

Effects of Halothane, Enflurane, and Isoflurane on Somatosensory Evoked Potentials during Nitrous Oxide Anesthesia

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The effects of 0.5, 0.75, and 1 MAC of halothane, enflurane, and isoflurane in 60% nitrous oxide on somatosensory cortical evoked potentials were studied in 30 patients undergoing corrective surgery for scoliosis. The evoked potentials were averaged at the scalp from the electroencephalogram following repeated bilateral posterior tibial nerve stimulation at the ankle. Latencies and amplitudes of the resulting potentials were measured and compared with the post-induction control values. Graded increase in latencies and graded decrease in amplitudes were found with increasing concentrations of all the three agents ($P < 0.05$), confirming that the effects were dose related. Reductions in amplitudes were more marked than increase in latencies. The authors conclude that, during nitrous oxide-based anesthesia, enflurane, and isoflurane resulted in less alteration of somatosensory cortical evoked potentials than halothane. In conjunction with 60% nitrous oxide, 0.5 and 0.75 MAC of halothane, 0.5, 0.75, and 1.0 MAC of isoflurane and enflurane, respectively, were found to be compatible with the generation of waves adequate for evaluation. (Key words: Anesthetic gases: nitrous oxide. Anesthetics, volatile: enflurane; halothane; isoflurane. Brain: somatosensory evoked potential monitoring. Surgery: scoliosis.)

SOMATOSENSORY CORTICAL EVOKED potentials (SCEPS) are a measure of neural transmission in afferent spinal cord pathways. In anesthetized patients, posterior tibial nerve SCEPS are used to monitor neuronal function in the spinal cord during scoliosis surgery.^{1,2} Monitoring of SCEP is also useful in intracranial vascular surgery and plexus injuries.^{3,4} It is generally held that volatile anesthetics attenuate SCEPS severely, and are to be avoided as anesthetic agents if such monitoring is planned.⁵ Sebel *et al.* reported that nitrous oxide caused graded changes in SCEPS.⁶ Recently, it has been shown that low doses of volatile anesthetics with fentanyl- or nitrous oxide-based

anesthesia are compatible with SCEP monitoring.^{7,8} Higher concentrations of volatile anesthetic agent, with or without nitrous oxide, appear to be compatible with median nerve SCEPS.⁹ As nitrous oxide is widely used during anesthesia, and posterior tibial nerve SCEPS are used to monitor spinal cord function during scoliosis surgery, we investigated the effects of halothane, enflurane, and isoflurane in clinically useful concentrations (0.5–1.0 MAC) with 60% nitrous oxide on posterior tibial nerve SCEPS. The purpose of the study was to determine the concentrations of volatile anesthetics at which such monitoring was still possible, whether the changes were dose-related, and whether at identical MAC levels the changes were different for the three agents.

Methods

Thirty otherwise healthy (ASA Class I) patients with idiopathic scoliosis and no underlying pulmonary, cardiac, or neurological problems, scheduled for operative correction of spinal deformities of 45–75°, were selected for the study. None of the patients were receiving any chronic medications. The study was approved by our Institutional Review Board. The 30 patients (18 women and 12 men) were randomly divided into three groups of ten each. The first group received halothane; the second, enflurane; and the third, isoflurane as the volatile anesthetic in addition to 60% nitrous oxide. The three groups did not differ in age: halothane group (range 15–45 yr), enflurane group (14–44 yr), and isoflurane group (15–45 yr).

All patients were premedicated with intramuscular secobarbital (2 mg/kg) and atropine (0.005 mg/kg) 90 min prior to surgery.

Two intravenous catheters for drugs, fluids, and blood, as well as a radial arterial cannula for measurement of blood pressure, and blood gas tensions were inserted in all patients.

Besides the SCEP monitor, other monitors included an ECG, esophageal temperature probe, esophageal stethoscope, and nerve stimulator. Blood loss and urine output were also measured. Maintenance fluids were calculated at a rate of $1.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ after cessation of oral intake, and 50% of this volume (D5/LR) was infused before induction of anesthesia.

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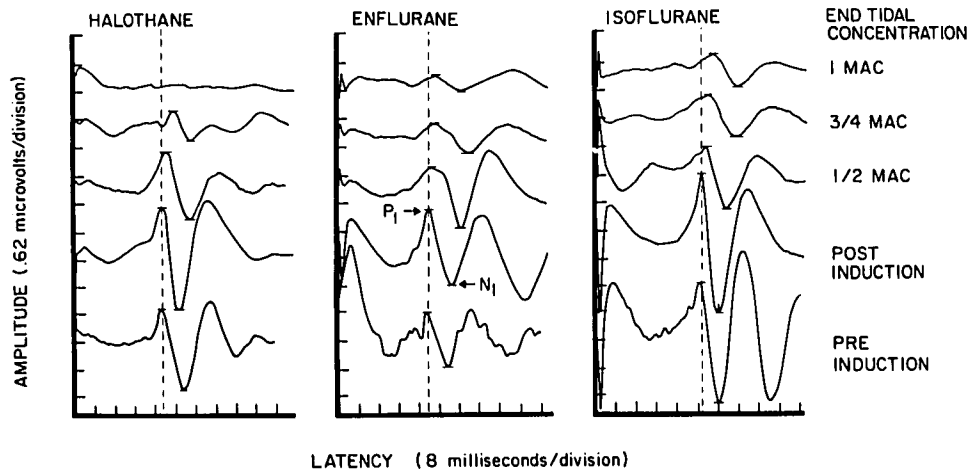


FIG. 1. Intraoperative SCEP records from three patients, each one receiving one of the volatile anesthetic agents plus 60% nitrous oxide. Peak latencies P_1, N_1 in msec; peak-to-peak P_1-N_1 amplitudes in microvolts. Post-induction SCEP serves as control. Note the increase in latencies and decrease in amplitudes with the increase of the MAC values of all three volatile anesthetics. Also note that, at 1.0 MAC of halothane, the SCEP is not measurable.

SCEPs were measured using a multichannel signal averager (Nicolet Pathfinder II®—Nicolet Biomedical, Madison, Wisconsin). A transcutaneous nerve stimulator was used to locate posterior tibial nerves at the ankle. The location was marked, and sterile stimulating needle electrodes were placed and the extremities were covered to prevent heat loss. Both extremities were stimulated simultaneously. The stimulus intensity delivered pre-induction was equal to the sum of sensory (S) and motor (M) thresholds. Sensory threshold was defined as the midpoint between the stimulus intensity needed for just detectable perception of stimulation and for just detectable loss of perception of stimulation. Motor threshold was defined as the point where twitching of a toe was just detectable. Post-induction, and on subsequent readings, the stimulus intensity was increased to three times the (S + M) threshold.^{10,11} This intensity produced a distinct toe twitch. Five hundred constant current stimuli of 200 microsecond duration¹² were delivered at a rate of 8.1 Hz. A time base of 80 msec following stimulus was analysed. Input filtering was set to a bandwidth of 5–1500 Hz. The acquired signals were amplified 120,000 times, corresponding to a sensitivity of 50 microvolts on the Pathfinder II. Following the 10–20 international system,¹³ the recording needle electrodes were placed at CZ (vertex) in reference to FPz. Ear clips served as ground. Electrode impedance was maintained at less than three Kohms. All recordings were repeated to verify their reproducibility. The data were stored on a magnetic disc for analysis. Three to five minutes were required to acquire each average. High voltage artifact was automatically rejected by the computer. Averaging was halted during periods of frequent use of electric cautery. Waveforms were recorded immediately prior to induction. Anesthesia was then induced with 3–5 mg/kg iv of thiopental and 0.1 mg/kg of pancuronium iv, and the trachea was intubated. Anesthesia was maintained with 60% $N_2O/40\% O_2$, with a total fresh gas flow of approximately 8 l/min. After positioning the prone patient on the frame, a second set of

waveform recordings (approximately 30 min post-induction) was obtained. After these averages were obtained, the volatile agent (0.5 MAC) under study was added. The same investigator administered anesthesia in all cases and performed the entire SCEP analysis using the same apparatus and technique. The MAC values used were the commonly accepted MAC values for each agent for age 30 yr.

End tidal concentrations were measured by EMMA (Engstrom—Multigas Monitor for Anesthesia) and gas chromatography. End tidal 0.5 MAC (halothane 0.4%; enflurane 0.85%; isoflurane 0.6%)¹⁴ was achieved and maintained for 30 min before the third set of waveforms was recorded. The same procedure was repeated at 0.75 MAC and 1 MAC levels. The post-induction and 0.5 MAC recordings were made prior to incision, while 0.75 MAC and 1.0 MAC recordings were made post-incision.

Peaks of the primary complex were labelled (fig. 1) P_1 (positive) and N_1 (negative). The latencies of peaks P_1 and N_1 were measured in msec from the time of stimulus. In addition, the peak-to-peak amplitudes of P_1-N_1 were measured in microvolts and were recorded for each of the sample periods. For each patient, the post-induction record served as control.

Pancuronium ($1/5$ of the initial dose) was administered as indicated by the peripheral nerve stimulator and the surgical circumstance. No other drugs were used during the study period.

Ventilation was adjusted to maintain $PaCO_2$ at 40 ± 2 mmHg. Body temperature in each case was maintained at $35 \pm 2^\circ C$ by warming the fluids administered, controlling the ambient temperature, and covering the extremities with blankets. Systolic blood pressure was maintained within 20% of the preoperative values by infusion of fluids and replacement of lost blood ml/ml. Urine output was measured and kept within 0.5–1.0 ml/kg/hr.

A one-way analysis of variance was performed to identify any significant ($P < 0.05$) differences in latencies or

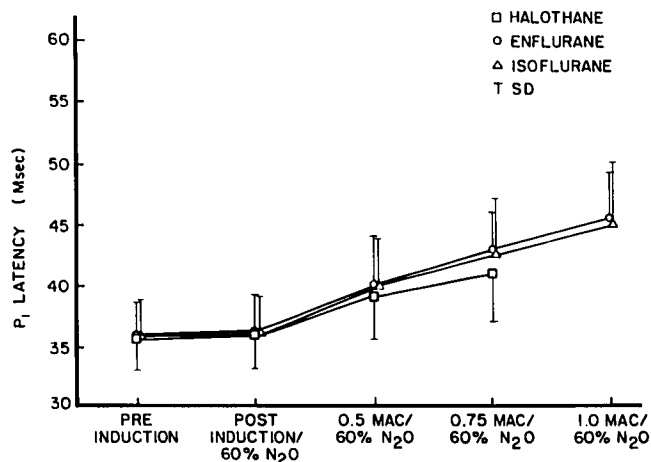


FIG. 2. Values are mean \pm SD. P₁ latencies in msec pre-induction, post-induction, and at various MAC levels of halothane, enflurane, and isoflurane with 60% nitrous oxide. Post-induction P₁ latencies serve as control. Within each agent group latency increases significantly with increasing MAC levels ($P < 0.05$). Note that, at 1.0 MAC of halothane, the P₁ latency is not measurable.

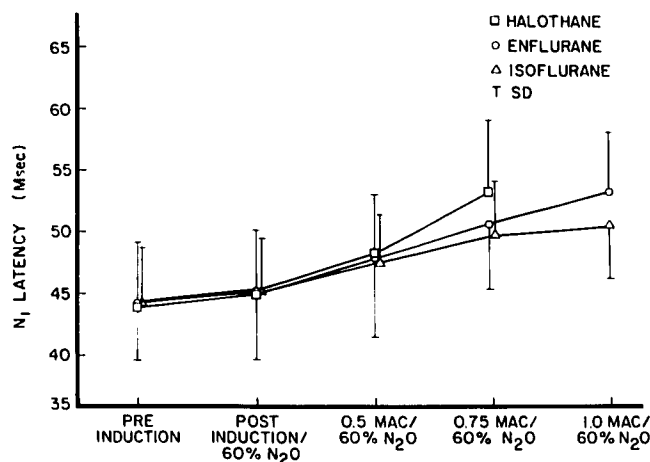


FIG. 3. Values are mean \pm SD. N₁ latencies in msec pre-induction, post-induction, and at various MAC levels of halothane, enflurane, and isoflurane with 60% nitrous oxide. Post-induction N₁ latencies serve as control. Within each agent group latency increases significantly with increasing MAC levels ($P < 0.05$). Increases with halothane 0.75 MAC are significantly greater than the increases with enflurane and isoflurane ($P < 0.05$). At 1.0 MAC latency increases with enflurane are greater than the increases with isoflurane ($P < 0.05$).

amplitudes among the three patient groups prior to and following induction. The analysis was followed by Tukey's HSD multiple comparison procedure,¹⁵ when significant differences were detected. Changes in latencies and amplitudes seen with increasing MAC of volatile anesthetics within a group were analysed using a repeated measures analysis of variance followed by tests for linear trends in the data using orthogonal components.¹⁵

At 1.0 MAC halothane, P₁-N₁ amplitudes were so small as to be unmeasurable. For the purpose of data analysis, these amplitudes were considered to be less than 0.01 microvolts, and the Mann-Whitney U nonparametric tests were employed to calculate the statistical significance between groups.¹⁶ Since the P₁ and N₁ peaks could not be identified for halothane subjects at 1.0 MAC, the latencies of these peaks could not be determined, and these were not included in the data analysis.

Results

There were no intergroup differences in post-induction esophageal temperature, and there was no significant change in temperature during the course of the study. All the patients in all the three groups were hemodynamically stable during the course of the study, and did not require any vasoactive agents for maintenance of systolic blood pressure within 20% of the pre-induction level.

Recordable and reproducible data was obtained prior to and following induction in all patients.

Figure 1 shows the effects of halothane, enflurane, and isoflurane in the presence of 60% nitrous oxide on SCEPS in three different patients undergoing corrective surgery for scoliosis. As the concentrations of the volatile agents

are increased, the amplitudes become smaller and the latencies longer.

There were no significant differences in latencies and amplitudes between the three groups prior to induction (figs. 1-4). Sixty per cent nitrous oxide, the induction agents, and an increase in stimulus intensity increased P₁, N₁ latencies and P₁-N₁ amplitudes, but the increases were not significantly different between the three groups

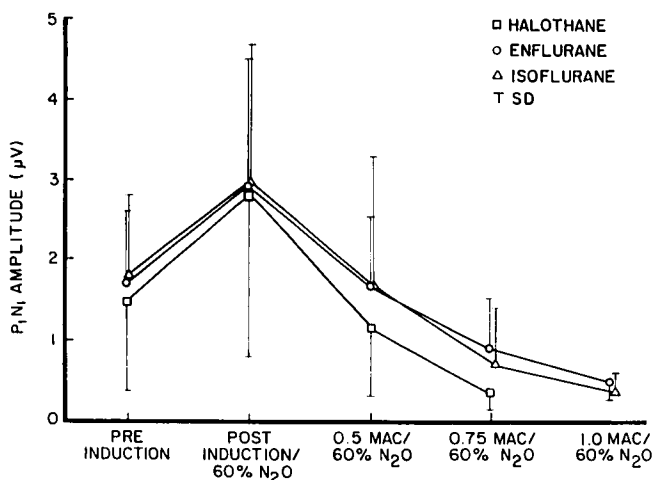


FIG. 4. Values are mean \pm SD. P₁-N₁ peak-to-peak amplitudes in microvolts pre-induction, post-induction, and at various MAC levels of halothane, enflurane, and isoflurane with 60% nitrous oxide. Post-induction P₁-N₁ amplitudes serve as control. Within each agent group amplitude decreases significantly with increasing MAC levels ($P < 0.05$). At 1.0 MAC halothane amplitude depression is significantly greater ($P < 0.01$) than for enflurane and isoflurane.

such that the three groups were comparable at post-induction (figs. 1–4).

Each increment in MAC level of halothane enflurane or isoflurane, in 60% nitrous oxide, resulted in statistically significant ($P < 0.05$) increases in P_1 and N_1 latencies and statistically significant ($P < 0.05$) decreases in P_1 - N_1 amplitudes (figs. 1–4) when evaluated from post-induction and tested for a linear trend following this post-induction.

The SCEPS were present at all MAC levels in patients receiving enflurane and isoflurane. With halothane, SCEPS were present at 0.5 and 0.75 MAC in all patients, but, at 1.0 MAC, the amplitudes were so small that neither the amplitudes nor the latencies could be measured. At 1.0 MAC, halothane depressed P_1 - N_1 amplitudes more than enflurane or isoflurane ($P < 0.01$). At 0.75 MAC, halothane increased N_1 latencies more than enflurane ($P < 0.05$) or isoflurane ($P < 0.01$). At 0.5 and 0.75 MAC, enflurane and isoflurane had similar effects on P_1 , N_1 latencies and P_1 - N_1 amplitudes. At 1.0 MAC, enflurane increased N_1 latencies more than isoflurane ($P < 0.05$). However, increases in P_1 latencies and decreases in P_1 - N_1 amplitudes were similar.

Discussion

Under the conditions of this study, we had no difficulty in obtaining pre- as well as post-induction data. Awake patients tolerated stimuli equal to the sum of sensory plus motor threshold, and were fairly comfortable. Increasing the stimulus strength intraoperatively (*i.e.*, three times sensory plus motor threshold) was advantageous, as the amplitudes of the waveforms were larger and easier to evaluate. Such stimulus intensity would be too painful for awake patients, but is usually employed for intraoperative recordings and evaluations.^{10,11} The accuracy and speed of SCEP measurement are directly proportional to the size and distinctiveness of the waveform.

A number of variables are known to alter SCEP waveforms. Besides anesthetics and neural injury, the amplitude and latency of the waveform may also change with age,⁵ body temperature,¹⁷ P_{aCO_2} ,⁵ and blood pressure.^{5,18} Our three groups were comparable in age and temperature, and P_{aCO_2} was maintained in the same range.

Brodkey *et al.*¹⁸ studied cortical evoked potentials elicited by posterior tibial nerves in anesthetized cats, and found that a combination of spinal compression (distraction) and hypotension (systolic blood pressure reduced to 50% of its original value) produced reversible depression of SCEPS. Neither spinal cord compression nor hypotension, when applied individually, depressed SCEPS. Although the primary treatment for spinal cord injury involves removal of distraction, avoidance of hypotension is critical due to its concomitant lowering of spinal cord blood flow. Therefore, in our study, we did not allow systolic blood pressure to fall below 20% of the pre-induction value.

Anesthetics are known to attenuate SCEPS.^{5–9} Some investigators⁵ found the action of volatile anesthetics on SCEPS so depressive that they advocated total avoidance of volatile anesthetics when anesthetizing patients monitored with SCEPS. Our results are at variance with the above,⁵ and the discrepancy may relate to different monitoring equipment, specific premedications, and some differences in the anesthetic techniques. Our results demonstrate that, in 60% nitrous oxide, concentrations of enflurane or isoflurane up to 1.0 MAC, or halothane up to 0.75 MAC, allow generation of SCEP waves adequate for monitoring. Furthermore, our results are qualitatively consistent with those of Salzman *et al.*⁸ and Peterson *et al.*,⁹ while some quantitative differences remain. Peterson *et al.* found that enflurane produced the greatest, and halothane the least, depressing effect on median nerve evoked SCEPS. However, we found that enflurane produced the least, and halothane the greatest, depressing effect on posterior tibial nerve evoked SCEPS. Petersen *et al.*⁹ examined the effects of halothane, enflurane, and isoflurane in increasing end tidal concentrations from 0.5–1.5 MAC with and without 60% nitrous oxide on median nerve (arm) evoked SCEPS. Salzman *et al.*⁸ examined the effects of halothane (0.5–2% inspired concentration) in 66% nitrous oxide-based anesthesia on SCEPS evoked by stimulating posterior tibial nerves at the knee. The only differences are quantitative in nature and are largely attributable to different sites of stimulation (arm *vs.* leg and knee *vs.* ankle), and some differences in recording and stimulating parameters. We could not compare the results of our study with those of McPhersen *et al.*,⁷ who studied the effects of fentanyl-based enflurane and isoflurane with very little control over the volatile anesthetic concentrations and found little or no change on SCEPS.

All three volatile anesthetic agents caused a dose-related decrease in amplitude and increase in latency. The changes were most pronounced with halothane. Changes seen with enflurane and isoflurane were almost identical, except the increase in N_1 latency at 1.0 MAC level. At present, we have no explanation why halothane depresses amplitudes more than enflurane or isoflurane. Similarly, we have no explanation for the fact that halothane at 0.75 MAC level increases N_1 latency more than enflurane or isoflurane, and enflurane at 1.0 MAC level increases the N_1 latency more than isoflurane.

The results of the present study suggest that, when using our stimulus and recording parameters, the administration of halothane up to 0.75 MAC, and enflurane or isoflurane up to 1.0 MAC (each with 60% N_2O), should be compatible with effective SCEP monitoring in normal subjects. If the amplitudes of the preoperative SCEPS are very small, halothane less than 0.75 MAC, and enflurane or isoflurane less than 1.0 MAC in conjunction with 60% nitrous oxide, should be administered. As far as possible, end tidal concentrations of volatile anesthetics should be

kept at a constant level during critical periods of monitoring. However, if alterations in end tidal concentrations occur, changes in latency and amplitude should be anticipated and considered in interpretation.

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