Comparison of the effects of halothane, isoflurane and methoxyflurane on the electroencephalogram of the horse

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Summary
We have investigated in eight ponies the effects of three different end-tidal concentrations of halothane, isoflurane and methoxyflurane on median (F50) and 95% spectral edge (F95) frequencies of the EEG and the second differential (DD) of the middle latency auditory evoked potential (MLAEP). The three concentrations of each agent were chosen to represent approximately the minimum alveolar concentration (MAC), 1.25 MAC and 1.5 MAC for each agent. During halothane anaesthesia, F95 decreased progressively as halothane concentration increased, from mean 13.9 (SD 2.6) at 0.8% to 11.9 (1.1) at 1.2%. DD was lower during anaesthesia with the highest concentration (21 (6.5)) compared with the lowest (27.6 (11.4)). There were no significant changes in F50. During isoﬂurane anaesthesia, there was a small, but significant increase in F95 between the intermediate and highest concentrations (10.2 (1.5) to 10.8 (1.6)). There were no changes in F50 and DD. Values of F95, F50 and DD at all isoﬂurane concentrations were similar to those of halothane at the highest concentration. During methoxyflurane anaesthesia, F95 and F50 decreased progressively as methoxyflurane concentration was increased, from 21.3 (0.7) and 6.5 (1), respectively, at 0.26%, to 20.1 (0.6) and 5.6 (0.8), respectively, at 0.39%. DD was lower during anaesthesia with the highest concentration of methoxyflurane (25.7 (7.8)) compared with the lowest (39.7 (20.6)). Values of F95, F50 and DD at all methoxyflurane concentrations were higher than those seen with halothane at the lowest concentration. The different relative positions of the dose–response curves for EEG and MLAEP changes compared with antinociception (MAC) changes suggest differences in the mechanisms of action of these three agents. These differences may explain the incomplete adherence to the Meyer–Overton rule. (Br. J. Anaesth. 1998; 81: 748–753).

Keywords: anaesthetic volatile, halothane; anaesthetic volatile, isoflurane; anaesthetic volatile, methoxyflurane; monitoring, electroencephalography; horse

In humans, the effects of inhalation agents on the EEG have been studied under various conditions. In surgical patients, frequency spectra obtained under adequate and increased end-tidal isoflurane concentrations have been graded.1 The progressive changes in frequency spectra were then colour-coded to produce a colour index of depth of anaesthesia. Graded changes in power spectra with increasing arterial halothane concentrations have also been found in infants undergoing facial surgery.2 Despite these changes, the EEG recorded before the start of surgery could not be used to predict movement in response to surgical stimulation.3 This confirmed similar results in the rat.4

The effects of 0.5%, 1% and 1.5% halothane and 0.5%, 1%, 1.5% and 2% isoflurane were compared as part of a balanced anaesthetic technique on the EEG.5 It was found that most of the change in EEG variables with isoflurane occurred at concentrations less than MAC. In contrast, halothane produced progressive EEG changes with increasing \( P_{	ext{Hal}} \) at values greater than MAC. The values found for isoflurane from MAC onwards were similar to each other in magnitude and to those found with halothane at 1.5%.

In the horse, the EEG effects of isoflurane, halothane, methoxyflurane and enflurane have been compared.6 A gradual change from control high frequency–low amplitude patterns to high amplitude slow waves was found with halothane and methoxyflurane. In contrast, enflurane and isoflurane anaesthesia were characterized by slow wave activity throughout with periods of burst suppression, occurring with increased concentrations. These effects were not fully described in terms of quantitative EEG variables. The effects of halothane in anaesthetized horses without surgery have been demonstrated quantitatively after induction of anaesthesia using xylazine–ketamine7 and thiopental.8 Both studies found progressive changes in derived EEG variables with increasing \( P_{	ext{Hal}} \). The EEG effects of halothane have been compared with those of isoflurane in horses undergoing orthopaedic surgery.9 Similar EEG values were found in both groups, however, more changes were seen in response to surgery with halothane than with isoflurane.

In humans, the middle latency auditory evoked potential (MLAEP) has been found to change in a dose-related manner with inhalation anaesthetic agents.10–12 Although most of the depression in the MLAEP occurs at sub-MAC anaesthetic concentrations, graded changes have been described for concentrations of up to 2 MAC of halothane and...
enflurane.10 12 In contrast, depression of the MLAEP with isoflurane appears to be complete by 1 MAC.11 There are no data available on the effects of anaesthesia on the equine MLAEP.

The aim of this study was to compare the quantitative effects of isoflurane, halothane and methoxyflurane on the equine EEG at concentrations greater than MAC, without surgical stimulation. This would provide a direct comparison of the effects of each agent on three different measures of CNS function and also provide comparative information allowing the EEG effects of the three agents to be compared with each other. Halothane and isoflurane were chosen as they are the two main agents used in clinical equine anaesthesia. Methoxyflurane was used as it is analgesic at sub-MAC concentrations13 and so may have quantitatively different effects from the other two agents.

**Materials and methods**

We studied eight pony geldings, aged 5–10 yr (mean 7 yr), weighing 270–325 kg (mean 305 kg). The ponies all had the right carotid artery raised surgically to a subcutaneous position. The study was carried out in accordance with the Animals (Scientific Procedures) Act, 1986 (Home Office Licence 80/666).

After placement of a 14-gauge cannula in the left jugular vein, anaesthesia was induced on three occasions by i.v. injection of thiopental 3 g. Additional thiopental was given as required in 0.5- or 1-g increments to allow tracheal intubation, resulting in a mean dose of 12 (sd 2) mg kg⁻¹. The ponies were placed in the left lateral recumbent position. Anaesthesia was maintained by inhalation of halothane, isoflurane or methoxyflurane from a circle breathing system (JD Medical). A 20-gauge cannula was placed in the raised carotid artery. The order in which each pony was given each anaesthetic agent was not randomized, but at least 2 weeks were left between subsequent anaesthetics in each animal.

\[ \text{MAC multiple} \]

<table>
<thead>
<tr>
<th>Approximate MAC multiple</th>
<th>Halothane</th>
<th>Isoflurane</th>
<th>Methoxyflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8%</td>
<td>1.2%</td>
<td>0.26%</td>
</tr>
<tr>
<td>1.25</td>
<td>1.0%</td>
<td>1.5%</td>
<td>0.32%</td>
</tr>
<tr>
<td>1.5</td>
<td>1.2%</td>
<td>1.8%</td>
<td>0.39%</td>
</tr>
</tbody>
</table>

The active (non-inverting) electrode was placed in the midline over the suture of the parietal bones 2–3 cm rostral to the convergence of the temporalis muscles. The reference (inverting) electrode was placed over the bony prominence of the right zygomatic arch. The ground electrode was placed 5–6 cm caudal to the poll, 5–6 cm to the right of the midline. This positioning of electrodes gave reliable EEG recordings and a well defined MLAEP. Electrodes were positioned as soon as practicable after induction of anaesthesia and were not moved or disconnected for the duration of the study. Data were recorded to a personal computer (450L, Dell) via a digital signal processing card (DSP with sub-board and 64k RAM, Loughborough Sound Instruments). Data recording software was used which was developed specifically for this hardware combination (Auditory Evoked Response Program, Chris Jordan, Northwick Park Hospital).

EEG data were recorded with a sample rate of 1 kHz and a passband of 0.5–400 Hz. Data were divided into 2-s epochs and artefact rejection was performed manually off-line by inspection of the raw data. Any epochs containing artefact were rejected before further processing. Data blocks containing
Table 2  Arterial pH, \(P_{CO_2}\), \(P_{O_2}\) and mean arterial pressure (AP) for each agent concentration during EEG recording (mean (SD)). *\(P<0.05\) denote values significantly different from each other.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Concentration</th>
<th>pH</th>
<th>(P_{CO_2}) Mean</th>
<th>(P_{O_2}) Mean</th>
<th>Mean AP Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>0.8%</td>
<td>7.325 (0.081)</td>
<td>6.1 (1)</td>
<td>36.1 (14.1)</td>
<td>10.9 (1.3)</td>
</tr>
<tr>
<td></td>
<td>1.0%</td>
<td>7.329 (0.104)</td>
<td>6.1 (1.2)</td>
<td>39.2 (15.8)</td>
<td>11.7 (1.3)</td>
</tr>
<tr>
<td></td>
<td>1.2%</td>
<td>7.297 (0.138)</td>
<td>6.7 (1.9)</td>
<td>32.2 (16.8)</td>
<td>11.8 (1.5)</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.2%</td>
<td>7.387 (0.029)</td>
<td>5.3 (0.2)</td>
<td>42.6 (12.5)</td>
<td>10.3 (1.2)</td>
</tr>
<tr>
<td></td>
<td>1.5%</td>
<td>7.39 (0.037)*</td>
<td>5.4 (0.4)*</td>
<td>46.6 (16.4)</td>
<td>10.5 (1.3)</td>
</tr>
<tr>
<td></td>
<td>1.8%</td>
<td>7.405 (0.036)*</td>
<td>5.1 (0.5)*</td>
<td>46.8 (18.5)</td>
<td>10.5 (1.1)</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>0.26%</td>
<td>7.382 (0.02)</td>
<td>5.9 (0.6)</td>
<td>48.9 (7.3)</td>
<td>16.1 (1.9)*</td>
</tr>
<tr>
<td></td>
<td>0.32%</td>
<td>7.375 (0.021)</td>
<td>5.9 (0.5)</td>
<td>48.3 (7.3)</td>
<td>12.8 (2.6)</td>
</tr>
<tr>
<td></td>
<td>0.39%</td>
<td>7.382 (0.034)</td>
<td>5.7 (0.6)</td>
<td>43.6 (8.4)</td>
<td>12.1 (19)*</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.8%</td>
<td>7.405 (0.036)*</td>
<td>5.1 (0.5)*</td>
<td>46.8 (18.5)</td>
<td>10.5 (1.1)</td>
</tr>
</tbody>
</table>

Results

There were no data after isoflurane anaesthesia for one pony as this experiment was abandoned because of repeated violent movements at both 1.2% and 1.5% isoflurane. EEG data from one pony during halothane anaesthesia were not included as they were found to be contaminated by high frequency (50 Hz) artefacts. There were no arterial blood-gas data after halothane anaesthesia for two of the ponies because of a malfunction of the blood-gas analyser.

There were no significant differences in pH, \(P_{O_2}\), \(P_{CO_2}\) or mean AP recorded during administration of the three concentrations of halothane. There were statistically significant reductions in \(P_{CO_2}\) and increases in pH between 1.5% and 1.8% end-tidal isoflurane. There was a statistically significant decrease in AP between 0.26% and 0.39% end-tidal methoxyflurane. All blood-gas data are shown in table 2.

Values for F95, F50 and DD with halothane are shown for all animals in table 3. Values for individual animals are illustrated in figure 1. When all animals were considered together, there was a progressive reduction in F95 which was statistically significant for all three \(P_{EEG}\). There were no significant changes in F50 with increasing \(P_{EEG}\). There was a statistically significant reduction in DD between 0.8% and 1.2% \(P_{EEG}\).

Values for F95, F50 and DD with isoflurane are shown for all animals in table 4. Values for individual animals are illustrated in figure 2. When all animals were considered together, there was a significant increase in F95 between 1.5% and 1.8% \(P_{EEG}\).
Effects of halothane, isoflurane and methoxyflurane on the EEG of the horse

were no significant differences in F50 or DD. Values of F95, F50 and DD with isoflurane at all $P_{\text{Hal}}$ were similar to those seen with halothane at 1.2%.

Values for F95, F50 and DD with methoxyflurane are shown for all animals in table 5. Values for individual animals are illustrated in figure 3. When all animals were considered together, there was a significant decrease in F95 and F50 between 0.26% and 0.39% $P_{\text{Meth}}$. DD at 0.39% was significantly less than that at 0.26%. Values for F95, F50 and DD seen with methoxyflurane at all $P_{\text{Meth}}$ were greater than those seen with halothane at 0.8%.

Burst suppression was a feature of the EEG during isoflurane anaesthesia. There was an increasing incidence with increasing $P_{\text{Iso}}$. Burst suppression was not seen during halothane or methoxyflurane anaesthesia.

**Discussion**

We have shown that the EEG effects of the three inhalation agents halothane, isoflurane and methoxyflurane were quantitatively different from each other compared with the MAC of these agents. Within the concentration window studied, halothane produced a progressive reduction in F95, F50 and DD while the values for isoflurane were all at one extreme of the halothane curve and the values for methoxyflurane all at the other extreme. As a progressive increase in the incidence of burst suppression was seen with increasing $P_{\text{Iso}}$, the values for isoflurane may represent maximal depression of F95, F50 and DD.

Data were collected in the order 1 MAC, followed by 1.25 MAC, followed by 1.5 MAC. In a previous

**Table 4** Change in F95, F50 and DD with $P_{\text{Iso}}$ (mean (sd)). $^*P<0.05$ denotes values significantly different from each other

<table>
<thead>
<tr>
<th>$P_{\text{Iso}}$</th>
<th>1.2%</th>
<th>1.5%</th>
<th>1.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>F95</td>
<td>10 (1.7)</td>
<td>10.2 (1.5)*</td>
<td>10.8 (1.6)*</td>
</tr>
<tr>
<td>F50</td>
<td>2.4 (0.4)</td>
<td>2.4 (0.3)</td>
<td>2.4 (0.5)</td>
</tr>
<tr>
<td>DD</td>
<td>23.3 (6.8)</td>
<td>23.2 (6.8)</td>
<td>22.7 (9.2)</td>
</tr>
</tbody>
</table>

**Table 5** Change in F95, F50 and DD with $P_{\text{Meth}}$ (mean (sd)). $^*P<0.05$ denotes values significantly different from each other; $^†P<0.05$ denotes values significantly different from all others in group

<table>
<thead>
<tr>
<th>$P_{\text{Meth}}$</th>
<th>0.26%</th>
<th>0.32%</th>
<th>0.39%</th>
</tr>
</thead>
<tbody>
<tr>
<td>F95</td>
<td>21.3 (0.7)$^†$</td>
<td>20.6 (0.9)$^†$</td>
<td>20.1 (0.6)$^†$</td>
</tr>
<tr>
<td>F50</td>
<td>6.5 (1)$^†$</td>
<td>6.1 (1)$^†$</td>
<td>5.6 (0.8)$^†$</td>
</tr>
<tr>
<td>DD</td>
<td>39.7 (20.6)$^*$</td>
<td>31.7 (18.6)</td>
<td>25.7 (7.8)$^*$</td>
</tr>
</tbody>
</table>
study investigating the effects of increasing concentrations of halothane on the EEG, the order in which the different concentrations were given was randomized. Both F95 and F50 showed a progressive reduction with increasing halothane concentration, but the changes with F50 were not as marked as those with F95. More recently, it was suggested that F50 may respond to changes in anaesthetic concentration in a sluggish manner (D. Sapsford, personal communication). Consequently, the order of anaesthetic agent concentrations in this study was not altered between animals in an attempt to standardize this possible source of error. The similarity in the halothane results between this and the previous study suggest that a sluggish response in F50 did not contribute to the results in either case.

The progressive decrease in F95 and DD with increasing concentrations of halothane were similar to previous findings. The lack of change with isoflurane and methoxyflurane and the progressive appearance of periods of burst suppression with isoflurane were also similar. As the EEG variables for isoflurane at all three $P_{F50}$ were similar to those for halothane at 1.2%, it is probable that the slope of the isoflurane dose–response curve for CNS depression occurs at a lower concentration in terms of multiples of MAC than that for halothane. Similarly, the EEG variables for methoxyflurane at all three $P_{Meth}$ demonstrated less CNS depression than 0.8% halothane, suggesting that CNS depression occurs at higher concentrations in terms of multiples of MAC with methoxyflurane than either isoflurane or halothane. The difference in the relative positions of the dose–response curves for CNS depression and antinociception with halothane and isoflurane would explain the finding in the horse that the CNS was more responsive during surgery with halothane anaesthesia than isoflurane anaesthesia.

The MAC of an anaesthetic agent is related to the ability of that agent to prevent response to a noxious stimulus. This is a measure of the antinociceptive potential of the anaesthetic agent. The degree of depression of the EEG variables investigated is incomplete at 1 MAC of halothane whereas with isoflurane, depression of these variables is complete by 1 MAC. The EEG variables did not appear to be completely depressed at any of the three methoxyflurane concentrations. In terms of multiples of MAC, there appears to be a spectrum of potency for CNS depression from methoxyflurane (least potent) through halothane to isoflurane. This suggests that methoxyflurane is more antinociceptive than isoflurane as response to a standard nociceptive stimulus is prevented by a concentration of methoxyflurane which induces less CNS depression than the required concentration of isoflurane. Halothane would appear to have an intermediate antinociceptive effect.

Traditionally, the inhalation agents have been the anaesthetic agents to which others have been compared. The concept of depth of anaesthesia which led to the classic signs and stages of anaesthesia was developed from experience with ether and modified as other inhalation agents appeared. The inhalation agents are all volatile compounds with low molecular weight. Because of the Meyer–Overton theory which links potency to fat solubility, it has been suggested that they have a similar site of action within a lipophilic biophase. This, together with the concept of pressure reversal, has led to the belief that general anaesthesia with the inhalation agents is a result of a physical effect in the cell membrane rather than a receptor-mediated effect and as such affects all cells.
in the body. This would lead to a global effect on the CNS producing a generalized depression of function rather than specific, pharmacologically localized effects.

These data appear to question the usefulness of comparing effects of anaesthetic agents other than that of antinociception in terms of multiples of MAC. If the different effects of inhalation anaesthetic agents occur at different concentrations relative to each other, there must be pharmacologically localized kinetic or dynamic differences between them. Effects of inhalation anaesthetic agents at differing sites or even receptors may explain the incomplete adherence of these agents to the Meyer–Overton rule.

Acknowledgements

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References