A Minimal Physiological Model of Thiopental Distribution Kinetics Based on a Multiple Indicator Approach

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ABSTRACT:

Currently available models of thiopental disposition kinetics using only plasma concentration-time data neglect the influence of intratissue diffusion and provide no direct information on tissue partitioning in individual subjects. Our approach was based on a lumped-organ recirculatory model that has recently been applied to unbound compounds. The goal was to find the simplest model that accounts for the heterogeneity in tissue partition coefficients and accurately describes initial distribution kinetics of thiopental in dogs. To ensure identifiability of the underlying axially distributed capillary-tissue exchange model, simultaneously measured disposition data of the vascular indicator, indocyanine green, and the marker of whole body water, antipyrine, were analyzed together with those of thiopental. A model obtained by grouping the systemic organs in two subsystems containing fat and nonfat tissues, successfully described all data and allowed an accurate estimation of model parameters. The estimated tissue partition coefficients were in accordance with those measured in rats. Because of the effect of tissue binding, the diffusional equilibration time characterizing intratissue distribution of thiopental is longer than that of antipyrine. The approach could potentially be used in clinical pharmacokinetics and could increase our understanding of the effect of obesity on the disposition kinetics of lipid-soluble drugs.

It has long been a goal to understand the determinants of the distribution kinetics of intravenous anesthetics, such as thiopental, and to relate them to the duration of narcosis (Brodie et al., 1952; Shideman et al., 1953; Price, 1960). Now it is well recognized that modeling of drug distribution kinetics within the first 2 min (front-end kinetics) is of special importance (Krejcie and Avram, 1999; Avram and Krejcie, 2003). Recirculatory models with a chain of compartmental subsystems that adequately characterize pulmonary first-pass distribution and initial mixing have been successfully applied to thiopental kinetics (Avram et al., 2002). These models can explain the effect of changes in cardiac output but do not account for the role of tissue partitioning and intratissue diffusion as determinants of systemic distribution kinetics of thiopental. Physiologically based models, in contrast, are very useful in explaining the effect of various physiological and anatomical factors on thiopental disposition using model simulation (Wada et al., 1997). However, they are far too complex to be fitted to plasma concentration-time data. To better understand the physiological determinants of thiopental kinetics in a clinical setting we need a model that is able to describe both front-end and disposition kinetics with parameters that can be estimated on the basis of plasma concentration-time data. Accordingly, we have recently developed a minimal physiological circulation model using a multiple indicator approach in which the lumped organs of the systemic circulation were described by an axially distributed capillary-tissue exchange model that accounts for intratissue concentration gradients (Weiss et al., 2007). However, until now this model has only been applied to inulin and antipyrine, compounds that do not bind to tissue constituents (Weiss et al., 2006, 2007). The aim of this article is to test the suitability of this model for the evaluation of thiopental disposition kinetics in dogs and to explain the difference between distribution kinetics of thiopental and antipyrine. We expect that tissue binding of thiopental leads to a slowing down of intratissue diffusion (Weiss, 1999b). Another interesting question is whether the heterogeneity in partitioning of the lipophilic compound thiopental in tissues will be consistent with the lumping of systemic organs into one subsystem.

Materials and Methods

Experimental Design of Multiple Indicator Experiments. The blood concentrations of the physiologic markers and drug used in the present analyses were taken from a study of the dispositions of markers of intravascular space [indocyanine green (ICG), total body water (antipyrine), and thiopental] in five halothane-anesthetized male dogs, weighing 32 to 42.3 kg (36.7 ± 4.6 kg) (Avram et al., 2002), that had been approved by the institutional Animal Care and Use Committee. The preparation and conduct of the studies have been described in detail previously (Krejcie et al., 1999; Avram et al., 2002).

Briefly stated, at time $t = 0$ min, 5 mg of ICG, 25 mg of antipyrine, and 100 mg of thiopental were flushed into the right atrium within 4 s. Arterial blood samples were collected every 0.05 min for the 1st min and every 0.1 min for the next minute. Subsequently, 30 arterial blood samples were drawn manually to 600 min.

Plasma ICG concentrations were measured by high-performance liquid chromatography (Henthorn et al., 1992) as were plasma antipyrine concentrations (Krejcie et al., 1996a) and plasma thiopental concentrations (Avram and Krejcie, 1987). Plasma ICG concentrations were converted to blood concent-
trations by multiplying them by \(1 - \text{hematocrit}\). Plasma antipyrine and thiopental concentrations were converted to blood concentrations using an in vivo technique that corrects for partitioning into erythrocytes (Krejcie et al., 1996a,b).

**Model.**

**Model 1.** The minimal physiological circulation model has been described in detail previously (Weiss et al., 2007). Based on circulatory transport (Weiss et al., 1996; Weiss, 1999a) and tissue diffusion of drugs (Weiss and Roberts, 1996), it consists of two subsystems, the pulmonary and the systemic circulation, which are characterized by transit time density (TTD) functions (Fig. 1). The lumped organ model of the systemic circulation that accounts for flow heterogeneity and the noninstantaneous mixing/distribution in the blood and tissue phases are characterized by the TTD \(f_s(s)\) (in the Laplace domain), whereas an empirical model (inverse Gaussian density) is used for the pulmonary circulation \(f_p(s)\). Both TTDs determine the arterial concentration-time curve after rapid bolus injection (dose \(D_{iv}\)) of the drug

\[
\hat{C}(s) = \frac{D_{iv}}{Q} \frac{\hat{f}_p(s)}{1 - (1 - E)\hat{f}_p(s)\hat{f}_s(s)}
\]

where \(Q\) is cardiac output and \(E\) the extraction ratio of drug in the systemic circulation that determines the total body clearance \(CL = QE\). Assuming that diffusion through the extravascular space is the rate-limiting distribution process, \(\hat{f}_p(s)\) is given by (Weiss and Roberts, 1996; Weiss et al., 2007)
where $\tilde{f}_{ha}(s)$ denotes the Laplace transform of the TTD of vascular marker ICG, $v = V_d/V_o$ represents the tissue steady-state distribution volume ($V_d$) as a fraction of the vascular volume ($V_o$) and $d = L/2D_{ha}$ is the characteristic time constant of the radial intratissue diffusion process that is determined by the effective tissue diffusion coefficient ($D_{ha}$) and the characteristic diffusion path length ($L$). To apply the diffusion approach (eq. 2) to thiopental, it is assumed that binding to tissue constituents occurs very rapidly compared with the diffusion time scale. This slows down the diffusion process, i.e., decreases $D_{ha}$.

The Laplace transform of the density function of the inverse Gaussian distribution that is used as the empirical TTD function for the vascular marker across the systemic or pulmonary circulation denoted by $\text{FTD}_R$ (Crank, 1975; Weiss, 1999b). The tissue distribution volume of thiopental can be expressed in terms of its blood/tissue partition coefficient $K_p$ and the tissue volume, i.e., the distribution volume of the unbound solute antipyrine $V_{T,AP}$.

$$V_T = K_pV_{T,AP}$$

(3)

The Laplace transform of the density function of the inverse Gaussian distribution is flow-limited; i.e., $CL_{M}$ increases in proportion to cardiac output, $Q$

$$CL_{M} = \frac{2Q}{RD_{P}^2 - 1}$$

(9)

### Parameter Estimation

The simultaneous administration of ICG, antipyrine, and thiopental (multiple indicator approach) allows the estimation of model parameters from indicator disposition data, which are subsequently fixed in fitting the thiopental data. These are for ICG the parameters $Q$, $V_o$, $RD_{P}^2$, $V_{T,AP}$, and $RD_{T}^2$, which describe the intravascular mixing process (estimated by fitting eqs. 1 and 4 to the ICG data). From the parameters estimated by fitting eqs. 1, 2, and 4 (with parameters $V_o$ and $RD_{T}^2$) to the antipyrine data, only $V_{T,AP}$ (tissue water volume) is used in the thiopental model. Thus, for model 1, five parameters $V_o$, $RD_{T}^2$, $K_p$, $d$, and $E$ remain to be estimated by fitting eqs. 1, 2, 3, and 4 to the thiopental data. Note that $V_o$ and $RD_{T}^2$ account for the distribution kinetics in the pulmonary circulation: $K_p$ for tissue binding, $d$ for the diffusional tissue distribution, and $E$ for the systemic extraction of thiopental. In the case of model 2, we have six adjustable parameters: $V_o$, $RD_{P}^2$, $K_{p,NF}$, $K_{p,ENF}$, $d_{NF}$, and $E$. For the fraction of blood flow to FT, a value $d_p = 0.15$ was used (Eibling et al., 1994; Brown et al., 1997).

Because the model equation (eq. 1) is only available in the Laplace domain, a numerical inverse Laplace transformation has to be performed to obtain the concentration-time curve in the time domain. $C(t) = L^{-1}\tilde{C}(s)$. We implemented Talbot’s algorithm into ADAPT II (D’Argenio and Schumitzky, 1997) and tested the accuracy and precision of parameter estimation using this method of numerical inverse Laplace transformation (Schalla and Weiss, 1999). Furthermore, using SCIENTIST (Micromath, Salt Lake City, UT) we made sure that other numerical Laplace inversion routines led to the same result. All parameters were estimated using maximum likelihood analysis with the variance model.

$$VAR = \left[\sigma_\text{a} + \sigma(C(t)_{i})\right]^2$$

(10)

where $VAR$ is the variance of the $i$th data point and $C(t)_{i}$ is the model prediction. “Goodness of fit” was assessed using the Akaike information criterion (AIC) and a visual examination of the distribution of residuals. The quality of parameter estimates was evaluated by their coefficients of variation (CVs). As criteria for evaluating the numerical identifiability of estimates, we used $CV < 0.5$ and a correlation coefficient threshold of 0.8.

Sensitivity analysis provides useful information for parameter estimations as a model parameter $p$ may be most accurately gained at time points with a high sensitivity of $C(t)_{i}$ to the parameter $p$. The sensitivity function

$$S_p(t) = \frac{\partial C(t)_{i}}{C(t)_{i}}\frac{\partial C(t)_{i}}{\partial p}$$

(11)

determines the relative change in $C(t)$ caused by a small relative change in the model parameter $p$. Because $Sp$ is nondimensional, it allows a comparison of results obtained for different parameters. Thus, $S_p(t)$ represents the relative importance of parameter $p$ to model output. The sensitivity functions (eq. 8 substituting eq. 1) were calculated using MAPLE 8 after implementing a numerical method of inverse Laplace transformation (Schalla and Weiss, 1999).

### Results

As shown previously in other dogs, the disposition kinetics of ICG (Weiss et al., 2006) and antipyrine (Weiss et al., 2007) were well described by the model (Fig. 2). To demonstrate the goodness of fit, dogs with an AIC value that was closest to the group median value was selected in all graphs (“representative fits”). The parameter estimates that were subsequently used as fixed parameters in fitting the thiopental data are listed in Table 1. These and all other parameters of ICG and antipyrine kinetics are not significantly different from those estimated in a previous study (Weiss et al., 2007). Representative fits of models 1 and 2, respectively, to the thiopental data are shown in Fig. 3, A and B. Model 1 holds with the exception of dog 4, for which it fails to fit the disposition curve (Fig. 4A). Model 2 significantly improved the fits to the data for four of the five dogs, as judged by their lower AIC values (Table 2). Most importantly, it also fitted the...
Account for the heterogeneity in partitioning of thiopental into non-fat tissue. The corresponding parameters of model 2 that restricts the first minutes after injection as shown for dog 4 (Figs. 3B and 4B). Third, model identification is achieved by the multiple indicator dilution methodology using ICG as marker of vascular mixing and antipyrine to determine the tissue water volume.

**Model 1.** As previously shown for antipyrine (Weiss et al., 2007), diffusional resistance in tissue determines whole body distribution kinetics and, as suggested by theory (Crank, 1975; Weiss, 1999b), tissue binding of thiopental slowed down this diffusional transport. Thus, the observed 2.5-fold increase in the relaxation time of the diffusional equilibration process, compared with that of the unbound drug antipyrine, can be explained by a decrease in the apparent tissue diffusion coefficient because $D_{ct}/D_{ct,AP} = d_{AP}/d$ is obtained from $d = L^2/D_{ct}$. Because organs of the systemic circulation were lumped into a single subsystem, the estimated values for $d$ and the tissue partition coefficient $K_p$ represent measures averaged over all organs excluding the lung. If one calculates the organ mass-weighted average of thiopental tissue partition coefficients measured in 11 organs of the systemic circulation in rat (Ebling et al., 1994), one obtains a value of $K_p = 1.35$ that is well in accordance with our estimate of $1.49 \pm 0.19$. Note that a comparison of tissue partition coefficients between rat and dog appears justified because the successful scaling up of thiopental pharmacokinetics from rat to human (Wada et al., 1997) suggests that tissue partition coefficients show little variation among species. The estimates of the model-independent parameters CL and $V_{ss}$ are not statistically significant different from those estimated previously with a different circulatory model (Avram et al., 2002).

**Model 2.** Although the lower AIC indicates a better fit for all data sets, the most striking advantage of model 2 is that it also describes the terminal phase in dog 4. It is not surprising that, in contrast to antipyrine, a neglect of partition coefficient heterogeneity in model 1 is only a crude approximation for thiopental. Interestingly, lumping the systemic organs into two subsystems, NFT and FT, with different partition coefficients, $K_{p,NF}$ and $K_{p,FT}$ respectively, where the tissue system FT is assumed to represent 15% of body mass with fractional blood flow $q_F = 0.15$, is a suitable extension that solves this limitation. The estimates of $K_{p,NF}$ and $K_{p,FT}$ (10.4 and 0.89) are again in reasonable agreement with thiopental organ partition coefficients measured in rats (Ebling et al., 1994). Thus, we obtain a weighted average of partition coefficients of 7.4 in the tissue group with high $K_p$ (fat, kidney) and an average partition coefficient of 0.72 for the rest of the body (nine organs). Also our assumption of the fractional blood flow to FT is in accordance with that of $q_F = 0.17$ in rats (Ebling et al., 1994). Furthermore, a fractional blood flow to fat of 9.7% has been reported for the dog (Brown et al., 1997), a value of 11% has been estimated for perfusion of the slowly equilibrating compartment (Avram et al., 2002), and a value of 25% has been assumed for the tissue pool with the higher distribution volume in a circulatory compartment model of thiopental kinetics in sheep (Upton and Ludbrook, 1999). The diffusional equilibration time in nonfat tissues, $d_{NF} = 11.7$ min, is shorter than that in fat, $d_F = 131.4$ min. The latter has been calculated by means of eq. 6, which follows from the fact that the effective diffusivity is inversely proportional to the tissue partition coefficient (Weiss, 1999b).

Our model simulation (Fig. 7) showed that the maximum amount of thiopental in FT (38% of dose) appeared with a delay of approximately 2 h relative to that in plasma and exceeded that in the rest of the body. This is in accordance with the observations in rats (Shideman et al., 1953) and dogs (Brodie et al., 1952).

Although we have no clear-cut explanation for the extremely high $K_{p,F}$ value of 17 corresponding to the long terminal half-life in dog 4, in partition coefficients significantly improves the fit obtained with model 1 and also describes the extremely long terminal half-life in dog 4 (Figs. 3B and 4B).
the possibility that this dog has a higher portion of fat tissue cannot be excluded and this may have led to an overestimation of $K_{p,F}$, because blood flow per unit weight of fat tissue is reduced in obesity (Coppack, 2005). This result means that a value of approximately 8 would have been obtained if the mass of fat tissue would have been doubled. After omission of dog 4, the mean of $K_{p,F}$ (8.8 $\pm$ 1.9) is nearer to the literature value mentioned above (7.4), and the variance is reduced. The mean $V_{ss}$ value of 61.0 $\pm$ 6.4 l is then in better agreement with that obtained with model 1 (47.2 $\pm$ 3.5 l); however, only the $V_{ss}$ estimated with model 2 is correct because model 1 did not cover the terminal phase for dog 4. This finding is also obvious from Fig. 6. Our result is in accordance with the lumping procedure used to predict the $V_{ss}$ of drugs (Björkman, 2002).

The effect of obesity on plasma concentration has been simulated in Fig. 8 for a dog with a 5-fold higher FT (i.e., 60% overweight), assuming that cardiac output increases proportional to body weight and $q_L$ doubles. Obviously, due to the high capacity for thiopental uptake into fat, the slower terminal decay of plasma concentration is determined by the release of thiopental from FT. Note the similarity to thiopental disposition curves in obese patients (Jung et al., 1982). In contrast, the simulation showed only a minor effect on initial distribution, with a concentration peak that appeared approximately 10 s earlier.

If we calculate the distribution clearance of thiopental and anti-

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**TABLE 1**

Parameter estimates of ICG and antipyrine

<table>
<thead>
<tr>
<th>Dog</th>
<th>ICG</th>
<th>Antipyrine</th>
</tr>
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<tr>
<td>-----</td>
<td>-----</td>
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</tr>
<tr>
<td></td>
<td>l/min</td>
<td>liters</td>
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<tr>
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**FIG. 3.** Representative fits of model 1 (A) and model 2 (B) to arterial thiopental data (dog 5). The inset shows the early concentrations.

**FIG. 4.** The superiority of model 2 (B) is obvious for dog 4 for which model 1 (A) fails to fit the disposition curve.
pyrine (eqs. 6 and 7) as a function of cardiac output, it becomes obvious that the flow-limited approach holds (since $RD_{s}^{2}/H_{11015}$ and $E$ and the slope is given by $2/(RD_{s}^{2}/H_{11002})$. This supports the notion that the whole body distribution of thiopental is flow-limited, as previously discussed for antipyrine (Weiss et al., 2007). Note that flow-limited distribution does not imply instantaneous tissue equilibration. As pointed out above, this process occurs with an equilibration time of 19 min (model 1) or 12 min in NFT and 131 min in FT of model 2, compared with a time constant of 8 min for antipyrine. If we define an apparent permeability-surface product that is determined by tissue diffusion according to $PS_{\text{diff}} = V_{p}/d$ (Weiss et al., 2007), flow limitation essentially means $PS_{\text{diff}} >> Q$ (eq. 8). The similarity of the initial distribution kinetics of the two drugs (Avram et al., 2002), on the other hand, is due to nearly identical parameters of the pulmonary subsystem (Tables 1 and 2).

Our goal here was to develop a minimal physiologic model of thiopental kinetics, i.e., a conceptual model in which physical processes are described from first principles and thus captures the essence of distribution behavior in a more realistic way. The multiple indicator approach made it possible for the model parameters to be estimated from plasma concentration-time data. The most important findings are the following. First, it could be shown that a slower diffusion in tissue

![TABLE 2](https://example.com/table2.png)

<table>
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<th>$RD_{p}^{2}$</th>
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<th>$K_{p}$</th>
<th>$E$</th>
<th>$CL_{a}$</th>
<th>$V_{ss}^{b}$</th>
<th>$dd_{SF}$</th>
<th>AIC</th>
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<th>$K_{p,F}^{c}$</th>
<th>$E_{NF}$</th>
<th>$CL_{d}$</th>
<th>$V_{ss}^{e}$</th>
<th>$dd_{SF}/d_{SF}$</th>
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*a CL = $E \times Q$.

*b $V_{ss} = V_{p} + V_{AX} + K_{p} \times V_{T,\text{AP}}$.

c $d_{NF}$: eq. 6.

d CL = $E_{NF} \times 0.15 \times Q$.

e $V_{ss} = V_{p} + V_{AX} + (K_{NF} \times 0.85 + K_{F} \times 0.15) \times V_{T,\text{AP}}$.

**FIG. 5** Normalized sensitivity of the thiopental disposition curve $C(t)$ with respect to diffusional equilibration time in nonfat tissues ($d_{NF}$), partition coefficients in nonfat ($K_{p,\text{NF}}$) and fat ($K_{p,F}$) tissues, and the volume of distribution of the pulmonary circulation ($V_{p}$) (inset).
can account for the difference in distribution kinetics between thio-
pental and antipyrine. Second, for the thiopternal model the heteroge-
nenity of organ partition coefficients has to be considered by treating
fat tissue as a separate subsystem. The results suggest that it may be
possible to estimate organ-averaged tissue partition coefficients and
equilibration times of tissue diffusion for thiopternal without taking
tissue samples, which makes the approach suitable for clinical studies.
This would imply, however, a multiple indicator approach including
frequent early arterial blood sampling, similar to the study by Avram

Regarding a comparison with other recirculatory models, it is not
surprising that we get different answers depending on how we reduce
the complexity of the system. Instead of assuming different compart-
mental organ models for different drugs (e.g., flow-limited versus
membrane-limited), the present model provides a unified approach
that describes a continuous transition between the limiting cases of
whole body distribution kinetics, i.e., from diffusion-limited (\(PS_{\text{diff}} \ll Q\)) to flow-limited (\(PS_{\text{diff}} \gg Q\)) tissue distribution (Weiss et al.,
2006, 2007). However, the price to be paid for the assumption of
noninstantaneous distribution in the vascular and tissue space is the
use of a vascular indicator and the lumped organ approach, respec-
tively, i.e., the reduction of the systemic circulation to only one or two
subsystems.

In conclusion, analysis of simultaneously measured disposition
curves of ICG, antipyrine and thiopternal in dogs allowed the estima-
tion of physiologically meaningful kinetic parameters. The estimated
partition coefficients of thiopternal in adipose and nonadipose tissues
are in good agreement with those obtained by direct tissue sampling
in rats. Since the model is only based on plasma concentration data, it
could potentially be used in clinical pharmacokinetics.

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