The Effect of Increasing Age on Thiopental Disposition
and Anesthetic Requirement

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The dose of thiopental required to induce anesthesia in adults decreases with age. The pharmacokinetic and pharmacodynamic properties of thiopental were studied in two groups of surgical patients to determine the mechanism of this decrease. In one group (29 patients 19–88 yr of age), thiopental was infused at a rate of 75–150 mg/min until the electroencephalogram (EEG) demonstrated early burst suppression (phase III). Arterial blood samples were obtained frequently during and after the infusion to measure serum thiopental concentrations, and power spectral analysis was used to calculate the spectral edge (Hz), defined as the frequency below which 95% of the EEG power is located. Pharmacodynamic modeling was used to relate the serum thiopental concentrations to the spectral edge in order to estimate the individual patient’s brain sensitivity to thiopental. In a second group (28 patients 24–88 yr of age), pharmacokinetics were determined after a bolus or rapid infusion of thiopental. Arterial blood samples were obtained frequently to characterize the initial distribution phases, sampling continued for 24–48 h to characterize elimination processes.

The dose of thiopental required to achieve early burst suppression on the electroencephalogram (EEG) decreased linearly and significantly with age. Pharmacodynamic modeling also demonstrated that brain sensitivity to thiopental does not change with age. The age-related decrease of the thiopental dose requirement is due to a change in the initial distribution of the drug. That is, the initial distribution volume (central compartment, or $V_1$) of thiopental decreases exponentially with age. This smaller initial distribution volume in the elderly results in higher serum levels after a given dose of thiopental. (Key words: Age factors. Anesthetics, intravenous: thiopental. Brain: electroencephalography. Pharmacodynamics: thiopental. Pharmacokinetics: thiopental.)

Because life expectancy and median age of the population are steadily increasing, more elderly patients are undergoing surgery. Although surgical mortality rates for these patients have improved, they are still higher than for any age group.1 A greater understanding of the unique anesthetic problems presented by the elderly patient will improve perioperative management and thus decrease surgically related mortality and morbidity.

Several physiologic changes with age have important implications for anesthesia. For example, cardiac output decreases and, hence, hepatic and renal blood flows.2 The cerebral, coronary, and skeletal muscle circulations receive a greater percentage of cardiac output.3 Also, total body water, plasma volume, extracellular fluid, and lean body mass decrease. By age 65 yr, women have approximately 5 kg less lean body mass, and men have 12 kg less lean body mass relative to younger subjects.4 These physiologic changes might affect not only end-organ responsiveness but also anesthetic drug disposition and elimination.

From clinical experience some anesthetists believe that elderly (i.e., over 65 yr of age) patients are more “sensitive” to the effects of thiopental than are younger patients.5 Although previous studies have demonstrated that the dose of thiopental required to induce or maintain a light level of anesthesia decreases with increasing age,5,6 no study has adequately documented this apparent greater sensitivity. The decreased dose requirement could be attributable to either age-related changes in pharmacodynamics (what the drug does to the body, e.g., brain response) or altered pharmacokinetics (what the body does to the drug, e.g., distribution and/or elimination processes).

This study examines the relationship between age (20–90 yr) and the dose of thiopental necessary to induce surgical anesthesia, and quantitates the influence of age on the pharmacokinetics and pharmacodynamics of thiopental. We used a recently developed model that characterizes the relationship between serum concentration of thiopental and its effect on the brain.8 This model, which quantitates the degree of brain sensitivity to thiopental based upon electroencephalographic slowing, has been used to evaluate acute tolerance to thiopental.9

Methods

Patient Population

The protocol was approved by the Stanford institutional review board, and informed consent was obtained
from all subjects. We studied two groups of subjects. In 29 ASA physical status I or II patients (19–88 yr of age; mean weight ± SD, 77 ± 13 kg), pharmacodynamic data were obtained. In this group the dose of thiopental required to reach early burst suppression was determined. In 21 of these subjects (surgical patients) we measured arterial thiopental serum concentrations and used power spectral analysis of the EEG to calculate the spectral edge, and a pharmacodynamic model was applied to determine if brain sensitivity to thiopental changed with age. The other eight subjects (volunteers) had been studied in earlier investigations, and their data were included in the current analysis because they were predominantly younger (20–40 yr) and increased the amount of data available in this age range. These volunteers were studied in an identical manner to the surgical patients except that venous blood was used to measure the serum thiopental concentrations.

In a second group of 28 surgical patients (23–88 yr of age; mean weight ± SD, 71.6 ± 10.6 kg), pharmacokinetic data were obtained. After receiving either a bolus or rapid infusion of thiopental, serum concentrations were obtained for 24–48 h for pharmacokinetic analysis. Fourteen of these patients were also members of Group 1 and, therefore, had both pharmacokinetic and pharmacodynamic data collected.

All of the surgical patients in the two groups were scheduled for minor elective surgical procedures requiring general anesthesia and were not expected to have an appreciable blood loss. Patients having a history of cardiac or renal disease, anemia, hypoproteinemia, liver dysfunction (manifested by elevated serum transaminase levels), drug or alcohol abuse, or obesity were excluded from the study.

Experimental Protocol

Pharmacodynamic Study

Group 1 surgical patients fasted overnight and arrived unmedicated in the operating room. After an intravenous catheter was placed for thiopental administration, an indwelling radial arterial catheter was placed in the contralateral arm for blood sampling and continuous blood pressure monitoring. A precordial stethoscope and electrocardiographic and electroencephalographic leads were applied.

The baseline EEG was recorded for approximately 5 min, after which time sodium thiopental was infused at the rate of 75, 100, or 150 mg/min. When the EEG produced a burst suppression pattern with isoelectric periods of approximately 1–3 s, the infusion was stopped, and the EEG was allowed to recover to a pattern of high frequency, low voltage (Stage 1)9 Recording of the EEG was then stopped, and anesthesia was reestab-

lished with methohexital 1.5–2.0 mg/kg as needed. Enflurane 1–2% (inspired) in 70% nitrous oxide was used to maintain anesthesia for the surgical procedure.

Arterial blood samples for measurement of serum thiopental concentrations were obtained at 0.5-min intervals during the thiopental infusion and then every 1–3 min after termination of the infusion for the next 20–30 min. Ventilation was assisted with an anesthesia circuit and 100% oxygen if the respiratory rate decreased below 10 breaths/min. An arterial blood sample for blood gas analysis was obtained at the end of the thiopental infusion. The subject was removed from the study if the arterial blood sample for blood gas analysis was not obtained at the end of the thiopental infusion. The subject was removed from the study if $P_{aCO_2}$ was not maintained.

The study protocol for the eight volunteers has been described elsewhere.9 It differed from the above only in the site of blood sampling (venous vs. arterial) and in the fact that the volunteers did not subsequently receive general anesthesia after completion of the thiopental infusion. All of the volunteers were between 20 to 40 yr of age and did not differ statistically from the surgical subjects of comparable age in demographic variables.

Pharmacokinetic Study

After an overnight fast, Group 2 patients arrived unmedicated in the operating room. An intravenous catheter was placed for drug administration. An indwelling radial arterial catheter in the contralateral arm was used to obtain blood samples and to monitor blood pressure continuously. A precordial stethoscope and electrocardiographic leads were applied. In 11 of the 28 patients, thiopental 4–5 mg/kg was administered as a bolus over 15 s. Blood samples were obtained at 1, 2, 3, 5, 10, 15, 30, and 45 min, and then at 1, 1.5, 2, 3, 5, 7, 10, 15, 20, 30, 40, and 48 h after the bolus. In the remaining patients, thiopental 4–9 mg/kg was given as an infusion over 1–5 min. Blood samples were taken at 0.5- to 1-min intervals during the infusion and then every 1–3 min for the next 20 min. Blood samples were also obtained at 30 and 45 min, and at 1, 1.5, 2, 3, 5, 7.5, 10, 15, 20, 30, 40, and 48 h after termination of the infusion. In all patients in this group, arterial sampling was used for the first 2–4 h to accurately characterize the distribution/redistribution phases. Venous sampling from a central venous catheter or a peripheral arm venous catheter was then subsequently used to characterize the terminal elimination phase, since it was not possible to have access to arterial blood samples for 48 h. In the patients who did not have electroencephalographic measurements after thiopental administration, succinylcholine 1.0 mg/kg was given, the trachea intubated, and enflurane 1–2% (inspired) with 70% nitrous oxide was given. If the EEG was recorded, then anesthetic management proceeded as in the pharmacodynamic study.
FIG. 1. Pharmacokinetic and pharmacodynamic models are illustrated. The former consists of the following: $V_1$, $V_2$, and $V_3$ represent the central and the rapidly and slowly equilibrating compartments, respectively. $K_{12}$, $K_{23}$, $K_{13}$, and $K_{21}$ are rate constants that characterize the intercompartmental transfer of drug. $K_{10}$ is the rate constant for drug clearance from the body. $Q_0$ ($K_{10} \times V_1$) and $Q_0$ ($K_{10} \times V_2$) are the rapid and slow intercompartmental clearances. The pharmacokinetic model, which is linked to the pharmacodynamic model by the effect compartment, consists of the following: The concentration of drug in the effect compartment ($C_{e_0}$) is determined by the rate constant $K_{e_0}$, which characterizes the temporal lag of serum concentration ($V_1$) and the measured spectral edge. $C_{e_0}$ can be related to the spectral edge by using the inhibitory sigmoid $E_{\text{max}}$ model (see text). A graphic representation of this equation and its parameters are indicated.

**Analytic Techniques**

Total (free and protein bound) serum thiopental concentrations were measured using a high-performance liquid chromatographic assay sensitive to 100 ng/ml. The degree of protein binding was determined with a previously described ultrafiltration technique at two different thiopental concentrations (10 and 30 µg/ml).

**EEG Waveform Analysis**

The progressive electroencephalographic stages produced by thiopental administration were described by Kiersey et al. In stage 1, frequency and amplitude increases. Patients are usually awake or drowsy but easily aroused. In stage 2, amplitude increases further and frequency decreases. Patients lose consciousness early in this stage. Later in stage 2 they lose the corneal reflex, do not withdraw from painful stimuli, and will tolerate surgical incision. Stage 3 is characterized by bursts of electrical activity separated by isoelectric periods of less than 3 s ("burst suppression"). Early stage 3 was the endpoint for drug administration and was used to terminate the thiopental infusion. This defined the thiopental dose requirement.

Since the electroencephalographic pattern seen with thiopental was similar for all leads, either a left fronto-central lead or a central-occipital lead was used for signal processing. Electroencephalographic signals were amplified by a Beckman Accutrace® EEG machine and were recorded on magnetic tape using an eight-channel recorder (Vetter Model A®). A PDP 11/23 computer (Digital Equipment Corporation) was used for the waveform analysis. The signal was first digitized (200 Hz) and then Fourier analyses of consecutive 3-s periods were computed to describe the frequency (resolved to 0.4 Hz) and amplitude of the electroencephalographic waveform. A power versus frequency histogram results from this analysis.

The spectral edge (i.e., the frequency below which 95% of the power lies in each 3-s epoch) was calculated from the power spectrum. A moving arithmetic mean of 10 consecutive epochs of the spectral edge data was used for curve smoothing.

**Pharmacodynamic Data Analysis**

The following inhibitory sigmoid $E_{\text{max}}$ pharmacodynamic model (fig. 1) and nonlinear regression were used to relate arterial serum thiopental concentrations to the spectral edge:

$$\text{Spectral Edge}_t = E_o - \frac{E_{\text{max}} \cdot C_{e_t} \gamma}{IC_{50} \gamma + C_{e_t} \gamma}$$

where $t =$ time; $E_o$ (Hz) is the spectral edge during Stage 1 of the thiopental EEG; $E_{\text{max}}$ (Hz) is the maximal decrease of the spectral edge induced by thiopental; $\gamma$ is a power function describing the steepness of the sigmoid curve; $IC_{50}$ (µg/ml) is the steady state thiopental serum concentration that causes one-half of the maximal EEG slowing; and $C_{e_t}$ is the concentration of drug in the effect site at time $t$.

Using arterial sampling, we found that a temporal lag or hysteresis existed between the thiopental serum concentration and spectral edge, preventing us from directly using the thiopental serum concentration in equation (1). Therefore, we postulated a biophase or "effect" compartment ($C_{e_t}$) that has a first-order rate constant ($K_{e_0}$) that characterizes the rate of equilibration between the thiopental serum concentration and the change in spectral edge. $T_{1/2}K_{e_0}$ (0.699/$K_{e_0}$) is the half-time of equilibration between the serum concentration and pharmacologic effect. The concept of an "effect compartment" and sigmoid-shaped equation to relate drug concentration to a drug effect under nonsteady-state conditions has been extensively used in the area of muscle relaxant pharmacokinetics and dynamics.

The $E_{\text{max}}$ parameter quantitates the brain's maximal responsiveness to thiopental, whereas $IC_{50}$ is a measure of the brain's sensitivity to the drug. The maximal degree of EEG slowing that can be quantitated by the waveform analysis and spectral edge calculation occurs.
at early burst suppression. As the EEG becomes isoelectric during burst suppression, the waveform analysis can no longer determine an underlying frequency. The IC50 was calculated for both total thiopental concentration and the free fraction using the degree of protein binding. Nonlinear regression was used to determine the parameters of this pharmacodynamic model from the serum thiopental concentrations and spectral edge data.

**Pharmacokinetic Data Analysis**

Data for total thiopental serum concentration versus time for each patient were fit to two- and three-compartment pharmacokinetic models using extended least-squares nonlinear regression (ELSFIT). In all cases, a three-compartment model using log-likelihood values and chi-square distribution was statistically preferable. Extended least-squares analysis differs from conventional weighted least-squares analysis in that the optimal weighting is determined by the statistical criteria of the regression program instead of being arbitrarily defined by the user. From the three-compartment model (fig. 1), values for the following variables were derived using standard pharmacokinetic formulas: rapid and slow distribution half-lives; terminal elimination half-life; the volume of the central compartment (Vc); the volume of distribution at steady-state (Vdss); total plasma clearance (Cl); the microrate constants describing the rate of drug transfer between the central and the rapidly and slowly equilibrating compartments (K12, K21, K13, K31); Qfast, the intercompartmental clearance to the rapidly equilibrating compartment (Qfast = Vc · K12); and Qslow, the intercompartmental clearance to the slowly equilibrating compartment (Qslow = Vc · K13). Using the free fraction as a measure of thiopental protein binding, we derived the unbound volume of distribution at steady-state and the unbound (intrinsic) clearance.

**Statistical Analysis**

All descriptive and linear regression statistical analyses were performed by the BMDP (1983) statistical package. All nonlinear regression analyses were performed using the ELSFIT data analysis program. The pharmacokinetic and pharmacodynamic variables were first examined for any relationship to body weight. Since no such relationship was found, these variables were not adjusted to body weight. Linear regression was used to determine if a significant ($P < 0.05$) relationship existed between age and pharmacokinetic and pharmacodynamic variables. If such a relationship did exist, nonlinear regression was used to determine if an exponential equation better characterized the data, using the log likelihood value to determine the optimal regression relationship.

**Results**

**Dose Response Relationship**

The dose of thiopental (mg/kg) required to produce burst suppression (isoelectric periods of 1–3 s on the EEG) decreased significantly and linearly with age (fig. 2). The thiopental dose (mg) needed to reach burst suppression was significantly related to body weight, therefore the dose was weight adjusted. In figure 2 the eight volunteer subjects are indicated separately from the 21 surgical patients. Adding the data from the eight volunteers did not change the slope or intercept values of the dose versus age regression relationship (dose [mg/kg] = 12.4 − 0.10 × age [yr], $r^2 = 0.74$, $F = 51.6$). For each 10-yr increase in age, the dose of thiopental required to achieve early burst suppression on the EEG decreased approximately 1 mg/kg.

During the thiopental infusion no age-related changes in mean arterial pressure or heart rate occurred when preanesthetic hemodynamic values were compared with the values at the time of the peak thiopental concentrations at the end of the infusion. Mean (±SD) arterial blood pressure decreased from $110 ± 14$ mmHg (control) to $95 ± 16$ mmHg, and heart rate increased from a mean of $74 ± 13$ beats/min to $83 ± 12$ beats/min; these differences were not statistically significant. Assisted ventilation was occasionally necessary at lighter levels of thiopental anesthesia, as was controlled ventilation during

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FIG. 3. The concentration of thiopental versus 1) time and 2) spectral edge in an elderly patient (top figure) and in a younger patient (bottom figure). Solid horizontal bars represent the length of thiopental infusion. Dots represent the measured thiopental concentration (linear scale), and the solid line next to them, the fitted data from the pharmacokinetic model. The axis for spectral edge has been inverted for visual clarity.

deepest levels. At the peak thiopental effect, arterial blood–gas values for each patient did not demonstrate hypercarbia or hypocarbia.

PHARMACODYNAMICS

Figure 3 characterizes the thiopental infusions and the resulting serum concentrations of the drug and changing spectral edge in a representative elderly and young patient. As the serum levels of thiopental increased, the predominant electroencephalographic frequences slowed and the spectral edge decreased progressively. Although thiopental levels and values for spectral edge were similar, there was a short delay in equilibration between onset of infusion and the beginning of the effect on EEG. When the spectral edge was plotted against the measured arterial plasma concentration of thiopental in the surgical patients, a delay in equilibration was evident in all patients except one (27 yr of age). The half-time for equilibration of the thiopental concentration and effect (t_{1/2K_{eo}}) on EEG was 0.67–2.5 min (table 1). No relationship was found between t_{1/2K_{eo}} and age. Because there was no significant equilibration delay between venous thiopental concentrations and manifestations on EEG for the eight volunteers, t_{1/2K_{eo}} was not estimated in these subjects.

No relationship was found between age and the following: 1) the baseline spectral edge (E₀); 2) the maximal slowing (E_{max}) induced by thiopental; or 3) γ, the power function of the concentration–response relationship. When the measure of brain sensitivity was examined, no relationship was found between the serum concentration of thiopental needed to cause one-half of the maximal EEG slowing (IC_{50}) based on the total drug concentration (fig. 4; table 1) or on the free, pharmacologically active portion of the drug concentration (table 1). The pharmacodynamic data indicate that although the thiopental dose requirement to reach the same electroencephalographic endpoint decreased with age, brain sensitivity did not change. The altered dose requirement must be due to a change in the pharmacokinetic processes of thiopental.

Within 1–5 min of starting the thiopental infusion, the difference in dose requirements to reach stage 3 on

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**TABLE 1. Values for Thiopental Pharmacodynamic Variables Showing No Age Relationship**

<table>
<thead>
<tr>
<th>Pharmacodynamic Parameters</th>
<th>Mean ± SD</th>
<th>Coefficient of Variation (%)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>E₀ (Hz)</td>
<td>24.6 ± 4.4</td>
<td>18</td>
<td>23.8</td>
<td>17.1–35.3</td>
</tr>
<tr>
<td>E_{max} (Hz)</td>
<td>14.5 ± 5.6</td>
<td>39</td>
<td>15.4</td>
<td>6.0–28.6</td>
</tr>
<tr>
<td>γ</td>
<td>4.9 ± 2.9</td>
<td>59</td>
<td>4.38</td>
<td>1.5–10.4</td>
</tr>
<tr>
<td>Total IC_{50} (µg/ml)</td>
<td>19.4 ± 6.8</td>
<td>35</td>
<td>18.0</td>
<td>10.3–54.6</td>
</tr>
<tr>
<td>Free IC_{50} (µg/ml)</td>
<td>2.7 ± 1.0</td>
<td>37</td>
<td>2.63</td>
<td>1.48–5.64</td>
</tr>
<tr>
<td>T_{1/2 K_{eo}} (min)</td>
<td>1.2 ± 0.4</td>
<td>37</td>
<td>1.09</td>
<td>0.67–2.5</td>
</tr>
</tbody>
</table>

Twenty-nine subjects were studied for each analysis, except for *, for which one outlying value of 49 was excluded from analysis; and †, in which n = 20 because for the eight volunteers (venous blood sampling) and one surgical patient (arterial blood sampling) t_{1/2K_{eo}} was not able to be measured.
the EEG between the young and the elderly patients became apparent. Because pharmacodynamic variables were unaffected by age, the occurrence of this difference in drug requirement over such a short time frame implies a change in early drug distribution. Figure 5 displays, on an expanded time axis, all of the serum levels obtained during the infusion of thiopental in a young and the elderly patient shown in figure 3. The difference in the shape of the serum concentration curves in figures 3 and 5 arises from the use of a linear concentration scale in figure 3 and a log concentration scale in figure 5. One minute after the start of the infusion, the elderly patient had significantly higher serum levels of thiopental than the younger patient. As the infusion continued, the elderly patient achieved adequate serum levels for burst suppression much sooner than the younger patient, an occurrence that accounts for the decreased thiopental dose requirement. The increase in thiopental concentration is much slower in the younger patient. The high serum levels relative to the dose given were the result of a smaller $V_1$ in the elderly patient than in the younger patient (fig. 6). The first-order rate constants for drug leaving the central compartment increased significantly with age (figs. 7 and 8; table 2). The rate constants $K_{12}$ and $K_{13}$ characterize the rate at which the rapid and slow compartments equilibrate with the central compartment. $K_{10}$ characterizes the rate of drug elimination (metabolism) from the body. The relationships between $V_1$, $K_{12}$, $K_{13}$, and $K_{10}$ were better characterized by an exponential equation than by a linear equation (table 2). Because the initial

![Graph showing the relationship between serum concentration and time for young and elderly patients.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931410/)  

![Graph showing the relationship between volume of the central compartment and age.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931410/)

**Fig. 5.** Serum thiopental concentration (log scale) versus time for the young (filled circles and bars) and the elderly (unfilled circles and bars) patients shown in figure 3. All of the measured thiopental concentrations for the patients are indicated in this figure, whereas all data could not be displayed in figure 3. The horizontal bars represent length of the thiopental infusions; solid lines represent fitted data from the pharmacokinetic model.

**Fig. 6.** Volume of the central compartment ($V_1$) versus age. The dots represent the $V_1$, derived from the pharmacokinetic analysis for each patient. The solid curve was derived using nonlinear regression of $V_1$ versus age to an exponential equation (see table 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Regression Equation</th>
<th>Coefficient of Determination ($r^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$ (L)</td>
<td>9.6 ± 8.0</td>
<td>$V_1 = 64.9e^{-0.339 \text{ age (yr)}}$</td>
<td>0.79</td>
</tr>
<tr>
<td>$K_{12}$ (min$^{-1}$)</td>
<td>0.3268 ± 0.3299</td>
<td>$K_{12} = 0.0312e^{0.697 \text{ age (yr)}}$</td>
<td>0.59</td>
</tr>
<tr>
<td>$K_{13}$ (min$^{-1}$)</td>
<td>0.1023 ± 0.1217</td>
<td>$K_{13} = 0.00426e^{-0.048 \text{ age (yr)}}$</td>
<td>0.57</td>
</tr>
<tr>
<td>$K_{10}$ (min$^{-1}$)</td>
<td>0.0436 ± 0.0505</td>
<td>$K_{10} = 0.00711e^{-0.0059 \text{ age (yr)}}$</td>
<td>0.80</td>
</tr>
<tr>
<td>Rapid distribution half-life (min$^*$)</td>
<td>2.3 ± 1.5</td>
<td>$t_{1/2} = 5.46 - 0.0548 \text{ age}$</td>
<td>0.49</td>
</tr>
</tbody>
</table>

$n = 28$ for all variables, except for $*$, for which one outlying value of 17.2 min was excluded from analysis.
rapid distribution half-life is determined by the parameters characterizing the initial distribution process (i.e., $V_1$, $K_{12}$, $K_{13}$, $K_{10}$), it also was age related but in a linear fashion.

The rate constants for drug transfer from the peripheral compartment back to the central compartment ($K_{21}$, $K_{31}$) were not significantly related to age (table 3). The decrease in $V_1$ with age was compensated for by an increase in $K_{12}$ or $K_{13}$ such that rapid and slow intercompartment clearance ($Q_{\text{fast}}$, $Q_{\text{slow}}$) did not change with age, the latter being the product of $V_1$ and $K_{12}$ or $K_{13}$. Total body clearance ($K_{10} \times V_1$) did not change with age (fig. 8) because of the reciprocal change in $V_1$ and $K_{10}$. The steady state distribution volume, slow distribution half-life, and the terminal elimination half-life were also not affected by age (table 3). Because protein binding did not change with age, neither did intrinsic clearance and the unbound steady state distribution volume.

**Discussion**

Previous studies have reported a lower thiopental dose requirement in the elderly for both induction and maintenance of anesthesia. The clinical endpoint for induction of anesthesia was loss of the eyelash reflex and, for maintenance of anesthesia, "satisfactory operating conditions" or the elimination of "signs of light anesthesia" (sweating, lacrimation, tachycardia, increased blood pressure). Comparing our study with these studies reveals that use of the EEG as a measure of anesthetic effect of thiopental has several advantages.

**Fig. 7.** $K_{12}$ and $K_{13}$, the first-order rate constants characterizing rate of drug transfer between the central compartment and the rapidly and slowly equilibrating compartments, versus age. The dots represent actual $K_{12}$ and $K_{13}$ values calculated from the pharmacokinetic analysis for each patient. The solid curve was determined using nonlinear regression of $K_{12}$ and $K_{13}$ versus age to an exponential equation (see table 2).

**Fig. 8.** $K_{10}$ and clearance versus age. Dots represent the rate constants or clearance derived from the pharmacokinetic analysis derived for each patient. $K_{10}$, the first-order rate constant of drug elimination (metabolism) from the body, has an exponential relationship with age. This relationship (solid curve) was determined using nonlinear regression (see table 2). Because clearance is the product of $K_{10}$ and $V_1$, clearance and age are not related.
For example, the EEG is a continuous and noninvasive measure of light-to-deep thiopental anesthesia, whereas the quantal measures (presence or absence of an anesthetic endpoint) of previous studies are not. Additionally, in determining the dose requirement, we selected an endpoint (burst suppression) that closely approximated surgical anesthesia, a deeper anesthetic state than that represented by loss of the corneal reflex.

The dose requirements for the eight volunteers were compatible with the data from the surgical patients. The regression relationship of age to thiopental dose requirement did not change when data for the relatively young volunteers were added to the data analysis. It should be noted that the dose requirement in figure 2 results when thiopental is infused over 3–10 min. This dose requirement is higher than it would be were the drug administered as a rapid iv bolus.

As described previously, the use of arterial blood sampling results in a temporal lag or delay in equilibration between serum thiopental concentrations and the spectral edge. This delay was present in all but one of our surgical patients from whom arterial blood samples were obtained. We have previously shown that the pharmacodynamic modeling of thiopental’s electroencephalographic effects is not altered when venous or arterial blood sampling is used except for this delay in equilibration. Arterial blood sampling allows for the calculation of accurate drug distribution data and the estimation of a useful pharmacodynamic parameter \( t_{1/2}K_{eq} \) that quantitates the rate of blood:brain equilibration. The values for \( t_{1/2}K_{eq} \) ranged from 0.6 to 2.5 min and did not change with age. This suggests that the brain equilibrates relatively rapidly with blood (the \( t_{1/2}K_{eq} \) for muscle relaxants is approximately 5–8 min). Because \( t_{1/2}K_{eq} \) is thought to be determined by blood perfusion to the drug site of action and the blood: tissue partitioning of drug, our data suggest that with age, cerebral blood flow and thiopental blood:brain partitioning is maintained.

The inhibitory sigmoid \( E_{max} \) pharmacodynamic model allows an estimation of brain sensitivity as measured by the \( E_{max} \) and IC\(_{50}\). Using this model and its parameters, we could not demonstrate a change in brain sensitivity to thiopental with age. This was surprising because an age-dependent increase in brain sensitivity has been reported for the inhalational agents. Because previously methods have not been adequate to estimate the sensitivity of the human brain to intravenously administered drugs, little information exists with which to compare our results.

The markedly altered dose requirement of thiopental in the elderly can be explained by the altered early distribution processes, and, specifically, the smaller initial distribution volume (or central compartment). The specific physiologic composition of the initial distribution space that is derived from a pharmacokinetic model cannot be known exactly. Generally, the initial distribution space or central compartment is composed of the blood volume and vessel-rich group tissues (lungs, heart, brain, liver, kidney) that have high perfusion and therefore very rapid equilibration with the blood volume. The assumption that thiopental’s central compartment is composed of these tissues is compatible with the several physiologic pharmacokinetic models that have been derived for this drug. The rapidly and slowly equilibrating compartments \( V_S, V_T, V_3 \) (fig. 2) may represent muscle and fat, respectively.

To accurately characterize the initial distribution/ redistribution of thiopental for the pharmacokinetic analysis, it was critically important to obtain arterial blood. Numerous studies have shown that venous blood can significantly underestimate the initial blood concen-
trations of a drug from either a bolus or rapid intravenous infusion because of several factors.\textsuperscript{24,25} These include a lag time due to drug transport from the injection site to the sampling site, mixing of drug in the blood circulation, and drug extraction by the sampling tissue.\textsuperscript{25} The last factor is of special importance, since arteriovenous differences are very prominent immediately after drug administration. Our use of arterial blood sampling obviated these problems and resulted in the measurement of drug concentration being delivered to the site of action (brain) and other tissues for distribution and redistribution. We have previously shown that the arteriovenous difference for thiopental is minimal within 10–20 min after a bolus\textsuperscript{26} or rapid infusion\textsuperscript{8} and that one can obtain comparable steady state pharmacokinetic parameters (clearance, steady state volume of distribution, terminal elimination half-life) when the combination of arterial then venous sampling is compared with totally venous blood sampling for thiopental's pharmacokinetic analysis.\textsuperscript{26}

The uptake of thiopental into any tissue is determined by the blood: tissue solubility, blood flow relative to volume of tissue, and the arteriovenous concentration difference across the tissue. Based on data from the present study, it is not possible to comment on an aging effect on vessel-rich tissue solubility for thiopental. However, other characteristics of the vessel-rich group (central compartment) do change with age. For example, with age the liver weight becomes a progressively smaller portion of total body weight and hepatic blood flow decreases.\textsuperscript{5} Renal blood flow also decreases with age.\textsuperscript{2,4} The age-related decrease in cardiac output occurs at the expense of decreased regional blood flow to some of the vessel-rich tissues such as the liver and kidney.\textsuperscript{2,4}

In addition, total body water, extracellular fluid volume, and plasma volume decrease with age. A combination of these factors could explain the progressively smaller initial distribution space seen with increasing age.

Thiopental's initial distribution volume decreased from 15 to 30 l in the 20–40-year-old patients to 3–7 l in the 60–90-yr-old patients. These values for thiopental's initial distribution volume may appear to be unphysiologic, since the blood volume is approximately 5 l in humans. The initial distribution volume of thiopental, a lipophilic compound that can rapidly penetrate membranes, includes both the blood volume and the partitioning into tissues that have very high perfusion and whose equilibration with blood is so rapid that it is not detectable with conventional blood sampling at one-half-minute intervals. The calculation of the initial distribution volume assumes that the blood to tissue partition coefficient is one. Therefore, if the true blood:tissue partition coefficient is greater than one for some highly perfused tissues, this will translate into an initial distribution volume that is greater than the blood volume as seen in the young patients. If blood flow is decreased to some of the highly perfused tissues, as we are postulating in the elderly, then both the mixing and delivery of thiopental to tissues and the blood contained in these tissues will be delayed, along with the tissue uptake of thiopental. This will translate into a smaller initial distribution volume as we found in the elderly. This volume could be less than the blood volume, since the flow of blood to all tissues is not an instantaneous process and drug mixing in the blood circulation is also not instantaneous. The total blood volume could well be divided into several different pharmacokinetic pools, depending upon the degree of tissue perfusion.

A smaller central compartment has not been reported previously in the other studies of thiopental pharmacokinetics in the elderly.\textsuperscript{20,27,28} In all of these studies, venous blood was used for the pharmacokinetic analysis. Because of arteriovenous equilibration factors and the frequency of blood sampling after drug administration, these studies may have "missed" characterizing a smaller initial distribution volume in the elderly. However, Thomson et al.\textsuperscript{29} found a decreased central compartment for lidocaine given by bolus or infusion in patients with overt congestive heart failure. They stated that this decreased distribution volume might be explained by decreased perfusion (secondary to the disease state) to various tissues. Perhaps a similar hemodynamic mechanism of decreased perfusion could explain our finding of a decrease in the central compartment volume of thiopental with age.

Despite the smaller central volume, the intercompartment clearance of drug (the volume of plasma containing drug transferred from the central compartment per unit time) from the central compartment to the rapidly and slowly equilibrating peripheral compartments remained the same. Redistribution from the smaller central compartment is faster in the elderly, thus preserving the efficiency of clearing drug from the central to the peripheral compartments. The increase in $K_{12}$, $K_{13}$, and $K_{10}$ with unchanged intercompartmental clearance is compatible with the fact that as age increases, some tissues in the vessel-rich group (such as liver, kidney, portal circulation) in effect "move" from the instantaneously mixing central compartment to a more slowly equilibrating peripheral compartment. Because these tissues become "redistribution sites" instead of the initial rapid equilibration "mixing site," the rate constants for drug transfer out of the central compartment ($K_{12}$ and $K_{13}$) would be expected to increase.

We were not able to demonstrate a progressive increase in the Vd of thiopental with age. One might expect an increase in this volume because the percentage of lean body mass decreases with age,\textsuperscript{5} and thus highly
lipid-soluble drugs would have a proportionately larger volume through which to distribute themselves. In addition, the patients in the present study showed no significant change in total body clearance of the drug with age. Thus, the overall elimination half-life of the drug did not change. This result differs from that of Jung et al., who reported higher $V_d$ values in elderly women than in young women. The difference in results between the two studies may be attributable to the fact that women lose proportionately less of their lean body mass with age than men.† The patient population in the present study (total, 28) included only three women. They did not appear pharmacokinetically different, although they represented only a small fraction of the total number of patients.

Christensen et al. also found an increase in $V_d$ in an elderly group of patients. In their study, elderly women had a higher value for $V_d$ than elderly men; both elderly men and women had a higher value for $V_d$ than younger men and women. It is difficult to compare the results of the present study with results from Christensen et al. for several reasons. First of all, experimental design between the two studies, including the drug administration protocol, length of sampling, and data analysis differed significantly. In addition, the value for $V_d$ found by Christensen et al. in younger men (mean 0.7 ± 0.2 l/kg) was significantly smaller than the $V_d$ reported by other authors, which, in a comparable age group, ranged from 1.5 to 3.3 l/kg. These latter values are much closer to the mean value of 2.3 ± 1.0 l/kg found in the 10 youngest patients in the present study (23–43 yr of age). An increase in $V_d$ would not explain, however, the marked decrease in thiopental dose requirement that occurred after 1–5 min of thiopental infusion, because $V_d$ becomes maximally significant after distribution is completed (1–4 h). Our finding of a decreased central compartment volume, however, easily explains the altered dose requirement.

The protein binding of thiopental was not affected by increasing age. Jung et al. found a statistically significant increase in the free fraction of thiopental with age in his female patients. Sex differences may play a more important role in protein binding of thiopental than age alone, as is the case with diazepam. However, decreased protein binding of thiopental with age would not account for the absence of a significant change in brain sensitivity (IC$_{50}$) to thiopental with age. If decreased protein binding were an important factor, one might expect to see the total IC$_{50}$ levels decreasing with increasing age and the free IC$_{50}$ values unchanged with age. This was not the case.

In summary, the pharmacodynamic and pharmacokinetic properties of thiopental were studied in a population of predominantly male patients 19–88 yr of age. Alteration in brain sensitivity to thiopental as a function of age could not be demonstrated. However, a statistically significant decrease in the initial distribution space of thiopental with age was found. This pharmacokinetic difference explains the clinical impression of “increased sensitivity” of the elderly to thiopental. Having a smaller central compartment, the elderly develop high serum levels of thiopental quickly and require less drug to show an effect. Thus, the dose of thiopental required to reach a surgical level of anesthesia significantly decreased with increasing age.

References