AN INCREASE IN THE HALF-LIFE OF PENTOBARBITONE WITH THE ADMINISTRATION OF HALOTHANE IN SHEEP

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SUMMARY
The effect of halothane on the half-life of pentobarbitone was studied in sheep. Pentobarbitone was given in a dose of 20 mg/kg and halothane was administered via a mask for periods from 30 min up to 2 hr. Concentrations of pentobarbitone in whole blood were measured and the half-life determined. In cross-over tests giving pentobarbitone alone, and pentobarbitone and halothane to eight sheep, increases in the half-life with halothane ranging from 4 to 323% (mean 71%) were observed.

Although halothane and barbiturates are often used together in anaesthesia, there is little information available on the effects of halothane on barbiturate metabolism. Brown (1971) has demonstrated that halothane has an action on the oxidative metabolism of certain drugs, that of pentobarbitone being depressed in vitro. Halothane is also known to decrease liver perfusion during anaesthesia in man (Epstein et al., 1965). Rahn, Dayton and Frederickson (1969) have shown that halothane has no effect on thiopentone half-life in man, but since redistribution, rather than metabolism, is responsible for the decline in thiopentone levels (Goldstein and Aronow, 1960; Price et al., 1960) this result would be expected.

In this study we have compared the half-life of pentobarbitone when used as the sole anaesthetic agent, with that obtained in the presence of halothane, in cross-over experiments in the same animals. Sheep were chosen because they are known to metabolize pentobarbitone rapidly (dos Santos, 1972).

MATERIALS AND METHODS

Animals.
Scottish blackface sheep, weighing between 29 and 52 kg, were used. The animals were divided into two groups. Group 1 was given pentobarbitone (Abbott) and halothane (ICI) on the first occasion, group 2 pentobarbitone alone. On the second occasion this was reversed, group 1 receiving pentobarbitone alone and group 2 pentobarbitone and halothane. A period of 4 weeks was allowed to elapse between the two procedures in the same animal to reduce effects due to enzyme induction.

Pentobarbitone was given in a dose of 20 mg/kg on each occasion by slow, intravenous injection. Halothane was administered using a Fluotec vaporizer via a mask for periods from 30 to 120 min beginning 10–15 min after pentobarbitone administration and in sufficient concentration to allow spontaneous respiration in the absence of a pedal reflex. Body temperature was measured using an electric thermometer and a rectal probe. Blood samples were collected from a jugular vein at intervals from 20 min following pentobarbitone injection for up to 5 hr.

Estimation of pentobarbitone in blood.

Pentobarbitone concentrations in whole blood were measured by the differential spectrophotometric method of Broughton (1956) in solutions at pH 13 and pH 10. The half-life of pentobarbitone was determined from the semilog plot of at least five measurements of blood pentobarbitone concentrations.

Estimation of halothane in blood.

Halothane levels were measured on a gas chromatograph by the method of Cousins and Mazze (1972). Blood samples were collected from sheep nos. 3, 4, 6, 7 and 8 in vacutainers and halothane concentrations were measured immediately by the injection of 5 μl of blood directly on to the column. The glass column was packed with 5% OV101 on chromosorb W, and was operated at 40°C with a flame ionization detector.

RESULTS

Repeat determinations of pentobarbitone half-life.

Measurements were made in three sheep to observe the variations which might be expected in the half-life of pentobarbitone on repeated occasions in the

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TABLE I. The effect of halothane on the half-life of pentobarbitone in the sheep.

<table>
<thead>
<tr>
<th>Regimen*</th>
<th>Sheep no.</th>
<th>Duration of halothane administration (min)</th>
<th>Half-life of pentobarbitone (min)</th>
<th>% Increases with halothane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alone</td>
<td>With halothane</td>
</tr>
<tr>
<td>Group 1</td>
<td>1</td>
<td>30</td>
<td>68</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>45</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>60</td>
<td>56</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>60</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>4 (repeat)</td>
<td>60</td>
<td>34</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>60</td>
<td>36</td>
<td>54</td>
</tr>
<tr>
<td>Group 2</td>
<td>6</td>
<td>60</td>
<td>72</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>7 (repeat)</td>
<td>60</td>
<td>62</td>
<td>100†</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>90</td>
<td>34</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>120</td>
<td>64</td>
<td>70</td>
</tr>
</tbody>
</table>

*Group 1. 1st experiment: Pentobarbitone + halothane
2nd experiment: Pentobarbitone alone

Group 2. 1st experiment: Pentobarbitone alone
2nd experiment: Pentobarbitone + halothane
†Body temperature maintained at 39°C.

same animal. In two sheep, nos. 3 and 4, this observation was made during a repeat of the whole experiment (table I). There was a difference of 6 min between the two determinations. A second administration of pentobarbitone to sheep no. 8 gave a half-life of 68 min compared to 64 min obtained previously. There was an interval of at least 4 weeks between these determinations in all three sheep.

Halothane levels.

It was not possible to maintain anaesthesia with a constant concentration of halothane in the inspired gas mixture. Concentrations of halothane in blood measured in five sheep ranged between 3.0 mg/100 ml and 8.5 mg/100 ml and showed variations during the course of each experiment. It was, therefore, not possible to determine whether a correlation existed between the concentration of halothane in the blood and the extent of prolongation of the half-life of pentobarbitone observed.

Rectal temperature.

Decrease in rectal temperature with pentobarbitone alone never exceeded 0.6°C. During halothane administration the maximum decrease observed (sheep no. 3) was 2.9°C. In this sheep, when hypothermia was prevented, by external warming, a half-life of 100 min was obtained (table I).

Effect of halothane on half-life of pentobarbitone.

Results obtained in eight sheep are shown in table I. In all sheep an increase was observed in pentobarbitone half-life after halothane. In five sheep the increase was greater than could be accounted for by variation on repeat determinations.

DISCUSSION

From our results, halothane appears to cause variable increases in pentobarbitone half-life. This effect may be due to: (1) inhibition of hepatic microsomal enzymes (Brown, 1971); (2) increased hypothermia; (3) reduced hepatic blood flow caused by halothane (Epstein et al., 1965); (4) altered distribution of pentobarbitone; or a combination of all, or some, of these.

From the in-vitro studies of Brown (1971), an increase in the half-life of pentobarbitone might be expected, due to inhibition of microsomal enzymes by halothane. In our experiments blood halothane levels varied during anaesthesia, and would probably be reflected in varying concentrations of halothane in the liver. This variation may account for the wide differences in the effects on pentobarbitone half-life observed.

Prolongation of half-life might also be due, at least in part, to increased hypothermia. When the body temperature was maintained at 39°C in one animal, there was a slight decrease in the half-life compared with the previous result (table I). It appears unlikely, however, that this factor could account entirely for the increases observed.

The results of these observations suggest that the administration of halothane will prolong the clear-
ance of those barbiturates whose duration of action depends on their metabolism. It seems unlikely that this phenomenon will only involve barbiturates and we would suggest that further examination of the importance of this effect on other drugs which might be used in conjunction with halothane anaesthesia is desirable.

REFERENCES


