EVOKE POTENTIALS DURING ISOFLURANE ANAESTHESIA

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No single, reliable, and easily applied neurophysiological measure of anaesthetic depth is currently available. Although a number of techniques of EEG analysis, which involve visual inspection of the EEG trace and increasingly sophisticated methods of signal processing, have been proposed (Evans and Davies, 1984), all have limitations in that the changes observed are generally agent-specific and do not always correlate well with the general state of the patient. Measurements of evoked potentials have been suggested as a means of monitoring the depth of anaesthesia (Uhl et al., 1980) and graded changes in the early cortical auditory evoked responses have been demonstrated for halothane, enflurane and etomidate (Thornton et al., 1983; Navaratnarajah et al., 1983). We have previously studied the effects of increasing concentrations of nitrous oxide on visual, somatosensory and auditory evoked responses (Sebel, Flynn and Ingram, 1984). Nitrous oxide caused a dose-related decrease in the amplitudes of the visual (VEP) and somatosensory evoked potentials (SEP), but there was no effect on latency. The current study was devised to quantify the effects of isoflurane on conventional evoked potential measurements.

PATIENTS AND METHODS

Following the approval of the local ethics committee, informed consent was obtained from 10 healthy patients (mean age 50.9 ± 10.8 yr, 4 male) scheduled for elective surgery. No premedication was given and anaesthesia was induced with sufficient thiopentone to obtund the eyelash reflex. The trachea was intubated following vecuronium 6–8 mg and the lungs were ventilated with isoflurane in oxygen using a Manley ventilator. Vecuronium 2 mg was given every 30 min. Inspired isoflurane concentration was adjusted to maintain an end-tidal isoflurane concentration of 0.55% for 15 min and 1.1% for 15 min (approximating to 0.5 and 1.0 MAC), as determined with an Engstrom EMMA. The Engstrom EMMA was removed from the circuit every 5 min, and the zero readjusted to account for any negative zero drift associated with the presence of water vapour. The minute volume was adjusted to maintain the end-tidal carbon dioxide tension at 4–5 %, using a Gould infra-red analyser.

SUMMARY

Somatosensory, visual and brainstem auditory evoked potentials were recorded in 10 unpremedicated patients anaesthetized with isoflurane in oxygen. Recordings were made at 0.5%, 1.1% and 1.65% (six patients) end-tidal isoflurane concentration. There were statistically significant increases in the latencies of the somatosensory (N20), visual and brainstem auditory potentials (waves III and V) with increasing concentrations of isoflurane. The central conduction time was prolonged. Amplitudes of the somatosensory and visual potentials were reduced with increasing concentrations of isoflurane. The effects of isoflurane on evoked potentials are similar to those of halothane and enflurane. It is possible that changes in evoked potential measurements may be useful as a neurophysiological indicator of anaesthetic depth.
Surgery was commenced when the end-tidal isoflurane concentration had been stable at 1.1% for 10 min. If time permitted, the isoflurane concentration was increased to 1.65% for 15 min (six patients), approximating to 1.5 MAC. In two patients 70% nitrous oxide was given after induction of anaesthesia and at the end of each 15-min period. Standard electrode derivations and filter settings were used, and have been described previously (Sebel, Flynn and Ingram, 1984). Stimulus parameters were as follows: brainstem auditory evoked response (BAER), 10-Hz square wave clicks at 80 dBHL for 1024 repetitions; VEP, 2-Hz stroboscopic flash stimulation for 128 repetitions; SEP, 100-μs constant current pulse applied over the median nerve at 2 Hz for 256 repetitions. A Medelec Sensor and Apple microcomputer were used to average and store the evoked responses. At least two recordings were made for each modality at each level. On occasions when the identification of the peaks was difficult, further traces were obtained. Peak latencies of waves I, III and V of the BAER, the latencies of the first major negative peak of the VEP and of the cervical peak (N13) was used to derive a measure of the central conduction time (CCT), which was taken as the difference between N20 and N13 peaks (five patients). The amplitudes of cortical SEP and VEP were measured between the first major negative peak and the greatest succeeding positive peak occurring before 60 ms (SEP) and 250 ms (VEP). All measurements were made by two independent observers.

Data are presented as mean (± SD). Regression analysis was carried out for waveform latencies and amplitudes against end-tidal isoflurane concentrations. A t test was used to test the difference of the mean slopes from zero.

## RESULTS

Satisfactory evoked potentials could be recorded in all subjects. On occasion, the peaks were not easily identified or did not replicate well. In these patients, no data have been reported. Nasopharyngeal temperature did not alter by more than 0.5 °C in any patient. No undue hypotension (systolic pressure less than 75% of control) occurred in any patient.

### Somatosensory evoked potentials

Latencies and amplitudes are shown in table I. All patients showed the same trend. With increasing concentrations of isoflurane, there was a graded reduction in amplitude and the first major negative cortical component (N20) showed a graded increase in latency (fig. 1). These changes were statistically significant: for the amplitude, the mean slope was $-3.14 (±2.3) \mu V %^{-1}$ ($P < 0.005$) and for the latency, the mean slope was $1.76 (±0.75) ms %^{-1}$ ($P < 0.005$). In the five subjects in whom CCT was measured, a graded

| Table I. Measurements of somatosensory evoked potentials. — Indicates that no measurement was made or could be made. End-tidal isoflurane concentrations are shown as 0, 0.55, 1.1, 1.65% |
|-----------------|-----------------|-----------------|-----------------|
| Subject | Latency (ms) | Amplitude (ms) | CCT (ms) | Slope |
| | 0 | 0.55% | 1.1% | 1.65% | 0 | 0.55% | 1.1% | 1.65% | 0 | 0.55% | 1.1% | 1.65% |
| 1 | 22 | 23.6 | 24.8 | 11 | 6.5 | 3.8 | — | — | — | — | — | — |
| 2 | 17.2 | 18.4 | 19.6 | 21.4 | 13.5 | 7.8 | 3.4 | 4.4 | — | — | — | — |
| 3 | 18.8 | 20.0 | 20.0 | 20.0 | 4.5 | 1.5 | 1.0 | — | — | — | — | — |
| 4 | 20.4 | 20.4 | 21.6 | 22.8 | 6.0 | 2.1 | 2.2 | 2.3 | — | — | — | — |
| 5 | 19.6 | 19.6 | 20.0 | 20.0 | 4.1 | 3.6 | 2.8 | — | — | — | — | — |
| 6 | 20.4 | 21.6 | 22.2 | 23.6 | 9.3 | 8.5 | 4.2 | 1.7 | 5.2 | 6.4 | 7.0 | 8.4 | 1.85 | 4.93 | 1.85 |
| 7 | 20.2 | 21.4 | 23.6 | 23.6 | 1.5 | 1.5 | 0.9 | 1.8 | 5.4 | 5.8 | 8.0 | 8.0 | 2.25 | 0.5 | 1.82 |
| 8 | 20.0 | 22.4 | 22.6 | 20.0 | 2.0 | 1.8 | 1.1 | — | 5.8 | 8.0 | 8.2 | — | 2.36 | 0.82 | 2.15 |
| 9 | 21.0 | 22.1 | 23.0 | 24.6 | 4.4 | 3.2 | 1.5 | 0.9 | 8.0 | 7.1 | 7.2 | 8.8 | 2.13 | 2.35 | 0.45 |
| 10 | 21.5 | 22.3 | 23.0 | 23.0 | 9.5 | 7.0 | 3.8 | 3.0 | 8.2 | 8.8 | 9.2 | 8.7 | 0.95 | -4.13 | 0.35 |
| Mean | 1.76 | -3.14 | 1.33 | | | | |
| SD | 0.75 | 2.13 | 0.86 | | | | |
| P < | 0.005 | 0.005 | 0.005 | | | | |
FIG. 1. Recordings of somatosensory evoked potentials from one subject. Upward deflection indicates a negative potential. The lines marked control... 1.65% show the potentials recorded at the end of each phase of the study. Latencies were measured from time of stimulus to the vertical markers. Measurements of amplitude were made between the horizontal markers in the control trace. The horizontal markers have been omitted from the subsequent traces for clarity. These recordings show an increase in latency and a decrease in amplitude with increasing concentrations of isoflurane.

increase in latency with increasing isoflurane concentrations was observed also; the mean slope was 1.33 (±0.86) ms %⁻¹ (P < 0.005).

Visual evoked potentials

Latencies and amplitudes are shown in table II. With increasing concentrations of isoflurane, the amplitude decreased sequentially and the latency increased (fig. 2). As with the SEP, these changes were statistically significant, for the group. Mean slope for the amplitude was −7.16 (±4.53) μV %⁻¹ (P < 0.05) and for the latency the mean slope was 17.55 (±8.21) ms %⁻¹ (P < 0.005).

Brainstem auditory evoked responses

BAER latencies are shown in table III. There were no consistent changes in the latency of wave
I although, during anaesthesia, this peak was frequently difficult to identify. With increasing concentrations of isoflurane, the latencies of both wave III and wave V increased (fig. 3). The changes in amplitude of peaks III and V were not greater than the expected inter-trial variability. For the group as a whole, the latencies of both wave III and wave V were increased significantly, mean slope for wave III was 0.788 (±0.549) ms⁻¹ (P < 0.05) and wave V was 0.317 (±0.088) ms⁻¹ (P < 0.005).

**Effect of nitrous oxide**

In the two patients in whom 70% nitrous oxide was added to 1.1% isoflurane, a further small increase in latency and a decrease in amplitude of the SEP were observed (fig. 4). This resulted in small but recognizable SEP, but the VEP in both patients was reduced below the level of background noise. BAER did not alter with the addition of nitrous oxide.

**DISCUSSION**

The data obtained in this study support the concept that anaesthetic agents generally produce increases in the latency of cortical evoked potentials and decreases in their amplitude. Previous studies have demonstrated that halothane produces graded increases in VEP latency (Uhl et al., 1980) and that halothane, enflurane (Thornton et al., 1983) and isoflurane (Navaratnarajah et al., 1985) cause increases in BAER latencies, and dose-dependent increases in the latency and reductions in the amplitude of the early cortical components of the BAER. The i.v anaesthetics Althesin (Heneghan et al., 1984) and etomidate (Navaratnarajah et al., 1983) do not affect BAER, but exert an effect similar to that of the inhalation agents on the early cortical components of the auditory response. Similarly, large doses of fentanyl have no effect on BAER (Samra et al., 1984). Nitrous oxide does not affect cortical...
FIG. 4. Somatosensory evoked potential from one subject in whom 70% nitrous oxide was added to 1.1% isoflurane. Upward deflection indicates a negative potential. Latencies were measured from the time of stimulus to the vertical markers. Amplitudes were measured between the horizontal markers. The changes following isoflurane are the same as seen in figure 1. Addition of nitrous oxide caused a further small increase in latency and reduction in amplitude of the evoked potential.

evoked potential latencies, but produces dose-dependent decreases in the amplitudes of VEP and SEP (Sebel, Flynn and Ingram, 1984). In view of the consistency of the observations that the amplitude of cortical potentials are reduced and their latencies increased and that the changes do not appear to be agent-specific, it may be feasible to derive an index of the depth of anaesthesia from these measurements.

Cortical, rather than brainstem evoked potentials, are the most useful for monitoring anaesthesia. They tend to be of large amplitude, show little inter-trial variation and exhibit clear changes which can be measured at various levels of surgical anaesthesia. BAER are not so useful, since the changes seen in BAER latencies with isoflurane in this study, as with halothane and enfurane (Thornton et al., 1984), are of small magnitude and do not occur with the i.v. agents (Navaratnarajah, 1983; Heneghan et al., 1984; Samra, 1984). They are of small amplitude and the amplitude measurements demonstrate great inter-trial variability, which makes them difficult to record in the operating theatre because of increased background noise. The middle latency, early cortical evoked responses have been suggested as the most suitable for measuring depth of anaesthesia (Thornton et al., 1984), but the peaks are not easily definable at increased depths of anaesthesia. In addition, interfering myogenic potentials of latency similar to that of the early cortical responses may make them difficult to record and, in our experience, this limits their usefulness.

VEP can be effectively monitored during anaesthesia only using flash stimuli. Even in the alert conscious subject, variations in latency of the first major negative peak and variation in the morphology of the waveform are known to occur (Raudzens, 1982). For this reason, minor changes in latency are difficult to interpret during anaesthesia; however, the decreases in amplitude are reliable and easy to measure.

SEP do not have these limitations. They show consistent changes in amplitude and latency in the cortically derived potentials. They have the advantage of allowing conduction time within the central nervous system (CCT) to be measured. The CCT shows increases in latency which parallel the changes observed in cortical potentials.

The effects on BAER of isoflurane and isoflurane-nitrous oxide have been studied (Manninen, Lam and Nicholas, 1985). Between awake and 1% end-tidal isoflurane concentration, statistically significant increases in the latencies of waves III, IV and V were found. Increasing the concentration of isoflurane to 1.5% end-tidal resulted in a further, but not statistically significant, increase in latency. Therefore, a plateau effect occurred and no further increase was found beyond 1.5%. Nitrous oxide was found not to affect BAER further. The findings in our current study are consistent with these observations. As we did not increase end-tidal concentration beyond 1.65%, we may have only just reached the plateau concentration. Our alterations in wave V latency were similar, being less than 1.0 ms. We also observed no effect of nitrous oxide on BAER, although cortical evoked potentials were affected by the addition of nitrous oxide to the isoflurane.

Nitrous oxide alone has no effect on latency of cortical evoked potentials (Sebel, Flynn and Ingram, 1984), but figure 4 shows that the addition of 70% nitrous oxide to 1.1% isoflurane causes a further increase in latency in SEP, which suggests an additive effect of nitrous oxide when used in conjunction with isoflurane. Under these
conditions VEP were unrecordable. This lends support to the view that SEP are likely to be most useful in monitoring anaesthetic depth, as they can be readily recorded, even at relatively deep levels of anaesthesia when VEP and early cortical auditory responses may not be present (Thornton et al., 1984).

In this study, owing to time constraints, reversal of the changes was not monitored specifically. However, graded reversal has been shown to occur with nitrous oxide (Sebel, Flynn and Ingram, 1984), and with halothane and enfurane (Thornton et al., 1984).

In conclusion, isoflurane produced graded increases in the latency of the SEP, CCT, VEP and waves III and V of BAER. The amplitudes of the VEP and cortical SEP were reduced by isoflurane. The most consistent and reliable changes occurred in SEP and the effects were similar to those observed with other anaesthetics, suggesting that the monitoring of evoked potentials may provide a suitable neurophysiological index of the depth of anaesthesia.

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REFERENCES


