The effects of enflurane and halothane on the electroencephalogram (e.e.g.) were studied in 10 cats. Animals underwent at least 2 MAC-hours of anaesthesia with either agent, and the e.e.g. was monitored continuously. Arterial blood-gas tensions were maintained within normal limits. In addition, e.e.g. and behaviour were monitored during the period following anaesthesia, at fixed intervals, for 4 weeks. Despite the production of the central stimulatory effects of enflurane during anaesthesia, no animal demonstrated any central nervous system sequelae on any occasion following the anaesthetic.

The introduction of enflurane into clinical anaesthesia was followed by several reports detailing unexpected central nervous system activity associated with its use. These effects ranged from motor hyperactivity to frank electroencephalogram (e.e.g.) seizure patterns, and were made worse by hypocarbia or increased depth of anaesthesia, or both (Neigh, Garman and Harp, 1971). Although the existence of enflurane-induced central nervous system stimulation is not disputed (Virtue et al., 1966; Joas, Stevens and Eger, 1972), its clinical significance is unclear. In fact, there is evidence that the anaesthetic can act both to inhibit as well as to excite epileptic foci (Leibowitz, Blitt and Dillon, 1972; Gallagher, Galindo and Richcy, 1978).

Unexplained seizures have been reported in two patients, 6 and 8 days after an enflurane anaesthetic (Ohm et al., 1975) and, more recently, Kruczek and his associates (1980) reported a solitary convolution occurring 1 h after anaesthesia. In both reports, the patients had not experienced any previous seizures. In cats, both e.e.g. and behavioural abnormalities have been demonstrated following the administration of enflurane (Julien and Kavan, 1972; Kavan, Julien and Lucero, 1972). However, since these accounts did not include control of the many variables that can affect the central nervous system during and after anaesthesia, we undertook the present study in animals so that the anaesthetic and post-anaesthetic effects of enflurane alone could be clarified, and compared with those of halothane.

METHODS

Ten adult female cats, weighing between 2.7 and 5.28 kg (mean 3.58 kg), and anaesthetized with sodium pentobarbitone, had bipolar 40-gauge stainless-steel electrodes implanted in the prepyriform cortex, septum, ventral hippocampus, dorsal hippocampus, basolateral amygdala and lateral geniculate body. In addition, electrical activity from the sensory-motor and occipital (striate) cortices was recorded from small stainless steel screws embedded in, but not penetrating the calvaria. The prepyriform cortical electrode was implanted by observing the characteristics of potentials evoked in the target site by electrical stimulation of afferent pathways (Fairchild, Jenden and Mickey, 1975). Electrodes in subcortical structures were positioned using standard stereotaxic procedures. After implantation, all electrode leads were soldered to a 20-pin plug which was permanently fixed to the skull with acrylic plastic. The animals were allowed to recover for at least 1 month before starting the series of experiments with enflurane and halothane.

On the day of the experiment, the unpremedicated, fasting cat was weighed, connected to the e.e.g. input circuit by a low-noise flexible cable, and placed in an observation area for a 5-min recording of awake electrical activity. At the conclusion of this control period, the animal was placed on an operating table and restrained gently. Anaesthesia was induced, using a mask, by the inhalation in oxygen of the agent being studied. When a suitable plane of anaesthesia had been achieved, the trachea was intubated and a pneumograph was attached to monitor...
respiratory rate. A femoral arterial catheter was inserted for the continuous monitoring of arterial pressure and to permit blood sampling for blood-gas and pH determinations. A heating blanket and rectal thermistor permitted maintenance of normal body temperature.

Anaesthesia was administered for 2 h using a Mapleson E anaesthetic system. Because of the variation in inspired anaesthetic concentrations necessary to prevent responses to frequent tail clamping, the MAC-hours of anaesthesia administered varied from 2.2 to 6.2 for halothane, and from 4.8 to 8.1 for enflurane (table I). Ventilation was augmented where necessary to maintain arterial carbon dioxide tension at less than 6.7 kPa. Arterial pressure remained greater than 40 mmHg in all animals (table I). Halothane or enflurane was delivered in oxygen by a Vemitrol vaporizer which was calibrated by gas chromatography. No drug, other than the anaesthetics under study, was administered during the 3 months of experimentation.

Inspired concentrations of each anaesthetic were measured by gas chromatography. E.g., arterial pressure, and respiratory rate were recorded continuously during the experiment and stored on analog tape for subsequent analysis.

At the conclusion of each investigation, the anaesthetic was discontinued and the animal allowed to awaken with the endotracheal tube in situ. When the cat had recovered consciousness sufficiently, as assessed both clinically and by e.g., the trachea was extubated and the animal was disconnected from the e.g. cable. At this stage, the cat was observed closely for early behavioural abnormalities such as excitability or unusual movements. Ten animals were randomly assigned to two groups of five. Cats in the first group received halothane during the initial set of experiments and enflurane during the second. The order was reversed for the subsequent series. Thus all 10 cats received both anaesthetics and served as their own controls. The two groups of experiments were performed over a 3-month period, with 40–46 days separating the administration of the two anaesthetics. After each experiment, the cat's e.g. and behaviour were monitored for 30 min at 24, 48, and 96 h, thence bi-weekly for an additional 4 weeks. The follow-up e.g. were visually inspected to identify unusual alterations in frequency spectra and to detect the presence of abnormal sharp wave activity. Behavioural observations were recorded following each 1-min period.

RESULTS

Enflurane and halothane were both associated with the development of a "fast rhythm" in the prepyriform cortex and amygdala which ranged between 12 and 50 Hz (fig. 1). This unusual finding appeared to be dose-related in individual cats and could be produced by varying the inspired concentration. Although the rhythm occurred most commonly during induction, it also appeared at deeper planes of anaesthesia. Halothane produced the phenomenon more often, but with enflurane it could easily have been masked by the synchronous spiking and periods of postictal silence present in the e.g. at surgical planes of anaesthesia.

Induction with enflurane was characterized by the appearance of this "fast rhythm" in the prepyriform cortex and amygdala, while at the same

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**Table I.** Femoral arterial pressure, Po2, PCO2 and pH presented as the range of measurements obtained during the experiments. The MAC-hours of anaesthesia are given for each type of volatile anaesthetic. N/A = data not available because of equipment malfunction.

<table>
<thead>
<tr>
<th>Cat</th>
<th>MAC-hours of anaesthesia</th>
<th>Femoral arterial pressure range (mm Hg)</th>
<th>PaO2 range (kPa)</th>
<th>PaCO2 range (kPa)</th>
<th>pH range (unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Halothane</td>
<td>Enflurane</td>
<td>Halothane</td>
<td>Enflurane</td>
<td>Halothane</td>
</tr>
<tr>
<td>1</td>
<td>6.2</td>
<td>4.8</td>
<td>58–66</td>
<td>58–64</td>
<td>75–78</td>
</tr>
<tr>
<td>2</td>
<td>3.7</td>
<td>5.8</td>
<td>54–76</td>
<td>78–95</td>
<td>60–69</td>
</tr>
<tr>
<td>3</td>
<td>3.4</td>
<td>6.0</td>
<td>60–86</td>
<td>50–64</td>
<td>69–72</td>
</tr>
<tr>
<td>4</td>
<td>4.7</td>
<td>6.5</td>
<td>44–52</td>
<td>80–84</td>
<td>51–70</td>
</tr>
<tr>
<td>5</td>
<td>4.4</td>
<td>7.1</td>
<td>76–82</td>
<td>48–70</td>
<td>57–71</td>
</tr>
<tr>
<td>6</td>
<td>3.8</td>
<td>7.8</td>
<td>61–80</td>
<td>N/A</td>
<td>53–58</td>
</tr>
<tr>
<td>7</td>
<td>2.2</td>
<td>8.1</td>
<td>N/A</td>
<td>47–60</td>
<td>58–65</td>
</tr>
<tr>
<td>8</td>
<td>5.1</td>
<td>7.4</td>
<td>47–59</td>
<td>61–58</td>
<td>67–69</td>
</tr>
<tr>
<td>9</td>
<td>2.5</td>
<td>7.5</td>
<td>45–52</td>
<td>52–74</td>
<td>70–77</td>
</tr>
<tr>
<td>10</td>
<td>3.4</td>
<td>7.0</td>
<td>41–64</td>
<td>64–74</td>
<td>50–77</td>
</tr>
</tbody>
</table>
time slow waves began to appear in other brain areas. Spiking activity followed in quick succession in all zones, first infrequently, then more often until each lead was recording numerous spikes. Gradually, the spiking activity became synchronous throughout the brain, and brief episodes of silence appeared. As the cat reached a light surgical plane of anaesthesia, groups or trains of spikes, with progressively longer periods of silence, gave way to very large amplitude single or double synchronous spikes, and motor phenomena such as limb clonus occurred. At this stage, grand mal convulsions could be elicited by repetitive peripheral stimuli such as handclapping near the animal's ear or flicking the ear itself (fig. 2). Occasionally, hippocampal structures appeared resistant to the epileptogenic action of enflurane. This is in direct contrast to the usual behaviour of the hippocampus which normally has a relatively low convulsive threshold.

During induction with halothane, the “fast rhythm” was evident in the prepyriform cortex and amygdala. Soon thereafter, slow wave activity became progressively dominant in all areas monitored. Both the dorsal and ventral hippocampi developed the type of large amplitude sharp waves which are usually detected in the unanaesthetized sleeping cat. These were probably unmasked by halothane as a result of a decrease in the fast-frequency components of the e.e.g. As anaesthesia was deepened, changes were detected in the occurrence and frequency of this “fast rhythm” in those cases where it did occur. As halothane anaesthesia progressed, there was a gradual, overall decrease in e.e.g. amplitude which, although evident in all animals, was particularly obvious in three.

During the observation period following anaesthesia, no cat exhibited any abnormality in e.e.g. or behaviour. The animals were normal not only during the planned periods of assessment, but also during additional “chance” observations.

DISCUSSION

This cross-over study in cats with halothane and enflurane failed to demonstrate any e.e.g. abnormalities following the administration of enflurane such as those previously reported in cats by Julien and Kavan (1972). In their experiments, administration of enflurane for 30 min resulted in high voltage spikes in the cortex and thalamic nuclei plus behavioural abnormalities for up to 16 days following the anaesthetic. This study has been extensively quoted as evidence for long-term, enflurane-induced central nervous system abnormalities.

There were important differences in methodology between our study and that of Julien and Kavan. First, we administered enflurane in 100% oxygen, whereas they used a 2:1 mixture of air and oxygen. Second, the cats in our experiments had the trachea intubated while the animals used by Julien and Kavan were anaesthetized via masks. Finally, in our animals, arterial pressure and blood-gas tensions were maintained within fixed limits throughout.
Hand Clapping 1 s

**FIG. 2** Production of grand mal seizures in the enflurane-anaesthetized cat by repetitive hand clapping near the animal's ear. In this cat, the seizure period of approximately 10 s was followed by electrical silence lasting more than 20 s. AP = femoral arterial pressure; other abbreviations as figure 1.

Although speculative, it is possible that the delayed e.e.g. and behavioural abnormalities observed by Julien and Kavan could have resulted from inadvertent cerebral hypoxia during the anaesthetic, hypoventilation while breathing a lower inspired oxygen concentration, or undocumented hypotension.

When Burchiel and co-workers (1977) administered enflurane anaesthesia to 12 human volunteers for 9.6 MAC-hours, frank e.e.g. and motor seizure activity was apparent during narcosis and diffuse slowing of the e.e.g.—but no epileptiform activity—persisted for 6–30 days in the period following anaesthesia. The inability to demonstrate epileptiform activity after enflurane anaesthesia in human volunteers does not, of course, exclude the possibility that such activity could have been observed had implanted depth electrodes been utilized or a large group of volunteers studied.

The repeated association of enflurane with the occurrence of epileptiform e.e.g. activity during anaesthesia is at variance with the theory that all anaesthetics act by global depression of the central nervous system. In fact, the central effects of enflurane classify it, together with chloralose and gammahydroxybutyrate, as a stimulant anaesthetic. When the latter two agents are given to animals, loss of consciousness coincides with the appearance of an epileptiform pattern on the e.e.g. Rather than depressing neural activity, the stimulant anaesthetics may inhibit control systems (Killam, 1968), or may alter circulation of activity through various neuronal networks so that a hypersynchronized state exists (Verzeano, 1972).

We noted no e.e.g. or behavioural abnormalities following halothane anaesthesia. This lack of central nervous system effect after halothane is in agreement with the observations made by Kavan, Julien and Lucero (1972), when they anaesthetized cats with halothane, methoxyflurane and diethyl ether.

In conclusion, we have been unable to document any e.e.g. or behavioural abnormalities following the administration of enflurane or halothane to cats. We believe that, if seizure activity occurs after an enflurane anaesthetic, other precipitating factors such as hypoxia should be considered.

**ACKNOWLEDGEMENTS**

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We thank Marie Lipot for secretarial assistance.
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SUMMARY

Enflurane and Halothane were studied in cats during anesthetic induction. The electroencephalogram (EEG) was monitored continuously throughout the anesthesia. No seizures were observed, and the EEG was stable throughout the experiment. After the use of enflurane and halothane, the cats showed no signs of neurological sequelae. The cats were observed for at least 4 weeks postoperatively and no lasting neurological effects were noted.

RESUME

Nous avons étudié les effets de l'enflurane et de l'halothane sur l'électro-encéphalogramme (e.e.g.) de 10 chats. Les animaux ont été soumis à au moins 2 MAC-heures d'anesthésie avec l'un ou l'autre agent, et l'e.e.g. a été surveillé de façon continue. Les valeurs des gaz du sang artériel ont été maintenues dans les limites de la normale. De surcroît, l'e.e.g. et le comportement ont été surveillés pendant la période suivant l'anesthésie, à intervalles réguliers pendant 4 semaines. Malgré l'apparition des effets stimulateurs centraux de l'enflurane au cours de l'anesthésie, aucun animal n'a manifesté de séquelles au niveau du système nerveux central, à quelque occasion que ce soit après l'anesthésie.

SUMMARY

Se estudian en 10 gatos los efectos del enflurano y del halotano sobre el encefalograma (e.e.g.). Los animales fueron sometidos a por lo menos 2 horas-MAC de anestesia con cualquiera de los dos agentes, y se verificó e.e.g. continuamente. Se mantuvieron las tensiones de gases del sangre arterial dentro de limites normales. Además, se verificaron el comportamiento y el e.e.g. durante el periodo que siguió la anestesia a intervalos fijos durante 4 semanas. A pesar de la producción de efectos estimuladores centrales del enflurano durante la anestesia, ningún animal demostró secuelas del sistema nervioso central en alguna oportunidad después de la anestesia.