Plasma Levels of Thiopental Necessary for Anesthesia

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This study determined the plasma levels of thiopental necessary for anesthesia in human patients. In Group I, corneal reflex (CR) and trapezius muscle response (TMR) showed highly significant correlations (P < 0.001) with response to surgical stimulation, the usual measure of MAC, in patients anesthetized with nitrous oxide, 67 per cent, and thiopental. Losses of CR and TMR were then used to measure the plasma levels of thiopental necessary for anesthesia. In Group II, anesthesia was induced in 36 informed patients with thiopental, 2–2.5 mg/kg, and maintained with a constant infusion of 1–1.5 mg/kg/min, a rate chosen to give a slowly increasing arterial blood level of thiopental. Total and free (unbound) arterial plasma thiopental levels were measured by gas chromatography at losses of eyelid reflex (ER), CR, and TMR.

For CR loss, thiopental requirements were 39.4 ± 2.5 μg/ml (mean ± SE) for total plasma thiopental and 5.9 ± 0.4 μg/ml for free plasma thiopental. For TMR loss, thiopental requirements were 42.4 ± 2.8 μg/ml for total plasma thiopental and 6.3 ± 0.6 μg/ml for free plasma thiopental. Nitrous oxide, 67 per cent, decreased these requirements 67–71 per cent. Age, sex, and weight of the patient and serum albumin level had little effect on thiopental requirements. Mean percentage of free thiopental was 14.4 ± 0.3 per cent of total. It is concluded that: 1) losses of corneal reflex, trapezius muscle reflex, and response to surgical stimulation all define essentially the same depth of thiopental anesthesia; 2) total plasma thiopental levels of 39–42 μg/ml and free plasma thiopental levels of 5.9–6.3 μg/ml produce surgical anesthesia in human subjects. (Key words: Anesthesia: depth. Anesthetics, intravenous: thiopental. Reflexes: corneal.)

Thiobarbiturates have been used for intravenous anesthesia for more than 30 years. During this time, various studies have established the amount of thiobarbiturate needed for induction of anesthesia,1 the plasma level of thiopental upon awakening,2,3 and the amount of thiopental necessary to abolish verbal counting.4,5 However, concentrations of thiopental necessary for clinical anesthesia have not been established. This study was undertaken to determine the free and total arterial plasma concentrations of thiopental necessary for surgical anesthesia so that the anesthetic potency and cardiovascular effects of thiopental could be compared with those of inhalational anesthetics.

Materials and Methods

All subjects were healthy, ASA-I, surgical patients, 21 to 50 years of age, with no significant drug history. This study utilized an informed consent agreement approved by the Human Investigation Committee at the University of Mississippi Medical Center. Patients were divided into two groups.

Group I

Corneal reflex (CR) and response to a hard squeeze of the trapezius muscle (TMR) were correlated with response to surgical stimulation in 37 patients anesthetized with nitrous oxide, 67 per cent, and thiopental. This group was subdivided into 13 patients who received only atropine, 6 μg/kg, and 24 patients who received atropine, 6 μg/kg, hydroxyzine, 1.3 mg/kg, and meperidine, 1.3 mg/kg, as premedication. Anesthesia was induced with sodium thiopental, 3–4 mg/kg, and maintained with nitrous oxide, 67 per cent. Repeated small doses of thiopental (0.7–1.4 mg/kg) were given as necessary to maintain anesthesia during the surgical preparation. CR and TMR were tested repeatedly throughout the surgical preparation, especially just prior to and after surgical stimulation. Surgical stimulation consisted of incision of the skin (50 per cent) or cervical dilatation (50 per cent). Ninety-three forearm or hand venous blood samples were drawn just before or after testing CR, TMR, and response to surgical stimulation. Time of testing was recorded.

Group II

This group consisted of 36 patients. Half received atropine, 7 μg/kg, and half received atropine, 7 μg/kg, and meperidine, 1.2 mg/kg, as premedication. The weight, height, sex, age, hemotocrit, and total protein and serum albumin values of each patient were recorded. Prior to induction of anesthesia, a sample of arterial blood was drawn from an indwelling arterial catheter. Anesthesia was induced with thiopental, 2–2.5 mg/kg, followed by an intravenous infusion of 1–1.5 mg/kg/min delivered from a Harvard infusion pump. Rate of infusion was estimated to give a slowly increasing arterial blood level of thiopental. Patients were observed for loss of eyelid reflex (ER), loss of CR, and loss of TMR. Thiopental infusion was then stopped and anesthesia con-
continued with nitrous oxide and halothane, enfurane or narcotic drugs. Arterial blood samples were drawn immediately with losses of ER, CR, and TMR and 15 min after infusion.

Free or unbound plasma thiopental levels were obtained by ultrafiltration through membrane cones; total and free plasma levels of thiopental were assayed by gas chromatography as previously described.$^6$

Data Analysis

In Group I, presence or absence of CR, TMR, and response to surgical stimulation were tabulated in $2 \times 2$ matrices and analyzed by chi-square tests to determine the correlations between these three measures of anesthetic depth. The anesthetic dose of venous plasma thiopental when 50 per cent of the patients did not respond to a particular stimulus (AD$_{50}$) was estimated by probit analysis.$^7$ In Group II, pertinent variables, free and total thiopental levels at losses of the various measures of anesthetic depth, and dose of thiopental administered were all recorded on a Hewlett-Packard 9830-A programmable calculator. A statistical program sorted data into various subgroups and determined probabilities of independence of these subgroups with a Student's $t$ test. For both groups, the average rates of changes in thiopental levels were calculated from plasma levels and sampling times.

Results

Group I

The three measures of depth of anesthesia (CR, TMR, and response to surgical stimulation) showed a low probability of independence and thus were closely correlated (table 1). A Fisher exact test for small samples gave probabilities of independence of these three measures approximately half as large as the probabilities listed for the chi-square test. The concentrations of venous total plasma thiopental when 50 per cent of the patients did not respond to a particular stimulus (AD$_{50}$) averaged 12.6 $\mu$g/ml for unpremedicated patients and 6.5 $\mu$g/ml for premedicated patients (table 2). In patients who needed no further thiopental between repeated tests of CR, TMR, and response to surgical stimulation, the average rate of decrease in thiopental concentration was 0.6 $\mu$g/ml/min. Some patients needed additional small doses of thiopental during the surgical preparation. In these patients, the average rate of increase in plasma thiopental was 2.4 $\mu$g/ml/min.

$^6$ Amicon Corporation, Lexington, Mass.
TABLE 2. Anesthetic Dose-50 (AD50) Values for Venous Total Plasma Thiopental

<table>
<thead>
<tr>
<th>Movement in response to</th>
<th>Premedicated (µg/ml)</th>
<th>Unmedicated (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>surgical stimulation</td>
<td>8.0</td>
<td>12.6</td>
</tr>
<tr>
<td>Corneal reflex</td>
<td>6.4</td>
<td>11.5</td>
</tr>
<tr>
<td>Trapezius response</td>
<td>5.1</td>
<td>13.8</td>
</tr>
<tr>
<td>AVERAGE</td>
<td>6.5</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Discussion

In Group I, a very close correlation between CR, TMR, and response to surgical stimulation was found by chi-square testing (Table 1) and by probit analysis of plasma levels of thiopental (Table 2). In addition, plasma levels of thiopental were changing slowly at the time of surgical stimulation, and CR and TMR used for the chi-square test were measured immediately before or after surgical stimulation; thus, both CNS and plasma levels of thiopental were essentially steady in this very short testing interval. Therefore, losses of CR and TMR should define essentially the same depth of anesthesia as loss of response to surgical stimulation, the usual measure of MAC, with thiopental and nitrous oxide anesthesia.

The results in Group I allowed the use of CR and TMR to measure anesthetic depth in patients in Group II. This avoided the use of excessive doses of thiopental between induction of anesthesia and surgical stimulation. In Group II, free plasma thiopental levels of 5.9–6.3 µg/ml and total plasma thiopental levels of 39–42 µg/ml produced loss both of CR and TMR (Table 3).

However, before concluding that the concentrations of thiopental necessary for loss of CR and TMR represent the same extent of CNS depression as that found with 1.0 MAC inhalational agents, the questions of brain/plasma equilibration, steady-state conditions, and equivalency of thiopental-plus-nitrous oxide anesthesia and thiopental-only anesthesia must be answered. In the case of thiopental, brain equilibrates in less than a minute with plasma, and then brain–plasma ratios remain essentially constant.8,9 Thus, plasma levels of thiopental, especially free or unbound plasma levels, should be accurate predictors of brain levels of thiopental and thus, of anesthetic depth.10,11

Steady-state conditions were not achieved due to patient variations and to the inability to analyze thiopental levels rapidly. Indeed, patients in Group II had increasing thiopental levels. However, those patients who had rapidly increasing thiopental levels and short infusion times needed essentially the same free and total thiopental levels for loss of both CR and TMR as those patients with slowly increasing levels and longer infusion times (Table 3; Fig. 1). Thus, in this study there was time for equilibration of brain and plasma levels of thiopental even though true steady-state conditions were not achieved.

Patients in Group I received nitrous oxide, 67 per cent, and thiopental. They needed 71 per cent less thiopental for loss of CR and 67 per cent less thiopental for loss of TMR than patients in Group II who received only thiopental. This is almost exactly what would be predicted for the additive effects of inhalational agents on MAC requirements.12 Thus, losses of CR and TMR with thiopental-plus-nitrous oxide anesthesia and thiopental-only anesthesia should define the same depth of anesthesia. Therefore, levels

<table>
<thead>
<tr>
<th>Thiopental Administered</th>
<th>Eyelid Reflex</th>
<th>Cornal Reflex</th>
<th>Trapezius Response</th>
<th>15 Minutes after Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Dose (µg/kg)</td>
<td>Number</td>
<td>Total ± SE (µg/ml)</td>
<td>Free ± SE (µg/ml)</td>
<td>Number</td>
</tr>
<tr>
<td>All subjects</td>
<td>36</td>
<td>8.9 ± .5</td>
<td>36</td>
<td>22.7 ± .3</td>
</tr>
<tr>
<td>Unmedicated vs.</td>
<td>19</td>
<td>9.5 ± .7</td>
<td>19</td>
<td>26.1 ± 2.3</td>
</tr>
<tr>
<td>Premedicated</td>
<td>17</td>
<td>8.2 ± .8</td>
<td>17</td>
<td>18.9 ± 2.2</td>
</tr>
<tr>
<td>Infusion &gt; 2 min vs.</td>
<td>26</td>
<td>10.1 ± .5</td>
<td>26</td>
<td>21.0 ± 2.1</td>
</tr>
<tr>
<td>Infusion &lt; 2 min</td>
<td>10</td>
<td>5.8 ± .5</td>
<td>10</td>
<td>27.1 ± 2.3</td>
</tr>
</tbody>
</table>

*P < .05, Student's t test, one-sided.
of thiopental producing losses of CR and TMR in Group II should produce a level of anesthesia equivalent to that produced by 1.0 MAC inhalational agents.

As expected from the work on MAC\textsuperscript{13,14} premedication decreased thiopental requirements. In Group II, in premedicated patients, free and total thiopental levels were 3 per cent lower for loss of CR and 13–14 per cent lower for loss of TMR, or about 9 per cent lower overall (table 3). These changes were not significant, but were similar to the 7 per cent decrease in halothane MAC found with addition of morphine, 8–15 mg.\textsuperscript{12} Thiopental levels were significantly lower for loss of ER. However, ER is lost at light levels of anesthesia\textsuperscript{15} and was almost absent in several premedicated patients prior to anesthesia. In Group I, thiopental levels were approximately 50 per cent lower in premedicated patients (table 2). Assuming that thiopental accounted for 33 per cent of the anesthetic depression in unpremedicated patients in this group, the 50 per cent decrease would correspond to about a 16–17 per cent decrease in requirements in Group II. Since patients in Group I received a narcotic drug and an anxiolytic drug, these results are not surprising.\textsuperscript{14}

Fraioli et al.\textsuperscript{16} recently determined the 0.5 MAC equivalent for thiopental using thiopental infusion, nitrous oxide, 60 per cent, and movement as their measure of anesthetic depth. In their study they found a 0.5 MAC equivalent of 38.5 \(\mu\text{g/ml}\) serum thiopental using a chloroform extraction and spectrophotometric assay method of Brodie.\textsuperscript{17} In this study, plasma thiopental concentrations of 39–42 \(\mu\text{g/ml}\) produced a depth of anesthesia equivalent to 1.0 MAC. Half of this concentration is 20–21 \(\mu\text{g/ml}\), much less than the concentration determined by Fraioli et al. but, interestingly enough, very similar to that (25 \(\mu\text{g/ml}\)) at which their patients regained movement after the thiopental infusion was stopped. The discrepancies between my results and the findings of Fraioli et al. can probably be explained by differences in methodology; however, they used an induction bolus of thiopental, 4 mg/kg, and a minimum infusion time of 30 min prior to determining response to surgical stimulation. Some acute tolerance to thiopental may have developed in their patients, since acute tolerance is related to the peak brain level of thiopental obtained.\textsuperscript{18}

In this study, the small induction dose of thiopental (2–2.5 mg/kg), the slowly increasing plasma level of thiopental, the small total dose of thiopental, the short period from induction to loss of the various signs of anesthesia, and the utilization of the corneal reflex, which is little affected by acute tolerance,\textsuperscript{10} avoided the problem of acute tolerance.

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**Fig. 1.** Free plasma thiopental levels and infusion times at loss of eyelid reflex (ER), corneal reflex (CR), and trapezius muscle response (TMR) in seven subjects. Infusion times, and thus rates of increase of plasma levels of thiopental, have little effect on thiopental levels at loss of each of the various signs of anesthesia.

From this study, it is concluded that: 1) losses of corneal reflex, trapezius muscle response, and response to surgical stimulation all define essentially the same depth of thiopental anesthesia; 2) total plasma thiopental levels of 39–42 \(\mu\text{g/ml}\) and free plasma thiopental levels of 5.9–6.3 \(\mu\text{g/ml}\) are necessary for loss of corneal reflex and loss of trapezius muscle response in unpremedicated patients; 3) the depth of anesthesia produced by these thiopental concentrations is roughly equivalent to that produced by 1.0 MAC inhalational agents; 4) nitrous oxide, 67 per cent, decreases these requirements 67–71 per cent; 5) age, sex, weight, and serum albumin level all have little effect on thiopental requirements; 6) the mean percentage of free thiopental is 14.4 per cent of total.

**References**