EEG by nitrous oxide, with [7] or without [8] changes in cerebral blood flow (CBF), has been demonstrated in animals. In their recent study in patients, Algotsson and colleagues [10] reported an increase in CBF, with a decrease in cerebral vascular resistance and an activation pattern in the EEG when 1.7% isoflurane–air was replaced by 0.85% isoflurane–nitrous oxide–oxygen. However, the EEG was not studied during constant concentrations of isoflurane. The present result, with constant isoflurane concentrations, is in accordance with our earlier study [6] showing that, although the frequency of EEG rhythm decreased when 65% nitrous oxide was added to 1.5% isoflurane anaesthesia, EEG suppressions were not seen. In the present study, addition of 0.7% (0.6 MAC) isoflurane instead of nitrous oxide, would probably have produced continuous EEG suppression in most of our patients [4].

The mechanism of activation of the EEG by nitrous oxide is interesting. Algotsson and colleagues [10] proposed a secondary effect of nitrous oxide on the brainstem reticular centres, which could also explain the result obtained in our study.

Four of our 13 patients showed an increase in the duration of EEG suppression during nitrous oxide. In two of these subjects the operation was abdominal, while in the two others it was breast surgery. The level of surgical stimulation in intra-abdominal surgery may differ from that of breast surgery. The type of surgery, however, seemed not to have any influence on the results.

Previous human studies on the effect of nitrous oxide on the EEG have often applied spectral analysis [1–3, 6]. Some of these results may also be interpreted as nitrous oxide-induced activation of the EEG. Spectral analysis is, however, sensitive to the bandpass characteristics of the recording system [11]. Furthermore, in addition to the spectral content of EEG, changes may occur in the topographical distribution and waveform of the EEG. This was demonstrated in our earlier study [6] which gave controversial results: nitrous oxide slowed the rhythm of EEG activity during isoflurane anaesthesia. Visual inspection of the raw EEG signal, however, showed that this was caused by frontal rhythmic delta activity, which may be interpreted as lightening of anaesthesia [12]. The waveform of the raw EEG signal, and transients (spikes, short suppressions), are lost in transformation to the power spectrum. Moreover, power spectrum analysis assumes a stationary signal, which is not present during burst suppression. Time domain analysis of EEG is thus more suitable for burst suppression EEG studies.

We used propofol for induction of anaesthesia. Propofol is claimed to have an effect on the EEG for only about 10 min after induction [13]. In our study, 45 min elapsed from administration of propofol to the recordings. Thus it is unlikely that propofol had any effect on the EEG during our measurements.

The burst involves d.c. shift in the EEG, which could be seen with increased bandwidth—a longer time constant in recording [14]. Usually, because of the high-pass filter, this d.c. shift is seen only as a small notch in the end of the burst. We used that notch as the definition of the suppression onset point, as it marks the end of the burst, which otherwise is difficult to determine.

In conclusion, we have shown that, during isoflurane burst suppression, nitrous oxide activated the EEG. The effect of nitrous oxide should be taken into consideration when isoflurane burst suppression is used as an indicator for depth of anaesthesia.
REFERENCES