THE EFFECT OF THIOPENTONE ON ENFLURANE-INDUCED CORTICAL SEIZURES

F. A. FURGANG AND J. J. SOHN

SUMMARY

The effect of thiopentone 0.5 and 1.0 mg/kg on the enflurane-induced cortical spike discharge has been examined. Seven cats were anaesthetized with enflurane in oxygen and ventilation was controlled to maintain eucapnia during e.e.g. recording. End-tidal enflurane concentrations of between 1.2 and 2.2% provoked dose-dependent spontaneous spike discharges reproducibly. It was found that, during light enflurane anaesthesia, intravenous thiopentone could exacerbate e.e.g. signs of seizure activity. However, at a greater depth of anaesthesia spike activity was suppressed. The e.e.g. changes following thiopentone resembled the effects of still greater concentrations of enflurane.

Enflurane (Ethrane) provokes dose-dependent seizure activity in the brain of animals (Virtue et al., 1966; deJong and Heavner, 1971; Joas, Stevens and Eger, 1971; Julien and Kavan, 1972; Julien, Kavan and Elliott, 1972; Kavan, Julien and Lucero, 1972) and man (Lebowitz, Blitt and Dillon, 1970, 1972; Linde et al., 1970; Neigh, Garman and Harp, 1971). Although uncommon, the associated movements (Botty et al., 1968; Dobkin et al., 1969; Lebowitz, Blitt and Dillon, 1970, 1972; Linde et al., 1970) may interfere with surgery. The anaesthetist may attempt to control the seizure by the i.v. injection of a rapidly acting barbiturate. However, the interaction between barbiturates and enflurane-induced cortical seizure activity has not been described previously. This study demonstrates that a small dose of thiopentone can either augment or suppress the seizure activity, depending upon the level of enflurane anaesthesia.

METHODS

Twelve adult cats of either sex, weighing in the range 1.9–2.7 kg, were anaesthetized with enflurane in oxygen. Tracheotomy was performed and a T-tube, with an internal catheter for gas sampling, was inserted. Ventilation was controlled with a small animal respirator. Arterial and venous catheters were inserted into the femoral vessels. The arterial catheter was connected via a three-way stopcock to a pressure transducer. Four stainless steel self-tapping screw electrodes were placed bilaterally in the frontal and parietal bones for e.e.g. recording. A heating lamp was applied to maintain the body temperature at 38 °C. Ventilation was adjusted to maintain normocapnia (Herbert and Mitchell, 1971). End-tidal gas samples were analysed immediately with a gas chromatograph (Hewlett-Packard 7610A). E.e.g., arterial pressure and heart rate were monitored continuously and recorded on a multi-channel system. Small doses of pancuronium (Pavulon) were given as required to prevent movement artefacts.

The time required to obtain a relatively stable end-tidal enflurane concentration was noted. The range of enflurane concentrations which included the threshold for the high-voltage spike activity was determined in a preliminary experiment. With this information, each cat was allowed to reach equilibrium with a predetermined inspired concentration for 20 min. In seven cats, thiopentone (Pentothal) 0.5 mg/kg was injected i.v. following a 45-s control e.e.g. After injection, the e.e.g. was recorded continuously for 75 s, and intermittently for 15 s at 2, 4, 8 and 16 min. With a minimum of 20 min between injections, thiopentone 1.0 mg/kg was administered with both a control and post-injection e.e.g. being recorded as before. End-tidal enflurane and arterial blood-gases were analysed before, during and after the e.e.g. sequence. This protocol was repeated at three additional enflurane concentrations; increasing from one level to the next in four cats and decreasing in three cats. Five control cats received pancuronium 0.1 mg/kg i.v. on an identical protocol at four enflurane concentrations, except that the e.e.g. was recorded for up to 4 min after the injection.

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E.e.g. was recorded at 2.5 cm/s paper speed and 200 μV-cm amplification, and the number of spikes/15-s interval was counted. A "spike" was defined as a waveform with a mean segmental velocity (rate of voltage change) equal to or greater than 10 μV/ms for at least 100 μV peak-to-peak amplitude. The number of spikes in the right and left fronto-parietal leads was added, except when they were simultaneous. End-tidal enflurane concentrations (mean ± SD) were grouped as follows: level I: 1.2 ± 0.1%; level II: 1.5 ± 0.1%; level III: 1.8 ± 0.1%; and level IV: 2.2 ± 0.2%. Data were pooled for each level for the thiopentone 0.5 mg/kg and 1.0 mg/kg dose, respectively. Each post-thiopentone spike count was paired with its control count and the mean differences were calculated; the t test for paired data was applied and the results were evaluated for significance at P<0.05. The two control counts obtained at each level were paired similarly and tested to determine if a significant difference existed.

RESULTS

Qualitative

The induction of anaesthesia was rapid and smooth. Licking movements of the tongue were followed quickly by excitement and loss of muscle tone. Thereafter, all the cats developed twitching of variable severity involving the extremities, back or face. At times, gross clonic movements or extensor tonic rigidity was observed. To facilitate surgery, it was necessary to administer pancuronium 0.1 mg/kg. Additional amounts of pancuronium were needed at levels I and II, but rarely at levels III or IV, to prevent movement and e.e.g. artefacts.

Spike appeared infrequently at level I, being of low amplitude, less than 300 μV from baseline. The e.e.g. was characterized by low-voltage fast activity. Thiopentone produced transient slowing and synchronization with a small increase in spike rate and occasional spindle formation. At level II, e.e.g. activity became slower with greater amplitude (fig. 1). Tall, sharp waves appeared, and the spike rate increased slightly and was enhanced further by thiopentone. At level III, frequent spikes occurred on a generally "spikey" background. Spikes were often bilateral with amplitudes between 300 and 500 μV. Thiopentone increased the spike rate and occasionally produced short periods of suppression. At level IV (fig. 2), the e.e.g. exhibited a burst-suppression pattern. Bursts were characterized by 2-5-s periods containing 1 or 2/s high voltage (often greater than 500 μV), usually multi-phasic, bilaterally synchronous.
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TABLE I. Conditions of study (mean ± SD)

<table>
<thead>
<tr>
<th>Level of anaesthesia</th>
<th>Enflurane concentration (%)</th>
<th>pH</th>
<th>PCO₂ (kPa)</th>
<th>PO₂ (kPa)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7</td>
<td>7.38 ± 0.03</td>
<td>4.27 ± 0.15</td>
<td>58.13 ± 0.107</td>
<td>38.2 ± 0.8</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>7.40 ± 0.03</td>
<td>4.27 ± 0.21</td>
<td>55.33 ± 0.080</td>
<td>38.0 ± 0.6</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>7.41 ± 0.05</td>
<td>4.27 ± 0.17</td>
<td>55.73 ± 0.120</td>
<td>37.6 ± 0.9</td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
<td>7.40 ± 0.05</td>
<td>4.13 ± 0.16</td>
<td>54.80 ± 0.107</td>
<td>37.8 ± 0.8</td>
</tr>
</tbody>
</table>

spike discharges. Frequently, spikes initiated and terminated the bursts. Suppressions from 1 to 3 s were interrupted occasionally by single spikes. Thiopentone increased the duration of the suppressions with a resulting decrease in spike rate. Spikes were usually, but not invariably, associated with slow waves. At times, jerky limb movements could be precipitated by loud hand clapping or tapping on the skull and occurred simultaneously with spikes at level IV.

Quantitative

The conditions of the study are shown in Table I. The effects of thiopentone on arterial pressure and heart rate were slight (Table II and III).

No significant difference was observed between the two control spike rates at a given level (all $P > 0.3$).

The previous injection of thiopentone 0.5 mg/kg had little effect on the control e.e.g. activity recorded before the 1.0-mg/kg dose 20 min later. Level I e.e.g. exhibited a spike rate of $2.4 ± 0.9$ (mean number of spikes/min ± SEM). With increasing concentrations of enflurane the spike rate increased to $9.2 ± 2.1$, $39.6 ± 8.3$ and $53.2 ± 8.8$ for levels II, III and IV, respectively (fig. 3).

At level I, thiopentone produced a small increase in spike rate which was statistically significant for $1.0$ mg/kg for the first 60 s following injection; $6.0$/min was the greatest significant change (GSC). At level II a larger increase in rate occurred, significant following $0.5$ mg/kg for 30 s (GSC $16.0$/min) and $1.0$ mg/kg for 75 s (GSC $25.6$/min). Level III showed a similar increase, although it was not significant. A depression of spike discharge at level IV was...
TABLE II. Effect of thiopentone 0.5 mg/kg on heart rate (beat/min) and arterial pressure (mm Hg) during enflurane anaesthesia (mean ± SD)

<table>
<thead>
<tr>
<th>Level of anaesthesia</th>
<th>Control</th>
<th>1 min</th>
<th>16 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>AP</td>
<td>Rate</td>
</tr>
<tr>
<td>I</td>
<td>189 ± 33</td>
<td>119 ± 18</td>
<td>185 ± 32</td>
</tr>
<tr>
<td>II</td>
<td>173 ± 29</td>
<td>105 ± 28</td>
<td>169 ± 29</td>
</tr>
<tr>
<td>III</td>
<td>156 ± 26</td>
<td>93 ± 33</td>
<td>150 ± 20</td>
</tr>
<tr>
<td>IV</td>
<td>155 ± 24</td>
<td>81 ± 15</td>
<td>148 ± 22</td>
</tr>
</tbody>
</table>

TABLE III. Effect of thiopentone 1.0 mg/kg on heart rate (beat/min) and arterial pressure (mm Hg) during enflurane anaesthesia (mean ± SD)

<table>
<thead>
<tr>
<th>Level of anaesthesia</th>
<th>Control</th>
<th>1 min</th>
<th>16 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>AP</td>
<td>Rate</td>
</tr>
<tr>
<td>I</td>
<td>190 ± 32</td>
<td>119 ± 20</td>
<td>182 ± 23</td>
</tr>
<tr>
<td>II</td>
<td>174 ± 31</td>
<td>110 ± 27</td>
<td>166 ± 29</td>
</tr>
<tr>
<td>III</td>
<td>155 ± 24</td>
<td>90 ± 16</td>
<td>149 ± 18</td>
</tr>
<tr>
<td>IV</td>
<td>153 ± 24</td>
<td>99 ± 15</td>
<td>146 ± 19</td>
</tr>
</tbody>
</table>

![Fig. 3. Seizure activity with enflurane.](image)

The ability of a small dose of thiopentone to increase the enflurane-induced cortical spike rate is not too surprising. Thiopentone can produce a dose-dependently reproducible discharge. Small doses of thiopentone during light enflurane anaesthesia can exacerbate transiently the electroencephalographic signs of seizure activity. At a greater depth of anaesthesia, thiopentone diminishes seizure activity.

DISCUSSION

Our data show that, in the cat, end-tidal enflurane concentrations between 1.2 and 2.2% provoke reproducible dose-dependent spontaneous spike discharges. Small doses of thiopentone during light enflurane anaesthesia can exacerbate transiently the electroencephalographic signs of seizure activity. At a greater depth of anaesthesia, thiopentone diminishes seizure activity.

The e.e.g. spike is regarded as a typical sign of seizure disorder. It is usually defined as an isolated waveform of duration 80 ms or less (Kooi, 1966). Spikes with amplitudes less than 50 µV may be unrecognized against background activity (Kooi, 1971). Earlier investigators suggested a threshold for the enflurane-induced discharge from 1.75 to 2.25% in the cat (deJong and Heavner, 1971), and about 2% in man (Neigh, Garman and Harp, 1971); its high-voltage nature has been emphasized repeatedly. However, in the present study waveforms meeting the above definition of a spike were observed at all levels. The spike amplitude and, therefore, the segmental velocity were observed to increase as the enflurane concentration was increased. Our more restricted definition of a spike, based upon segmental velocity, was useful for quantitation. Thereby, we excluded some conventional spikes from counting at level I, while virtually all were included at level IV. Nevertheless, the enflurane spike threshold in the cat appears to be less than 1.2% end-tidal concentration. Except for this finding, our electroencephalographic observations agree with those of deJong and Heavner (1971).

The ability of a small dose of thiopentone to increase the enflurane-induced cortical spike rate is not too surprising. Thiopentone can produce a dose-
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30
20
10
-10
-20

Uval • Uval III
• Uval II • Uv*I IV

0.5
30
20
10
0
-10
-20

-10
-20

0
0
0
0

1 2 4 8 16 0.5 1 2 4 8 16

min p thiopentone 0.5 mg/kg min p thiopentone 1.0 nig'kg

FIG. 4. Effect of thiopentone on enflurane-induced seizure activity.

dependent sequence of e.e.g. changes from an initial rapid rhythm, to spindles and polymorphic slow waves, and burst-suppression. The initial activation is thought to result from direct stimulation of the mesencephalic reticular formation and rapid propagation of the effect throughout the brain (Rosner and Clark, 1973). Barbiturates have been observed to activate epileptic discharges; methohexitone has been used to elicit cortical spikes in epileptic patients before temporal lobe resection (Wilder, 1971). During light barbiturate anaesthesia an increase in cortical reactivity to direct electrical stimulation has been observed also (Merlis, 1965).

Depth electrode studies in the cat during enflurane inhalation have demonstrated prominent seizure activity in the amygdala and hippocampus (deJong and Heavner, 1971; Julien and Kavan, 1972; Julien, Kavan and Elliott, 1972; Kavan, Julien and Lucero, 1972), structures with a particularly low threshold to seizure discharge (Gloor, 1960; Green, 1960). We may speculate that the widespread initial excitation and increase in cortical reactivity by barbiturates would stimulate further a sub-cortical enflurane seizure focus or augment the cortical responsiveness to ascending activity. Interestingly, the e.e.g. changes which we observed following thiopentone resembled the effects of a still greater concentration of enflurane. Even the reduction in spike rate and lengthening of suppressions by thiopentone at level IV are consistent with published e.e.g. observations (deJong and Heavner, 1971) and our findings in experiments at deeper enflurane concentrations (2.25–5%).

Preliminary observations in three cats receiving pentobarbitone 1.0 mg/kg i.v. have shown an increase in cortical spike rate at levels II and III, and a depression of activity at level IV, the effect lasting for up to 1 h. Therefore, the phenomenon observed is not unique to thiopentone, but may be a property of barbiturates in general.

ACKNOWLEDGEMENTS
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**EFFET DU THIOPENTONE SUR LES CRISSES CORTICALES PROVOQUÉES PAR L’ENFLURANE**

**RESUMEN**

On a étudié l’effet du thiopentone administré à raison de 0,5 et 1,0 mg/kg sur l’écoulement cortical de pointe provoqué par l’\textit{Enflurane}. On a anesthésié sept chats à l’aide d’\textit{Enflurane} dans de l’oxygène et on a contrôlé la ventilation de manière à maintenir l’eucapnie pendant l’enregistrement de l’électro-encéphalogramme. Les concentrations d’\textit{Enflurane} dans l’air de respiration final, situées entre 1,2 et 2,2%, ont produit des écoulements de pointe reproductibles et spontanés en fonction de la dose. On a trouvé que pendant l’anesthésie légère à l’\textit{Enflurane}, le thiopentone administré par voie intraveineuse pouvait aggraver les signes de l’électro-encéphalogramme de l’activité de la crise. On a néanmoins pu supprimer l’activité de pointe par une anesthésie plus profonde. Les variations de l’e.e.g. à la suite de l’administration de thiopentone, ont ressemblé aux effets de concentrations encore plus grandes d’\textit{Enflurane}.

**DIE WIRKUNG VON THIOPENTON AUF DURCH ENFLURAN HERVORGERUFENE KORTIKALE ANFÄLLE**

**ZUSAMMENFASSUNG**

Untersucht wurde die Wirkung von Thiopenton 0,5 und 1,0 mg/kg auf die durch Enfluran hervorgerufene korticale Spitzenentladung. Sieben Katzen wurden mit Enfluran in Sauerstoff narkotisiert, und die Belüftung wurde kontrolliert, um während des e.e.g.’s Eukapnie zu bewahren. Enflurankonzentrationen zwischen 1,2 und 2,2% im Atemendvolumen riefen dosisbedingte spontane Spitzenentladungen hervor. Es wurde festgestellt, dass Thiopentone bei intravenöser Verabreichung während einer leichten Enflurananarkose die e.e.g.-Anzeichen einer Anfallsaktivität verschärfen konnte. Bei tieferer Narkose jedoch war die Spitzenaktivität unterdrückt. Die e.e.g.-Veränderungen auf Thiopentone ähnelten den Wirkungen noch stärkerer Enflurankonzentrationen.

**EL EFECTO DE TIOPENTONA SOBRE LOS ACCESOS CONVULSIVOS INDUCIDOS CON ENFLURANO**

**SUMARIO**

Se ha examinado el efecto de la tiopentona 0,5 y 1,0 mg/kg sobre la descarga de espiga cortical inducida con enflurano. Se anestesiaron siete gatos con enflurano en oxígeno y se reguló la ventilación para mantener la eucapnia durante el registro e.e.g. Las concentraciones de volumen residual de enflurano de entre 1,2% y 2,2% provocaron descargas de espiga espontáneas dosis-dependientes de manera reproducible. Se halló que durante la anestesia ligera con enflurano, la tiopentona endovenosa podía exacerbar los signos de actividad convulsiva mostrados en el e.e.g. Sin embargo, con una mayor profundidad de anestesia se suprimía la actividad de espiga. Los cambios en el e.e.g. tras la tiopentona se asemejaron a los efectos de concentraciones aún mayores de enflurano.