LACK OF EFFECT OF HALOTHANE ON THE METABOLISM OF THIOPENTONE IN MAN

BY

ELKE RAHN, P. G. DAYTON AND E. L. FREDERICKSON

SUMMARY

In subjects without evidence of liver disease, given 500–700 mg doses of thiopentone, the half-life was shorter than reported previously with doses ranging from 1 to 4 g. Halothane was shown not to have a significant effect on the metabolism of thiopentone.

Previous studies of the half-life of thiopentone ($T_{\frac{1}{2}}$) in man were performed using higher than usual doses (1–4 g) (Brodie et al., 1950, 1951; Brodie, 1952). This was necessary because there was no method available to measure low plasma concentrations of the drug. It has been shown that $T_{\frac{1}{2}}$ of certain drugs may depend on the dose (Weiner et al., 1950; Brodie et al., 1952; Dayton et al., 1967a). Since a sensitive spectrofluorometric method is now available, we decided to measure the $T_{\frac{1}{2}}$ of thiopentone in man using therapeutic doses.

Thiopentone is metabolized mainly in the liver (Winters et al., 1955; Cooper and Brodie, 1957; Spector and Shideman, 1959; Mark et al., 1965). There is evidence that halothane alters liver perfusion in normal volunteers (Epstein et al., 1965; Price et al., 1966). This effect of halothane might influence thiopentone metabolism; therefore, we studied patients receiving both drugs.

PATIENTS AND METHODS

Eight healthy patients without evidence of liver disease and not taking chronic medication, participated in the study. Group I consisted of five patients who had anaesthesia for minor surgery (four cystoscopy and one biopsy). Group II was made up of three patients who underwent surgical procedures, lasting from 2.5 to 6 hours. In these three patients anaesthesia was maintained with halothane in nitrous oxide and oxygen after induction with thiopentone.

Halothane was vaporized in concentrations (1.0–2 per cent) adequate to maintain moderately deep anaesthesia. Ventilation was assisted to prevent accumulation of carbon dioxide. Thiopentone was always given intravenously in doses ranging from 5 to 12 mg/kg within the first 10 minutes. No marked hypotensive episodes were observed.

Since the initial decay of plasma levels was not followed, samples of venous blood were drawn intermittently starting 1 hour after the administration of the drug. Samples were drawn intermittently from subjects in group I for as long as 12 hours after the drug was administered. At least four samples were drawn from subjects in group II during halothane anaesthesia. Two to six hours after discontinuation of halothane, four more samples were taken from these subjects. Thiopentone in plasma was measured by a method previously described (Dayton et al., 1967b). For the analysis it was more convenient to use glass distilled N hexane (Burdick & Jackson Laboratories, Muskegon, Mich.) and NaOH supplied by Mallinckrodt than randomly purchased reagents. This resulted in lower blanks.

RESULTS

The initial rapid decline in plasma concentration primarily due to distribution of the drug throughout the body was not measured. The slow decline due to metabolism of thiopentone is a single
exponential curve, as shown in figure 1. The rate of decay calculated from this and other curves obtained in seven additional subjects ranged from 16 to 24%/hr (table I) (mean 18.4%/hr ±1.0). Thus, $T_{\frac{1}{2}}$ ranged from 2.1 to 3.1 hours (table I); the mean was 2.6 ±0.1 hours. The rate of decay during halothane anaesthesia did not differ from the values obtained after halothane was discontinued (fig. 2; table I).

![Graph](https://academic.oup.com/bja/article-abstract/41/6/503/252565)

**Fig. 1**
Plasma levels of thiopentone after the intravenous dose of 500 mg of thiopentone-sodium (Subject 1). Though the dotted extrapolation to zero time in order to give a hypothetical volume of distribution might suggest immediate "equilibrium", actually distribution is a complex phenomenon (Bischoff and Dedrick, 1968).

**Fig. 2**
Plasma levels of thiopentone during (dots) and after (triangles) halothane anaesthesia (Subject 8). Halothane was given during the time period indicated by $<=>$. Extrapolation to time zero as in figure 1.

**TABLE I**
Data on individual subjects.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Dose* (mg/kg)</th>
<th>$\mu g/ml$†</th>
<th>Rate of decay (%/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GROUP I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>83.7</td>
<td>6</td>
<td>3.8</td>
<td>19 (2.6)</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>F</td>
<td>65.3</td>
<td>11</td>
<td>6.6</td>
<td>18 (2.8)</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>F</td>
<td>60.3</td>
<td>12</td>
<td>5.1</td>
<td>16 (3.1)</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>F</td>
<td>49.5</td>
<td>11</td>
<td>5.4</td>
<td>21 (2.4)</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>F</td>
<td>58.2</td>
<td>8</td>
<td>3.4</td>
<td>18 (2.8)</td>
</tr>
<tr>
<td><strong>GROUP II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>M</td>
<td>116</td>
<td>5</td>
<td>4.1</td>
<td>17 (3.0)</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>F</td>
<td>51</td>
<td>10</td>
<td>4.4</td>
<td>22 (2.3)</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>M</td>
<td>86.5</td>
<td>6</td>
<td>3.4</td>
<td>24 (2.1)</td>
</tr>
</tbody>
</table>

* As sodium salt of thiopentone. $T_{\frac{1}{2}}$ (hr) in parentheses. † Extrapolated level at $t=0$.

**DISCUSSION**
It has been shown that thiopentone is metabolized in the liver (Winters et al., 1955; Cooper and Brodie, 1957; Spector and Shideman, 1959; Mark et al., 1965; Shideman et al., 1949). In this study with routine clinical anaesthesia it was found that halothane does not affect the $T_{\frac{1}{2}}$. This could be explained on the basis that, though halothane may have decreased hepatic blood flow and even oxygen tension in the hepatic veins, the
metabolism of the drug was not diminished. It is known that oxygen is involved in the metabolism of thiopentone (Cooper and Brodie, 1957; Spector and Shideman, 1959; Mark et al., 1965).

Brodie and others (1950, 1951) and Brodie (1952) have reported a $T_1/2$ of thiopentone ranging from 10 to 15%/hr after doses of 1–4 g. In the present study, following doses of 500–700 mg, $T_1/2$ ranged from 16 to 24%/hr. The subjects studied by Brodie and co-workers were not described as being normal in regard to liver function; in fact, it was then believed that even in cirrhosis there was no alteration in the rate of drug metabolism (Brodie, Burns and Wiener, 1959). However, recently it has been shown that differences in the rate of drug metabolism may depend on differences in liver function and pre-treatment with unrelated drugs (Levi, Sherlock and Walker, 1968). Thus, some subjects in whom $T_1/2$ was studied by Brodie and co-workers may have had altered function. An alternative explanation for the present results is that metabolism is dose-dependent, being more rapid at lower levels. Weiner and associates (1950) had found such a phenomenon in humans using dicoumarol and similar findings were reported by Brodie and associates (1952) for ethylbiscoumacetate. Dayton and associates (1967a) have demonstrated dose dependence in dogs for several drugs. Brodie and associates (1952) suggested as an explanation for the dose-dependence of $T_1/2$ of drugs the saturation of a biochemical mechanism. In the case of thiopentone, the drug-metabolizing enzymes in the liver microsomes may be saturated at higher doses of the drug.

REFERENCES


ABSENDEFFETTEHLHALOTHANENMETABOLISMEUTHIOPTENTONECHEZL'HOMME

SOMMAIRE

Chez des sujets sans signes d'affection hépatique, recevant des doses de 500–700 mg de thiopentol, le temps de demi-vie était plus court que rapporté précédemment avec des doses de 1 à 4 g. Il a été démontré que l'halothane n'a pas d'effet significatif sur le métabolisme du thiopentol.

MANGELNDE WIRKUNG VON HALOTHAN AUF DEN THIOPENTALSTOFFWECHSEL BEIM MENSCHEN

ZUSAMMENFASSUNG

Bei Individuen ohne nachweisbare Lebererkrankung, denen 500–700 mg Dosen von Thiopentol gegeben wurden, war die Halbwertszeit kürzer als es früher mit Dosen zwischen 1 und 4 g berichtet worden war. Es wurde gezeigt, dass Halothan keine signifikante Wirkung auf den Thioptenalstoffwechsel hat.