Summary

We have studied in 12 patients the effect of desflurane in nitrous oxide on the electroencephalogram (EEG) and the early cortical auditory evoked response (AER). After induction with desflurane, patients' lungs were ventilated to maintain three different end-expiratory concentrations of desflurane (1.5, 3 and 6%) during four consecutive 10-min periods before surgery. As the end-expiratory concentration of desflurane was increased, Pa and Nb (AER) amplitudes decreased and their latencies increased, and spontaneous EEG showed an increase in amplitude and a slowing of frequency. A linear relationship was demonstrated between log₁₀ concentration of desflurane and all variables (P<0.001). Pa amplitude showed the greatest linearity followed by the derived variable F95 of the EEG. From regression slopes, mean percentage changes of each variable were calculated for a 1 MAC change in desflurane concentration. Pa amplitude showed the largest change (mean 49% (95% confidence interval 40–56%) decrease for a 1 MAC increase). This was greater than that of F95 for a similar confidence interval, indicating better resolution. This study confirms that the early cortical AER is affected by desflurane in a similar manner to that of other anaesthetic agents and as such remains the most promising EEG derived measure of depth of anaesthesia. (Br. J. Anaesth. 1997; 78: 282–285).

Key words

Previous studies have shown that increasing concentrations of inhalation1,2 and i.v.3,4 anaesthetic agents produce graded reductions in amplitude and prolongation of the latency of waves Pa and Nb of the early cortical auditory evoked response (AER). These changes are not agent specific and are antagonized by surgical stimulation,5 suggesting that the AER may be a useful measure of anaesthetic depth. The electroencephalograph (EEG) has been shown to slow with increasing concentration of anaesthetic, although enflurane has an opposite effect.6 EEG data may be analysed to provide quantitative indices. Variables can be derived from the power spectra of the EEG, for example median frequency or F50, which is the frequency below which 50% of the signal power is present,7 and spectral edge frequency or F95 which is the frequency below which 95% of the signal power is present.8 Spectral edge and median frequencies have been shown to decrease with increasing concentrations of thiopentone,9 etomidate,10 isoflurane11 and desflurane.12

The EEG and AER effects of new agents have to be characterized if they are to remain useful tools for monitoring depth of anaesthesia. The aims of this study were to investigate the effects of desflurane on the early cortical AER and to compare these with changes in median frequency and spectral edge of the EEG.

Patients and methods

We studied 12 patients, aged 31–65 yr, undergoing elective surgery requiring tracheal intubation. All gave informed consent to participate in the study, the design of which was approved by the Harrow District Ethics Committee.

After premedication with morphine 10 mg and atropine 0.4 mg i.m., anaesthesia was induced by inhalation of desflurane and 66% nitrous oxide (end-tidal) in oxygen. When anaesthesia was achieved, vecuronium 0.1 mg kg⁻¹ was given and the patient's trachea intubated. The lungs were ventilated with desflurane and 66% nitrous oxide in oxygen, a concentration selected according to a predefined sequence to which patients had been allocated randomly. Patients received either 1.5, 3 or 6% desflurane (end-expiratory concentrations) for 10 min and then the concentration was changed. All patients received each of the three possible concentrations. During a fourth period, the concentration of the preceding period was repeated. This study
design ensured that each concentration of desflurane followed every other concentration, including itself, an equal number of times so that overall, any “carry over” effect of one period to the next would be cancelled. It also allowed interactions between dose and time to be studied. Fresh gas flow was adjusted to maintain end-expiratory carbon dioxide partial pressure at 4.5–5 kPa. Neuromuscular block was maintained at a level of two responses on the train-of-four by infusion of vecuronium. End-expiratory concentrations of nitrous oxide, carbon dioxide and desflurane were measured using a calibrated Datex Ultima gas analyser.

The EEG and AER recorded from adhesive silver–silver chloride electrodes attached to the mastoid and forehead were stored and analysed on a PC-based system described previously. The auditory stimulus was a rarefaction click at 6 per second delivered to both ears via close fitting ear pieces, 75 dB above the average hearing threshold. The EEG signal was analogue filtered on input with bandwidths of 25–500 Hz to produce the AER recording. Although the EEG and AER were recorded continuously throughout the study, only the last 2 min 40 s (1024 sweeps of AER) of each period, when equilibrium was considered to have occurred, were used to derive the data. From the printed AER waveforms, Pa and Nb amplitudes and latencies were measured by an observer blind to the dose of desflurane.

For statistical analysis, all AER variables were normalized by log10 transformation. To test for a significant effect of dose and period on the AER and EEG variables, we used analysis of variance (ANOVA) with the restricted maximum likelihood (REML) procedure in Gentstat. The Wald statistic (REML) which follows an approximate chi-square distribution with 1 degree of freedom tested for linearity with log dose.

Results

Of the 12 patients studied, eight were females undergoing major gynaecological surgery and four were males undergoing major orthopaedic surgery. Mean age was 46 (range 31–62) yr and mean weight 77 (SD 10) kg.

As the end-expiratory concentration of desflurane was increased, Pa and Nb amplitudes decreased and their latencies increased, and the EEG showed an increase in amplitude and a slowing of frequency. An example from one patient is shown in figure 1.

A linear relationship was demonstrated between log10 dose and all variables over the concentration range studied. For example, mean Pa amplitude and F95, plotted against end-expiratory desflurane concentration (log10 scale) are shown in fig. 2.

For all variables the Wald statistic was highly significant at \( P<0.001 \) (table 1). The Wald statistic

<table>
<thead>
<tr>
<th>Variable</th>
<th>Direction of change</th>
<th>Mean % change</th>
<th>95% CI for change</th>
<th>Wald statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pa latency</td>
<td>Increase</td>
<td>9.9</td>
<td>4.5–15.5</td>
<td>13.0</td>
</tr>
<tr>
<td>Nb latency</td>
<td>Increase</td>
<td>8.0</td>
<td>3.1–13.1</td>
<td>10.1</td>
</tr>
<tr>
<td>Pa amplitude</td>
<td>Decrease</td>
<td>40–56</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Nb amplitude</td>
<td>Decrease</td>
<td>43–52</td>
<td>43.6</td>
<td></td>
</tr>
<tr>
<td>F50</td>
<td>Decrease</td>
<td>25–32</td>
<td>11–37</td>
<td></td>
</tr>
<tr>
<td>F95</td>
<td>Decrease</td>
<td>33–41</td>
<td>14.6</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Geometric mean (95% confidence intervals) for Pa and Nb amplitude and F50 and F95 to illustrate the effect of period

<table>
<thead>
<tr>
<th>Period</th>
<th>Pa amplitude</th>
<th>Nb amplitude</th>
<th>F50</th>
<th>F95</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>0.21</td>
<td>0.20</td>
<td>2.82</td>
<td>10.88</td>
</tr>
<tr>
<td>2</td>
<td>0.21</td>
<td>0.26</td>
<td>1.80</td>
<td>8.78</td>
</tr>
<tr>
<td>3</td>
<td>0.15</td>
<td>0.26</td>
<td>1.01</td>
<td>7.92</td>
</tr>
<tr>
<td>4</td>
<td>0.16</td>
<td>0.12</td>
<td>1.06</td>
<td>7.96</td>
</tr>
</tbody>
</table>

Probability \( P<0.001 \)

![Figure 1](image-url) An example from one subject, showing the effect of increasing end-expiratory desflurane on the AER and EEG. In the AER the amplitudes of Pa and Nb decreased and their latencies increased. The EEG shows an increase in amplitude and slowing of frequency.
tests for linearity and the larger the number the more linear the relationship. Pa amplitude, had the highest value, followed by F95. Regression slopes (with SEM) for each variable with log10 dose were calculated. From these, the percentage change and 95% confidence intervals were calculated for a 1 MAC increase in desflurane concentration. For example, a 1 MAC increase in desflurane concentration produced a 49% (95% confidence interval 40–56%) decrease in Pa amplitude, and a 33% (25–41%) decrease in spectral edge. Percentages are appropriate rather than the original units because the AER and EEG variables were log10 transformed for data analysis.

A period effect was seen for Pa and Nb amplitudes, and F50 and F95 (P=0.009, 0.01, 0.003 and <0.001, respectively). The means of these variables were significantly lower in the later periods of administration (table 2). In the case of Pa amplitude and F95, a significant interaction between dose and period was seen (P=0.05 and <0.001, respectively). For the low desflurane concentration these variables decreased in the later periods. At medium and high concentrations no clear trend emerged.

Discussion

Desflurane reduced the amplitudes of waves Pa and Nb of the AER and increased their latencies. Median frequency (F50) and spectral edge (F95) were reduced by desflurane. In all cases these effects were linearly dose related.

The significant effect of period on the variables Pa and Nb amplitude and F50 and F95 (P=0.009, 0.01, 0.003 and <0.001, respectively). The means of these variables were significantly lower in the later periods of administration (table 2). In the case of Pa amplitude and F95, a significant interaction between dose and period was seen (P=0.05 and <0.001, respectively). For the low desflurane concentration these variables decreased in the later periods. At medium and high concentrations no clear trend emerged.

No trend was seen for the medium and high concentrations. As the low desflurane concentration could only follow a higher concentration (except in the first period) this effect could be attributed to a carry over effect from the preceding period. If this were true one would expect to see the converse effect in the high desflurane concentration group. However, such an effect was not observed. There are two possible explanations for this: first, the same equilibration effects cannot be assumed during wash-in and wash-out; second, for the EEG variables, the effect may have been too subtle to detect at the higher desflurane concentrations where the average curves were much flatter.

Changes in the early cortical AER were similar to those of other anaesthetics we have studied previously.1–4 Halothane, enflurane, isoflurane, etomidate and propofol reduced amplitude and increased the latency of the Pa and Nb waves of the AER in a dose-related manner. Confirmation that new anaesthetic agents produce similar changes in the AER strengthens its value as a method of monitoring depth of anaesthesia.

Changes in the AER were more marked when the concentration of desflurane decreased from 3% to 1.5% compared with changes in EEG variables (see fig. 1). Thus the AER may be a more sensitive indicator of anaesthetic depth at low desflurane doses than the EEG.

Pa amplitude showed the best linear relationship with desflurane concentration (largest Wald statistic, F95 was the next largest (table 1)). Also, Pa amplitude showed a larger percentage change for 1 MAC desflurane compared with F95 for the same confidence intervals, suggesting greater resolution of measurement.

Rampil and colleagues investigated the quantitative effects of desflurane on the EEG12 and found a progressive decrease in these variables with increasing concentration. However, at comparable desflurane concentrations, F50 and F95 were higher in their study compared with ours. Patients in our study were deeper for equivalent desflurane concentrations, possibly because of premedication with morphine and atropine as an adjunct to induction.

Figure 2 Mean (95% confidence intervals) Pa amplitude and F95, plotted against desflurane concentration (log scale).

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**Figure 2** Mean (95% confidence intervals) Pa amplitude and F95, plotted against desflurane concentration (log scale).
with desflurane. We used this premedication and nitrous oxide for comparison with data from our previous studies with other volatile agents.\textsuperscript{1,2} In addition, the higher mean age of the patients in this study of 45.8 yr compared with 23.8 in the study of Rampil and colleagues would contribute to this difference. Burst suppression was not seen in our study.

In summary, we observed that desflurane had similar actions on the early cortical AER as other anaesthetic agents studied previously and it compared well with EEG spectral analysis variables. Pa amplitude (AER) showed better linearity and resolution than the best of the EEG variables (F95). The results also suggested that the AER may be a more sensitive indicator of anaesthetic depth at low desflurane doses and the EEG more sensitive at higher desflurane concentrations. As such, the early cortical AER remains the most promising EEG derived measure of depth of anaesthesia.

References

11. Schwilden H, Stoeckel H. Quantitative EEG analysis during anaesthesia with isoflurane in nitrous oxide at 1.3 and 1.5 MAC. \textit{British Journal of Anaesthesia} 1987; 59: 738–745.