PHARMACOKINETICS OF THIOPENTONE IN A GROUP OF YOUNG WOMEN AND A GROUP OF YOUNG MEN

J. H. CHRISTENSEN, F. ANDREASEN AND J. A. JANSSEN

SUMMARY

The average induction dose of thiopentone did not differ significantly when eight young women were compared with eight young men. In neither group did the dose increase with increased body weight. Clearance of thiopentone from venous blood was described by a three-compartment open model. The average volumes of $V_1$ and $V_2$ were greater in the females, but only the difference between the $V_3$ values was significant ($P < 0.05$). Significant correlations ($P < 0.01$) were found between the initial drug concentrations and the $k_{13}$ values. The slopes of the regression lines were 0.0029 for the women and 0.0038 for the men ($0.1 < P < 0.2$). It is suggested that the redistribution rate constant $k_{13}$ is predominant in determining the sleep dose rather than the initial distribution volume $V_1$.

It is accepted that the age, sex and body weight of a patient influence the dose of thiopentone required to maintain anaesthesia (Dundee, 1954). When investigating the dose of thiopentone necessary for the induction of anaesthesia, Christensen and Andreassen (1978) found that, although the apparent difference between men and women was not significant when individual age groups were compared, the average dose for all the men was significantly greater than that for the women. Moreover, there was a considerable individual variation in groups of patients comparable with respect to age, sex, body weight and surgical disease.

In the only complete pharmacokinetic study of thiopentone in patients Ghoneim and Van Hamme (1978) studied the effect of enflurane, nitrous oxide and surgery on the pharmacokinetics of the drug. The present investigation compared a group of young women with a group of young men with respect to dose and to pharmacokinetic data obtained by conventional compartmental analysis based on concentrations of thiopentone in peripheral venous blood.

Since the individual variation may be related to the method of drug administration, the drug was administered exactly as in our previous study of 1978.

PATIENTS AND METHODS

Eight male and eight female patients gave informed consent to the study. The age range was 20–40 yr. The women underwent minor gynaecological operations, the men orthopaedic procedures. The diseases were not of an acute nature: No patient showed evidence of a disease other than the surgical disease condition.

Pethidine 1 mg plus diazepam 0.1 mg per kg body weight and atropine 0.5 mg were given i.m. 0.5–1 h before the induction of the anaesthesia. Anaesthesia was induced with thiopentone as described in detail below. Suxamethonium 100 mg was given to facilitate tracheal intubation and anaesthesia was maintained with nitrous oxide in oxygen and halothane. The lungs were ventilated artificially and every anaesthetic was administered by the same anaesthetist (J.H.C.). The duration of anaesthesia was 55–220 min for the men and 50–120 min for the women.

The thiopentone solution was injected to a vein on the back of the hand until the eyelash reflex was obtunded. The first 250 mg was given over 25 s. After that repeated doses of 50 mg were injected over 2 s every 20 s. Before each injection the patient was examined to determine the presence or absence of the eyelash reflex. The total dose administered (induction dose) was injected over 85–145 s.

Blood samples for the determination of thiopentone were withdrawn from an indwelling catheter placed in a large cubital vein in the arm opposite to the
injection. A control sample was taken before induction. The first sample was drawn 40 s after the last injection of thiopentone (20 s after the observation of an absent eyelash reflex). Further samples were taken at 5, 10, 20, 30, 45, 60 and 90 min and 2, 3, 4, 6, 8, 12-14 and 18-20 h. The blood was allowed to coagulate; serum was obtained by centrifugation and kept refrigerated for 1-2 days before analysis.

Thiopentone was analysed by high performance liquid chromatography (Christensen and Andreasen, 1979). The sensitivity of the method was 0.1 μg ml⁻¹. None of the drugs given to the patients interferes with the assay.

Calculations of pharmacokinetic data

A three-compartment open model with elimination from the central compartment only was used to describe the disappearance of thiopentone from the serum. The model was fitted to the time (t)–serum concentration (Cₜ) data by numerical solution of coupled differential equations describing the concentration changes in the central compartment (equation (1)), in the “shallow” peripheral compartment (equation (2)) and in the “deep” peripheral compartment (equation (3)):

\[
\begin{align*}
\frac{dC_1}{dt} &= \frac{k'_{10}}{V_1} - (k_{10} + k_{13} + k_{12})C_1 + k_{21}C_2 + k_{23}C_3 \\
\frac{dC_2}{dt} &= k_{13}C_1 - k_{21}C_2 \\
\frac{dC_3}{dt} &= k_{12}C_1 - k_{31}C_3
\end{align*}
\]

The meanings of V₁, k₁₀, k₁₂, k₁₃, k₁₉ and k₂₁ are as accepted normally and k'₁₀ is the infusion rate. The value of k'₁₀ was changed with time during the numerical solution according to the administration schedule. The hybrid rate constants π, α and β were calculated as the roots of equation (4):

\[x^3 - ax^2 + bx - c = 0\]

where the values of a, b and c appear from equations (5), (6) and (7) (Gibaldi and Perrier, 1975):

\[
\begin{align*}
a &= k_{10} + k_{13} + k_{21} + k_{18} + k_{91} \quad (= \pi + \alpha + \beta) \\
b &= k_{12}k_{21} + k_{12}k_{31} + k_{19}k_{31} + k_{21}k_{22} + k_{31}k_{19} \quad (= \pi \alpha + \pi \beta + \alpha \beta) \\
c &= k_{12}k_{21}k_{31} \quad (= \pi \alpha \beta)
\end{align*}
\]

The main differences between the serum concentration–time curve obtained in the present study and the serum concentration–time curves utilized in the majority of other studies is that we have given repeated bolus injections of the drug with short intervals initially and took the first sample of blood from an arm vein 40 s after the last injection. A possible influence, on the initial distribution of the drug, of individual differences in haemodynamics would not be reflected in the calculated parameters if no blood concentrations were measured during the first few minutes. Therefore, we performed the calculations with inclusion of the first (40-s) blood sample as well as with its exclusion (beginning with the 5-min value).

RESULTS

The dose of thiopentone required to induce anaesthesia did not increase significantly with the body weight of the patients (fig. 1). For neither men nor women is the slope of the regression line different from 0. As is shown in figure 1 and table I, the average dose was greater in men. However, if the dose is adjusted for the differences in body weight, this apparent difference disappears.

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose injected (mg)</td>
<td>319 ± 37</td>
<td>388 ± 52</td>
</tr>
<tr>
<td>Dose injected (mg per kg body weight)</td>
<td>5.43 ± 0.64</td>
<td>5.25 ± 1.05</td>
</tr>
</tbody>
</table>

The concentration of thiopentone in serum in one of the patients (table III) is shown as a function of time in the semilogarithmic plot in figure 2. Similar relationships between the serum concentrations and time were found for all 16 patients and in all patients the decline of the serum concentration could be described by a three-compartment open model—and not by a one- or a two-compartment model.

The pharmacokinetic data obtained by analysis of the serum concentration curves are listed in tables II and III. The average values for V₁ and V₃ were greater in the female group, but only the difference between the V₃ values was significant (P<0.05). The average values of the serum half-lives were greater in the women than in the men, but only the difference
between the $T_{1/2}^a$ values was statistically significant ($P<0.05$, Mann–Whitney). Significant correlations ($P<0.01$) were found between the initial values of the serum concentration and the $k_{13}$ values for both women and men (fig. 3). The apparent difference in slope (slope 0.0029 for women and 0.0038 for men) was not statistically significant ($0.1<P<0.2$). The averages of the $k_{13}$ values were not significantly different either. It was tested whether a three-compartment model could be used if the initial serum concentration value was disregarded. For both groups of patients, a three-compartment model could still be used to describe the serum concentration curves, but significant correlations between the initial serum concentration (5 min) and $k_{13}$ were no longer present.

**Table II. Pharmacokinetic parameters for thiopentone in eight male patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Body weight (kg)</th>
<th>$V_1$ (litre)</th>
<th>$V_2$ (litre)</th>
<th>$V_3$ (litre)</th>
<th>$k_{13}$ (min$^{-1}$)</th>
<th>$k_{13}$ (min$^{-1}$)</th>
<th>$k_{10}$ (min$^{-1}$)</th>
<th>$T_{1/2}$ (min)</th>
<th>$T_{1/2}$ (min)</th>
<th>$T_{1/2}$ (min)</th>
<th>$Cl$ (litre min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>36</td>
<td>77</td>
<td>3.88</td>
<td>10.59</td>
<td>30.57</td>
<td>0.237</td>
<td>0.060</td>
<td>0.035</td>
<td>1.7</td>
<td>28</td>
<td>296</td>
<td>0.136</td>
</tr>
<tr>
<td>■</td>
<td>21</td>
<td>52</td>
<td>4.58</td>
<td>5.97</td>
<td>19.38</td>
<td>0.169</td>
<td>0.042</td>
<td>0.018</td>
<td>2.1</td>
<td>23</td>
<td>305</td>
<td>0.082</td>
</tr>
<tr>
<td>○</td>
<td>26</td>
<td>69</td>
<td>3.41</td>
<td>10.45</td>
<td>21.78</td>
<td>0.311</td>
<td>0.066</td>
<td>0.034</td>
<td>1.4</td>
<td>25</td>
<td>262</td>
<td>0.116</td>
</tr>
<tr>
<td>■</td>
<td>20</td>
<td>71</td>
<td>14.46</td>
<td>10.16</td>
<td>32.31</td>
<td>0.048</td>
<td>0.008</td>
<td>0.011</td>
<td>5.5</td>
<td>57</td>
<td>388</td>
<td>0.159</td>
</tr>
<tr>
<td>△</td>
<td>39</td>
<td>81</td>
<td>6.61</td>
<td>22.93</td>
<td>44.32</td>
<td>0.128</td>
<td>0.021</td>
<td>0.025</td>
<td>3.4</td>
<td>71</td>
<td>473</td>
<td>0.165</td>
</tr>
<tr>
<td>▲</td>
<td>23</td>
<td>73</td>
<td>3.04</td>
<td>10.68</td>
<td>39.79</td>
<td>0.257</td>
<td>0.073</td>
<td>0.057</td>
<td>1.6</td>
<td>28</td>
<td>313</td>
<td>0.173</td>
</tr>
<tr>
<td>▼</td>
<td>29</td>
<td>88</td>
<td>5.97</td>
<td>12.09</td>
<td>22.35</td>
<td>0.198</td>
<td>0.031</td>
<td>0.032</td>
<td>2.0</td>
<td>31</td>
<td>206</td>
<td>0.191</td>
</tr>
<tr>
<td>▼</td>
<td>40</td>
<td>95</td>
<td>16.97</td>
<td>18.11</td>
<td>42.58</td>
<td>0.081</td>
<td>0.021</td>
<td>0.017</td>
<td>4.1</td>
<td>53</td>
<td>373</td>
<td>0.288</td>
</tr>
</tbody>
</table>
**DISCUSSION**

**Dose–effect relationship**

Our comparison of a group of young women with a group of young men showed a greater but not statistically significant sensitivity to thiopentone in women; this apparent difference disappeared when the dose was corrected for differences in body weight. A large individual variation in sensitivity in the groups did not disappear by correction of the dose for differences in body weight (range for the women 4.5–6.6 and for the men 3.6–7.0 mg/kg body weight). Edwards and Ellis (1973) found even larger variation (range 1–4.5 mg kg\(^{-1}\)) in induction doses between male Ghanaian patients with a larger age range (mean 34.2 yr ± 11.9 SD) and with different chronic diseases. Becker (1978) gave thiopentone as an infusion to 36 comparable individuals. He found that 26 patients required 10.1 ± 0.5 mg kg\(^{-1}\) for induction while in 10 5.8 ± 0.5 mg kg\(^{-1}\) was adequate.

The finding in the groups that additional weight does not necessarily mean decreased sensitivity to a given dose may be in good agreement with Wulfsohn and Joshi (1969) who found that the induction dose correlated better with the lean body mass than with the body weight.

**Kinetic considerations**

Valuable information about the distribution and elimination patterns in the average patient have been obtained by measuring thiopentone concentrations in different anatomically or physiologically defined regions. By doing this Price and colleagues (1960) and Bischoff and Dedrick (1968) found excellent agreement between the concentrations actually measured and concentrations predicted—by assuming certain values for flow and volume from data available in the literature. One of our objects was to elucidate and explain the reasons for the large individual

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**FIG. 3.** The initial value of the venous serum concentration of thiopentone as a function of the rate constant \(k_{12}\). The apparent difference in slope between the regression lines for men and women is not statistically significant.

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**TABLE III. Pharmacokinetic parameters for thiopentone in eight women**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Body weight (kg)</th>
<th>(V_1) (litre)</th>
<th>(V_2) (litre)</th>
<th>(k_{11}) (min(^{-1}))</th>
<th>(k_{12}) (min(^{-1}))</th>
<th>(k_{10}) (min(^{-1}))</th>
<th>(T_{11}) (min)</th>
<th>(T_{12}) (min)</th>
<th>(T_{10}) (min)</th>
<th>(Cl) (litre min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>36</td>
<td>64</td>
<td>4.25</td>
<td>9.00</td>
<td>0.148</td>
<td>0.046</td>
<td>0.011</td>
<td>2.7</td>
<td>43</td>
<td>273</td>
<td>0.047</td>
</tr>
<tr>
<td>25</td>
<td>53</td>
<td>5.48</td>
<td>6.17</td>
<td>36.07</td>
<td>0.163</td>
<td>0.041</td>
<td>0.022</td>
<td>2.0</td>
<td>23</td>
<td>368</td>
<td>0.121</td>
</tr>
<tr>
<td>25</td>
<td>62</td>
<td>11.00</td>
<td>14.24</td>
<td>53.54</td>
<td>0.088</td>
<td>0.016</td>
<td>0.011</td>
<td>4.0</td>
<td>56</td>
<td>626</td>
<td>0.121</td>
</tr>
<tr>
<td>25</td>
<td>52</td>
<td>10.44</td>
<td>17.90</td>
<td>53.47</td>
<td>0.101</td>
<td>0.020</td>
<td>0.020</td>
<td>3.7</td>
<td>49</td>
<td>417</td>
<td>0.209</td>
</tr>
<tr>
<td>23</td>
<td>57</td>
<td>11.12</td>
<td>10.55</td>
<td>43.61</td>
<td>0.058</td>
<td>0.026</td>
<td>0.012</td>
<td>4.9</td>
<td>33</td>
<td>407</td>
<td>0.133</td>
</tr>
<tr>
<td>31</td>
<td>56</td>
<td>12.82</td>
<td>23.35</td>
<td>165.20</td>
<td>0.063</td>
<td>0.019</td>
<td>0.012</td>
<td>5.8</td>
<td>71</td>
<td>1312</td>
<td>0.154</td>
</tr>
<tr>
<td>22</td>
<td>72</td>
<td>15.55</td>
<td>9.07</td>
<td>38.30</td>
<td>0.036</td>
<td>0.010</td>
<td>0.011</td>
<td>6.5</td>
<td>49</td>
<td>379</td>
<td>0.171</td>
</tr>
<tr>
<td>25</td>
<td>56</td>
<td>2.37</td>
<td>9.02</td>
<td>36.79</td>
<td>0.264</td>
<td>0.067</td>
<td>0.038</td>
<td>1.6</td>
<td>35</td>
<td>501</td>
<td>0.090</td>
</tr>
</tbody>
</table>
variation in response to a given dose of thiopentone. In the present study we found it crucial to utilize fully the interpretation of the curves illustrating the decline in the venous serum concentrations of thiopentone; this method of obtaining information was the only one possible.

For none of our patients could the serum concentration curves be adequately described by a one- or a two-compartment model. However, they could all be described by a three-compartment model. After thiopentone 3.5 mg/kg body weight injected over 30 s, Ghoneim and Van Hamme (1978) found that the kinetics of the venous concentration curve could be described by a three-compartment open model in nine subjects and by a two-compartment model in three subjects. We found that the $V_3$ values were significantly greater in the women than in the men ($P < 0.05$). Also the terminal serum half-lives were significantly longer in the women (range 4.5–22 h in women and 4–8 h in men). Ghoneim and Van Hamme (1978) found an average elimination half-life of 5.14 h in three young women and three young men.

The individual variation in serum concentration found by us 20 s after the disappearance of the eyelash reflex was as large as the individual variation in dose per kg body weight. Becker (1978) gave thiopentone by i.v. infusion and found that the arterial concentration needed to abolish the eyelash reflex was small and rather constant $(22.7 \pm 1.7 \mu g \text{ ml}^{-1})$. We found a considerably greater and not very constant venous concentration 20 s after the disappearance of the eyelash reflex (average $49.8 \pm 19.7 \mu g \text{ ml}^{-1}$ in men and $38.6 \pm 24.1 \mu g \text{ ml}^{-1}$ in women). The average value found by Becker (1978) was close to our value 5 min after the last injection of thiopentone (4 min and 40 s after the disappearance of the eyelash reflex $(21.0 \pm 5.7 \mu g \text{ ml}^{-1})$. Becker (1978) found also that the dose was high and rather variable (see above); he gave 150 mg initially followed by infusion of $90 \text{ mg min}^{-1}$ whereas we gave 250 mg initially followed by $150 \text{ mg min}^{-1}$ in repeated, rapidly injected doses of 50 mg every 20 s. It seems likely that the slow administration caused a general increase in the dose necessary for induction and nullified the importance of individual variations in the initial distribution phase. This point of view is supported by the significant correlations we found for men and for women between the $k_{12}$ and the venous serum concentrations 20 s after the disappearance of the eyelash reflex. There was no correlation between the $k_{12}$ values, calculated without the initial serum concentration value, and either the initial or the 5-min values. Thus, the omission of the initial value loses valuable information. We suggest that patients with small values of $k_{12}$ will reach the necessary serum concentration sooner than patients with large $k_{12}$ values, who possess the ability to distribute the drug more effectively to organs unimportant for the observed effect.

REFERENCES


PHARMACOCINETIQUE DU THIOPENTONE ETUDEE SUR UN GROUPE DE JEUNES FEMMES ET DE JEUNES HOMMES

RESUME

La dose moyenne d'induction du thiopentone n'a pas différé de façon significative lorsqu'on a fait une comparaison entre huit jeunes femmes et huit jeunes hommes. La dose n'a été augmentée ni dans un groupe ni dans l'autre en fonction du poids du corps. L'élimination du thiopentone du sang veineux a été décrite par un modèle ouvert à trois compartiments. Les volumes moyens de $V_1$ et de $V_2$ ont été plus élevés chez les femmes, mais seul l'écart entre les valeurs de $V_2$ a été significatif $(P < 0.05)$. On a trouvé des corrélations significatives $(P < 0.01)$ entre les concentrations initiales du médicament et les valeurs de $k_{12}$. Les pentes des lignes de régression ont été de 0.0029 pour les femmes et de 0.0038 pour les hommes $(0.1 < P < 0.2)$. On laisse entendre que la constante $k_{12}$ du taux de redistribution prédomine dans la détermination de la dose pour le sommeil, plutôt que le volume $V_1$ de répartition initiale.
Die durchschnittliche Narkoseeinleitungsdois von Thiopenton unterschied sich nicht wesentlich bei einer Gruppe junger Frauen und einer Gruppe junger Männer (jeweils 8). Bei keiner der Gruppen stieg die Dosis bei erhöhtem Körpergewicht. Die Ausscheidung der Droge aus dem venösen Blut wurde mittels eines offenen Modells mit drei Kammern beschrieben. Die Durchschnittsvolumen von $V_1$ und $V_3$ waren bei den Frauen größer, doch war nur der Unterschied zwischen den $V_1$ Werten signifikant ($P<0,05$). Signifikante Korrelationen ($P<0,01$) bestanden zwischen den anfänglichen Drogenkonzentrationen und den $k_{12}$ Werten. Das Gefälle der Absteigelinien war 0,0029 bei den Frauen und 0,0038 bei den Männern ($0,1<P<0,2$). Es wird gefolgert, dass die Wiederverteilungskonstante $k_{12}$ bestimmend bei Feststellung der Schlafdosis ist, eher als das anfängliche Verteilungsvolumen $V_1$.