Isoflurane compared with nitrous oxide anaesthesia for intra-operative monitoring of somatosensory-evoked potentials

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Intraoperative monitoring of somatosensory-evoked potentials is a routine procedure. To determine the depressant effect of nitrous oxide relative to isoflurane, the authors recorded the scalp, cervical and brachial plexus-evoked responses to stimulation of the median nerve under different anaesthetic conditions. Eight subjects, age 35 ± 6 (SD) yr, weight 68 ± 12 kg, were studied. Following recording of awake control responses, anaesthesia was induced with thiopentone 5 mg · kg^{-1} and fentanyl 3 μg · kg^{-1} and was followed by succinylcholine 1 mg · kg^{-1}. During normocapnia and normothermia, and with a maintenance infusion of fentanyl 3 μg · kg^{-1} · hr^{-1}, evoked potential recording was repeated under three different anaesthetic conditions; 0.6 MAC nitrous oxide, 0.6 MAC nitrous oxide ± 0.6 MAC isoflurane, and 0.6 MAC isoflurane. Among the anaesthetic conditions, the combination of nitrous oxide-isoflurane had the most depressant effect on the cortical amplitude (67 ± 4% reduction, P < 0.05). Nitrous oxide decreased the cortical amplitude more than an equipotent dose of isoflurane (60 ± 4% vs 48 ± 7%, P < 0.05). The latency was unchanged by nitrous oxide, but increased slightly by isoflurane and isoflurane-nitrous oxide anaesthesia (1.0 and 0.9 msec respectively, P < 0.05). We conclude that somatosensory-evoked potential monitoring is feasible both during nitrous oxide anaesthesia and isoflurane anaesthesia, but the cortical amplitude is better preserved during 0.6 MAC of isoflurane alone relative to 0.6 MAC of nitrous oxide alone. The depressant effect is maximal during nitrous oxide-isoflurane anaesthesia but less than the predicted additive effect.

Le monitorage des potentiels évoqués somato-sensoriels est une technique utilisée couramment. Pour comparer les effets dépresseurs du protoxyde d'azote à ceux de l'isoflurane, les auteurs ont enregistré sur le scalp et les plexus cervical et brachial, les réponses évoquées à la stimulation du nerf médian sous différentes méthodes d'anesthésie. Il ont étudié huit sujets, âgés de 35 ± 6 (SD) ans, pesant 68 ± 12 kg. Après l'enregistrement des réponses vigiles (contrôle), l'anesthésie a été induite avec du thiopentone 5 mg · kg^{-1} et du fentanyl 3 μg · kg^{-1} suivi de succinylcholine 1 mg · kg^{-1}. Sous normocapnie et normothermie avec une perfusion d'entretien de fentanyl 3 μg · kg^{-1} · hr^{-1}, ils ont répété l'enregistrement des potentiels évoqués pendant trois méthodes d'anesthésie: protoxyde d'azote 0,6 MAC, protoxyde d'azote 0,6 MAC + isoflurane 0,6 MAC, et isoflurane 0,6 MAC. Parmi ces méthodes, le protoxyde d'azote-isoflurane a l'effet dépresseur le plus marqué sur l'amplitude corticale (baisse de 67 ± 4%, P < 0,05). Le protoxyde l'azote diminue l'amplitude corticale d'une façon plus importante qu'une concentration équipotente d'isoflurane (60 ± 4% vs 48 ± 7%, P < 0,05). Sous protoxyde d'azote, la période de latence demeure inchangée, mais augmente légèrement sous isoflurane et sous isoflurane-protoxyde d'azote (1,0 et 0,9 MAC respectivement, P < 0,05). Les auteurs concluent que le monitorage des potentiels somato-sensoriels évoqués est réalisable pendant l'anesthésie au protoxyde d'azote et à l'isoflurane, mais que l'amplitude est mieux préservée pendant 0,6 MAC d'isoflurane seul comparativement à 0,6 MAC de protoxyde d'azote. L'effet dépresseur est maximal pendant l'anesthésie au protoxyde-isoflurane mais il est moindre que la somme arithmétique des effets de chacune des substances.

Key words

ANAESTHETICS, INHALED: isoflurane, nitrous oxide;
MONITORING: evoked potentials, somatosensory-evoked potential.

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Somatosensory-evoked potentials (SSEPs) are frequently monitored intraoperatively in surgical procedures where the brain or spinal cord is considered to be at risk.[1,2] The underlying assumption is that ischaemia or retraction damage to the structures being monitored would result in a delay in conduction and decrease in amplitude of the specific potential. Although there is still debate about the relative sensitivity of amplitude versus latency changes as indices of ischaemia, both experimental and clinical studies suggest that amplitude change is a better and more reliable correlate with neuronal ischaemic changes.[3,4] A 50% reduction in amplitude is generally considered to be a clinically important change that, if persistent, may result in postoperative neurological deficit.[4,5] To optimize the recording and interpretation of SSEP changes, the anaesthetic regimen should depress the amplitude minimally.

Potent inhaled anaesthetics depress the amplitude of the cortical response of SSEP in a dose-related manner,[6-9] but in low doses, SSEPs are generally recordable.[1,6-9] On the other hand, nitrous oxide in combination with a narcotic-based anaesthetic, a technique frequently used for intraoperative SSEP monitoring, also decreases the amplitude of the scalp-recorded cortical response.[10,11] Although it is clear that nitrous oxide and potent inhaled anaesthetics have an additive depressant effect on the amplitude of the cortical response,[6,7,12] the comparative influence of nitrous oxide with an equipotent dose of isoflurane has received limited attention. Accordingly, our investigation was carried out to determine the optimal anaesthetic regimen for intraoperative monitoring of SSEPs by comparing the influence of 0.6 MAC nitrous oxide with an equipotent dose of isoflurane. In addition, we also investigated the influence of nitrous oxide in combination with isoflurane to assess the additive effects of these two agents at low doses.

Methods

The study was approved by the Human Subject Review Committee of the University of Washington. With written informed consent, eight ASA I or II patients without neurological disease, age 35 ± 6 yr, weight 68 ± 12 kg (SD) admitted for peripheral extremity surgery were entered into the study.

Recording of SSEP

Somatosensory-evoked potentials were recorded from a scalp electrode placed over the right parietal cortex (C4' in the international 10–20 system) referenced to the forehead in response to contralateral median nerve stimulation using a square wave current of 200 μsec duration at 2 mA above the motor threshold. The stimulus was delivered at a frequency of 5.1 Hz. Additional electrodes were placed over the C_7 spine and Erb's point to record the cervical spinal and the peripheral responses. Frequency filters were set at 30 and 1500 Hz. An analysis time of 50 msec was used and at least 500 sweeps were averaged. All recordings were performed in duplicate. The impedance was checked periodically to ensure that it was below 3000 ohms.

Study protocol

All patients were premedicated with midazolam 0.03 $mg \cdot kg^{-1}$ *iv* 30 min before the study. In the supine position, the stimulating and recording electrodes were placed and impedance checked to ensure satisfactory conductance. Monitors including electrocardiogram, pulse oximetry, and non-invasive blood pressure were then attached. Following recording of control awake SSEPs in duplicate, anaesthesia was induced with thiopentone 5 $mg \cdot kg^{-1}$ and fentanyl 3 $\mu g \cdot kg^{-1}$. Succinylcholine 1 $mg \cdot kg^{-1}$ was administered to facilitate tracheal intubation, after which a fentanyl infusion was begun at 3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ and maintained for the duration of the study. Muscle paralysis was maintained with vecuronium as needed. Mechanical ventilation was adjusted to maintain end-tidal CO_2 between 35 and 40 mmHg. Body temperature was measured via an oesophageal stethoscope with a thermistor tip. Thermal blanket and warmed intravenous infusion were used to maintain body temperature as close to the awake value as possible. During normocapnia and normothermia, SSEPs were repeated under three conditions: (1) 0.6 MAC (minimum alveolar concentration) isoflurane; (2) 0.6 MAC isoflurane + 0.6 MAC nitrous oxide; and (3) 0.6 MAC nitrous oxide. The first and the last condition are therefore equipotent in terms of anaesthetic depth, and the second condition represents the additive effect of nitrous oxide and isoflurane anaesthesia. The patients received approximately 38% inspired oxygen throughout the study, with the balance either in nitrogen or nitrous oxide depending on the study conditions. For the purpose of this study, MAC of isoflurane was assumed to be 1.15%,[13] and that of nitrous oxide 104%.[14] The entry sequence was randomized such that half of the patients received isoflurane first and the other half received nitrous oxide first. The combination of nitrous oxide-isoflurane was always studied in the middle. End-tidal nitrous oxide and isoflurane concentrations were monitored with a Perkin-Elmer mass spectrometer which was calibrated before the study. A steady end-tidal anaesthetic concentration was achieved for at least 15 min at each study condition before SSEPs were recorded in duplicate. Because of time constraints it was not always possible to wash out nitrous oxide and isoflurane com-

pletely during re-equilibration at different stages of the study, but nitrous oxide was always <6% and isoflurane <0.1% before they were considered to have been eliminated. To avoid the influence of surgical stimulation, the study was completed before surgery was allowed to begin.

Analysis of data

The recordings were analyzed for amplitude and latency of N_{20} (cortical component, scalp electrode), N_{13} (cervical spinal component, C_7 spine), and N_{10} (peripheral component, Erb's point). The values from the duplicate recordings were averaged before statistical computation. Because of the inherent variability of the magnitude of the N_{20} amplitude among individuals,[15] the normalized values (expressed as percentages of awake values) were also computed for analysis. The latter analysis was considered to be more important since the percentage changes were less influenced by the baseline values.[16] Moreover, percentage change from baseline is generally used as the criterion for clinically important changes.[5] All data were then analyzed using ANOVA for repeated measures, and where statistical significance was found, a multiple comparison procedure was used for further analysis (Fisher's PLSD). A P value of < 0.05 was considered significant.

Results

Heart rate and blood pressure were higher during "awake" than "under anaesthetic" conditions. Mean blood pressure was higher during 0.6 MAC nitrous oxide than during the other anaesthetic study conditions. Despite the lower values during isoflurane and nitrous oxide-isoflurane anaesthesia, the mean blood pressure was always above 60 mmHg and therefore well above the lower limit of cerebral autoregulation. There were no other differences between the different anaesthetic conditions (Table I).

Anaesthesia decreased the amplitude of the N_{20} cortical response (Table II). The SSEP recordings from a representative patient are shown in Figure 1. The decrease in amplitude was the greatest with nitrous oxide-isoflurane anaesthesia and the least with isoflurane alone. However, due to the variability of the baseline amplitude, there were no differences in absolute amplitude among the three anaesthetic conditions. Expressed as a percentage of the awake amplitude, which yielded changes less dependent on the baseline values, 0.6 MAC nitrous oxide reduced the amplitude more than 0.6 MAC isoflurane (60 ± 4% vs 48 ± 7% reduction, $P < 0.05$) (Figure 2). The decrease in amplitude was maximal with the nitrous oxide-isoflurane combination (67 ± 4% reduction) although this was not different from the change recorded during nitrous oxide alone. Nitrous oxide alone did not change the latency, but both nitrous oxide-isoflurane and isoflurane anaesthesia increased the latency by approximately 1.0 msec from the awake value (Table II).

With the N_{13} and N_{10} components, there were no differences in latency observed between the anaesthetic conditions and awake control. However, both nitrous oxide anaesthesia alone and nitrous oxide-isoflurane anaesthesia caused a reduction in amplitude (Table II).

TABLE I Blood pressure, heart rate and temperature

	Awake	*0.6 MAC N_2O*	*0.6 MAC N_2O + 0.6 MAC ISO*	*0.6 MAC ISO*
HR (bpm)	72 ± 5	59 ± 4	62 ± 4	59 ± 5
MABP (mmHg)	90 ± 6	89 ± 6*	66 ± 4	67 ± 3
Temp (°C)	36.5 ± 0.2	36.0 ± 0.4	36.0 ± 0.4	36.3 ± 0.3

All values are mean ± SE, $n = 8$.
*$P < 0.05$ compared with other anaesthetic conditions.

TABLE II Amplitude and latency of N_{20}, N_{13} and N_{10} responses

	Awake	*0.6 MAC N_2O*	*0.6 MAC N_2O + 0.6 MAC ISO*	*0.6 MAC ISO*
Amplitude (μv)				
N_{20}	2.70 ± 0.4	1.10 ± 0.16*	0.89 ± 0.16*	1.35 ± 0.24*
N_{13}	3.00 ± 0.30	2.59 ± 0.22*	2.60 ± 0.28*	2.96 ± 0.33
N_{10}	5.00 ± 0.75	5.28 ± 0.86	4.93 ± 0.75	5.0 ± 0.77
Latency (msec)				
N_{20}	20.3 ± 0.6	20.4 ± 0.5	21.2 ± 0.5*	21.3 ± 0.5*
N_{13}	14.0 ± 0.5	14.0 ± 0.7	14.1 ± 0.6	14.2 ± 0.5
N_{10}	10.6 ± 0.4	10.4 ± 0.5	10.5 ± 0.4	10.6 ± 0.4

All values are mean ± SE, $n = 8$.
*$P < 0.05$ compared with awake value.

Discussion

Potent inhaled anaesthetics decrease the amplitude of the cortical response of the somatosensory-evoked potentials in a dose-related manner, and although low doses are compatible with monitoring, high doses can abolish the response.[6,7] Consequently, some authors advocate that inhaled anaesthetics should be avoided in favour of nitrous oxide-narcotic anaesthesia whenever intraoperative monitoring of SSEP monitoring is undertaken.[2,5] However, nitrous oxide at 50% concentration has been shown to cause a more than 50% reduction in the cortical amplitude.[10,11] Moreover, in many patients the use of nitrous

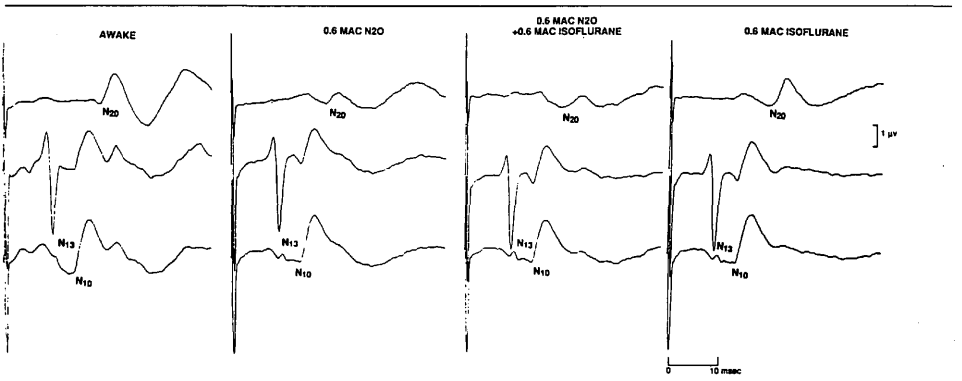

FIGURE 1 Recordings from a representative patient. The cortical, spinal and peripheral components are labeled. The reduction in N_{20} amplitude with anaesthesia is evident. The amplitude was preserved better with 0.6 MAC isoflurane than with 0.6 MAC of nitrous oxide.

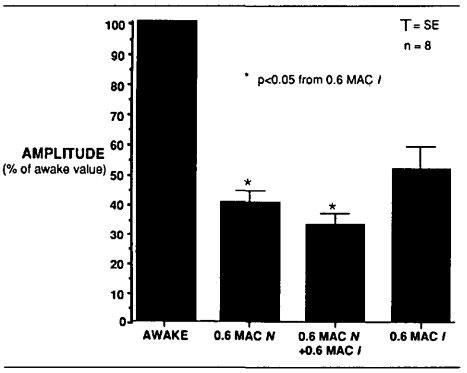

FIGURE 2 Change in relative amplitude of N_{20} with the three anaesthetic conditions. The amplitude was reduced from awake value in all three conditions, but the amplitude was better preserved during 0.6 MAC of isoflurane than with an equipotent dose of nitrous oxide or the nitrous oxide-isoflurane combination. (N = nitrous oxide, I = isoflurane.)

oxide may be contraindicated; these may include patients with intracranial air, or patients who require a high inspired oxygen concentration for adequate oxygenation. In this study we have demonstrated that SSEP monitoring is not only feasible during low-dose isoflurane anaesthesia, but that the cortical amplitude is better preserved than with an equipotent dose of nitrous oxide anaesthesia. We also observed that the depressant effect of nitrous oxide-isoflurane anaesthesia at the dose we studied (0.6 MAC + 0.6 MAC) was less than the additive effects of each agent alone.

Although a direct comparison between the influence of nitrous oxide and that of an equipotent dose of isoflurane on SSEPs monitoring has not been investigated before, our results are consistent with previous investigations on the influence of isoflurane-nitrous oxide anaesthesia.[6-8] Both Pathak *et al.*[6] and Peterson *et al.*[7] have demonstrated that 1.0 MAC isoflurane caused a reduction in the cortical amplitude, and that the addition of 60% nitrous oxide caused even more deterioration. Since the completion of our study, Thornton *et al.*[17] have reported their work on the comparative effects of isoflurane and nitrous oxide on evoked potentials. Their primary aim was to investigate the use of evoked potentials as a measure of depth of anaesthesia, but both the experimental design and results were remarkably similar to ours. Although they only allowed ten minutes of anaesthetic equilibration time, they too reported that nitrous oxide (0.6 MAC) caused a greater reduction of cortical amplitude with no influence on latency than 0.6 MAC of isoflurane. However, since they did not record awake responses, the magnitude of reduction by each anaesthetic regimen could not be quantified.

To approximate the clinical situation more closely, in addition to nitrous oxide and/or isoflurane, we also included a background fentanyl infusion. As fentanyl has negligible influence on SSEPs,[18,19] and all patients received an infusion for all anaesthetic conditions, this should have no bearing on the findings. It is often observed during intraoperative monitoring that there is a time-related deterioration of the amplitude response. Consequently we randomized the study entry sequence so that the time of study would not introduce a bias. Surgical stimulation may also introduce an unpredictable variable,

therefore we elected to complete the whole study during steady-state conditions before surgical stimulation was allowed. Although there was a slight reduction in body temperature during anaesthesia, this was not different from the awake condition. Thus, our findings represent an accurate comparison of the influence of nitrous oxide relative to an equipotent dose of isoflurane. We only studied the cortical potential of median nerve stimulation and did not examine the cortical potential of posterior tibial nerve stimulation which is commonly used for spinal cord monitoring. Although we believe the results can be generalized and should equally apply to posterior tibial nerve stimulation, the latter needs to be confirmed.

The slight increase in latency of N_{20} by nitrous oxide-isoflurane and isoflurane anaesthesia, although statistically significant, is clinically insignificant. Moreover, because of the relative lack of sensitivity, the latency is seldom used as a criterion for change during intraoperative monitoring of SSEPs.[4,5]

The cervical and the brachial plexus potentials are not utilized as often as the cortical potential in intraoperative monitoring. However, the former may be used to allow calculation of the central conduction time (difference between the latency of N_{13} and N_{20}), which is indicative of conduction between brainstem and the cortex, and the latter may be useful in evaluation of peripheral nerve conduction during surgery on the brachial plexus. Hence, we examined these responses as well during this study. With the exception of N_{13}, the amplitude of which showed a modest 13% reduction during nitrous oxide and nitrous oxide-isoflurane anaesthesia, anaesthesia had a minimal effect on these components compared to the cortical response. These differential findings are not unexpected as similar observations have been reported previously.[8,20] It is postulated that generation of these responses is more dependent on axonal conduction than synaptic transmission, therefore they are less influenced by general anaesthesia.[8]

In summary, based on our observations, we conclude that (1) SSEPs monitoring is feasible both during nitrous oxide and low-dose isoflurane anaesthesia; (2) nitrous oxide at 0.6 MAC decreases the cortical N_{20} amplitude more than an equipotent dose of isoflurane; (3) the combination of nitrous oxide (0.6 MAC) and isoflurane (0.6 MAC) anaesthesia decreased the cortical amplitude less than what is expected from the additive effects of each agent, but more than 0.6 MAC isoflurane alone. To optimize intraoperative recording of SSEPs, these factors must be taken into consideration, particularly in patients with low cortical amplitude baseline recordings.

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