Effects of Halothane, Enflurane, and Isoflurane in Nitrous Oxide on Multilevel Somatosensory Evoked Potentials

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The effects of halothane, enflurane, and isoflurane were studied at 0.5, 0.75, and 1 MAC in 60% N₂O on subcortical sensory evoked potentials recorded at the popliteal fossa (PF), the spine (L-3, C-6) and on cortical potentials recorded at the scalp (SC) following bilateral posterior tibial nerve stimulations at the ankle in 28 patients undergoing scoliosis surgery. Latencies and amplitudes of the resulting potentials at each level were compared with postinduction control values. With increasing MAC, latency and amplitude changes seen at C6 (subcortical) were also compared with those at SC (cortical). Increasing the concentrations of each agent resulted in a graded increase in latency and a graded decrease in amplitude, at all levels. At SC each increase in MAC with each agent resulted in an increase in latency (P < 0.05) and a decrease in amplitude (P < 0.005), respectively. The increases in SC latency at 0.75, 1 MAC were larger than the increase in latency at C6 (P < 0.005) and the decreases in SC amplitudes at 0.5, 0.75 and 1 MAC were greater than the decrease in amplitude at C6 (P < 0.01). Halothane, enflurane, and isoflurane in 60% N₂O altered subcortical potentials less than cortical potentials. Enflurane and isoflurane at 0.5, 0.75, and 1 MAC, and halothane at 0.5, 0.75 MAC maintained subcortical and cortical potentials that were adequate for evaluation. However, 1 MAC of halothane suppressed cortical potentials but maintained subcortical potentials. Subcortical C6 potential may serve as an additional monitor. (Key words: Anesthetic gases; nitrous oxide. Anesthesics, volatile: halothane, enflurane, isoflurane. Monitoring, somatosensory evoked potential: peripheral nerve; spinal; scalp. Surgery: scoliosis.)

Because surgical correction of spinal deformities carries the risk of paraplegia, monitoring for early indications of potential spinal cord damage is of utmost importance. Several reports have described intraoperative cortical (scalp) sensory evoked potential (SEP) recordings to monitor spinal cord function during corrective surgery of kyphoscoliosis. Interindividual variability in absolute SEP amplitudes and latencies of scalp recorded potentials make it necessary for each patient to serve as his/her own control. To reduce interindividual variability inherent in noninvasive scalp recorded evoked potential and to eliminate spurious findings associated with cortical recordings, several invasive methods have been adopted and simultaneous multilevel subcortical recordings have been suggested. However, preoperative and postoperative records cannot be obtained without causing pain, which makes invasive methods unpopular.

Effects of anesthetics on percutaneous scalp recorded potentials and invasive epidurally recorded spinal potentials have been reported, but the data on noninvasive percutaneous recorded, peripheral nerve, and spinal evoked potentials are scanty and incomplete. Therefore, we examined the effects of the halothane, enflurane, and isoflurane in clinically useful concentrations in 60% nitrous oxide (N₂O) on skin recorded potentials at the popliteal fossa, the spine (L-3 and C-6), and the scalp. Because C6 and scalp recording sites are located above the level of spinal fusion for scoliosis, we also compared the effects of the anesthetics at these two sites. Our objective was to determine whether the volatile anesthetics act differently on subcortically and cortically recorded potentials. Clinically, such subcortically recorded potentials may provide an additional noninvasive assessment of functional integrity of the spinal cord during surgery.

Methods

Twenty-eight (ASA physical status 1) patients with no underlying pulmonary, cardiac, or neurologic 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 28 patients (16 women and 12 men) between the ages of 15 and 45 yr were randomly divided into three groups of 10, 9, and 9. Patients in the first group received halothane, in the second group enflurane, and in the third group isoflurane as the volatile anesthetic. In addition, all patients received 60% N₂O.

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

In addition to the SEP monitor, other monitors included an ECG, esophageal temperature probe, esophageal stethoscope, and a nerve stimulator. Blood loss and urine output were also measured. Maintenance fluids were calculated at a rate of 1.5 ml.kg⁻¹.h⁻¹ after cessation of oral intake, and 50% of this volume (D₆/LR) was infused before induction of anesthesia.

SEP were measured using a multichannel signal aver-
ager (Nicolet Pathfinder II, Nicolet Biomedical, Madison, Wisconsin). A transcutaneous nerve stimulator was used to locate both posterior tibial nerves at the ankles. The location was marked, sterile stimulating needle electrodes inserted, and the extremities covered to prevent heat loss. Both posterior tibial nerves were simultaneously stimulated. Before induction the stimulus intensity was equal to the algebraic sum of the sensory and motor thresholds. This intensity produced a distinct toe twitch. After induction the stimulus intensity was increased three times the (stimulus + motor) threshold. Five hundred constant current stimuli of 200 ms duration were delivered at a rate of 8.1 Hz. A time base of 80 ms following the stimulus was analyzed. Input filtering was set to a band width of 150–1500 Hz for subscalp and 30–250 Hz for scalp recordings. The recording needle electrodes were placed at the right popliteal fossa in reference to negative electrodes placed across the same knee for the peripheral nerve evoked potential, at the L-3 and C-6 spinous processes in reference to the right hip and the right shoulder, respectively, for spinal evoked potentials and at the scalp in reference to FPz for cortical recordings. Ear clips served as ground. Electrode impedance was maintained at less than 3 kohm. All recordings were repeated to verify their reproducibility. Data were stored on a magnetic disc for analysis. High voltage artifact was automatically rejected by the computer. Averaging was halted during periods of frequent use of electrocautery. Waveforms at all levels were recorded immediately prior to induction of anesthesia.

Anesthesia was then induced with 3–5 mg/kg of thiopental iv, and following 0.1 mg/kg of pancuronium iv the trachea was intubated. Anesthesia was maintained with 60% N₂O/40% O₂, with a total fresh gas flow of approximately 8 l/min. Having positioned the prone patient on the frame, a second set of waveform recordings (approximately 30 min postinduction) was obtained, after which the volatile agent (0.5 MAC) under study was added. The same investigator administered anesthesia in all cases and performed the entire SEP analysis using the same apparatus and technique. The MAC values used were those commonly accepted values for each agent for age 30. 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%) was achieved and maintained for 30 min before the third set of waveforms were recorded. The same procedure was repeated at 0.75 MAC and 1.0 MAC levels. The postinduction and 0.5 MAC recordings were made prior to incision while 0.75 MAC and 1.0 MAC recordings were made after incision. Peaks of the subcortical and primary cortical complex were marked (fig. 1). The latencies of the peaks were measured in milliseconds from the time of stimulus. In addition, the peak to peak amplitudes were measured in microvolts and were recorded for each of the sample periods. For each patient the postinduction record served as control.

Pancuronium (one-fifth of the initial dose) was administered as indicated by the peripheral nerve stimulator and surgical need. No other drugs were used during the study period.

Ventilation was adjusted to maintain $P_{\text{aCO}_2}$ at 40 ± 2 mmHg. Body temperature was maintained at 36 ± 1 °C by warming the administered fluids 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).

One way analysis of variance was performed to identify any significant differences ($P < 0.05$) in latency and amplitude among the three patient groups at each recording location for postinduction (baseline) and each MAC level, and for preinduction at scalp level only. Mean ages and changes in patient temperature during the study were similarly analyzed for intergroup differences. When significant differences were detected, the analysis was followed by multiple paired $t$ tests to confirm increases in latency and decreases in amplitude with increasing MAC of volatile anesthetics in each group and for comparison between recording locations. $P$ values have been adjusted according to Bonferroni methods to reflect significance for multiple comparisons. At 1.0 MAC halothane scalp amplitudes were small and unmeasurable. For the purpose of data analysis, these amplitudes were considered to be less than 0.1 mV and the Mann-Whitney U nonparametric
test was employed to establish statistical significance between the patient groups.17

Results

The three groups did not differ significantly with respect to age (28.7 ± 9.8 yr for the halothane group, 26.6 ± 10.2 yr for the enflurane group, and 27.8 ± 8.9 yr for the isoflurane group). Similarly, there was no significant difference in esophageal temperature between the three groups obtained postinduction (36.3 ± 0.1° C for the halothane group, 36.1 ± 0.1° C for the enflurane group, and 36.2 ± 0.1° C for the isoflurane group). Furthermore, there was no significant change in temperature during the course of the study. The maximum observable decrease in esophageal temperature found in two patients (one from the halothane group and one from the enflurane group) was of 0.3° C. All the patients 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 preinduction level.

Preinduction measurable data could easily be obtained at scalp level but not at P-F, L-3, and C-6 because of extreme noise (fig. 1). The preinduction values for scalp latency were as follows: halothane group, 35.7 ± 0.7 ms; enflurane group, 35.8 ± 0.8 ms; and isoflurane group, 35.8 ± 0.8 ms; and for scalp amplitude: halothane group, 1.4 ± 1.2 μV; enflurane group, 1.7 ± 0.8 μV; and isoflurane group, 1.8 ± 1.0 μV. There were no statistically significant differences between the groups at preinduction.

Following induction reproducible data were obtained in all patients at all locations, namely, popliteal fossa, L-3, C-6 and scalp, which served as baseline (control) data for further comparisons. There were no statistically significant differences between the three groups at postinduction.

Figure 1 shows the effects of halothane with increasing concentrations (MAC) in the presence of 60% N2O on popliteal fossa, L-3, C-6, and scalp recorded evoked potentials in a patient undergoing corrective surgery for scoliosis.

As the distance from the ankle increases, the latency increases being shortest at popliteal fossa and longest at scalp in all patients. The amplitudes are high at popliteal fossa, lower at L-3, remain the same at C-6, and then increase again at scalp. As the concentration of volatile anesthetic increases, the amplitudes decrease and latencies increase at each recording location. The effect is obvious at scalp location as compared to other locations.

Figure 2 shows the effect of recording location on evoked potential amplitude at postinduction (60% N2O). The amplitudes become smaller at L-3 compared to popliteal fossa in all three groups (P < 0.05), remain at the same level at C-6, and then increase at scalp compared to C-6 in all the three groups (P < 0.05). There are no intergroup differences seen at any recording location.

Figure 3 shows the effect of recording location on evoked latency at postinduction (60% N2O). As the distance from the ankle increases, the latency also increases (P < 0.005) such that the largest value is observed at the scalp. There are no intergroup differences at any recording location.
The difficulty in obtaining preinduction subcortical waveforms was attributable to the operating room electrical noise and muscle artifacts. These findings are similar to those of El-Negamy and Sedgewick,18 and in contrast to those of Lastimosa et al.,19 who obtained their measurements in electrically shielded and soundproofed rooms.

Data obtained postinduction were qualitatively similar to that of Lastimosa et al., although quantitatively different.19 These differences may have resulted from differences in recording sites (L-3 vs. L-5) and recording and stimulating parameters.

Each anesthetic increased the latencies and decreased the amplitudes of peripheral nerve, spinal (L-3, C-6) and scalp recorded evoked potentials. The dose-related effects were minimal at peripheral nerve, L-3, and C-6 locations and maximal at the scalp location. These findings are sim-

**Fig. 5.** Effect of increasing the concentration of volatile anesthetics + 60% N2O on multilevel recorded SEP amplitude. Postinduction data serve as control. Values are mean ± SD. Note that at all locations each MAC increase decreases amplitudes. *P < 0.005. Note that the maximum effect at SC amplitude decrease at SC > C6 (P < 0.01) in all three groups. At 1.0 MAC halothane, SC amplitude depression is significantly greater (P < 0.01) than for enflurane or isoflurane.

**Discussion**

Our results demonstrate that under the conditions of this study, we had no difficulty in obtaining preinduction cortical, postinduction cortical, and subcortical SEP data.
ilar to those of Thurner et al.,\textsuperscript{13} who studied the effects of fentanyl and enflurane on cortical and subcortical evoked potentials.

There are fewer intervening synapses involved in the generation of the subcortical potentials than that of cortical potentials. The greater number of synapses involved in generation of cortical potentials may explain why they are more affected by anesthetic agents.

Our results further show that at each MAC multiple, the three volatile anesthetics similarly affected the evoked response at subcortical poplitéal fossa, L-3, and C-6 level. However, at the cortical level, enflurane and isoflurane had similar effects, whereas halothane depressed SC potentials more than enflurane and isoflurane. At 1.0 MAC halothane SEP were barely recognizable or measurable. This potent effect of halothane may be due to its greater inhibition of GABA metabolism at synapses as compared to enflurane or isoflurane.\textsuperscript{20}

The subcortical potentials were largely unaffected by increasing concentrations of all three volatile anesthetics. Peterson et al.\textsuperscript{8} seemed to show similar results. However, their data are incomplete because no measurements of subcortical amplitudes are provided. Similarly, comparative analysis of subcortically versus cortically recorded data with isoflurane and enflurane are not shown by Peterson et al.\textsuperscript{8}

In contrast to previous studies by us\textsuperscript{9} and investigations by McPherson et al.,\textsuperscript{7} Peterson et al.\textsuperscript{8} stated that they could not record cortical waveforms with 1 MAC of enflurane in 67% of the cases. The same investigators could not record usable cortical waveforms in two of seven patients at 1.5 MAC isoflurane. They concluded that depression of cortical waveforms was most pronounced with enflurane and least with halothane. However, previous studies by us\textsuperscript{9} showed that halothane at 1 MAC caused more depression of cortical waveforms than did enflurane or isoflurane.

Furthermore, Peterson et al.\textsuperscript{8} found that halothane even at 1.5 MAC did not depress median nerve potentials, whereas we as well as Salzman et al.\textsuperscript{10} found that higher concentrations of halothane depressed cortically recorded posterior tibial nerve potentials to the extent that they became unmeasurable. We have no explanation why Peterson's results differ so strikingly from our,\textsuperscript{9} McPherson's\textsuperscript{7} and Salzman's\textsuperscript{10} findings.

Although monitoring of skin recorded scalp potentials has proven to be a useful surgical adjunct in scoliosis surgery, the technique has limitations with occasional reports of false-negative findings.\textsuperscript{1,2} It has been suggested that multilevel noninvasive skin recordings that monitor the same neural pathways may make the methodology more reliable.\textsuperscript{13} The two recordings obtained below the level of fusion may reflect spinal cord injury. Even though neck (C-6) potentials are less affected than scalp potentials by volatile anesthetics, their sensitivity to spinal cord injury needs to be demonstrated and should be compared with the sensitivity of scalp potentials. Schramm et al.\textsuperscript{21} studied the effects of graded compression (distraction) on both spinal and cortical recorded potentials in cats and reported that both potentials were depressed by spinal cord compression. Spinal potentials were depressed at an earlier stage of compression than the cortical potentials (60% vs. 80% of total compression applied to abolish both potentials). Brodkey et al.\textsuperscript{16} studied the effects of spinal compression (distraction) and vascular compromise (hypotension-systolic blood pressure reduced to 50% of its original value) on cortically recorded potentials and found that a combination of both factors was essential to depress cortical evoked potentials. The results of the present study suggest that in normal subjects when using our stimulus and recording parameters, the administration of halothane, enflurane, and isoflurane in increasing concentrations up to 1.0 MAC (each with 60% N\textsubscript{2}O) should be compatible with subcortical poplitéal fossa, L-3, and C-6 recorded evoked potentials. The administration of halothane up to 0.75 MAC and enflurane or isoflurane up to 1.0 MAC (each with 60% nitrous oxide) should be compatible with cortically recorded evoked potentials.

If the amplitudes of the preoperative scalp recorded potentials are small, the anesthetic concentration of halothane should be limited to less than 0.75 MAC and of enflurane or isoflurane at less than 1.0 MAC in conjunction with 60% N\textsubscript{2}O. During critical periods of monitoring, end-tidal concentrations of volatile anesthetics should be kept constant. However, if alterations in end-tidal concentrations occur, changes in latency and amplitudes should be anticipated and considered in interpretation. Because the C-6 spinal recorded evoked potential is located above the level of fusion and is less affected by volatile anesthetics, an additional recording site may be provided, which may help reduce false-negative reports and increase the reliability of the methodology.

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References