EFFECT OF ISOFLURANE ON THE AUDITORY EVOKED RESPONSE IN MAN

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The use of sympathetic and haemodynamic signs to assess the depth of anaesthesia in paralysed patients is unsatisfactory, and results in an incidence of awareness of up to 7% (Breckenridge and Aitkenhead, 1983). The development of i.v. anaesthetic drugs with minimal side effects may compound the problem because weight-related infusion rates can produce widely different blood concentrations (Sear and Prys-Roberts, 1979; Thornton et al., 1985, 1986). In these circumstances awareness or overdose are equally likely, and are undetectable in the absence of side effects (Hug, 1985). There is, therefore, a need for an objective measure of the depth of anaesthesia and, in an attempt to find such a measure, we have been studying the effects of general anaesthetic drugs on the auditory evoked response (AER).

The characteristics of an ideal index of the depth of anaesthesia include the following: the index must be graded, so that the approach of awareness can be detected before its onset; it should be applicable to all anaesthetic agents, and to mixtures of agents; and it should be unaffected by non-anaesthetic drugs, such as β-adrenoceptor blocking agents and myoneural blocking drugs.

Initially, we attempted to establish whether the AER was affected similarly by the commonly used anaesthetic drugs—since there is evidence that different anaesthetic agents affect the somatosensory evoked response differently. For example, enflurane appears to increase the amplitude of some waves, which are decreased by most other agents (Clark and Rosner, 1973). So far, we have shown (Thornton et al., 1983, 1984, 1985, 1986) that halothane, enflurane, etomidate and Althesin had similar effects on the early cortical (middle latency) components of the AER, decreasing the amplitudes and increasing the latencies of waves Pa and Nb.

We then wanted to test whether the effects of the inhalation agents halothane, enflurane and isoflurane on the AER were related to their potencies as assessed by their MAC values. An earlier comparison of halothane and enflurane revealed that, although halothane had more of an effect on most waves than did enflurane at the same end-tidal concentration, there were some discrepancies when precise MAC-related comparisons were made. It was hoped that the present study would elucidate this problem.

SUMMARY

We have examined the effects of isoflurane (0.6–2.9% end-tidal) on the auditory evoked response (AER) in six patients before elective surgery. Isoflurane produced significant dose-related changes in the AER: reductions in amplitude and increases in latency of the cortical waves Pa and Nb, and increases in the latency of the brainstem waves III and V. When isoflurane was compared with halothane and enflurane using an MAC-based comparison, we found no differences in the effect of the three agents on the amplitude of the early cortical waves, although the latencies showed significant differences. The consistent dose-related effect on the amplitudes of the cortical waves implies that the AER could be a promising index of the depth of anaesthesia.
A final reason for this project was to look at sites of action of anaesthetics. The AER is particularly useful for this, since the sites of generation of many of the waves have been located in the brainstem and cortex (Maurer, Leitner and Schafer, 1980). There is evidence that the important site of anaesthetic action of all these drugs is rostral to the brainstem, possibly cortical, and this concept is supported by studies of the effects of etomidate and Althesin on regional brain metabolism (Davis et al., 1984; R. A. Hawkins, personal communication).

We wished to determine whether the effects of isoflurane were similar to those of the other inhalation agents and, accordingly, have investigated its effect on the brainstem as well as the cortex.

PATIENTS AND METHODS
Six patients with normal hearing (aged 18–45 yr), scheduled for elective surgery expected to last 1–2 h, gave informed consent to participate in the study—the design of which had been approved by the Harrow District Ethical Committee. After premedication with morphine 10 mg and atropine 0.6 mg i.m., anaesthesia was induced with thiopentone 2–4 mg kg\(^{-1}\). Pancuronium 0.1 mg kg\(^{-1}\) was given, the trachea intubated and the lungs ventilated with 70% nitrous oxide in oxygen, isoflurane being added to the gas mixture as described below. Fresh gas flow and, hence, ventilation was adjusted to keep end-tidal carbon dioxide constant in the range 5.0–5.6 kPa (38–42 mm Hg) as measured with a Hewlett-Packard 47201A in-line carbon dioxide analyser. Temperature, measured with an oesophageal thermistor probe, was also kept constant, and heart rate and arterial pressure were monitored. An arterial pressure of less than 90 mm Hg systolic was treated by the infusion i.v. of lactated Ringer's solution; a decrease in arterial pressure to less than 80 mm Hg systolic would have necessitated the cessation of the administration of isoflurane and, hence, the abandonment of the study.

At 7 min after the induction of anaesthesia, isoflurane was added to the fresh gas flow in concentrations which increased in five equal steps of 0.75%, to a maximum of 3.75%, each inspired concentration being held for 10 min. The inspired and end-tidal concentrations were measured using an Engstrom EMMA, protected from the effect of water vapour by placing a condenser humidifier between the sensing probe and the patient.

The AER was recorded before and after the induction of anaesthesia, and in the second half of the 10 min at each inspired concentration of isoflurane. A 500-\(\mu\)s unidirectional rectangular wave pulse was generated by a Global Specialities Corporation 4001 pulse generator, and applied to acoustically shielded Telephonics TDH 39P headphones. This gave a binaural rarefraction click 75 dB above the normal hearing threshold, with a dominant frequency of 1 kHz. The EEG was recorded from silver–silver chloride disc electrodes, with the right and left mastoid and the inion placements being referred to the vertex. The EEG signal was amplified and filtered (25–3600 Hz) with a modified SLE 10/8 polygraph, and recorded on a Racal Store 4 FM tape recorder at 38 cm s\(^{-1}\) for subsequent analysis. The averaged AER for the 130-ms post-stimulus was derived from 2048 stimuli with a Datalab DL4000 averager. The AER variables examined were the latency and amplitude of waves I, III and V in the brainstem section of the response, and of waves Pa and Nb in the early cortical section. \(I – III, I – V\) and \(III – V\) intervals were also examined.

Regression analyses were carried out using the MINITAB programme (Ryan, Joiner and Ryan 1976), as previously described (Thornton et al., 1984). The MINITAB routines applied were: a test for a significant dose–response relationship with isoflurane for each variable for each patient, and then a derivation of a common dose–response slope representing all six patients, preceded by testing for parallelism. The comparison of dose–response slopes for the three different inhalation agents shown in table III was performed with a one-way analysis of variance on the individual patient's slopes.

All studies were completed before the start of surgery.

RESULTS
Table I shows the patients' demographic details. No study was discontinued on grounds of excessive hypotension (< 80 mm Hg systolic).

Increasing end–tidal concentrations of isoflurane increased the latency and reduced the amplitude of waves Pa and Nb in all patients. Figure 1 illustrates the early cortical waves in one patient, and in figure 2 Pa amplitude is plotted against end–tidal isoflurane concentration for all six patients. Increasing concentrations of isoflurane also increased the latency of brainstem waves III and V, as illustrated in figure 3.
TABLE I. Demographic data. All surgery was elective, the female patients undergoing major gynaecological surgery, the male patient major orthopaedic surgery.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63</td>
<td>9</td>
</tr>
<tr>
<td>Sex ratio (F/M)</td>
<td>5/1</td>
<td>--</td>
</tr>
</tbody>
</table>

End-tidal isoflurane concn

\[ 0.5 \mu V \]

Fig. 1. Effect of increasing end-tidal isoflurane on the early cortical components of the AER. The latencies of Pa and Nb increase, and the amplitudes decrease, with increasing isoflurane concentration. \( \nabla = \) Pa; \( \triangle = \) Nb.

In one patient in whom surgery was delayed, isoflurane was discontinued to establish whether the observed effects were reversed when the end-tidal concentration of isoflurane was decreased; 15 min after discontinuing the isoflurane, the end-tidal concentration had decreased to the value obtained at the end of the first 10-min period, and the changes in the configuration of the waves had reversed almost completely.

Table II shows the mean slopes of the graphs of change of amplitude and latency of all the waves.

End-tidal isoflurane concn

\[ 0.5 \mu V \]

Fig. 2. Pa amplitude plotted against end-tidal isoflurane concentration, expressed both in % and MAC units. In all six patients Pa amplitude decreased as end-tidal isoflurane increased.

End-tidal isoflurane concn

\[ 0.5 \mu V \]

Fig. 3. Effect of increasing end-tidal isoflurane concentration on the brainstem components of the AER. Vertical lines are drawn through waves I, III and V at 0% isoflurane. In this patient III and V latency increased progressively with increasing end-tidal isoflurane.
identified waves per unit change in end-tidal isoflurane concentration (%), together with $P$ values for the difference of the slopes from zero. There were significant concentration-dependent changes in the latency of waves V, Pa and Nb, and the I-V interval. The changes in III latency, and III-V interval approached statistical significance. Table III shows the results from our previous study of the effects of halothane and enflurane on the AER compared with those of the present study. The results are MAC, rather than concentration-related. The effects of the three agents on III and V latency and Pa and Nb amplitude did not differ significantly between the three agents, although the latencies of Pa and Nb were affected significantly.

**DISCUSSION**

This study shows that isoflurane affects the auditory evoked response (AER) by increasing the latencies of waves III, V, Pa and Nb, and reducing the amplitudes of waves Pa and Nb. These effects were dose related, and similar in all patients.

We have shown that isoflurane has effects on the early cortical waves of the AER similar to those of all the other agents that we have previously studied (Thornton et al., 1983, 1984, 1985, 1986): halothane, enflurane, etomidate and Althesin all increased the latency and decreased the amplitude of the early cortical waves in the AER reversibly and in a dose- or concentration-related manner. This point is important in relation to the measurement of depth of anaesthesia, because a technique which can be utilized during routine general anaesthesia must be similarly affected by all anaesthetic drugs. Various other indices which have been considered as measures of depth of anaesthesia all share the disadvantage of being differently affected by different anaesthetics (Jones, Heneghan and Thornton, 1985). Specific examples of this are EEG-power spectral analysis, and its derivatives the compressed spectral array and the spectral edge. Enflurane also affects the somatosensory evoked response differently from other agents, increasing the size of the P100 cortical component which the other agents suppress (Clark and Rosner, 1973). This difference in effect is not a problem with the early cortical components of the AER, as all the agents that we have so far studied, and now isoflurane, consistently reduce the amplitude and increase the latency of early cortical (middle latency) waves (Thornton et al., 1983, 1984, 1985, 1986).

We have examined the potency relationship of the effects of the inhalation agents on the brain stem and early cortical waves in table III. (There is no measure of anaesthetic potency that applies to the i.v. agents.) The effects of isoflurane are compared with those of halothane and enflurane from our previous study (Thornton et al., 1984), using MAC-corrected effects. This was done by

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**Table II. Relationship between end-tidal isoflurane concentration and latency and amplitude of waves indicated. Units of slopes of latencies and intervals are ms/% end-tidal isoflurane, and for amplitude $\mu V/%$ end-tidal isoflurane. Significance: **$P < 0.01$; *$0.1 > P > 0.05$; ns = not significant.**

<table>
<thead>
<tr>
<th>Wave</th>
<th>Function</th>
<th>Slope</th>
<th>SEM</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Latency</td>
<td>0.00</td>
<td>0.02</td>
<td>ns</td>
</tr>
<tr>
<td>III</td>
<td>Latency</td>
<td>0.22</td>
<td>0.05</td>
<td>*</td>
</tr>
<tr>
<td>V</td>
<td>Latency</td>
<td>0.32</td>
<td>0.04</td>
<td>**</td>
</tr>
<tr>
<td>Pa</td>
<td>Latency</td>
<td>18.7</td>
<td>2.4</td>
<td>**</td>
</tr>
<tr>
<td>Nb</td>
<td>Latency</td>
<td>29.6</td>
<td>3.4</td>
<td>**</td>
</tr>
<tr>
<td>I-III Interval</td>
<td>0.22</td>
<td>0.06</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>I-V  Interval</td>
<td>0.32</td>
<td>0.04</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>III-V Interval</td>
<td>0.10</td>
<td>0.03</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Amplitude</td>
<td>-0.02</td>
<td>0.01</td>
<td>ns</td>
</tr>
<tr>
<td>V</td>
<td>Amplitude</td>
<td>-0.04</td>
<td>0.01</td>
<td>ns</td>
</tr>
<tr>
<td>Pa</td>
<td>Amplitude</td>
<td>-0.21</td>
<td>0.03</td>
<td>**</td>
</tr>
<tr>
<td>Nb</td>
<td>Amplitude</td>
<td>-0.21</td>
<td>0.04</td>
<td>**</td>
</tr>
</tbody>
</table>

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**Table III. Comparison of the effects of isoflurane from the present study with those of halothane and enflurane (Thornton et al., 1984); results now expressed in MAC units rather than percentages (MAC values used: halothane 0.7%; enflurane 1.7%, isoflurane 1.2%); thus units are ms/MAC unit, and $\mu V$/MAC unit, as appropriate. Values are means (SD). Different from halothane: **$P < 0.001$; different from halothane and enflurane: $\dagger\dagger P < 0.001$.**

<table>
<thead>
<tr>
<th>Wave</th>
<th>Function</th>
<th>Halothane (n = 6)</th>
<th>Enflurane (n = 6)</th>
<th>Isoflurane (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Latency slope</td>
<td>0.23 (0.21)</td>
<td>0.27 (0.05)</td>
<td>0.26 (0.25)</td>
</tr>
<tr>
<td>V</td>
<td>Latency slope</td>
<td>0.23 (0.07)</td>
<td>0.40 (0.08)</td>
<td>0.37 (0.17)</td>
</tr>
<tr>
<td>Pa</td>
<td>Latency slope</td>
<td>6.8 (2.7)</td>
<td>20.1 (6.2)**</td>
<td>23.7 (4.9)**</td>
</tr>
<tr>
<td>Nb</td>
<td>Latency slope</td>
<td>8.9 (5.8)</td>
<td>18.3 (8.9)</td>
<td>37.1 (9.6)$\dagger\dagger$</td>
</tr>
<tr>
<td>Pa</td>
<td>Amplitude slope</td>
<td>-0.51 (0.15)</td>
<td>-0.43 (0.30)</td>
<td>-0.28 (0.14)</td>
</tr>
<tr>
<td>Nb</td>
<td>Amplitude slope</td>
<td>-0.23 (0.18)</td>
<td>-0.37 (0.23)</td>
<td>-0.27 (0.11)</td>
</tr>
</tbody>
</table>
ISOFLURANE AND THE AUDITORY EVOKED RESPONSE

comparing the slopes of III and V latency, and Pa and Nb latency and amplitude plotted against MAC multiples rather than vapour concentration. If the effects of these drugs exactly corresponded with their MAC values, then the mean slope for each individual variable for each drug would be identical. The slopes for III and V latency, and for Pa and Nb amplitude are not significantly different between the three agents, but there are differences for Pa and Nb latency. This indicates a quantitative difference in the effects of these drugs on the latencies of the early cortical waves, which in turn suggests that these variables will not be useful indices of the depth of anaesthesia. This is not the only interpretation; since these results are based upon small samples, these may be chance findings. The amplitude of waves Pa and Nb are the most promising candidates in the search for an index of depth of anaesthesia because they were not quantitatively differently affected by the three volatile agents and were qualitatively similarly affected by etomidate and Althesin.

Isoflurane has effects on the brainstem components of the AER similar to those of halothane and enflurane (Thornton et al., 1983, 1984), which also increase the latencies of the brainstem peaks III and V. This finding is in accord with a recent report which showed that isoflurane increased the latencies of the brainstem peaks (Manninen, Lam and Nicholas, 1985). However, these authors reported that isoflurane in oxygen had no further effect on the brainstem waves above a concentration of 1.5% end-tidal. On examination of these data, this was not the case for 1.5% enfurane in a 50% nitrous oxide mixture and, in our study, we found that with 70% nitrous oxide in oxygen there were increasing effects of isoflurane even up to 2.85% (fig. 3).

The similar effect of isoflurane, halothane and enfurane on the brainstem AER is in contrast to that of the i.v. agents etomidate (Thornton et al., 1985) and Althesin (Thornton et al., 1986), which exhibited no effect on the brainstem AER at a time when they had produced profound depression of the early cortical waves. This relative sparing of the brainstem AER occurs with two agents which are noted for their minimal effect on respiratory and cardiovascular homeostasis, and we have previously speculated (Thornton et al., 1985, 1986) that these effects may be related. The homeostatic stability observed during anaesthesia with these agents may result in part from an absence of effect on the brainstem.

These regional differences in the effects of different anaesthetics on the AER correspond to the regional differences in their effects on cerebral metabolism—despite the intense controversy that has surrounded the methods for measuring regional brain metabolism (Crosby and Sokoloff, 1983; Hawkins, Hass and Ransohoff, 1983). Hawkins and Biebuyck (1980) have shown that halothane reduces metabolism in both the medial geniculate and the inferior colliculus in the rat, and the effect on the inferior colliculus was also observed in primates (Shapiro et al., 1978). However, Althesin (Davis et al., 1984) and etomidate (R. A. Hawkins, personal communication) had a negligible effect on the inferior colliculus and more caudal parts of the auditory pathway compared with a striking effect on the cortex. This is not to say that all i.v. agents spare the brainstem. Barbiturates reduce uniformly the metabolism of the brain (Sokoloff, 1981), although the effect of thiopentone on the AER has not been studied in detail. Our own observations and those of others (M. F. M. James, personal communication) indicate substantial effects of thiopentone on both the brain stem and cortical components of the AER. Methohexitoline produces a significant increase in wave V latency (Kriss, Prasher and Pratt, 1982).

We conclude that all the anaesthetics that we have studied so far have a dose-related effect on the cortical part of the AER, whereas some spare the brain stem. These observations, together with studies of regional brain metabolism, lend support to the concept that loss of consciousness in anaesthesia may be more closely related to depression of cortical rather than brain stem function, and that this may be measured using the cortical components of the AER.

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