Computer Simulation of the Effects of Alterations in Blood Flows and Body Composition on Thiopental Pharmacokinetics in Humans

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Background: Understanding the influence of physiological variables on thiopental pharmacokinetics would enhance the scientific basis for the clinical usage of this anesthetic.

Methods: A physiological pharmacokinetic model for thiopental previously developed in rats was scaled to humans by substituting human values for tissue blood flows, tissue masses, and elimination clearance in place of respective rat values. The model was validated with published serum concentration data from 64 subjects. The model was simulated after intravenous thiopental administration, 250 mg, over 1 min, to predict arterial plasma concentrations under conditions of different cardiac outputs, degrees of obesity, gender, or age.

Results: The human pharmacokinetic model is characterized by a steady state volume of distribution of 2.2 l/kg, an elimination clearance of 0.22 l/min, and a terminal half-life of 9 h. Measured thiopental concentrations are predicted with an accuracy of 6 ± 37% (SD). Greater peak arterial concentrations are predicted in subjects with a low versus a high cardiac output (3.1 and 9.4 l/min), and in subjects who are lean versus obese (56 and 135 kg). Acutely, obesity influences concentrations because it affects cardiac output. Prolonged changes are due to differences in fat mass. Changes with gender and age are relatively minor.

Conclusions: The physiological pharmacokinetic model developed in rats predicts thiopental pharmacokinetics in humans. Differences in basal cardiac output may explain much of the variability in early thiopental disposition between subjects. (Key words: Anesthetics, intravenous; thiopental. Pharmacokinetics: thiopental.)

Thiopental is an intravenous drug commonly used to induce general anesthesia. When clinical doses are administered, thiopental reversibly depresses brain activity and causes loss of consciousness within 10–20 s for a duration of 5 – 8 min.† Drug disposition plays an important role in onset and offset of thiopental’s hypnotic effect. A greater understanding of the relationship between patient physiology and thiopental pharmacokinetics would enhance the scientific basis for the clinical usage of this drug.

Physiological pharmacokinetic models have provided insight into the physiological determinants of thiopental disposition. The first physiological model for thiopental disposition in humans suggested that ‘lean,’ i.e., chiefly muscle tissue, was primarily responsible for the depletion of thiopental from the central nervous system and consequent termination of thiopental’s anesthetic effect.‡ Others found that the role of muscle was equal to the combined contribution of metabolism and fat uptake and predicted changes in blood concentrations caused by hemorrhage,§ different metabolic rates,¶ apprehension, and different injection sites. However, these physiological models were validated with limited data. For example, predicted jugular venous blood concentrations, as a percent of the concentration at 1 min, were compared with 15 internal jugular vein concentrations measured between 2 – 16 min in six humans. Also, the models did not discriminate between arterial and
venous blood. Because thiopental induction can occur before thiopental distributes uniformly in blood, these models are limited in their ability to predict induction pharmacokinetics. More detailed pharmacokinetic models have incorporated protein binding and multiple tissues with distinction between arterial and venous blood, but did not validate or simulate the models extensively in humans.⁶,⁷

We have previously reported a physiological model that predicted accurately thiopental disposition in arterial plasma and 11 other tissues in rats between 1–360 min.⁸ The goals of the present investigation were first to improve the model in rats to predict plasma concentrations more accurately in the first minute, to scale the model to humans, and to validate the human model with published arterial serum data collected between 1 min to 24 h in 64 subjects.⁹–¹¹ Second, the validated human model was then used to predict arterial concentrations after a 1-min intravenous thiopental infusion, 250 mg, for subjects with different cardiac outputs, degrees of obesity, gender, and age. Our model complements and extends previous works by demonstrating that physiological pharmacokinetic models can be scaled to humans and can be used to investigate the putative physiological determinants of the induction pharmacokinetics of thiopental.

Methods

Rat Pharmacokinetic Model

We reported a physiological pharmacokinetic model for thiopental in rats, which predicted plasma concentrations accurately between 1–360 min after a 20 mg/kg infusion administered in 45 s, but predicted twice the measured concentrations during the infusion.⁸ In the current work, we used new information in an attempt to improve the early model predictions. Namely, we incorporated the time profile of thiopental-induced regional blood flows,¹² a blood–plasma partition coefficient of 0.95 ², and an increased total body blood volume.³ The modeling methodology is described elsewhere.⁶

Human Pharmacokinetic Model

The pharmacokinetic model for rats was scaled to human dimensions by substituting human values for elimination clearance, blood flows, organ weights, and great vessel blood volumes, while retaining the rat pharmacokinetic parameters for the individual tissues and organs. The scaling procedure has been described previously.¹³ Figure 1A displays the total body model, and Figure 1B displays the model of a typical organ. Because thiopental uptake in the lung of the rat could not be measured adequately,³ lung distribution clearance in humans was adjusted until first-pass retention of thiopental equaled 13.8%, a value directly measured in humans.¹₄ The blood–plasma partition coefficient was set to 0.94.¹⁵ ¹⁶ Organ masses and flows characteristic of a 75-kg man and 60-kg woman are presented in tables 1 and 2. The organ masses are increased slightly from reference values to account for the distribution of vascular volume.¹⁷ Organ masses and flows for a 67-kg human are averaged from the female and male data. Cardiac output ranges from 5.7 l/min in women to 6.8 l/min in men, with a value of 6.3 l/min in humans. Plasma elimination clearance (CLₑ) is assumed to be of metabolic origin and is modeled as a pathway exiting from the shallow parenchymal compartment of the liver with clearance rate CL₂₀. The value of CL₂₀ can be calculated from CLₑ, liver blood flow, the blood-to-plasma partition coefficient, and other liver pharmacokinetic parameters.⁶ Once CL₂₀ is determined, this same relationship allows calculation of CLₑ for different liver blood flows. The volume of distribution at steady state and distribution extraction were calculated using methods described previously.¹³ Volume of distribution describes the extent of thiopental partitioning in body tissues. Distribution extraction is the dose fraction that exits blood and enters tissue parenchyma on a single pass through the systemic circulation.

Model Validation

Arterial serum thiopental concentrations from 64 experiments in 58 surgical patients and 6 volunteers were used to validate the human pharmacokinetic model.⁹–¹¹ Subjects ranged in age from 23–88 yr (50 ± 13 SD), and the weight range was 52–118 kg (75 ± 13 SD). Four subjects were female. These data were used pre-

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(A) Body Model

Fig. 1. A, the total body pharmacokinetic model describing thioental disposition in humans. The model consists of multiple tissues and blood pools connected via the vasculature, and assumes venous injection and arterial blood sampling (Cb). The "clock" generates simulation times corresponding to the simulated blood concentrations. Regional blood flows are generated in the box in the lower right hand corner, and sum to cardiac output. Some anatomical simplifications are made. Peripheral venous injection and peripheral arterial sampling are assumed to be indistinguishable from the illustrated central venous injection and aortic sampling, after consideration of appropriate transport delays. The pancreas and spleen are represented as a common tissue. B, a typical pharmacokinetic model for an organ. Organs such as the brain or heart consist of two compartments representing vasculature and parenchyma. The rate of mass transfer between compartments is proportional to the concentration gradient; this proportionality constant is the distribution clearance. Tissue models for fat, muscle, and carcass are comprised of a single compartment which represents both vascular and parenchymal volumes. Organ models for kidney, gut, and liver require a third "deep" parenchymal compartment connected only to the "shallow" parenchymal compartment to describe prolonged retention of thioental.

Previously to develop a population pharmacokinetic model for thioental. In 16 experiments, the subject received an intravenous bolus (200–500 mg over 6 s), and arterial concentrations were measured intermittently for 24–48 h. In another 48 experiments, thioental was administered at a constant rate (60–200 mg/min) over 2–15 min to reach a hypnotic end-point defined by 1–3 s of isoelectric electroencephalogram. The mean infusion duration was 7.4 min. Arterial samples were collected during the first half-hour of the infusion experiments, and venous samples were collected up to 24–48 h thereafter. We excluded data after 24 h, and assumed that venous concentrations equaled arterial concentrations and that serum concentrations equaled plasma concentrations.

All subjects were American Society of Anesthesiologists' (ASA) physical status I or II without hepatic, respiratory, cardiovascular, or renal disease. Surgical subjects receiving an intravenous infusion were induced after 20–30 min with 1–2 mg/kg methohexitol, and general anesthesia was maintained with 1–2% inspired enflurane and 70% nitrous oxide. Surgical patients receiving a bolus were intubated after 3–5 min and maintained with enflurane and nitrous oxide. Eleven of the subjects receiving an infusion were chronic alcoholics participating in an inpatient alcohol rehabilitation program. The plasma elimination clearance for the physiological model was determined from the data of 51 of the 64 patients in whom plasma concentrations were mea-
sured for at least 24 h. Clearance was calculated for each subject as the ratio of dose to the area under the concentration versus time curve. The equation $C_l = 0.00336 \times \text{body weight}$ described a proportional relationship between clearance (l/min) and total body weight (kg). For the standard woman, man, and human, elimination clearance was 0.20, 0.25, and 0.22 l/min, respectively. The pharmacokinetic model was simulated using data for the standard human according to each subject’s infusion rate and duration. Arterial plasma concentrations were simulated and compared with respective measurements. Prediction error per sample (PE) was calculated as

$$PE = 100 \times \frac{C_{\text{measured}} - C_{\text{predicted}}}{C_{\text{true}}}$$

The mean and SD of the prediction error for all data were used as the principle measure of predictive performance. Median absolute prediction error was calculated to gauge predictive performance per individual. Simulations were repeated with clearances that were calculated from each individual’s concentration data or with

<table>
<thead>
<tr>
<th>Organ/Tissue Mass (kg)</th>
<th>Male</th>
<th>Female</th>
<th>Human</th>
<th>-15%</th>
<th>+50%</th>
<th>+100%</th>
<th>70 yr</th>
<th>90 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1.0</td>
<td>0.8</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
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</tr>
<tr>
<td>Brain</td>
<td>1.4</td>
<td>1.2</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Heart</td>
<td>0.5</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Liver</td>
<td>2.0</td>
<td>0.4</td>
<td>2.2</td>
<td>2.1</td>
<td>2.5</td>
<td>2.9</td>
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<td>Pancreas + spleen</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
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<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Gut</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
<td>1.2</td>
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</tr>
<tr>
<td>Kidney</td>
<td>0.4</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
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</tr>
<tr>
<td>Muscle</td>
<td>3.1</td>
<td>18</td>
<td>25</td>
<td>23</td>
<td>30</td>
<td>35</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Skin</td>
<td>3.4</td>
<td>2.3</td>
<td>2.9</td>
<td>2.6</td>
<td>3.4</td>
<td>3.9</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Fat</td>
<td>1.3</td>
<td>1.8</td>
<td>1.5</td>
<td>7</td>
<td>39</td>
<td>64</td>
<td>20</td>
<td>23</td>
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<tr>
<td>Carcass</td>
<td>1.6</td>
<td>1.3</td>
<td>1.5</td>
<td>14</td>
<td>18</td>
<td>21</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Great vessel blood*</td>
<td>3.0</td>
<td>1.8</td>
<td>2.4</td>
<td>2.3</td>
<td>2.9</td>
<td>3.4</td>
<td>2.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Total body mass (kg)</td>
<td>73</td>
<td>60</td>
<td>67</td>
<td>56</td>
<td>100</td>
<td>135</td>
<td>67</td>
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</tr>
</tbody>
</table>

*Great vessel blood is partitioned two thirds to venous blood and one third to arterial blood.

<table>
<thead>
<tr>
<th>Organ/Tissue Flows (ml-min⁻¹)</th>
<th>Standard Values (35 yr)</th>
<th>Weight</th>
<th>Cardiac Output</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Human</td>
<td>-15%</td>
</tr>
<tr>
<td>Lung (bronchial)</td>
<td>190</td>
<td>150</td>
<td>170</td>
<td>170</td>
</tr>
<tr>
<td>Brain</td>
<td>780</td>
<td>670</td>
<td>730</td>
<td>730</td>
</tr>
<tr>
<td>Heart</td>
<td>260</td>
<td>270</td>
<td>270</td>
<td>270</td>
</tr>
<tr>
<td>Liver (total)*</td>
<td>1,720</td>
<td>1,520</td>
<td>1,620</td>
<td>1,550</td>
</tr>
<tr>
<td>Pancreas + spleen</td>
<td>270</td>
<td>230</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Gut</td>
<td>1,000</td>
<td>940</td>
<td>970</td>
<td>920</td>
</tr>
<tr>
<td>Hepatic artery</td>
<td>450</td>
<td>350</td>
<td>400</td>
<td>380</td>
</tr>
<tr>
<td>Kidney</td>
<td>1,240</td>
<td>960</td>
<td>1,100</td>
<td>1,100</td>
</tr>
<tr>
<td>Muscle</td>
<td>1,140</td>
<td>680</td>
<td>910</td>
<td>850</td>
</tr>
<tr>
<td>Skin</td>
<td>400</td>
<td>280</td>
<td>340</td>
<td>310</td>
</tr>
<tr>
<td>Fat</td>
<td>350</td>
<td>490</td>
<td>420</td>
<td>210</td>
</tr>
<tr>
<td>Carcass</td>
<td>720</td>
<td>680</td>
<td>700</td>
<td>660</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>6,800</td>
<td>5,700</td>
<td>6,250</td>
<td>5,840</td>
</tr>
</tbody>
</table>

*Total liver blood flow is not included in cardiac output.
†Blood flow changes induced by thiopental.
gender- or age-specific physiologic data. The body composition and blood flow data for the gender and age simulations are presented in the next section.

Model Predictions

Arterial plasma concentrations were simulated over 120 min after intravenous thiopental administration, 250 mg in 1 min, with the following comparisons:

1. Cardiac output: low (3.1 l/min), standard (6.3 l/min), and high (9.4 l/min) cardiac outputs.
2. Obesity: lean (56 kg), standard (67 kg), overweight (100 kg), and obese humans (135 kg).
4. Age: standard (35-yr), elderly (70-yr), and geriatric (90-yr) adults.

Organ masses and flows are summarized in tables 1 and 2. Details of the simulations are as follows:

1. Cardiac output: humans with a 50% increase (high) or decrease (low) in cardiac output from the standard human, and humans with a 20% thiopental-induced decrease. The coefficient of variation of blood flows to brain, heart, skin, adipose, muscle, and the splanchnic region is reported to be 15–30% in adults. Consequently, to simulate the 50% increase or decrease in basal cardiac output, all regional blood flows were also changed 50%. To simulate dynamic blood flow changes during thiopental anesthesia, brain and renal blood flows were decreased by 50% and 30%, respectively. Coronary and skin blood flows were increased by 50% and 100%, respectively. Hepatosplanchnic tissues were not changed, and muscle, fat, and carcass flows were decreased by 50%. The resulting cardiac output decreased by 20% from 6.3 to 5.0 l/min. The blood flows were changed linearly with time to the new values during thiopental administration and fixed at the new level until the end of the simulation.

2. Obesity: humans with 50% excess weight (overweight), 100% excess weight (obese), and humans who are 15% underweight (lean). Of the absolute change in weight, 71% was allocated to fat and 29% to lean body mass. Gut and liver mass were increased by 50% for every 100% increase in body weight. Skin mass was increased in proportion to body surface area, which was calculated from body height and mass. The remaining increase in lean body mass was allocated to muscle and carcass, which were increased by 40% for every 100% increase in body weight. Organ blood flows were increased proportionately to organ size, resulting in a cardiac output ranging from 5.8 l/min in the lean patient to 8.8 l/min in the obese patient. Blood volume was changed in direct proportion to cardiac output.

3. Gender: Blood flows and body compositions or male and female adults are presented in tables 1 and 2.

4. Age: 35-yr (young), 70-yr (elderly), and 90-yr (geriatric) humans. Adipose mass was increased 9% per decade relative to the standard 35-yr human. Liver mass was decreased for patients older than 55 yr by 9% for every 10 yr in excess of 55 yr. Muscle mass was decreased to maintain body weight at 67 kg. Specific blood flows to kidney, hepatosplanchnic organs, brain, and adipose were decreased 5%, 8%, 8%, and 12% per decade, respectively. Coronary blood flow was changed in proportion to cardiac output. Specific flows to the muscle, skin, and remaining organs were not changed. The net effect on cardiac output is a decrease from 6.3 to 4.2 l/min as age increases from 35 to 90 yr.

The benefits of adjusting the thiopental dose to total body mass, lean body mass, or cardiac output were evaluated by calculating dose ratios. For a fixed peak plasma concentration $C_{\text{pmax}}$, the dose ratio for a particular patient type is $D/D$, where $D$ is the dose administered in 1 min that achieves $C_{\text{pmax}}$ in this patient, and $D$ is the dose that achieves $C_{\text{pmax}}$ in the standard human. $D$ and $D$ are expressed in mg, mg per kg of total body mass, mg per kg of lean body mass, or mg per l/min of cardiac output. A dose ratio close to unity indicates proper dose adjustment.

Results

Rat Pharmacokinetic Model

The revised pharmacokinetic model predicts arterial plasma concentrations more accurately than the old one between 0–1 min and at 420 min (fig. 2). Parameters of the model are reported in table 3. The improvement in the first minute is due to a revised blood–plasma partition coefficient of 0.95, and a blood volume of 8.3% of total body weight. Previously we had used values of 0.85 and 5.0%, respectively. The improvement at 420 min is due to inclusion of saturable metabolism with maximum elimination rate $V_m = 30.4$ $\mu$g/min and Mi-
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Fig. 2. Simulated and measured\(^a\) thiopental plasma concentrations in rats with the new (solid) and old (dashed) thiopental pharmacokinetic models. The inset displays the first 5 min in detail.

The Michaelis-Menten constant \(K_m = 5.14 \mu g/ml\), whereas the old model assumed first-order elimination kinetics.

**Human Pharmacokinetic Model**

The human pharmacokinetic model uses the rat parameters in table 3. The intrinsic metabolic clearance from liver parenchyma, \(CL_{S,T}\), is 0.13 l/min per kg of liver. The plasma elimination clearance is 0.22 l/min, the total volume of distribution is 2.2 l per kg of body weight, the distribution extraction is 76%, and the terminal half-life is 9 h.

**Model Validation**

Figures 3A and 3B demonstrate that the spread of the measured data covers the model simulations over 24 h after a bolus or short infusion. Figures 3C and 3D show that the prediction errors are distributed similarly, and that to a reasonable extent, the prediction errors are randomly and evenly spread about zero. The mean prediction error for all data points is 6% with an SD of 37%, and the spread of prediction errors always includes zero. Per subject, the mean prediction error ranges from -40% to 57%, and the median absolute prediction error ranges from 7% to 54%, with a population median of 19%.

The mean prediction error is based primarily on data collected in the first 6 h. The median sample time is 15 min, and only 15% of the measurements are taken after 6 h. There is a positive prediction error in the first 15 min (16% ± 37%), and a negative prediction error between 6–24 h (-14% ± 41%). The greatest prediction errors occur at 1 min in the bolus simulation (53% ± 120%) and the infusion simulation (-24% ± 35%).

When each subject is assigned an individualized clearance, the prediction error for all data points is 8% ± 33%. When gender- or age-related physiology is considered, the prediction errors are 10% ± 40% and 10% ± 35%, respectively.

Table 3. Thiopental Pharmacokinetic Parameters of the Organs and Tissues in a 67-kg, 35-yr Human and 355-g, 5-mo Rat

<table>
<thead>
<tr>
<th>Organ/Tissue</th>
<th>Distribution Clearances*</th>
<th>Distribution Volumes*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(CL_{S,T}) (l·min(^{-1})·kg(^{-1}))</td>
<td>(CL_{S,T}) (l·min(^{-1})·kg(^{-1}))</td>
</tr>
<tr>
<td>Lung</td>
<td>2.2</td>
<td>0.0017</td>
</tr>
<tr>
<td>Brain</td>
<td>2.0</td>
<td>0.0017</td>
</tr>
<tr>
<td>Heart</td>
<td>1.1</td>
<td>0.0017</td>
</tr>
<tr>
<td>Liver</td>
<td>1.2</td>
<td>0.0017</td>
</tr>
<tr>
<td>Pancreas + spleen</td>
<td>0.58</td>
<td>0.0061</td>
</tr>
<tr>
<td>Gut</td>
<td>0.60</td>
<td>0.010</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.8</td>
<td>0.010</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

* Distribution clearances and volumes are normalized to organ/tissue mass and referenced to arterial blood concentrations. Parameter definitions and model details are presented elsewhere.\(^{13}\)

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**Tissue Disposition**

Figure 4 displays the important organs governing the arterial plasma concentration curve after thiopental administration in the standard human. Figure 4A shows that thiopental predominantly resides in the great vessel blood and lung during the 1-min infusion. At 1 min, 39% of the dose resides in great vessel blood or the lung, 32% resides in the well-perfused organs liver, brain, heart, kidney, gut, pancreas, or the spleen, and 0.3% has been eliminated.

Figure 4C shows that the rate at which thiopental enters the lung and eventually the arterial blood is the sum of the infusion rate and the rate at which thiopental recircu-
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Fig. 4. Thiopental disposition after a 1-min intravenous infusion, 250 mg, to the “standard” human. A. Amount in selected tissues as a fraction of dose in the body over 10 min. Great vessels include arterial and venous blood. The solid bar indicates infusion duration. B. Amount in selected tissues or amount eliminated as a fraction of dose in the body over 180 min. C. Thiopental concentrations in selected tissues over 10 min. D. Thiopental concentrations in selected tissues over 180 min.

lates \textit{via} venous blood. At the time of peak arterial concentration, the venous concentration is 25\% of the arterial concentration. Therefore, peak arterial concentrations are determined primarily by the first pass of the infused thio- pental through the lung. The acute decrease in arterial concentrations immediately after the infusion stops is determined by the rate at which thiopental exits the lung and arterial blood. When the exit rate is increased by reducing the mass of the arterial blood and lung by 95\%, peak arterial concentrations decrease to 17 \( \mu \text{g/ml} \).

Figure 4A shows that the liver and muscle are important organs of distribution between 1 - 2 min, whereas metabolism is unimportant. During this time, 60 mg of thiopental is lost from blood and lung, of which 28\% enters the liver.
22% enters the muscle, and 4% has been metabolized. The well-perfused organs, excluding the liver, do not play a role during this time; the dose fraction in these organs increases negligibly from 19–20% between 1–2 min. Thiopental concentrations in the nonhepatic visceral organs peak between 1.2 and 1.6 min and follow a similar time course to venous blood concentrations.

Between 2 and 10 min, thiopental distributes out of blood and visceral tissues into muscle, fat, and carcass. At 10 min, 4% of the dose remains in great vessel blood, 65% has distributed to muscle, fat, or carcass, and 8% has been eliminated. Figure 4B shows that between 10 and 180 min, thiopental continues to distribute to fat or to be eliminated. Muscle concentrations peak at 10 min, and fat concentrations peak at 163 min in Figure 4D. After 180 min, all tissues are releasing thiopental back to the blood.

**Different Cardiac Outputs**

Figure 5A demonstrates the effect of changes in cardiac output on the early disposition of thiopental. As cardiac output decreases from 9.4 to 3.1 l/min, peak arterial concentrations increase by 103%. Between 1 and 1.5 min, arterial concentrations decrease 67% in the subject with a cardiac output of 9.4 l/min and decrease 51% in the subject with a cardiac output of 3.1 l/min.

Differences do not persist beyond 30 min because hepatic elimination is not much affected by large changes in cardiac output. When cardiac output is 9.4 l/min, the elimination clearance is 0.24 l/min, and 1% of the dose is eliminated at 30 min. When cardiac output is 3.1 l/min, the elimination clearance is 0.19 l/min, and 18% of the dose is eliminated at 30 min.

When cardiac output decreases, well-perfused tissues generally receive more thiopental despite lesser blood flows because tissue concentrations will increase to meet the increased arterial concentrations. For example, heart concentrations at 2 min increase from 14 to 18 μg/g as cardiac output decreases from +50% to −50%. Conversely, poorly perfused tissues generally receive less thiopental because the reduction in tissue perfusion overcompensates for the increased arterial concentrations. For example, the dose fraction in fat at 30 min decreases from 32% to 19% as cardiac output decreases from +50% to −50%.

A 20% thiopental-induced depression of cardiac output produces thiopental concentrations that are similar to those in the standard human during the infusion and in the subject with low cardiac output after the infusion. The change decreases within the boundaries imposed by variations in basal cardiac output.

**Obesity**

Figure 5B demonstrates the effect of obesity on arterial plasma concentrations. Peak arterial concentrations decrease from 54 to 35 μg/ml in the lean versus the 100% overweight (obese) subject. On average, arterial concentrations in the obese subject are 52% less than in the lean subject over the first 5 min and 73% less over 120 min. The decreased concentrations in the first 5 min are caused by increased cardiac output in heavier people. When the simulation for the obese subject is repeated with blood flows of the lean human, the arterial concentrations become 88% of those in the lean human over the first 5 min. The persistent difference over 120 min is primarily attributed to the capacity for thiopental uptake into fat. At 120 min, 69% of the dose resides in the fat in 100% overweight humans, but only 25% of the dose in lean humans. The difference is not explained by increased elimination clearance in obese people. Although elimination clearance increases from 0.21 to 0.29 l/min with increasing weight, the percent eliminated at 120 min is 39% in lean humans and 18% in 100% overweight humans.

**Gender**

Figure 5C indicates that gender has little effect on thiopental plasma concentrations. Peak arterial concentrations are 57 and 45 μg/ml in women and men, respectively. On average, arterial concentrations are 1% less in men than in women between 5–120 min. As discussed previously, altered peak concentrations are explained by the different cardiac outputs.

**Age**

Figure 5D shows that the age-related physiological changes have a relatively minor effect on peak plasma concentrations, with negligible differences after 2 min. Again, increasing peak concentrations are explained by cardiac output, which decreases from 6.3 l/min in the 35-yr-old human to 4.2 l/min in the 90-yr-old human. In contrast to the subjects with different cardiac outputs (fig. 5A), the curves converge rapidly. Blood flows affect the rate but not the extent of uptake by body tissues. Age-related changes in blood flows occur primarily to well-perfused tissues such as brain, kidney, and liver. Because peak thiopental concentrations in well-perfused tissues occur shortly after the end of infusion regardless of blood flow, age-related changes in blood flows will only have a transient effect on arterial concentrations.
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(A) Cardiac Output

(B) Obesity

(C) Gender

(D) Age

Fig. 5. Model predictions of arterial plasma concentrations after intravenous thiopental administration, 250 mg, in one min. A. Cardiac output (CO). Blood flows are increased or decreased 50% relative to the standard human, or altered dynamically to produce a 20% thiopental-induced decrease in cardiac output. The inset displays the predictions over 60 min. B. Obesity. Organ masses are increased or decreased relative to the standard human. The “lean” human is 15% underweight, OW denotes overweight. The inset displays the predictions over 120 min. C. Gender. Blood flows and body compositions are changed for females or males. D. Age. Blood flows and body compositions are changed for subjects of age 35, 70, and 90 yr.

Summary and Dosing Implications

Table 4 summarizes the simulation results. Thiopental distribution volume ranges from 1.7 to 3.5 l/kg, whereas elimination clearances are relatively constant, except in the geriatric subject with decreased liver mass. Terminal half-lives range from 7 to 25 h. Peak plasma are not
solely dependent on lean body mass, total body weight, or volume of distribution because the simulations with different cardiac outputs use identical body compositions but attain different peak concentrations. Elimination clearance and peak concentrations are indirectly related. Assuming that cardiac output is increased in conditions of increased liver blood flow, the increased liver blood flow will increase elimination clearance, and the increased cardiac output will decrease peak concentrations.

For a 1-min infusion, Table 5 presents the fractional increase or decrease in dose to achieve a specified peak plasma concentration, when the dose is chosen according to different factors. For example, in terms of absolute dose (mg), the obese subject requires 46% more and the subject with low cardiac output requires 35% less than the average human. When the thiopental dose is adjusted per kg of body mass, these two subjects require approximately 50% less than the average human. Adjusting the dose per kg of lean body mass corrects for patients of different weight, age, and gender. However, subjects with low cardiac output would require 35% less and those with high cardiac output 30% more. A dose adjusted to cardiac output is relatively consistent for all patients, except the subject with low cardiac output would require 30% more. The range in dose ratio is least when the dose is adjusted to cardiac output.

**Discussion**

A physiological pharmacokinetic model for thiopental has been scaled from rats to humans and validated with arterial concentrations after an intravenous bolus or short infusion. For a dose of 250 mg in 1 min, the model predicts greater peak arterial plasma concentrations in subjects who have a lesser cardiac output, a lesser degree of obesity, or who are female versus male or elderly versus young. The simulations confirm that cardiac output is an important physiological variable governing the peak and ensuing decrease in thiopental concentrations.

**Human Pharmacokinetic Model**

Physiological pharmacokinetic models in humans consist of organ models, in which the model parameters are scaled from other species or measured directly in humans. Our basic organ model (Fig. 1B) requires values for blood flow, vascular volume, apparent parenchymal volume, and distribution clearance. Organ blood flows and vascular volumes are measurable in humans, although vascular volumes are similar in humans and
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Table 5. Thiopental Dose Ratios* Following a 1-min Infusion in Different Patient Types: Effect of Adjusting Dose to Body Mass, Lean Body Mass, or Cardiac Output

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Absolute Dose (mg)</th>
<th>Body Mass (mg · kg⁻¹)</th>
<th>Lean Body Mass (mg · kg⁻¹)</th>
<th>Cardiac Output (mg · L⁻¹ · min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard human†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lean (-15%)</td>
<td>0.94</td>
<td>1.13</td>
<td>1.00</td>
<td>1.01</td>
</tr>
<tr>
<td>Overweight (50%)</td>
<td>1.23</td>
<td>0.82</td>
<td>1.04</td>
<td>1.03</td>
</tr>
<tr>
<td>Obese (100%)</td>
<td>1.46</td>
<td>0.72</td>
<td>1.06</td>
<td>1.04</td>
</tr>
<tr>
<td>Cardiac state</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (-50%)</td>
<td>0.65</td>
<td>0.65</td>
<td>0.65</td>
<td>1.30</td>
</tr>
<tr>
<td>High (+50%)</td>
<td>1.30</td>
<td>1.30</td>
<td>1.30</td>
<td>0.87</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.12</td>
<td>1.02</td>
<td>0.96</td>
<td>1.03</td>
</tr>
<tr>
<td>Female</td>
<td>0.90</td>
<td>1.00</td>
<td>1.09</td>
<td>0.98</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly (70-yr)</td>
<td>0.89</td>
<td>0.89</td>
<td>0.98</td>
<td>1.12</td>
</tr>
<tr>
<td>Geriatric (90-yr)</td>
<td>0.81</td>
<td>0.80</td>
<td>0.94</td>
<td>1.20</td>
</tr>
<tr>
<td>Range</td>
<td>0.65-1.45</td>
<td>0.65-1.30</td>
<td>0.65-1.30</td>
<td>0.87-1.30</td>
</tr>
</tbody>
</table>

* For a given patient type, the dose ratio is the adjustment required to achieve the peak plasma concentration attained in the standard human.
† A 35-yr, 67-kg human with cardiac output 6.3 L · min⁻¹.

rats. We assume that apparent parenchymal volume and distribution clearance, scaled to organ mass, are equal in rats and humans. Apparent parenchymal volume reflects tissue binding, and distribution clearance describes drug flux across endothelial barriers. Physical processes, such as tissue binding, often vary predictably with size across mammals, whereas metabolic processes often do not.³⁷

Alternative organ models assume instantaneous equilibration of drug between tissue vascular volume and parenchyma. Organs have been modeled as the parallel connection of a distributive unit and a physiologic shunt unit.³⁸ The anatomic variation in ventilation - perfusion ratio in the lung exemplifies this model. However, the fractional flow and blood volume of each unit is difficult to measure in humans. The axial dispersion organ model describes axial spreading of drug in blood during passage through a capillary.³⁹ Axial dispersion is a physical process that should scale across species, but this model is more difficult to implement.

For the standard human, the model predicts distribution volumes (1.8 L/kg in men to 2.6 L/kg in women) and terminal half-lives (9 h in men to 11 h in women), which lie in the range of literature values.¹⁰,¹⁶,¹⁰,⁴¹ The pharmacokinetic model also predicts that 76% of thiopental distributes to tissues on a single pass through systemic capillaries; 24% does not exit the blood. This substantiates a previous work that reported 58% single pass distribution of thiopental in dogs.‡‡ Other physiologic pharmacokinetic models for intravenous anesthetics generally assume that blood flow is the only limitation to tissue uptake.²,³,⁶,⁷,⁴² Intratissue limitations to drug uptake probably become detectable with sufficiently rapid tissue sampling.

**Model Validation**

The comparison of the pharmacokinetic simulations with the measured data (fig. 3) provides confidence to perform further simulations. With the exception of elimination clearance and lung distribution clearance, all organ pharmacokinetics are based on rat data, and all physiologic variables are based on literature values. Pharmacokinetics, when examined in detail, probably scales accurately across species because of a common physicochemical basis.

Minor systematic prediction errors exist. Measurements are 16% greater than model predictions in the first 15 min, and 14% less between 6-24 h. The early prediction error may be caused by inaccurate estimates of blood flows, whereas the later differences may be related to incorrect specification of the mass or partition of adipose tissue. Model predictions at 1 min dis-
play the most bias. In the bolus group, three subjects of aged 76–78 yr had prediction errors exceeding 190% at 1 min. Excluding these subjects, the error decreased from 53% to 9%. These three subjects may have had an unexpected age-related decrease in cardiac output, which contributed to the increased prediction errors. In the infusion group, many measurements were less than the prediction at 1 min. The rat data display a similar pattern, which could be caused by injection delays in the syringe (e.g., improper placement in the pump), the catheter (e.g., capacitance), or the body (e.g., vascular transit delays).

Subject-specific information, i.e., clearance, gender or age, did not substantially affect the predictive capability of the model. We did not incorporate subject weight because our obesity model is derived from subjects who were approximately 20–150% overweight, where the ideal weight is corrected for height, frame size, age, or gender.12–26 The obesity model is not valid for all humans. But the median absolute prediction error of 19% is comparable with the predictive capabilities of classical pharmacokinetic models.22 The error may be associated with variables, e.g., cardiac output, which could not be determined from the available data.

**Tissue Disposition**

The tissue disposition simulations (fig. 4) confirm previous predictions regarding the time course of thiopental distribution into visceral, muscle, and fat tissues,23 and the limited role of metabolism in the early decrease in arterial concentrations.3–4 In addition, our simulations agree with a clinical study in eight patients; this study demonstrated a marked difference between arterial and central venous plasma concentrations of thiopental for the first 2 min after a peripheral intravenous bolus injection, but minor differences thereafter.15 Our simulations yielded two new results. First, the liver is an important organ of uptake during the acute decrease from peak arterial concentrations between 1–2 min in figure 4A. Altered liver uptake may influence the termination of thiopental’s effect. Second, single-pass distribution extraction quantitates the initial extent of distribution. If 76% of the thiopental in arterial blood is distributed to systemic tissues on a single pass, then initial venous concentrations will be approximately 24% of arterial concentrations, which corresponds to the 23% ratio illustrated in figure 4C at the end of the infusion. Increased distribution extraction will enhance tissue distribution, and therefore is relevant to peak arterial concentrations and termination of effect.

**Cardiac Output**

We varied organ blood flows in proportion to changes in cardiac output to span the range of blood flows, which are observed in resting humans. No attempt was made to produce flows from representative patient types, e.g., the “hemorrhaged” patient, because comprehensive data are not available. Figure 5A shows predicted changes of ±30% in peak thiopental concentrations for a ±50% change in cardiac output, which is in accord with a previous work.2 This work predicted a change of ±50% in central nervous system uptake in the “hemorrhagic” or the “apprehensive” patient.2

Thiopental can decrease cardiac output in humans by 20%,42 however this change affects peak concentrations to a lesser extent than basal variations in cardiac output (fig. 5A). The main reason is that the cardiac output decreases gradually from baseline over the duration of the infusion. The full decrease of 20% is not effective until the infusion is complete.

Dilution is the process by which increased cardiac output decreases peak arterial concentrations. Thiopental is diluted in the volume of blood entering the pulmonary artery during the infusion period; this blood volume is directly proportional to cardiac output. Previous work in sheep demonstrated that peak pulmonary artery concentrations of indocyanine green after inferior vena cava injection were inversely proportional to cardiac output, but directly proportional to injection rate.42 After a bolus, cardiac output removes thiopental from the lung. Therefore, increased cardiac output decreases the amount of thiopental in lung tissue. Because arterial sampling sites are directly downstream from the lung, increased cardiac output accelerates the acute decrease from peak blood concentrations. Other studies reported a decreased distribution clearance of thiopental when cardiac output and blood pressure were decreased as an effect of treatment with dexmedetomidine,46 and a decreased distribution clearance in elderly versus young adults.47–51 In this context, distribution clearance is the clearance between two compartments of a classical compartmental pharmacokinetic model. Presumably the age-related results could be explained in part by decreased cardiac output with increasing age.

**Obesity**

Obesity is characterized by a disproportionate increase in adipose mass relative to lean body mass. Peripheral blood flows increase to supply the extra tissue; specific blood flows remain unchanged, and therefore cardiac output increases. The increased cardiac output
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decreases peak concentrations. Increased body fat acts as a depot that retains thiopental in the body. Obesity can be expected to increase terminal half-life and steady-state volume of distribution.

Our model predicts an increase in distribution volume from 1.6 to 3.3 l/kg in lean versus obese humans. Volume of distribution was reported to increase from 1.40 ± 0.46 to 4.72 ± 2.73 l/kg in lean versus obese young patients. The discrepancy may be due to an underestimate of the fat partition coefficient in our pharmacokinetic model. Our model uses a fat-plasma ratio of 6.0, whereas an omental fat-plasma ratio of 8.5 was found in humans after bolus administration of thiopental.

When using the greater fat partition in our model, the volume of distribution became 2.0 and 4.8 l/kg in lean versus obese humans. Measurements of thiopental concentrations in adipose from different body regions would be necessary to determine the average fat partition coefficient in humans.

Gender and Age

Gender and age are two patient stratifications in which pharmacokinetic differences may possibly be explained by differences in body composition and blood flows. Physiologically, aging entails a decrease in cardiac output, a lowered proportion of lean tissue in the body, and decreased blood flows to visceral and lean tissues. Together, these changes impair distribution of thiopental during and immediately after the infusion. The changes also have been described as causing prolonged intravascular mixing of thiopental in the elderly. In a standard pharmacokinetic model of thiopental disposition, this corresponds to a decreased clearance from the central to the shallow peripheral compartment.

Previous pharmacokinetic studies report an increased volume of distribution in women versus men, which is consistent with our model predictions. However, this study measured peripheral venous concentrations after repeated doses, so quantitative comparisons are not possible. Pharmacokinetic studies in the elderly indicate an increase in the volume of distribution at steady state. Distribution volume increased 60% in elderly (72 yr, 88 kg) versus young (31 yr, 95 kg) male patients. In nonobese female subjects, ranging in weight from 44-82 kg, a plot of volume of distribution versus age was reported. Visual examination of the plot indicates that distribution volume increased by approximately 100% in the elderly (70 yr) versus the young (35 yr). Our physiologic model predicts a 20% increase in distribution volume in the elderly versus young humans. This change may be less than demonstrated in the literature because of heterogenous thiopental partitioning in fat, differing degrees of obesity, or because the data used to derive the age-related changes in blood flows and tissue masses in our model were measured primarily in men.

Published studies suggest no effect of age on clearance. Our physiologic model predicts a 15% decrease in clearance in elderly humans compared with young humans. A decrease with age may be obscured by the 20-30% interindividual variability in clearance.

Dosing Implications

Assuming no pharmacodynamic differences, the dose ratios based on pharmacokinetic considerations (table 5) generally agree with findings in humans. Heavier people require more thiopental on a mg-per-kg basis, appear more sensitive when dose is adjusted proportionally to body weight, and should probably receive a dose proportional to lean body mass. Women and men require the same dose on a mg-per-kg basis. With increasing age, model predictions concur with investigations where thiopental was administered as a continuous infusion over 1-3 min until a held syringe was dropped, or as multiple boluses over 1-2 min to obtain eyelash reflex. However, the predictions do not explain the twofold reduction in dose required to reach an isoelectric electroencephalogram (EEG) between the ages of 20 and 80 yr. Because age did not affect thiopental's potency to attenuate the EEG, the dose reduction was attributed to pharmacokinetic differences. EEG studies typically require greater doses (5-10 mg/kg) and longer infusions (5-8 min). Age-related effects on dose requirement may be amplified during EEG studies because thiopental's effect on cardiac output in elderly patients could be greater with longer infusions and greater doses.

As previously suggested, patients may benefit by adjustment of the dose for cardiac output, especially when cardiovascular changes are incommensurate with body composition. Table 5 suggests that this approach will suffice for all subjects except for the subject with low cardiac output, who will require 30% additional thiopental.

Assumptions and Limitations

Our pharmacokinetic model has several limitations. First, the experimental rat model did not allow concentration measurements before the recirculation time of
blood (approximately 10 s in rats). Pulmonary uptake in humans and consequently arterial concentrations in the first 30 s in humans cannot be predicted from data measured solely in rats. Rapid sampling studies should be performed in larger species. Second, model predictions are sensitive to estimates of great vessel blood volumes. These are difficult to measure directly, and usually rely on a mass balance of total blood volume with blood accounted for in separate organs, or a calculation based on measured blood vessel geometry.

Our model will not necessarily predict the hypnotic effect of thiopental. Arterial blood–effect rate constants have been determined to predict an EEG measure or the time to achieve a hypnotic endpoint after a short infusion. However, the rate constants have not been validated with effect data from a bolus injection. It is tempting to use total brain concentrations to predict pharmacologic response, but these may not reflect concentrations at the neuronal sites of hypnotic effect.

Despite these limitations, physiologic models provide quantitative insight into factors that govern pharmacokinetics. In particular, physiologic models can explain the relationships of arterial concentrations to cardiac output, blood flows, pulmonary uptake, and blood volumes. This is not possible with classical compartmental models.

In summary, we have scaled a pharmacokinetic model from rats to humans, validated the model with published data, and used the model to predict arterial concentrations for alterations in blood flows and body composition. Model predictions agree quantitatively with published human data. The arterial concentration curve of thiopental during the time period relevant to anesthetic induction is produced by complex interplay between injection speed, cardiac output, lung uptake, and single-pass uptake in systemic tissues. Cardiac output is an important determinant of peak arterial concentrations and the ensuing decrease after a 1-min intravenous infusion. The thiopental model provides a scientific basis for mammalian pharmacokinetics and provides knowledge to support and guide the clinical usage of this drug.

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