EFFECTS OF HALOTHANE OR ENFLURANE WITH CONTROLLED VENTILATION ON AUDITORY EVOKED POTENTIALS

C. THORNTON, C. P. H. HENEGHAN, M. F. M. JAMES AND J. G. JONES

SUMMARY

The effects of increasing concentrations of halothane and enflurane on selected components of the auditory evoked response were studied in 12 patients; six received halothane and six enflurane. After the induction of anaesthesia with thiopentone, anaesthesia was maintained with 70% nitrous oxide in oxygen. Ventilation was controlled. The inspired concentration of the inhalation agent was increased incrementally, halothane in steps of 0.5% up to 2.5%, and enflurane in steps of 1% up to 5%. With both agents, linear dose-related increases were seen in the latencies of waves III, V, Pa and Nb and the interpeak intervals I—V and III—V, with decreases in the amplitudes of Pa and Nb. In five of the patients the inhalation agent was discontinued at the end of the test period, resulting in reversal of the changes in some or all of these waves. End-tidal carbon dioxide tension was controlled and variations of temperature and arterial pressure were insufficient to produce the observed changes. The results show that halothane and enflurane delay neural transmission along the brainstem and cortical sections of the auditory pathway and that the effects of these agents are approximately related to their known anaesthetic potencies.

Of the problems which arise commonly in association with general anaesthesia, that of assessing the depth of anaesthesia is particularly relevant. This is especially so during mechanical ventilation, where reliance on traditional signs may lead to an unacceptably high frequency of awareness. Thus, there is a need for an objective method, which is independent of these signs, with which to assess the depth of anaesthesia. Ideally, it should also be graded, to allow detection of approaching awareness, and should be applicable to all anaesthetic agents.

A number of methods have received attention, including the electroencephalogram (EEG) and some of its modifications such as the cerebral function monitor and power spectral analysis. These have not been altogether appropriate, largely because the varying effects of different anaesthetic agents make interpretation difficult (Bart, Homi and Linde, 1971; Clark and Rosner, 1973; Saunders, 1981). Another modification of the EEG signal, the auditory evoked response, has been studied and we have previously demonstrated graded changes in the brainstem and early cortical components of this response during graded increases in the end-tidal concentrations of enflurane in spontaneously breathing patients (Thornton et al., 1981, 1983). In the present study, ventilation was controlled, a normal end-tidal carbon dioxide concentration achieved and maintained, and the effects of halothane or enflurane, on the auditory evoked responses, measured.

PATIENTS AND METHODS

Subjects and anaesthesia

Twelve patients aged between 18 and 45 yr were investigated. Each patient had given informed consent to an experimental programme approved by the Northwick Park Hospital Ethics Committee. Only one volatile agent was given to each patient and the entire study was carried out before the start of surgery. Morphine 10 mg and atropine 600 ng were used as premedication and anaesthesia was induced with thiopentone 2-4 mg kg⁻¹. The trachea was intubated following pancuronium 0.1 mg kg⁻¹ and the lungs ventilated with 70% nitrous oxide in oxygen. The minute volume was adjusted to keep end-tidal carbon dioxide tension constant (4.5-5.5 kPa) (Godart 17070 infra-red analyser corrected for the effects of nitrous oxide). Seven minutes after the induction of anaesthesia the volatile agent was introduced at the lowest concentration and at 10-min intervals the concentration was increased. The auditory evoked response was recorded towards the end of the post-induction period, and at the end of each subsequent 10-min period. Five inspired vapour concentrations were administered: 0.5, 1.0, 1.5, 2.0, 2.5% for halothane.
and 1.0, 2.0, 3.0, 4.0, 5.0% for enflurane. These concentrations were thought to be approximately equipotent for the two agents (Eger, 1974). The end-tidal concentrations of anaesthetics were measured continuously using a mass spectrometer (BOC Medishield). Oesophageal temperature was measured with a thermistor, its tip being positioned at the level of the aortic arch. Arterial pressure was recorded at 5–10-min intervals.

Delays in the commencement of surgery in four of the patients receiving halothane and in one receiving enflurane allowed the administration of the volatile agents to be discontinued following administration of the highest concentrations; the administration of nitrous oxide was continued. The auditory evoked response was recorded throughout this “recovery” period, the duration of which ranged from 8 to 24 min.

Recording the auditory evoked response
The technique used to measure the auditory evoked response has been described previously (Thornton et al., 1983). In outline, click stimuli of 75 dB and 0.5 ms duration were applied at a rate of $6 \text{ s}^{-1}$ and the EEG was recorded using silver–silver chloride disc electrodes at mastoid, inion and vertex. The signals were recorded continuously using an F.M. tape recorder (RACAL 4).

Subsequently, the tapes were analysed to produce averaged auditory evoked responses using a Datalab DL 4000 averager. Each response was produced from 2048 stimuli averaged over the 0–80 ms interval following the stimulus. Values were derived for the latency and amplitude of waves I, III, V, Pa and Nb in the evoked response before anaesthesia, at the end of the induction period and at each anaesthetic concentration. In addition, spontaneous EEG activity was examined for these periods.

Statistical analyses
The statistical measurement of the data was similar to that described previously (Thornton et al., 1983). The mean end-tidal anaesthetic concentration was calculated for the period during which an averaged auditory evoked response was derived. For each of the waves I, III, V, Pa and Nb regression analyses were carried out for both latency and amplitude on end-tidal anaesthetic concentration. Data before anaesthesia, and following induction and the start of nitrous oxide administration, were not included in these analyses. The slopes of the regressions for each subject were examined. A computer program, MINITAB (Ryan, Joiner and Ryan, 1976) was used to calculate a common slope for each anaesthetic agent and to test whether it was significantly different from zero. Other variables examined were the times from wave I to III, I to V and III to V (i.e. interpeak intervals).

RESULTS
Changes in the brainstem and early cortical responses with anaesthesia
The mean latencies for waves I, III, V, Pa and Nb before anaesthesia in both groups combined are comparable to the values obtained by Picton and colleagues (1974), and to our previous data (Thornton et al., 1983) (table I). Typical changes in the brainstem and early cortical responses of individual subjects before and after the induction of anaesthesia and for roughly equipotent concentration ranges of the two agents are shown in figures 1 and 2.

Brainstem response (fig. 1). With increasing end-tidal concentration of both agents the latencies of waves I, III and V increased. Vertical lines have been drawn through these waves at the first increment of end-tidal anaesthetic concentrations.

Early cortical response (fig. 2). With increasing end-tidal concentration of both agents the latency of waves Pa and Nb increased and the amplitudes decreased. Samples of the EEG corresponding to the averaged evoked responses shown in figure 2 are shown in figure 3. In both cases there was a gradual increase in the number of large amplitude slow waves although, with enflurane, these appeared at a

<table>
<thead>
<tr>
<th>Wave</th>
<th>Picton and others (1974) $(n=20)$</th>
<th>Thornton and others (1983) $(n=6)$</th>
<th>Present study $(n=12)$</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>1.5</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>III</td>
<td>3.8</td>
<td>3.7</td>
<td>3.8</td>
</tr>
<tr>
<td>V</td>
<td>5.8</td>
<td>5.8</td>
<td>5.7</td>
</tr>
<tr>
<td>Pa</td>
<td>25</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Nb</td>
<td>36</td>
<td>39</td>
<td>39</td>
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<table>
<thead>
<tr>
<th></th>
<th>Latencies (ms)</th>
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<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Picton and others (1974) $(n=20)$</td>
<td>1.5</td>
</tr>
<tr>
<td>Thornton and others (1983) $(n=6)$</td>
<td>1.6</td>
</tr>
<tr>
<td>Mean</td>
<td>0.17</td>
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<tr>
<td>SD</td>
<td>0.23</td>
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AUDITORY EVOKED POTENTIALS: HALOTHANE AND ENFLURANE

lower equivalent concentration in proportion to their respective MAC values (Eger, 1974), than with halothane. In addition, at the highest concentration of enflurane, the EEG demonstrated the phenomenon of "burst suppression" (Clark and Rosner, 1973). This was not seen with halothane.

Regression of latency and amplitude on increasing anaesthetic concentration

The effect of halothane or enflurane on the latency of wave V of the auditory evoked response for each subject is shown in figure 4. Common slopes for the regression of latency and amplitude on concentration were derived for each wave, for each agent. The common slope for wave V latency is shown in figure 5. The common slopes are presented with their standard errors in table II. With increasing concentrations of both agents, there were significant increases in the latencies of waves III, V, Pa and Nb and of the interpeak latencies I–V, III–V and there were significant linear decreases in the amplitudes of Pa and Nb. In addition, for enflurane, the latency of wave I and the interpeak latency of I–III increased significantly and V amplitude decreased significantly, these changes being linearly related to anaesthetic concentration. For the variables where both common slopes were significantly different from zero, the ratio of the halothane slope to that of enflurane is also given in table II.

Deep body temperature, end-tidal carbon dioxide tension and arterial pressure

Small decreases in deep body temperature (max 0.5°C) did occur in some, but not all, subjects. With both agents there was minimal change in end-tidal carbon-dioxide tension. Arterial pressure never de-

Fig. 1. Averaged brainstem auditory evoked responses for one subject from each group: halothane (left panel), enflurane (right panel). The responses represent those obtained before anaesthesia, following induction of anaesthesia, and at different end-tidal concentrations of each agent. Vertical lines indicate the positions of waves I, III and V at the lowest concentration.
FIG. 2. Averaged early cortical auditory evoked responses for one subject from each group: halothane (left panel), enflurane (right panel). The traces represent responses obtained before anaesthesia, following induction, and at different end-tidal concentrations of each agent. Pa is denoted as ▼ and Nb as ▲.

FIG. 3. The EEG for the two patients referred to in figure 2 at the same concentrations of halothane and enflurane. The phenomenon of "burst suppression" occurs at the 2.5% concentration of enflurane. The low voltage spikes which are seen during the periods of EEG suppression are ECG complexes.
Fig. 4. Wave V latency (ms) plotted against end-tidal halothane (HI-6) or enflurane (El-6) concentrations (vol%) for each subject.

Table II. Regression analyses of latency (ms) and amplitude (μV) on end-tidal halothane and enflurane concentrations (vol %). Common slopes, standard errors of the regression coefficients and significance of slopes compared with zero are shown. The ratios of slopes for halothane and enflurane are also shown.
creased to less than 80 mmHg systolic. Table III gives the mean (± SEM) of the changes in end-tidal carbon dioxide tension and arterial pressure over the period of administration of the inhalation agents.

Reversal of anaesthesia

After withdrawal of the inhalation agent, some recovery of the brainstem components III and V was observed in the patient who received enflurane and in two of the four who received halothane. The brainstem responses of the other two did not recover after the withdrawal of halothane. In contrast, the early components, Pa and Nb, showed partial recovery in all patients. Figure 6 shows the responses of a patient who showed partial recovery of both brainstem and early cortical components.

DISCUSSION

Changes in the brainstem and early cortical components of the auditory evoked response have been demonstrated in patients receiving halothane or enflurane.

TABLE III. Changes in end-tidal carbon dioxide tension (kPa) and systolic arterial pressure (mm Hg) (mean and SEM) for the two groups of patients over the period of administration of the inhalation agents

<table>
<thead>
<tr>
<th>End-tidal CO2 (kPa)</th>
<th>Halothane (n = 6) (Mean ± SEM)</th>
<th>Enflurane (n = 6) (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−0.05 ± 0.02</td>
<td>0.03 ± 0.10</td>
</tr>
<tr>
<td>Systolic AP (mm Hg)</td>
<td>−28 ± 5.0</td>
<td>−28 ± 3.1</td>
</tr>
</tbody>
</table>

FIG. 5. Wave V latency (ms) for all subjects plotted against end-tidal halothane or enflurane concentrations (vol%). The common regression line for each group is shown with its equation. H or E, 1–6 are denoted by •, ○, △, ■, □ respectively.

FIG. 6. The averaged auditory evoked responses in a subject (H2) in whom halothane was discontinued following administration of the greatest concentration. The traces represent: before anaesthesia, three different end-tidal halothane concentrations (as indicated), and awake following surgery. The lowest halothane trace (0.25%) was recorded 24 min after halothane had been discontinued. The time axis is split into two linear parts, from 0 to 10 ms and from 10 to 150 ms, to allow clear illustration of both brainstem and early cortical components. Vertical lines are drawn through waves III, V, Pa and Nb at the lowest end-tidal halothane concentration to facilitate comparisons with the trace at the highest concentration, and with that after discontinuation of halothane.
flurane in association with artificial ventilation. For both agents, linear dose-related increases were seen in the latencies of waves III, V, Pa and Nb and the interpeak intervals I–V and III–V, with decreases in the amplitudes of waves Pa and Nb. These findings confirm our previous observations on the effects of enflurane on the auditory evoked response in spontaneously breathing patients (Thornton et al., 1981; 1983). The III–V interpeak interval is thought to represent brainstem transmission (Stockard, Stockard and Sharbrough, 1978) and Pa and Nb latency the arrival of the signal at the primary auditory cortex (Picton et al., 1974; Kaga et al., 1980). We are convinced, therefore, that these changes represent graded slowing of central nervous system transmission.

It has been suggested (Rosenblum, Gal and Ruth, 1982) that nitrous oxide could affect middle ear pressure sufficiently to produce the changes in the brainstem response observed in our previous study. However, the effect of nitrous oxide can be excluded on two counts: first, increasing middle ear pressure delays the waves by delaying wave I, which is generated in the acoustic nerve. This type of delay in wave I would be expected to leave the interpeak latencies undisturbed whereas, in our study, we saw dose-related increases in interpeak latencies I–V and III–V. Second, a pressure effect caused by nitrous oxide would be unaffected by discontinuing the volatile anaesthetic, whereas we observed a return towards the awake values of peak latencies and interpeak intervals when the volatile agent was discontinued (fig. 6). The auditory evoked response might also be affected by increases in $P_{aCO_2}$, decreases in body temperature (Stockard, Stockard and Sharbrough, 1978), or a reduction in cerebral perfusion. In the present study none of these factors could explain our findings. Cerebral perfusion was probably unaffected, since the systolic arterial pressure never decreased to less than 80 mm Hg (Lassen and Christensen, 1976); body temperature never decreased by more than 0.5°C, which was insufficient to produce the observed changes (Stockard, Stockard and Sharbrough, 1978); and $P_{aCO_2}$ was controlled by end-tidal monitoring. Thus, this study confirms that the previous findings were correctly attributed to the effect of enflurane on brainstem transmission.

This study extends the previous findings to include halothane, which had a similar dose-related effect upon both the brainstem and the early cortical components of the auditory evoked response. This can be interpreted as indicating that the drugs act in a similar manner on similar parts of the brain by slowing transmission within the central nervous system. There may be a generalized effect upon all the synapses of the auditory pathway, resulting in the observed slowing of transmission, or it is possible that the effect on the early cortical components results from a decrease in activity in the brainstem components sufficient to block further transmission to a higher level. There is a suggestion that the latter is not the true interpretation since in two of the patients in whom the inhalation agent was withdrawn there was some reversal of the early cortical changes in the evoked response, with no reversal of the brainstem effects. This cannot be explained by an effect of brainstem changes on higher centres and must be a direct cortical effect.

Previous reports have failed to show an effect of halothane (Duncan, Sanders and McCullough, 1979) and of enflurane (Rosenblum, Gal and Ruth, 1982) on the brainstem components of the auditory evoked response, although Dubois and colleagues (1982) have confirmed our previous observations on the effect of enflurane on the brainstem components. In the first of these studies (Duncan, Sanders and McCullough, 1979) designed to test whether audiometry using evoked responses was valid under halothane anaesthesia, the results were compared using unpaired t testing. It remains unclear whether a difference would have been detected in this study if the considerable between-subject variation had been removed using paired t testing and, therefore, it is unclear whether these data contradict our findings. In the second study (Rosenblum, Gal and Ruth, 1982) the measurements were made while surgery was in progress. Since any possible modifying effect of surgery on the components of the auditory evoked response has not been formally tested, the significance of their observations is unclear. It is possible that, during light anaesthesia with 1.5% enflurane, the auditory evoked response returned to normal in response to the stimulus of surgery.

In the present study the concentrations of the two inhalation agents administered to the patients were chosen to be approximately equipotent, this choice being based on their MAC values (Eger, 1974). The slopes of the lines relating end-tidal concentrations of the agent to its effect on the auditory response were, with only one exception, greater for halothane than enflurane. This indicated that halothane was more potent in its effect on the auditory evoked
response than enflurane, just as it is as an anaesthetic. However, the ratio of the slopes for the two agents was never as high as the ratio of the MAC values would predict. This may mean that the ratio of the effect of the two drugs on this response differs, in proportion, from the ratio of their anaesthetic potencies. There are other interpretations: the lower solubility of enflurane (Eger, 1974) could have resulted in its equilibrating more quickly in the 10 min allowed, with the result that its brain tension was closer to the alveolar tension than that of halothane at the same time. Thus, the observed ratio of potencies would not be as great as that predicted from the MAC values. It is also possible that the difference in ratios was attributable to a non-linearity of the dose-response curves relating volatile anaesthetics to the depth of anaesthesia. As MAC is, by definition, a single point, the use of this value to compare potency over the whole range of concentrations may not be valid. This problem requires further study.

As mentioned above, in two of the four patients in whom halothane was withdrawn, the early cortical components recovered partially without any recovery of the brainstem components. This may have been caused by a difference in the sensitivity to the drugs of the different parts of the brain, or may be attributed to a different rate of washout of the drug in the different regions of the brain. Further speculation based on the limited data here available would be fruitless.

It is necessary to consider whether the present findings support the use of the auditory evoked responses to measure depth of anaesthesia. (1) Are the observed changes a response to the anaesthetic drug? The fact that there is reversal of these changes when the inhalation agents are withdrawn shows that they are. (2) Can the magnitude of the changes be related to the known potencies of the two anaesthetic agents? Although there are minor discrepancies, the effects are not incompatible with the known potencies. (3) Do the changes correlate with "depth of anaesthesia"? To answer this question it should be shown that, with a given anaesthetic concentration, there is the same attenuation of response to a painful stimulus as there is in the auditory evoked response. This is planned as the next stage of the study. (4) Is the interpatient variability in the measurements sufficiently small for the technique to be of practical value? The variation in the slopes (i.e. in the quantitative effects of the anaesthetics on the response) is small, particularly compared with the variability of the existing clinical measurements. However, the variation in the baseline latencies or amplitudes means that a single measurement in an individual patient may not be a unique guide to the depth of anaesthesia. Consequently, it may be necessary to examine changes in latency and amplitude in relation to their starting values.

We believe that the technique shows sufficient promise to be worthy of further study and investigations to study other agents, and to validate the technique further as a method for assessing "depth of anaesthesia", are planned.

ACKNOWLEDGEMENTS

We are grateful to Mr Charles Rossiter and Mrs Caroline J. Dore of the Division of Computing and Statistics at the Clinical Research Centre for their statistical advice and help.

REFERENCES


EFFETS DE L'HALOTHANE OU DE L'ENFLURANE EN VENTILATION CONTROLEE SUR LES POTENTIELS AUDITIFS EVOQUES

RESUME
Les effets de concentrations croissantes d'halothane et d'enflurane sur des composantes choisies de la réponse auditive évoquée ont été étudiés chez 12 patients; six ont reçu de l'halothane et six de l'enflurane. Après une induction au thioptental, l'anesthésie générale était entretenu avec 70% de protoxyde d'azote dans l'oxygène en ventilation contrôlée. La concentration inspirée de l'agent volatile était ensuite augmentée par paliers, l'halothane par paliers de 0,5% jusqu'à 2,5%, l'enflurane par paliers de 1% jusqu'à 5%. Avec l'un et l'autre agent, on constatait des augmentations linéaires doses-dépendantes des latences des ondes I, V, Pa et Nb et des intervalles entre les pics I-V et III-V, ainsi que des diminutions d'amplitude de Pa et Nb. Chez certains patients, l'agent volatile a été arrêté à la fin de la période test ce qui a entraîné une disparition des modifications de certaines ondes voire de toutes. La pression partielle de dioxyde de carbone, en fin d'expiration, était surveillée et les variations de température et de pression artérielle n'étaient pas suffisantes pour produire les modifications observées. Les résultats montrent que l'halothane et l'enflurane retardent la transmission nerveuse dans le tronc cérébral et dans les parties corticales des voies auditives, et que les effets de ces agents sont approximativement corrélés à leur puissance anesthésique connue.

EFECTOS DEL HALOTANO O ENFLURANO CON VENTILACION CONTROLADA SOBRE LOS POTENCIALES AUDITIVOS EVOCADOS

SUMARIO
Se estudiaron los efectos de concentraciones crecientes de halotano y de enflurano sobre componentes seleccionados de la respuesta auditiva evocada en 12 pacientes de los cuales seis recibieron halotano y seis enflurano. Después de la inducción de anestesia con thiopentona, se mantuvo la anestesia con óxido nitroso al 70% en oxígeno. Se controló la ventilación. La concentración inspirada del agente de inhalación siguió aumentando por incrementos, el halotano en escalones del 0,5% al 2,5% y el enflurano del 1% al 5%. Con ambos agentes, los aumentos lineales relacionados con las dosis se tradujeron por las latencias en las ondas III, V, Pa y Nb y en los intervalos entre topes I-V y III-V, con descensos en las amplitudes del Pa y del Nb. En cinco de los pacientes, el agente de inhalación terminó al final del periodo de ensayo, lo que resultó en una inversión de los cambios en algunas o en todas estas ondas. Se controló la tensión terminal respiratoria del anhidrido carbónico y las variaciones de temperatura y de tensión arterial fueron insuficientes como para producir los cambios observados. Los resultados demuestran que el halotano y el enflurano atrasan la transmisión neural a lo largo del tallo cerebral y de las secciones corticales de la vía auditiva y que los efectos de dichos agentes tienen una relación aproximada con sus potencias anestésicas conocidas.