The Concordance of Early Antipyrine and Thiopental Distribution Kinetics

MICHAEL J. AVRAM, TOM C. KREJCIE, and THOMAS K. HENTHORN
Department of Anesthesiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois
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ABSTRACT
Studies of factors affecting the initial disposition of drugs with a rapid onset of effect following i.v. administration have used antipyrine as a surrogate for lipophilic drugs because it lacks cardiovascular effects. The present study tested the assumption that antipyrine is a useful surrogate for the flow-dependent tissue distribution of the lipophilic drug thiopental by comparing the recirculatory pharmacokinetic models of antipyrine and thiopental disposition after concomitant administration to five dogs anesthetized with 1.5% halothane. The pharmacokinetics of indocyanine green, a marker of the intravascular behavior of antipyrine and thiopental, and antipyrine in these dogs was nearly identical to that described previously in dogs anesthetized with 1.5% halothane but not given thiopental. The total volume of distribution of the highly lipophilic drug thiopental was more than 60% larger than that of antipyrine, 53 versus 33 liters, respectively. Nonetheless, the initial distribution kinetics of the two drugs, including the pulmonary tissue volume and the volume of the nondistributive pathway, as well as the clearance to it, were nearly identical. As a result, the fraction of cardiac output involved in distribution of the two drugs to peripheral tissues was similarly identical, although the distribution of cardiac output between clearance to the rapidly equilibrating tissues and clearance to the slowly equilibrating tissues differed slightly. This study validates the assumption that antipyrine is a useful surrogate for lipophilic drugs in pharmacokinetic studies in which physiologic stability is desirable to meet the assumption of system stationarity.

Antipyrine, a marker of total body water (Soberman et al., 1949), including pulmonary extravascular water (Brigham et al., 1971), distributes to a volume as large as total body water in a blood flow-dependent manner in many tissues and is thus a prototype for many lipophilic drugs, including intravenous anesthetics (Renkin, 1952, 1955). Unlike intravenous anesthetics, antipyrine has no systemic cardiovascular effects to affect its own disposition and thus is a useful surrogate for lipophilic drugs in pharmacokinetic studies in which physiologic stability is desirable to meet the assumption of system stationarity (Riggs, 1963).

Factors affecting the early arterial drug concentration versus time profile influence the intensity and timing of the onset of drug effect for rapidly acting drugs, such as intravenous anesthetics (Krejcie and Avram, 1999). We have developed a recirculatory pharmacokinetic model of drug disposition using antipyrine as a surrogate for lipophilic drugs, such as thiopental, to enable studies of factors affecting the initial disposition of drugs with a rapid onset of effect (Krejcie et al., 1996a). This model has been used to study antipyrine disposition in canine studies of various paradigms of altered cardiac output and blood flow distribution, including different levels of halothane (Avram et al., 1997) and isoflurane (Avram et al., 2000) anesthesia, volume loading as well as mild and moderate hypovolemia in awake dogs (Krejcie et al., 1999), and infusions of isoproterenol, nitroprusside, and phenylephrine in awake dogs (Krejcie et al., 2001). These studies have demonstrated that not only cardiac output but also its peripheral distribution affects the early antipyrine concentration history after rapid intravenous administration. Changes in early antipyrine distribution are not proportional to changes in cardiac output because regional blood flow changes depend not only on the altered cardiac output.
but also on the physiologic circumstances leading to these changes in cardiac output. The purpose of the present study was to test the assumption that antipyrine is a useful surrogate for the flow-dependent tissue distribution of lipophilic drugs, such as thiopental, by comparing the dispositions of antipyrine and thiopental after concomitant administration.

**Materials and Methods**

**Experimental Protocol.** Five male dogs, weighing 32 to 42.3 kg (36.7 ± 4.6 kg; Table 1), were studied in this Institutional Animal Care and Use Committee-approved study. Approximately 1 month before being studied, a Vascular-Access-Port (Access Technologies, Skokie, IL) was implanted with its catheter tip positioned near the aortic bifurcation via a femoral artery of each dog to facilitate frequent percutaneous arterial blood sampling (Garner and Laks, 1985). Details of the preparation and conduct of the studies have been described in detail previously (Krejcie et al., 1999).

After an overnight fast during which water was allowed ad libitum, the dogs were brought to the laboratory. Anesthesia was induced with ketamine (5 mg/kg i.v.) via a foreleg vein, and the trachea was intubated with a 9-mm tracheal tube; the animals were placed in the left lateral decubitus position. Mechanical ventilation was instituted at a tidal volume of 20 to 25 ml/kg and at a rate sufficient to maintain end-tidal carbon dioxide tension at 30 ± 5 mm Hg. Anesthesia was maintained with 1.5% halothane in oxygen. End-tidal halothane concentrations were monitored with a Saracak A.G. (PPG Industries Inc., Lenexa, KS) after its calibration with known standards.

A sheath introducer was placed percutaneously into the right external jugular vein. A flow-directed thermal dilution pulmonary artery catheter was inserted through the sheath introducer for later use to determine thermal dilution cardiac output as well as to facilitate right atrial thiopental and physiological marker administration. The side arm of the sheath introducer was used for maintenance fluid administration and the readministration of autologous blood. Hydration was maintained throughout the study by an infusion of 0.9% saline at a rate of 5 to 10 ml/kg/h to maintain a constant pulmonary artery diastolic pressure (≤ 2 mm Hg).

Following anesthetic induction and catheter placement, 150 ml of whole blood was removed from the dog through the arterial catheter and anticoagulated with 1000 U of heparin. This blood was immediately replaced with 600 ml of 0.9% saline solution administered intravenously over 30 min. During the first 10 min of the study (from time \( t = 0 \) min to \( t = 10 \) min), this autologous blood was reinfused to replace the blood removed during this period of frequent blood sampling.

The study was not begun until the dog was hemodynamically stable. This was defined as less than a 10% variation of cardiac output time data prior to evidence of recirculation (i.e., first-pass data) were measured continuously, and cardiac output was determined at least every 15 min. The dogs were hemodynamically stable approximately 1 h after the start of the study.

At the onset of the study (time \( t = 0 \) min), ICG (Cardio-Green; BD Biosciences, San Jose, CA; 5 mg in 1 ml of ICG diluent), antipyrine (Sigma-Aldrich, St. Louis, MO; 25 mg in 1 ml of ICG diluent), and thiopental (Abbott Laboratories, Abbott Park, IL; 100 mg in 2 ml of diluent), were placed sequentially in a 76-cm length of i.v. tubing (4.25 ml of priming volume) and connected to the proximal injection port of the pulmonary artery catheter. At the onset of the study (time \( t = 0 \) min), the 4-ml drug volume was flushed into the right atrium within 4 sec using 10 ml of a 0.9% saline solution, allowing the simultaneous determination of dye and thermal dilution cardiac outputs.

**Analytical Methods.** Plasma ICG concentrations of all samples obtained up to 20 min were measured on the study day by the HPLC technique of Grasela et al. (1987), as modified in our laboratory (Henthorn et al., 1992). Plasma antipyrine concentrations were measured in all samples using a modification of an HPLC technique developed in our laboratory (Krejcie et al., 1994, 1996a). Plasma thiopental concentrations were measured within 24 h of sample collection using an HPLC technique developed in our laboratory (Avram and Krejcie, 1987).

To interpret intercompartmental clearances in relation to blood flow, the recirculatory models were constructed on the basis of whole blood marker concentrations. Plasma ICG concentrations were converted to blood concentrations by multiplying them by 1 minus the hematocrit, as ICG does not partition into erythrocytes. Plasma antipyrine and thiopental concentrations were converted to blood concentrations using an in vivo technique that corrects for antipyrine and thiopental partitioning into erythrocytes by calculating its apparent dose, assuming a red blood cell/plasma partition coefficient of 1; the product of cardiac outputs and area under the first-pass concentration versus time curve for both the plasma antipyrine concentration versus time curve and the plasma thiopental concentration versus time curve equals dose when their red blood cell/plasma partitioning is 1 (Krejcie et al., 1996a,b).

**Pharmacokinetic Model.** The pharmacokinetic modeling method (Fig. 1) has been described in detail previously (Krejcie et al., 1996a; Avram and Krejcie, 1997). It is based on the approach described by Jacquez (1996) for obtaining information from outflow concentration histories, the so-called inverse problem. Antipyrine and thiopental distributions were analyzed as the convolution of their intravascular behavior, determined by the pharmacokinetics of concomitantly administered ICG, and tissue distribution kinetics (Krejcie et al., 1996a).

Arterial ICG, antipyrine, and thiopental concentration versus time data prior to evidence of recirculation (i.e., first-pass data) were weighted uniformly and fit to the sum of two Erlang distribution functions using TableCurve2D (version 3.0; SPSS Science, Chicago, IL) on a Pentium-based personal computer (Dell, Austin, TX); two parallel, lumped pathways with different transit characteristics re-

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**TABLE 1**

Subject characteristics and weight-normalized global pharmacokinetic parameters (\( N = 5 \))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value ± S.D.</th>
<th>( V_{SS} )</th>
<th>( V_{inf} )</th>
<th>( CL_{H} )</th>
<th>( CL_{R} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>kg</td>
<td>36.7 ± 4.6</td>
<td>0.077</td>
<td>8.94</td>
<td>0.76</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>%</td>
<td>38.8 ± 3.3</td>
<td>1.16</td>
<td>0.014</td>
<td>0.06</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>l/min</td>
<td>(1.86)</td>
<td>(1.3)</td>
<td>(0.18)</td>
<td>(0.06)</td>
</tr>
</tbody>
</table>

\( ^{a} \) Determined by thermal dilution.

\( ^{b} \) Antipyrine and thiopental \( V_{SS} \) and \( CL_{R} \) are presented here on the basis of plasma rather than blood concentrations.
for rejection of the null hypothesis. Possible model misspecification was sought by visual inspection of the measured and predicted marker concentrations versus time relationships.

In general, peripheral drug distribution can be lumped into identifiable (i.e., mathematically distinct) volumes and clearances: nondistributive peripheral pathways ($V_{ND}$ and $CL_{ND}$); rapidly equilibrating (fast) tissues ($V_{T-F}$ and $CL_{T-F}$); and slowly equilibrating (slow) tissues ($V_{T-S}$ and $CL_{T-S}$). The rapidly equilibrating (fast) and slowly equilibrating (slow) nondistributive peripheral pathways ($V_{ND-F}$ and $CL_{ND-F}$, $V_{ND-S}$ and $CL_{ND-S}$) represent intravascular circuits in the ICG model; the single identifiable nondistributive peripheral pathway in the antipyrine and thiopental models ($V_{ND}$ and $CL_{ND}$), determined by the recirculation peak, represents blood flow that quickly returns the lipophilic marker to the central circulation after minimal apparent tissue distribution (Krejcie et al., 1996a; Avram et al., 1997). In the antipyrine and thiopental models, the parallel rapidly and slowly equilibrating tissues are the fast and slow compartments of traditional three-compartment pharmacokinetic models, respectively, whereas the central circulation and nondistributive peripheral pathway(s) are detailed representations of the ideal central volume of the traditional multicompartmental model (Krejcie et al., 1994). Because of the direct correspondence between the recirculatory model and compartmental models, $CL_E$ was modeled from the arterial (sampling) compartment to enable comparison of these results with previous ones.

For purposes of comparison, observed plasma antipyrine and thiopental concentration versus time relationships were first modeled independently. Thiopental was then modeled with the parameters describing the central circulation and nondistributive peripheral pathway fixed to those of antipyrine, with the parameters describing the central circulation and nondistributive peripheral pathway and $CL_{T-F}$ fixed to those of antipyrine, and with the parameters describing the central circulation and nondistributive peripheral pathway and $CL_{T-S}$ fixed to those of antipyrine. The appropriateness of the choice of model was evaluated using the Akaike information criterion and the Schwarz-Bayesian information criterion (Cobelli and Foster, 1998; Foster, 1998).

**Results**

The pharmacokinetics of ICG and antipyrine in these dogs (Tables 1 and 2) were nearly identical to those described previously in dogs anesthetized with 1.5% halothane but not given thiopental (Avram et al., 1997). Blood ICG, antipyrine, and thiopental concentration versus time relationships were well characterized by the models from the moment of injection (Figs. 2–4). The one-sample runs test confirmed that there were no systematic deviations of observed data from calculated values.

The total volume of distribution ($V_{SS}$) of thiopental was more than 60% larger than that of antipyrine, reflecting differences in the volumes of both the rapidly and the slowly equilibrating tissue compartments, $V_{T-F}$ and $V_{T-S}$, respectively. Nonetheless, the initial distribution kinetics of the two drugs, including the pulmonary tissue volume and the volume of the nondistributive circuit, $V_{ND}$, as well as the clearance to it, $CL_{ND}$, were nearly identical. As a result, the fraction of cardiac output involved in the distribution of the two drugs to peripheral tissues was similarly identical, although the partitioning of cardiac output between clearance to the rapidly equilibrating tissues, $CL_{T-F}$, and clearance to the slowly equilibrating tissues, $CL_{T-S}$, differed slightly.

To further test the assumption that antipyrine is a useful surrogate for the flow-dependent tissue distribution of lipophilic drugs, such as thiopental, recirculatory thiopental

![Fig. 1. The general model for the recirculatory pharmacokinetics of ICG, antipyrine, and thiopental (Krejcie et al., 1996a). Cardiac output (CO) flows through the central circulation, which is defined by the delay elements ($V_c$). All delay elements are represented generically by rectangles surrounding four compartments, although the number of compartments needed in a delay varied between 2 and 30. The pulmonary tissue volumes ($V_{T-p}$), subsets of $V_c$, are calculated for antipyrine and thiopental by subtracting the $V_c$ of ICG from those of antipyrine and thiopental. Beyond the central circulation, cardiac output distributes to numerous circulatory and tissue pathways which lump, on the basis of their blood volume to flow ratios or tissue volume to distribution clearance ratios ($M/T$), into fast ($CL_{ND-F}$, $V_{ND-F}$) and slow ($CL_{ND-S}$, $V_{ND-S}$) peripheral blood circuits (ICG) or the nondistributive peripheral pathway ($CL_{ND}$, $V_{ND}$) and the fast ($CL_{T-F}$, $V_{T-F}$) and slow ($CL_{T-S}$, $V_{T-S}$) tissue volume groups (antipyrine and thiopental). ICG, which distributes only within the intravascular space, does not have fast and slow tissue volumes. The nondistributive flow for ICG was resolved into fast and slow components; antipyrine and thiopental do not have identifiable (i.e., mathematically distinct) second nondistributive peripheral pathways. The elimination clearances ($CL_E$) are modeled from the arterial sampling site without being associated with any particular peripheral circuit.

<table>
<thead>
<tr>
<th>$V_{T-p}$</th>
<th>$CL_{ND-F}$</th>
<th>$V_{ND-F}$</th>
<th>$CL_{ND-S}$</th>
<th>$V_{ND-S}$</th>
<th>$CL_{T-F}$</th>
<th>$V_{T-F}$</th>
<th>$CL_{T-S}$</th>
<th>$V_{T-S}$</th>
<th>$CL_E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipyrine</td>
<td>0.12</td>
<td>0.08</td>
<td>0.20</td>
<td>0.15</td>
<td>0.10</td>
<td>0.14</td>
<td>0.08</td>
<td>0.20</td>
<td>0.12</td>
</tr>
<tr>
<td>Thiopental</td>
<td>0.15</td>
<td>0.10</td>
<td>0.25</td>
<td>0.18</td>
<td>0.12</td>
<td>0.16</td>
<td>0.10</td>
<td>0.25</td>
<td>0.15</td>
</tr>
</tbody>
</table>
pharmacokinetics was modeled with several of its parameters fixed to those of the antipyrine model (Table 3). When the parameters describing the central circulation and nondistributive peripheral pathway were fixed to those of antipyrine, the recirculatory thiopental pharmacokinetic model was nearly identical to that of thiopental modeled independently; only \( V_{T-P} \) and \( CL_{T-S} \) differed from those estimated by the independent model by more than 10%. That these differences (a 40-ml distribution volume difference due to fixing \( V_{T-P} \) to the antipyrine volume and a 60 ml/min distributional blood flow difference in \( CL_{T-S} \)) had no practical significance is illustrated by the similarity of the fit of this model to the data to the fit of the independent model to the data (Fig. 4, dashed and solid lines, respectively). When the parameters describing the central circulation, the nondistributive peripheral pathway, and either \( CL_{T-F} \) or \( CL_{T-S} \) were fixed to those of antipyrine, the recirculatory thiopental pharmacokinetic model was quite different from that of thiopental modeled independently; \( V_{SS} \) decreased by more than 13% due largely to a more than 40% decrease in \( V_{T-F} \), and \( CL_{T-F} \) decreased by more than 10% with a corresponding increase in \( CL_{T-S} \) of more than 69%. The Akaike information criterion and the Schwarz-Bayesian information criterion provided no guidance as to the appropriateness of the choice of model as these parameters differed only in the third significant figure and even then did so inconsistently.

### Discussion

The physicochemical characteristics of antipyrine and thiopental are quite different. Antipyrine is a base with a \( pK_a \) of 1.4, hence its fraction ionized at physiologic pH is less than 0.1% (Wu et al., 1995), whereas thiopental is an acid with a \( pK_a \) of 7.6, hence its fraction ionized at physiologic pH is 61.3% (Dundee, 1974). Antipyrine is moderately lipophilic, with an octanol/pH 7.4 Krebs-Henseleit buffer partition coefficient of 1.738 (Wu et al., 1995), whereas thiopental, the prototypical highly lipid-soluble drug (Mühlebach et al., 1985), has an octanol/water partition coefficient of 631 (Steiner et al., 1991). Antipyrine is minimally bound by plasma proteins, with a free fraction of 94% (Wu et al., 1995),
analyses suggest that the heterogeneity of diffusion barriers may invalidate the simplistic assumption that tissue distribution clearances may be equated with blood flows. However, the limitations to thiopental diffusion into brain, heart, liver, and muscle were low in the report of Ebling et al. (1994) and lower or even absent in their corrected model (Wada et al., 1997). Blood flow to these tissues accounted for 57% of cardiac output (Wada et al., 1997), which compares favorably with the 55% of cardiac output represented by thiopental distributive clearances in the present recirculatory model [i.e., (\(CL_{T-F} + CL_{T-S}\))/\(CL_{t-to}\)] (Table 2).

The largest parenchymal diffusion barrier reported by Ebling et al. (1994) and Wada et al. (1997) was that of the skin. This corresponds to the observation of Renkin (1955) that blood flow to an isolated hindlimb equaled antipyrine distribution clearance only when the limb was skinned.

The parameters determining the initial distribution of antipyrine and thiopental in the present study were nearly identical (Table 2). The \(V_c\) and \(V_{ND}\) of antipyrine and thiopental differed by less than 5% and, like thiopental, antipyrine had minimal first-pass pulmonary uptake, which is consistent with the observations of Roerig et al. (1989). Nondistributive blood flow, \(CL_{ND}\), of the antipyrine and thiopental models differed by less than 8%. As further evidence of the concordance of the initial distribution kinetics of antipyrine and thiopental, when the parameters describing the central circulation and nondistributive peripheral pathway in the recirculatory thiopental pharmacokinetic model were fixed to those of antipyrine, the thiopental model was minimally affected (Table 3).

An important observation of our work with various paradigms of perturbed physiology is that not only cardiac output but also its distribution affects early drug concentrations, as reflected in the area under the curve in the first minutes after i.v. administration (Avram et al., 1997, 2000; Krejcie et al., 1999, 2001), and suggested by the report of Upton et al. (1999; Krejcie and Avram, 1999). The nondistributive peripheral pathway in the antipyrine model represents blood flow that returns the lipophilic drug to the central circulation after minimal apparent tissue distribution (Krejcie et al., 1996a; Avram et al., 1997). The fraction of cardiac output represented by \(CL_{ND}\) is an important determinant of early drug concentrations. Increased arterial drug concentrations

### TABLE 3
Pharmacokinetic variables for thiopental kinetic models (N = 5)
Values are mean (±S.D.).

<table>
<thead>
<tr>
<th>Model</th>
<th>(V_C)</th>
<th>(V_{TP})</th>
<th>(V_{ND})</th>
<th>(V_{TS})</th>
<th>(V_{SS})</th>
<th>(CL_{ND})</th>
<th>(CL_{TP})</th>
<th>(CL_{TS})</th>
<th>(CL_{E})</th>
<th>(\Sigma CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent</td>
<td>1.11</td>
<td>0.19</td>
<td>0.70</td>
<td>14.26</td>
<td>37.05</td>
<td>53.12</td>
<td>1.18</td>
<td>1.29</td>
<td>0.36</td>
<td>0.17</td>
</tr>
<tr>
<td>(CL_{ND}) fixed to AP</td>
<td>1.07</td>
<td>0.15</td>
<td>0.67</td>
<td>12.79</td>
<td>37.20</td>
<td>51.74</td>
<td>1.09</td>
<td>1.33</td>
<td>0.42</td>
<td>0.17</td>
</tr>
<tr>
<td>(CL_{ND} + CL_{TP}) fixed to AP</td>
<td>1.07</td>
<td>0.15</td>
<td>0.67</td>
<td>8.36</td>
<td>36.60</td>
<td>46.70</td>
<td>1.09</td>
<td>1.12</td>
<td>0.61</td>
<td>0.18</td>
</tr>
<tr>
<td>(CL_{ND} + CL_{TS}) fixed to AP</td>
<td>1.07</td>
<td>0.15</td>
<td>0.67</td>
<td>7.59</td>
<td>36.75</td>
<td>46.08</td>
<td>1.09</td>
<td>1.08</td>
<td>0.66</td>
<td>0.18</td>
</tr>
</tbody>
</table>

\(AP\), antipyrine.

\(^{a}\) Shown are the volumes (V) of the two parallel central (C) circuits, including the pulmonary tissue (T-P), the nondistributive (ND) pathway, and the rapidly equilibrating (fast) (T-F) and slowly equilibrating (slow) (T-S) tissues. The volume of distribution at steady state (\(V_{SS}\)) equals the sum of all volumes except the thiopental pulmonary volumes, which are represented in their \(V_c\) values but thiopental \(V_{TP}\) values are equal to the difference between the thiopental \(V_c\) values and the \(V_c\) described by ICG.

\(^{b}\) Shown are the clearances (CL) of the nondistributive (ND) pathway, and the rapidly equilibrating (fast) (T-F) and slowly equilibrating (slow) (T-S) tissues, elimination clearance (\(CL_E\)), and the sum of all clearances (\(\Sigma CL\)), which equals the ICG (dye dilution) cardiac output determined at the moment of marker injection.
resulting from a larger fractional CL_{ND} increases drug exposure of the sites of action of drugs with a rapid onset of effect, such as thiopental, and would be expected to produce a more profound and prolonged effect. An important observation of the present study is that the early disposition of antipyrine, including the central circulation, the nondistributive peripheral pathway, and the fraction of cardiac output represented by CL_{ND}, is nearly identical to that of thiopental. This concordance makes antipyrine a useful physiologically inert surrogate for certain rapidly acting lipophilic drugs in nondestructive studies of the effect of altered cardiac output and blood flow distribution on drug disposition in both animals and humans.

Peripheral distribution of antipyrine and thiopental, on the other hand, differed significantly. Although the total distributive blood flow (CL_{T-F} + CL_{T-S}) of antipyrine and thiopental differed by less than 8%, antipyrine CL_{T-F} was more than 13% less than that of thiopental, whereas antipyrine CL_{T-S} was 83% more than that of thiopental. Peripheral antipyrine distribution volumes (V_{T-P} and V_{T-S}) and V_{SS} were less than two-thirds those of thiopental. The characteristic distribution pattern of a given drug is dependent on not only blood flow to various tissues but also binding competition among them (Bickel and Gerny, 1980). Antipyrine binds minimally to extracellular and intracellular components (Bickel and Gerny, 1980), whereas thiopental binds weakly to both tissue and plasma (Bickel et al., 1987). Thiopental binds to splanchnic tissues, represented by V_{T-P}, which is twice as large as that of antipyrine, delays and prolongs equilibration with its V_{T-S}, which is only 50% larger than that of antipyrine, relative to that of antipyrine (Upton et al., 1996).

In addition to validating the use of antipyrine as a physiologically inert surrogate for rapidly acting lipophilic drugs, the results of the present study have another practical implication. Interindividual differences in the response to rapidly acting drugs, such as intravenous anesthetics, may have a pharmacokinetic or pharmacodynamic basis. Rapid i.v. drug injection is necessary to describe the pharmacokinetic basis for differences in the dose-response relationship using a recirculatory pharmacokinetic model. In contrast, the pharmacodynamic basis for such differences is best studied when the drug is infused relatively slowly, allowing description of the concentration-effect relationship during the onset and offset of effect. The use of antipyrine as a surrogate for a rapidly acting lipophilic drug like thiopental allows the conduct of pharmacokinetic-pharmacodynamic studies in which antipyrine is administered by rapid i.v. injection to describe early drug disposition, whereas thiopental is administered by continuous infusion to a pharmacodynamic endpoint to enable description of the concentration-response relationships and the tissue distribution and elimination clearance elements of the recirculatory pharmacokinetic model.

This study validates the assumption that antipyrine is a useful surrogate for lipophilic drugs in pharmacokinetic studies in which physiologic stability is desirable to meet the assumption of system stationarity (Riggs, 1963) and to enable accurate description of initial drug distribution in pharmacokinetic-pharmacodynamic studies of rapidly acting lipophilic drugs.

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References


**Address correspondence to:** Dr. Michael J. Avram, Department of Anesthesiology, Northwestern University, Feinberg School of Medicine, 303 E. Chicago Avenue, Ward Building 13-199, Chicago, IL 60611-3008. E-mail: mja190@northwestern.edu