Physiologic Disposition of Methohexital in Man

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The barbiturate methohexital (Brevital) has recently been introduced as an ultrashort acting intravenous anesthetic.1-8 In clinical behavior it is grossly similar to the other barbiturate anesthetics. Recovery appears to be slightly more rapid,1-8 although one group9 reported a longer sleeping time with methohexital. The distinguishing feature described by all investigators is the relatively complete alertness without "hangover" seen at awakening. At this time complex tasks could be accurately performed.9 As a consequence, recovery room care is simplified and the management of ambulatory patients facilitated.

This paper attempts to evaluate some physicochemical and pharmacologic factors that influence the course of clinical anesthesia with methohexital in man.

Methohexital is an oxybarbiturate whose chemical structure, 1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbiturate, contains two optically active carbon atoms, indicated by asterisks in figure 1. There are, therefore, four different stereoisomers. Methohexital consists of a racemic mixture of the α-α and α-β isomers. The β-α and β-β isomers produce excessive motor activity.10 In rats, mice, rabbits, monkeys, and dogs methohexital is three times as potent, one half as long in duration, and localized in tissues to a much lesser extent than thiopental.4

Chemical Assay Methods

The method described by Brodie and associates11 for thiopental was slightly modified for determining methohexital as follows:

One to 3 ml of plasma was placed in a 60-ml glass-stoppered bottle. If less than 3 ml were used, water was added to make a 3-ml volume. To this, 0.5 ml of 6 N HCl and 30 ml of heptane containing 1.5 per cent isomyl alcohol8 was added. This was shaken for one hour (at this point samples may be left overnight), and then centrifuged in test tubes. A 25-ml aliquot was transferred into another bottle containing 2 ml of 2.5 N NaOH. After shaking five minutes, an aliquot of the aqueous phase was transferred to a semimicro-cuvet and the optical density at 248 mu in an ultraviolet spectrophotometer (Beckman) was determined. The compound is unstable in 2.5 N NaOH, 5 per cent decomposing in 25 minutes. To correct for this, when the 2.5 N NaOH was added to the analyzed samples, a solution of 10 mg./liter of drug was prepared, and both fresh standard and samples were measured concurrently. To measure methohexital in fat a 20 per cent homogenate in 0.1 N NaOH was made, using glass homogenizers at a temperature of 5° C. or lower. The homogenate was centrifuged and the middle layer withdrawn quickly for analysis. Whenever possible, 3 ml samples were used. (Though the drug is more stable in dilute NaOH than in 2.5 N NaOH, speed was important.) Internal standards of 50 μg. were analyzed simultaneously. The procedure for plasma was modified by the introduction of a wash prior to extraction with NaOH, in

![Figure 1. Methohexital. Asterisks indicate optically-active carbon atoms.](image-url)
order to minimize "blank." As much as possible of the organic phase was shaken with an equal amount of pH 4.4 citrate (0.1 M) disodium phosphate (0.2 M) buffer, then 20 ml. of organic phase were extracted with NaOH. Recoveries were better than 95 per cent for plasma and 90 per cent for fat, when corrected for decomposition as described above. In a representative experiment, when a standard of 50 μg. was analyzed by the method (25 ml. of aliquot shaken into NaOH) a reading of 0.538 above blank was found; correcting for decomposition yielded 0.555, corresponding to a recovery of 95 per cent. The sensitivity of the method was limited by the plasma "blank" which was variable, but remained less than 0.200 for 3 ml.

**Rate of Biotransformation**

Four human subjects received methohexitol intravenously in 1 per cent solution in doses of 1.2 to 1.8 g. over a period of one hour. Plasma samples for determination of drug levels were drawn at intervals over a five and one-half hour period.

Figure 2 compares plasma decay curves representative of two of these four experiments with typical curves obtained previously for methitural and thiopental. The plasma concentrations of methohexitol in all patients declined rapidly for the first thirty minutes and then more slowly. The early rapid decline of plasma levels apparently represents a shift of drug from plasma to tissues as the drug is distributed throughout the body. As equilibrium is approached between plasma and tissues, the further decline is dependent on the rate of biotransformation which is quite slow, being 15 to 19 per cent per hour. This is comparable to the rate of 20 per cent per hour for methitural and is somewhat faster than that of 15 per cent per hour for thiopental (fig. 2).

**Localization in Tissues**

Samples of omental fat and plasma were obtained at intervals after a large dose (1.5 to 2.4 g.) of methohexitol was administered intravenously over a period of 30 to 60 minutes to six patients undergoing operation. Subsequently, light cyclopropane anesthesia and muscle relaxants were used as needed. Concentrations of methohexitol in fat increased with time, reaching values two to six times those in plasma after two to four hours (table 1).
In Vitro Studies

The distribution between oil and water was determined for methohexital, thiopental and methital respectively after distributing 10 mg. of each drug between 5 ml. of peanut oil and 100 ml. of pH 7.4 phosphate buffer. In this system the partition coefficient for methohexital was exceeded by that of both thiobarbiturates (table 2).

The pKa of methohexital, determined by the spectrophotometric method of Flexser et al.,13 was 7.9 at room temperature in water.

The degree of plasma binding was determined by equilibrium dialysis against isotonic phosphate buffer of pH 7.4 at 37° C. for eighteen hours. Visking membranes were utilized as dialysis bags. In human plasma, at a concentration of 100 mg./liter, 73 per cent of the drug was bound to the nondiffusible constituents of the plasma. The remaining 27 per cent of the compound free in plasma water presumably represents the pharmacologically active drug.

Passage into Brain

Changes in the electrical activity of the brain after intravenous injection of the drug

<p>| Table 1. Methohexital in Human Fat |
|-----------------------------|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Dose* (grams)</th>
<th>Time† (minutes)</th>
<th>Plasma (mg./liter)</th>
<th>Oriental Fat (mg./kg.)</th>
<th>Fat/Plasma Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 (60)</td>
<td>165</td>
<td>14.5</td>
<td>21.6</td>
<td>1.5</td>
</tr>
<tr>
<td>1.6 (60)</td>
<td>145</td>
<td>11.8</td>
<td>38.6</td>
<td>3.3</td>
</tr>
<tr>
<td>2.0 (60)</td>
<td>165</td>
<td>21.6</td>
<td>37</td>
<td>1.7</td>
</tr>
<tr>
<td>2.0 (55)</td>
<td>135</td>
<td>12.2</td>
<td>15.6</td>
<td>1.4</td>
</tr>
<tr>
<td>2.0 (55)</td>
<td>225</td>
<td>9.7</td>
<td>43.2</td>
<td>6.4</td>
</tr>
<tr>
<td>1.9 (30)</td>
<td>64</td>
<td>27</td>
<td>262</td>
<td>25</td>
</tr>
<tr>
<td>125</td>
<td>24.4</td>
<td>51</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>195</td>
<td>13.9</td>
<td>43</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>2.34 (40)</td>
<td>71</td>
<td>39.6</td>
<td>47</td>
<td>1.2</td>
</tr>
<tr>
<td>177</td>
<td>21</td>
<td>28.3</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>264</td>
<td>14</td>
<td>28.8</td>
<td>2.1</td>
<td></td>
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</tbody>
</table>

* As sodium salt. This value is multiplied by 262/285 (0.92) to calculate dose as free acid; concentrations are reported as free acid. Parentheses denote length of infusion in minutes.
† From beginning of infusion.
‡ Subcutaneous fat.

Table 2. Oil to Water Partition Ratios

<table>
<thead>
<tr>
<th></th>
<th>Methohexital</th>
<th>Thiopental</th>
<th>Methital</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg. of each compound distributed between peanut oil (5 ml.) and pH 7.4 phosphate buffer (100 ml.).</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

were studied in man and dog by means of a Grass four-channel electroencephalograph. Typical alterations as described for thiopental by Kiersley and associates14 appeared in the electroencephalographic patterns within 15 to 20 seconds after the intravenous injection of methohexital, coinciding with a loss of consciousness. This would suggest the prompt passage of the drug in effective concentrations from the blood into the brain.

Discussion

Physicochemical characteristics both account for and set limits to the clinical usefulness of anesthetic drugs. In the case of the barbiturates, the properties concerned include ionization, lipid solubility, protein binding, potency and rate of metabolism. The dissociation constant, pKa (i.e., that pH at which 50 per cent of the drug is present in the unionized state and 50 per cent in the ionized) for most barbiturates was between 7 and 8. Consequently, in the physiologically interesting range of pH, they exist to varying degrees as undissociated molecules. In this form, given a sufficient degree of lipid solubility, they penetrate biological “membranes” (e.g., the blood-brain barrier), ionizing promptly on the other side to an extent governed by the local pH encountered there. The amount of drug free to participate in such transfers is dependent upon the extent of binding to protein elements in the plasma (and tissues). The amount of drug required for anesthetic effect is governed in part by its potency, in part by the rapidity of its redistribution into nonnervous tissue elements and in part by the rate of its biotransformation to form pharmacologically inactive metabolites.

The present study attempts to assess the relative contribution of some of these physicochemical characteristics to an explanation of the similarities and differences in the clinical behavior of methohexital as compared to thiopental and methital. Although no precise
evaluation of potency was attempted, incidental observations during the investigations reported here were in general agreement with the estimates of others that the relative potency of methohexital in man is two to two and one-half times that of thiopental and five times that of methitural. 

The $pK_a$ of methohexital, as reported above, is 7.9 at room temperature in water, while that of thiopental is 7.6. Based on the Henderson-Hasselbalch equation, 61 percent of the thiopental present at pH 7.4 is unionized, whereas 76 percent of methohexital is unionized. For any given dose, somewhat more methohexital would be present in the unionized form, able to diffuse across membranes and arrive at sites of biological activity. Thus, comparatively less drug would be required to produce a desired effect. This may represent a minor contribution to the greater potency of methohexital as compared to thiopental.

In human plasma 73 percent of methohexital is bound to protein, as compared to 75 percent with thiopental. For practical purposes, these are identical. Methohexital has a slightly lower oil-to-water partition ratio than either thiopental or methitural (table 2). The order of lipid solubility of all three drugs is adequate to permit their rapid passage across the blood-brain barrier. Indeed, the time of onset of changes in the electroencephalogram and the time of loss of consciousness after injection of methohexital, thiopental and methitural are so close as to be indistinguishable.

On the other hand, the lower fat solubility of methohexital seems to be associated with less extensive localization in fat. It is recognized that the distribution of methohexital into various body tissues is influenced by concomitant factors such as the hemodynamic effects of the barbiturate and supplementary anesthetic agents (light cyclopropane, muscle relaxants) and the surgical operation itself. Methods currently available are not adequate to measure the magnitude of these influences. However, within broad limits, the experimental conditions were held uniform by meticulous attention to ventilation and blood pressure and the use of very light anesthesia. Under these circumstances concentrations of methohexital in human fat two to four hours after administration were two to six times those in plasma (table 1). The corresponding figures for thiopental ranged from 6.5 to 13 and for methitural reached 18. Consequently, proportionately less methohexital is sequestered in relatively inactive tissue and proportionately more remains circulating in the plasma for distribution to sites of action and for metabolism by microsomal enzymes in the liver. Conversely, since the thiobarbiturates are distributed more extensively into body fat, they may be less readily available for biotransformation. Indeed, slow release from fat depots may be a determining factor in the rate of their metabolism. This phenomenon is not unique in pharmacology. For instance, after the administration of dibenamine the drug rapidly disappears from plasma, due mainly to rapid metabolism but partly to deposition in fat. Subsequently, the unmetabolized drug is almost wholly present in fat, from which it diffuses very slowly into the blood stream. In other words, despite the ability of microsomal enzymes to metabolize dibenamine rapidly, plasma concentrations are maintained at low levels for a considerable period of time as the drug is released slowly from fat depots. A similar mechanism could account in part for the somewhat delayed awakening and the "hangover" effect seen in the patient who has received large doses of thiobarbiturates as compared with the more complete return to a state of alertness seen with methohexital. This finding is not unexpected in the case of thiopental, which is metabolized in man more slowly than methohexital. It is equally true, however, with methitural despite its more rapid rate of metabolism. Obviously rapid metabolism does not counterbalance the effect of slow release from fat. It may be that the ideal intravenous anesthetic requires a degree of lipid solubility sufficiently high for rapid passage into brain but not so high that extensive localization in fat depots results. One may speculate that the lesser accumulation in fat, the greater potency, the higher $pK_a$ and the slightly faster rate of metabolism help to provide an explanation for the marked alertness and lack of "hangover" observed after recovery from methohexital.

This study has been concerned, not with the mechanism of action of methohexital or the other barbiturates, but rather with the
mechanics of their distribution within and removal from the body. The findings help to account for the clinical behavior of these agents without considering their mode of action on a cellular level. It may ultimately prove more rewarding to seek within the central nervous system directly to explain the clinical differences observed among the anesthetic barbiturates. For example, the recent radioautographic studies by Roth and Barlow indicate that barbiturates enter certain parts of the brain more rapidly than others and that uniform distribution occurs much later than the onset of anesthesia. Non-uniform distribution of barbiturates in the brain at an early time might have been anticipated, since capillary density varies in different parts of the brain. This raises the possibility that differences between barbiturates may be correlated with differences not only in fat solubility but also in the time sequence of their patterns of distribution within the brain.

Summary and Conclusions

Some factors that influence the course of clinical anesthesia with methohexitol in man were investigated. The rate of biotransformation of methohexitol and the extent of its ionization are in the same range as but somewhat higher than those for thiopental. In binding to plasma proteins it is identical with thiopental. Its lipid solubility is high enough to permit rapid passage across the blood-brain barrier, but its accumulation in fat is less extensive than that of thiopental or metitalur.

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References