ANOTHER LOOK AT ACUTE TOLERANCE TO THIOPENTONE

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SUMMARY
The phenomenon of "acute tolerance" to thiopentone was re-examined in 82 subjects with induction doses of 2-15 mg kg\(^{-1}\). There was a strong positive correlation between the venous plasma thiopentone concentrations on recovery from anaesthesia and the induction dose, expressed as either mg kg\(^{-1}\) or mg m\(^2\). Recovery time was proportionately shorter with larger doses, being directly related to log\(_{10}\) of the plasma concentration at awakening.

There is great individual variation in the response to thiopentone, including the dose required to induce anaesthesia and the plasma concentration at which patients recover consciousness. The work of Brodie (1952) clarified the latter; each of four subjects was infused with two different doses and it was seen (table I) that the plasma concentration at recovery was greater when the larger dose of drug was given. These doses are outside the range used today, but Dundee, Price and Dripps (1956) described a phenomenon which they called "acute tolerance" to thiopentone. In 16 subjects given single doses of thiopentone ranging from 2 to 12 mg kg\(^{-1}\) they found that patients receiving the larger doses awakened at a greater arterialized venous plasma concentration of the drug than those given smaller doses.

With the availability of modern and less time-consuming analytical techniques (Toner et al., 1979) a further, more comprehensive examination of the phenomenon of acute tolerance was undertaken in 82 unselected, unpremedicated adults. The dose of thiopentone ranged from 2 to 15 mg kg\(^{-1}\) and venous blood was used for analysis. The findings of this study have been summarized by Dundee (1980) and Dundee and others (1980).

METHODS
Doses were allocated at random and injected rapidly over 2-5 s. The time was noted from injection to recovery (open eyes on command). In some patients the thiopentone was given well in advance of operation, the time to recovery was noted and anaesthesia was reinduced with nitrous oxide in oxygen and a further small dose of barbiturate. With larger doses a short operation was carried out during nitrous oxide in oxygen anaesthesia, but nitrous oxide was discontinued immediately and recovery usually took a further 3-5 min. Immediately on waking a venous blood sample (for thiopentone analysis) was drawn from the arm opposite to that used for injection. Plasma thiopentone concentration was estimated using an Anachem High Performance Liquid Chromatograph fitted with a fixed wavelength ultra-violet light detector (254 nm) with sensitivity set at 0.08. A reverse phase (15 cm x 0.3 cm i.d.) spherisorb 10 ODS column and a mobile phase of methanol-water 50 : 50 at a pressure of 7000 kPa was used (Toner et al., 1979).

In presenting the data, the dose of thiopentone is expressed as mg kg\(^{-1}\) except in figure 2. Student's
r-test and linear regression analyses were used as required.

RESULTS

Eighty-two patients were studied. The relationship between the plasma thiopentone concentration at awakening and the dose administered (mg kg\(^{-1}\)) is shown in figure 1. There was a positive linear relationship between these two factors (\(r = 0.694\)). With the dose expressed as mg m\(^{-2}\), a similar relationship was shown with a correlation value of \(r = 0.654\) (fig. 2). Hereafter, the dose will be expressed as mg kg\(^{-1}\).

Figure 3 groups the doses of thiopentone and table II shows the significance of the difference of average plasma concentrations in the thiopentone groups. Table II also shows average times to awakening and the significance of difference between groups.

In the group receiving less than 3.5 mg kg\(^{-1}\), seven patients did not go to sleep, but samples

<table>
<thead>
<tr>
<th>Dose (mg kg(^{-1}))</th>
<th>n</th>
<th>Average plasma thiopentone concn at wakening ((\mu g) ml(^{-1}) ± SEM)</th>
<th>P</th>
<th>Average time to wakening (min ± SEM)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.5</td>
<td>12†</td>
<td>6.5 ± 1.3</td>
<td>&lt;0.5</td>
<td>2.75 ± 0.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>3.5-5.5</td>
<td>15*</td>
<td>7.6 ± 0.7</td>
<td>&lt;0.1</td>
<td>5.2 ± 0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>5.5-7.5</td>
<td>19</td>
<td>9.9 ± 1.1</td>
<td>&lt;0.2</td>
<td>8.4 ± 0.6</td>
<td>* &lt;0.9</td>
</tr>
<tr>
<td>7.5-9.5</td>
<td>14</td>
<td>12.5 ± 1.0</td>
<td>&lt;0.5</td>
<td>8.6 ± 1.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>9.5-11.5</td>
<td>12</td>
<td>13.3 ± 0.7</td>
<td>&lt;0.01</td>
<td>11.3 ± 1.2</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>11.5+</td>
<td>11</td>
<td>19.1 ± 2.0</td>
<td>&lt;0.01</td>
<td>13.6 ± 3.1</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>
were taken between 1 and 2 min after injection; this also applies to one patient in the group receiving 3.5–5.5 mg kg\(^{-1}\). These concentrations were less than those of the patients who went to sleep (\(P<0.1\)).

Although averages of plasma concentrations and wakening times between consecutive groups were not significantly different (table II), a highly significant (\(P<0.02\)) difference was found between alternate groups. There was a less marked correlation (\(r = 0.56\)) between the dose of thiopentone and time to recovery.

However, using the grouping of doses shown in figure 3, a very good correlation (\(r = 0.98\)) between log\(_{10}\) average plasma thiopentone concentration on wakening and the average recovery time was obtained (fig. 4).

![Figure 4](https://academic.oup.com/bja/article-abstract/52/10/1005/295555)

**Fig. 4.** Relationship between log\(_{10}\), average plasma thiopentone concentrations at wakening (\(\mu g\) ml\(^{-1}\)) and average time to wakening (min).

**DISCUSSION**

A comparison of figures 1 and 2 suggests that there is little advantage in using mg m\(^{-2}\) as a means of expressing the dose of thiopentone rather than the more commonly used mg kg\(^{-1}\).

This paper does not elucidate the mechanism of the phenomenon of acute tolerance. The present study confirms the relationship found in the smaller series of Dundee, Price and Dripps (1956). Although the correlation coefficient in the earlier data was 0.74, based on only 16 patients, this compared favourably with \(r = 0.694\) in the 82 patients. One may question the validity of venous concentrations of thiopentone, but generally the blood was sampled 4–5 min after induction and by that time the difference between arterial and venous concentration should be negligible.

This study further substantiates the view that plasma thiopentone concentration is a poor guide to the depth of anaesthesia; the findings regarding concentrations at recovery support those of the previous study by Dundee, Price and Dripps (1956) and that by Brand and others (1961) who found no correlation between plasma thiopentone concentrations and the “depth” of anaesthesia as judged by the electroencephalogram.

The medico-legal implications of this finding are obvious. Serial plasma concentrations may be a guide to the depth of anaesthesia and to the speed of recovery, but isolated concentrations are meaningless.

![Figure 5](https://academic.oup.com/bja/article-abstract/52/10/1005/295555)

**Fig. 5.** Scatter of venous thiopentone concentrations at wakening.

**REFERENCES**


EXAMEN COMPLEMENTAIRE DE L'ACCOUTUMANCE AIGUE AU THIOPENTONE

RESUME
On a à nouveau examiné le phénomène de l'accoutumance aigue au thiopentone sur 82 sujets, en utilisant des doses d'induction de 2–15 mg kg⁻¹. On a constaté une forte corrélation positive entre les concentrations de thiopentone dans le plasma veineux au moment de la reprise de conscience, après l'anesthésie, et la dose d'induction, exprimée soit en mg kg⁻¹ soit en mg m⁻². Le temps nécessaire à la reprise de conscience a été proportionnellement plus court avec les doses les plus impotantes, celui-ci étant directement relié au log₁₀ de la concentration dans le plasma au moment du réveil.

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EINE WEITERE BETRACHTUNG DER AKUTEN TOLERANZ FÜR THIOPENTON

ZUSAMMENFASSUNG
Das Phänomen der akuten Toleranz auf Thiopenton wurde bei 82 Personen mit Narkosedosen von 2–15 mg kg⁻¹ neu untersucht. Es besteht eine starke positive Verbindung zwischen den venösen Plasma-Thiopentonkonzentrationen nach Aufwachen aus der Narkose und der Narkosedosis, ausgedrückt entweder in mg kg⁻¹ oder in mg m⁻². Die Erholungszeit war proportional kürzer mit größeren Dosen und stand in direktem Zusammenhang zu log₁₀ der Plasmakonzentration beim Erwachen.

UN NUEVO EXAMEN DE LA TOLERANCIA AGUDA A LA TIOPENTONA

SUMARIO
El fenómeno de “tolerancia aguda” a la tiopentona se volvió a examinar en 82 pacientes mediante dosis de inducción de 2–15 mg kg⁻¹. Tuvo lugar una fuerte correlación positiva entre las concentraciones de tiopentona en el plasma venoso al recuperarse de la anestesia y la dosis de inducción, expresada bien en mg kg⁻¹ o en mg m⁻². El tiempo de recuperación fue proporcionalmente más corto para las mayores dosis, viéndose relacionado directamente al log₁₀ de la concentración de plasma al momento de despertar.