The Relationship between the Myocardial Kinetics of Meperidine and Its Effect on Myocardial Contractility: Model-Independent Analysis and Optimal Regional Model

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ABSTRACT

The myocardial kinetics of meperidine and the relationship between these kinetics and the effect of meperidine on myocardial contractility (maximum rate of change of left ventricular pressure) were examined by analysis of previously published data collected in sheep after the i.v. injection of 100 mg of meperidine over 1 s. There was significant hysteresis between reductions in myocardial contractility and the arterial concentrations of meperidine, but not the coronary sinus blood (effluent from the heart) or calculated myocardial concentrations. The peak reduction in contractility occurred after the peak arterial concentration, at the time of the peak myocardial concentration, but before the peak coronary sinus concentration, suggesting that the site of drug action in the heart was not in equilibrium with either arterial blood or effluent blood from the heart. The most appropriate form of a dynamic model (a linear model with a threshold) was determined, without the need to assume a kinetic model, by directly fitting the observed reductions in myocardial contractility to the calculated myocardial concentrations. To determine the optimal kinetic and combined kinetic-dynamic models, a variety of one-, two-, and three-compartment models of the myocardium were fitted to the coronary sinus concentrations by using hybrid modeling. These included “tank in series” models that accounted well for drug dispersion and “peripheral compartment” models that accounted well for deep distribution. The most appropriate model was a “compilation” model, which incorporated features of both these extremes and was a better fit to the observed data than either a traditional single flow-limited compartment or a traditional membrane-limited model.

Previous reports have documented experimental data regarding the myocardial kinetics of meperidine as determined by measurements of the product of its arteriovenous concentration difference across the heart and myocardial blood flow after bolus administration in sheep (Huang et al., 1994a). In the same experiments, it also was shown that meperidine [at doses that are sufficiently low to avoid overt central nervous system (CNS) stimulation] caused transient reductions in myocardial contractility (Huang et al., 1994b). This was taken to be a direct effect on the heart, as reductions in contractile performance also have been documented in isolated heart tissues without CNS innervation (Rendig et al., 1980) and appears to be related to the action of meperidine on calcium currents rather than opioid receptors (Wu et al., 1997).

As part of developing a physiological model of meperidine disposition, these previously published data were examined to determine an optimal model of the myocardial kinetics of meperidine and its dynamic effect on myocardial contractility. The general strategy used first was to examine the kinetic-dynamic relationship by using model-independent methods based on the analysis of hysteresis loops. Previously, this approach has been used for lidocaine in the heart, with mass balance principles (Upton et al., 1988) used to calculate the lidocaine concentration in the myocardium. It was found that the reduction in myocardial contractility caused by lidocaine was better related to this myocardial concentration than to its concentration in either arterial or coronary sinus blood (effluent from the heart) blood (Huang et al., 1993). Second, an optimal dynamic model (e.g., linear, maximum effect ($E_{\text{max}}$), or sigmoid $E_{\text{max}}$) was determined by directly fitting the observed reductions in myocardial con-

ABBREVIATIONS: CNS, central nervous system; LV, left ventricle; LV $dP/dt_{\text{max}}$, maximum positive rate of change of left ventricular pressure; AUC, area under the curve; MSC, model selection criteria; Qh, myocardial blood flow; $C_{\text{art}}$, arterial meperidine concentration; $C_{\text{sas}}$, coronary sinus meperidine concentration.
tractility to the calculated myocardial concentrations, a method that required no assumptions about the underlying myocardial kinetics of meperidine. Third, the myocardial kinetics were studied in detail by determining the best fit to the data of a variety of one-, two-, and three-compartment models of myocardial kinetics (including a traditional single flow-limited compartment and a traditional membrane-limited model). These were also combined with the optimal dynamic model to produce a variety of kinetic-dynamic models. The optimal models were chosen based on hybrid modeling of the time courses of the coronary sinus concentrations of meperidine and changes in contractility together with deductions from the model-independent analysis.

There are some outstanding issues with respect to the modeling of myocardial kinetics and dynamics. It is not clear from the present literature whether multicompartment models of the myocardium can be resolved from data regarding the arteriovenous concentration difference across the myocardium, as collected previously for meperidine. Furthermore, it is not known whether a more realistic description of myocardial kinetics can be achieved by adding the extra compartments in series to represent dispersion (Robert et al., 1988) or by adding the extra compartments as “peripheral” or “deep” compartments as used in traditional membrane-limited models (Gerlowski and Jain, 1983). Finally, when considering the relationship of the model to simultaneous effect measurements in the heart, it is clear that the optimal model is one in which at least one of the compartments is in pseudoequilibrium with the site of drug action responsible for the effect. Clearly, increasing the number of compartments used to describe the myocardium provides greater flexibility when constructing such a combined kinetic-dynamic model. The aims of the present study were to explore these issues by examining our previously published data on the myocardial kinetics and dynamics of meperidine. The specific aims were to:

1. determine whether the time course of the effect of meperidine on myocardial contractility was better related to the time courses of its concentration in arterial blood or coronary sinus blood or its calculated mean concentration in the myocardium;

2. determine the optimal dynamic model describing the relationship between the calculated myocardial concentration of meperidine and changes in myocardial contractility;

3. determine whether data regarding the arteriovenous concentration difference of meperidine across the myocardium have sufficient information to distinguish between a variety of compartmental models of myocardial kinetics and, if so, determine which model is optimal for describing the data; and

4. determine whether such models also can describe the effects of meperidine on myocardial contractility.

The general principles elucidated here may be applicable to other models of drug kinetics and dynamics in individual organs.

Materials and Methods

Data Source

The data on the effect of meperidine on myocardial contractility and other cardiovascular parameters (Huang et al., 1994b) and on its blood and myocardial pharmacokinetics (Huang et al., 1994a) after bolus i.v. injection in adult female sheep have been reported previously. In this paper, the relationship between myocardial contractility and myocardial kinetics is examined for the first time. A summary of the study design and the experimental methods relevant to this paper is presented here for completeness.

Adult Merino sheep were prepared under anesthesia with chronic intravascular catheters in the aorta (for sampling afferent blood to the heart), the coronary sinus (for sampling efferent blood from the heart once the hemiazygous vein is ligated), and the right atrium (for drug administration). An ultrasonic Doppler flow probe was placed on the left main-stem coronary artery to measure myocardial blood flow and was calibrated ex vivo. A pressure transducer-tipped catheter was acutely placed in the left ventricle (LV) on experimental days via a chronic introducer catheter, and the pressure trace was integrated digitally to give the maximum positive rate of change of LV pressure (LV dP/dt max), an index of myocardial contractility.

On an experimental day, conscious sheep were administered 100-, 200-, or 300-mg i.v. doses of meperidine over 1 s. Myocardial blood flow and LV dP/dt max were recorded continuously for the next 10 min and at 15 min, while paired arterial and coronary sinus blood samples were taken at intervals of as short as 5 s for 15 min after the dose. Meperidine blood concentrations were determined by using a gas chromatographic method. The myocardial concentrations of meperidine were calculated by using mass balance principles (Huang et al., 1994a; Upton, 1994). By this method, the mass of meperidine in the myocardium at a given time is the integral of the difference in the flux of meperidine entering the myocardium [i.e., myocardial blood flow (Qh) times the arterial meperidine concentration, C arte ] and the flux leaving the myocardium (i.e., Qh times the coronary sinus meperidine concentration, C cs ). The myocardial concentration (C myo ) is this mass divided by the mass of the myocardium perfused by the left main coronary artery (M myo ), estimated previously (Huang et al., 1994a):

\[
C_{\text{myo}} = \frac{1}{M_{\text{myo}}} \int_0^t Q_h(C_{\text{arte}} - C_{\text{cs}}) dt
\]

Only the 100-mg data were analyzed in the present paper because the higher doses produced CNS agitation and sympathetic stimulation, which masked the underlying myocardial depressant effect of meperidine at clinically relevant doses (Huang et al., 1994b). Four sheep were studied.

Data Analysis

Hysteresis Analysis. For the model-independent analysis, the time course of changes in LV dP/dt max (expressed as percent reduction from baseline) were plotted against the time courses of the arterial, coronary sinus, and calculated myocardial concentrations of meperidine. To quantify the hysteresis, each plot was divided into two sections at the point of the maximum meperidine concentration, with one section representing concentration-effect relationships when meperidine concentrations were increasing and the other representing the relationships when the meperidine concentrations were decreasing. The area under the curve (AUC) of each section of the concentration-effect loop were calculated by using the trapezoid rule. Concentration-effect hysteresis was considered to be present when the differences between the AUC of these two sections of the hysteresis loop were statistically different. The times of the peak values of the concentrations and percent reduction in contractility also were compared.

Optimal Dynamic Model. To determine the optimal dynamic model, the relationship between the calculated concentration of meperidine in the myocardium and the contractility data was analyzed directly by using Scientist for Windows (Micromath Scientific Software, Salt Lake City, UT). The fit of linear, linear with a threshold, \( E_{\text{max}} \), and sigmoid \( E_{\text{max}} \) dynamic relationships to these data were
examined by using a least-squares method. The equations for all but
the linear with a threshold models are in common usage and have
been reported previously by our laboratory (Huang et al., 1998). The
equations of the threshold model (in a form common to many pro-
gramming languages) were as follows, where $C_{myo}$ is the calculated
myocardial concentration, “dpdt“ is the percent reduction in LV
dPdtemp from baseline, and “dpdtemp“ is a temporary variable:

$$dpdtemp = \text{slope} \times C_{myo} + \text{intercept}$$

$$\text{IF } dpdtemp < 0, \text{ then } dpdt = 0, \text{ else } dpdt = dpdtemp$$

For the least-squares curve-fitting, the best fit was determined as
that with the highest model selection criteria (MSC) and without
nonidentifiable parameters. The MSC is essentially the inverse of
the Akaike Information Criterion scaled to compensate for data sets
of different magnitudes (Scientist for Windows manual; Micromath
Scientific Software) and is calculated from the following formula:

$$\text{MSC} = \ln \left( \frac{\sum_{i=1}^{n} w_i (Y_{obsi} - Y_{cali})^2}{\sum_{i=1}^{n} w_i (Y_{obsi} - Y_{obsi})^2} \right) - \frac{2p}{n}$$

where $w_i$ is a weighting term and $p$ is the number of parameters. The
higher the value of the MSC, the better the fit. Note that this term
adjusts for the number of parameters of a model, so that models with
more parameters do not necessarily produce a higher MSC. No
weighting was considered necessary because there was no evidence
that the data were heteroscedastic.

Nonidentifiability (after the terminology of Jacquez, 1987) was
defined arbitrarily as when the coefficient of variation of a parameter
returned by the fitting program was greater than 100%. A model
with nonidentifiable parameters is “underdetermined” for a given
data set. i.e., the data do not contain sufficient information to esti-
mate the parameter with precision. The correlation coefficient be-
tween parameters was also recorded, and a correlation greater than
0.99 was taken to indicate that a pair of parameters was nonidenti-
fiable and could be mathematically combined into one parameter.

Optimal Kinetic and Combined Kinetic-Dynamic Models.
Models of myocardial kinetics with a maximum of three compart-
ments were considered. To illustrate the possible configurations,
consider methods for improving the fit of a single compartment
model by adding a second compartment—two compartments either
may be arranged “in series” to improve the description of the disper-
sion process (Roberts et al., 1988) or as a more traditional “mem-
brane-limited” model to account for deep distribution (Gerlowkski and
Jain, 1983). When three compartments are considered, it is clear
that a three-“tank in series” model, a “double” membrane-limited
model, and other arrangements that combine the features of both of
these extremes are possible. The resultant nine kinetic models are
shown in Figs. 1, 2, and 3; the equations describing the models are
shown in Appendix 1.

Kinetic models first were considered separately from combined
kinetic-dynamic models. Hybrid modeling was used to fit each ki-
etic model to the observed mean data as follows. The arterial
concentration and myocardial blood flow were designated $C_{art}$ and $Qh$,
respectively. The volume of the compartment in equilibrium with coro-
monary sinus blood ($C_s$) was always designated $V_c$. The additional compart-
ments were designated either $V_1$ or $V_2$ and had drug concentrations of $C_1$
and $C_2$, respectively. The permeability constant of these compartments
(units of flow) were PS1 and PS2, respectively.

Combined kinetic-dynamic models were examined by using an ex-
extension of the same process. The concentration in each compart-
ment in the model was, in turn, linked to the optimal form of the
dynamic model determined previously, and curve-fitting was used to
estimate the kinetic and dynamic parameters of the model from both
the coronary sinus and myocardial contractility data.

**Statistical Analysis**

Data in the text are presented as mean (lower to upper 95% confidence intervals),
assuming a $t$ distribution (Gardner and Alt-
man, 1989). Two means were considered significantly different at the
95% level if each of the means lay outside of the confidence intervals
of the other or if the 95% confidence intervals of the difference did not include zero.

**Results**

**Hysteresis.** The hysteresis loops of effects versus the various
concentrations are shown in Fig. 4. There was a pro-
nounced counter-clockwise hysteresis for the arterial concentra-
tions, a smaller clockwise hysteresis for the coronary sinus concentrations, and an again smaller clockwise hysteresis for the calculated mean myocardial concentrations. The
mean size of the hysteresis loops (and 95% confidence inter-
vals) as given by the difference between AUC under the
sections of the plots when the concentrations were increasing
and decreasing was 449 mg s l$^{-1}$ (242–655) for the arterial
concentrations. This statistically significant hysteresis is
clearly evident in Fig. 4A. Figure 4, B and C, shows the AUC
differences of 37 mg s l$^{-1}$ (39 to 113) for the coronary sinus
concentrations and 69 mg s l$^{-1}$ (12 to 150) for the calculated
myocardial concentrations; these later two sites were not statistically different from zero, suggesting no significant hysteresis.

The mean time (and 95% confidence intervals) of the maximum reduction in contractility was 56 s (39–73), which was significantly different from the times of the maximum arterial blood [20 s (10–30)] and coronary sinus blood [125 s (66–184)], but not the myocardial concentrations [75 s (54–96)] of meperidine.

It can be concluded from this section of the analysis that the arterial concentrations of meperidine were not temporally related to the changes in myocardial contractility. The coronary sinus concentrations were better related to these changes but were clearly delayed relative to the changes in contractility. This was not the case for the calculated mean myocardial concentrations.

This information was used to reduce the overall computation time of the subsequent kinetic-dynamic modeling. Any model that assumed that the contractility changes were related to the changes in myocardial contractility was excluded at this stage because it is impossible for a dynamic effect linked to this concentration to precede the coronary sinus concentration as suggested by the model-independent analysis.

**Optimal Dynamic Model.** The MSC of fits of the dynamic models to the data are shown in Table 1. Both the $E_{\text{max}}$ and sigmoid $E_{\text{max}}$ models were underdetermined for the value of $E_{\text{max}}$ leading to nonidentifiability for this parameter. Although it could be argued that using higher meperidine doses would allow the measurement of $E_{\text{max}}$, this is physically impossible for myocardial contractility in vivo. The maximum reduction in contractility is the balance between direct depressant effects and indirect CNS effects, as well as the risk of fatality. The linear model was a reasonable fit, but returned values for the slope of 3.12, S.D. 0.28, and an intercept of −7.53, S.D. 1.92. This negative intercept suggests a “threshold” effect for measurable contractility changes, which is broadly consistent with Fig. 4C. The final model chosen, therefore, was the linear model with a threshold such that at concentrations below the threshold the reductions in contractility were zero. This form of the dynamic relationship (but not the parameter values) therefore was used for the subsequent combined kinetic-dynamic models, which enabled a considerable reduction in the number of combined
The best fits of the dynamic models

The various dynamic models were used to relate the reductions in myocardial contractility to the calculated myocardial concentrations of meperidine. The higher the value of the MSC, the better the fit. Nonidentifiable parameters have a coefficient of variation of greater than 100% (see text).

Table 1. The best fits of the dynamic models

<table>
<thead>
<tr>
<th>Dynamic Model</th>
<th>MSC</th>
<th>Nonidentifiable Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>1.45</td>
<td>No</td>
</tr>
<tr>
<td>Linear and threshold</td>
<td>2.09</td>
<td>No</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>0.69</td>
<td>Yes</td>
</tr>
<tr>
<td>Sigmoid $E_{\text{max}}$</td>
<td>2.07</td>
<td>Yes</td>
</tr>
</tbody>
</table>

The general problem was a poor account of the time of the peak and “washout” coronary sinus concentrations (Fig. 5). The volume of the heart ($V_h$) was 0.73 S.D. 0.02 liter, which equated to an equilibrium half-life between arterial and coronary sinus blood of 4.13 min.

The “two tanks in series” model (model 2) was a good fit to both data sets with no nonidentifiable parameters (Fig. 5). $V_1$ was 0.031 S.D. 0.003 liter, and $V_h$ was 0.642 S.D. 0.014 liter.

The membrane-limited model (model 3) was a better fit to the data than the single flow-limited compartment model, but, again, gave a poor account of the time of the peak coronary sinus concentration (Fig. 5) and was underdetermined for the volume of the peripheral compartment ($V_p$), which was constrained to a minimum of 0.0001 liter. However, the additional compartment did improve the fit of the “washout” concentrations compared with the single flow-limited compartment model (Fig. 5). The values of $V_p$ and PS1 were 0.56 S.D. 0.04 liter and 0.63 S.D. 0.31 l/min, respectively.

Model 4, the “three tank in series” model, offered no better fit than the “two tanks in series” model and was underdetermined for the volume of the additional compartment ($V_1$), which was constrained to a minimum of 0.0001 liter. The values of $V_2$ and $V_h$ were 0.64 S.D. 0.06 liter and 0.032 S.D. 0.007 liter, respectively.

“Compilation” model A (model 5) was the best fit to the kinetic data (Fig. 5) and had the highest value of the MSC and the most random distribution of residuals (from serial correlation analysis of the residuals). It was a reasonable fit of the kinetic-dynamic data, but was one of the few models that fitted these data without nonidentifiable parameters. $V_1$ was 0.036 S.D. 0.004 liter, $V_h$ was 0.62 S.D. 0.02 liter, PS2 was 0.014 S.D. 0.004 l/min, and $V_2$ was constrained to the maximum of $10^4$ liters.

“Compilation” model B (model 6) was also good in these regards. For the kinetic data, $V_1$ was 0.040 S.D. 0.005 liter, $V_h$ was 0.58 S.D. 0.03 liter, PS2 was 0.011 S.D. 0.006 l/min, and $V_2$ was constrained to the maximum of $10^4$ liters. However, for the kinetic-dynamic data, the volume of peripheral compartment ($V_p$) was within the constraint limits but was nonidentifiable.

The double membrane-limited model in the A configuration (model 7) was not a good fit to the kinetic data, offering no advantage over the single membrane-limited model (model 3). The value of $V_h$ was 0.55 S.D. 0.05, PS1 was 0.57 S.D. 0.34, $V_1$ was 0.001 S.D. 0.009, $V_2$ was constrained to a maximum of $10^4$, and PS2 was $6.3 \times 10^{-16}$ S.D. $6.6 \times 10^{-15}$.

However, when used for the kinetic-dynamic data, the fit of this model was improved significantly, but with an underdetermined value for $V_h$.

The “triangular” model (model 8) was a reasonable fit of the kinetic data and had the highest MSC when applied to the kinetic-dynamic data. For the kinetic data, the value of $V_1$ was 0.061 S.D. 0.116 liter, $V_h$ was 0.33 S.D. 0.06 liter, $V_h$ was 0.06 S.D. 0.08 liter, and Q2 was 0.12 S.D. 0.03 l/min. Its shortcomings were underdetermined values for $V_1$ or $V_h$, which were correlated with a correlation coefficient of >0.99.

The double membrane-limited model in the B configuration (model 9) was not a good description of the kinetic or kinetic-dynamic data and was underdetermined for many parameters. For the kinetic data, $V_1$ was constrained to the minimum value of $10^{-4}$, $V_2$ was constrained to the maximum...
value of $10^5$, $V_1$ was 0.56 S.D. 0.05 liter, PS1 was 0.63 S.D. 0.37 l/min, and PS2 was $6.1 \times 10^{-16}$ S.D. $1.2 \times 10^{-14}$.

Summary of Model Performance. Note that across the range of models a good fit to the kinetic data did not necessarily mean a good fit to the kinetic-dynamic data, and vice versa. This is indicative of the fact that a good fit to the dynamic data generally arose when a compartment of the model linked to the dynamic model was “upstream” of the coronary sinus compartment. This is consistent with the model-independent analysis, which also showed that the effect preceded the coronary sinus concentrations.

By examining Table 2 and neglecting those models with nonidentifiable parameters, the rank order of the best kinetic models (from high to low MSC) was models 5, 6, 2, and 1. For the kinetic-dynamic data, the ranked models were models 2, 5, and 1. Of the three models suitable for both data sets, the mean MSC for both data sets was 3.63 for model 5, 3.54 for model 2, and 2.84 for model 1. Therefore, both models 5 and 2 were good at describing these data (although with a slight advantage to model 5) and had in common two compartments in series providing an element of dispersion to the model output. Interestingly, although model 1 (the single flow-limited compartment) fell well short of these two models in describing the data, it performed better than many more complicated models, in agreement with its widespread use in many physiological pharmacokinetic models.

Discussion

An initial observation from this analysis is the general utility of the mass-balance method for describing this type of regional kinetic-dynamic data. In this case, it was used to determine whether the mean myocardial concentration of a drug was related to its proposed effect on the myocardium and was able to do so even if there was incomplete equilibrium between the effect and the venous concentrations emerging from the organ. This itself is good evidence that a single-compartment description of the organ may not be appropriate, as this model assumes instantaneous equilibration between tissue and effluent venous drug concentrations.

A general picture also is emerging for a variety of drugs that changes in myocardial contractility caused by the drug are better related to its myocardial rather than arterial concentrations; this has been demonstrated for thiopental (Upton et al., 1996), lidocaine (Huang et al., 1993), verapamil (Huang et al., 1998), and, now, meperidine in the present study. The mass-balance method also was useful for determining the optimal dynamic model independent of any assumptions about the underlying myocardial (or effect-compartment) kinetics. It is not clear whether the observed threshold effect of meperidine on myocardial contractility was a real effect or was due to lack of sensitivity in the method. Although the error bars in Fig. 4 are relatively small, such a threshold effect has not been observed in vitro (Wu et al., 1997).

The opportunity was taken in this study to address a pertinent issue regarding the choice of kinetic models for individual organs or regions of the body such as the heart. In many physiological models of lipophilic drugs such as meperidine (Gabrielsson et al., 1986; Davis and Mapleson, 1993), the heart and many other organs or regions are represented as single flow-limited compartments. In agreement with the present data, it was found that the myocardic kinetics of fentanyl and alfentanil after a 1-min infusion to rats were better described by a single flow-limited compartment (equivalent to the present model 1) than either two- or three-compartment models equivalent to models 3 and 7 of the present paper, respectively ( Bjorkman et al., 1994). However, although single flow-limited compartment models are in broad agreement with the available data, there is some evidence that this single-compartment representation of an organ or region is too simple, particularly for data arising from bolus or impulse administration studies. For example, when drug kinetics in organs or regions are examined individually after impulse administration, it generally is noted that the concentration profile emerging from the organ is lagged, unimodal, asymmetric, and skewed to the right (Roberts et al., 1988; Krejcie et al., 1996). This shape arises from dispersion of the idealized impulse input in the organ due to laminar flow in the vasculature, turbulence at branch points, the distribution of vascular path lengths, and heterogeneity in the perfusion of the organ (Krejcie et al., 1996). More complex, stochastic “dispersion” models of the organ are required to account for these processes, often with models that need to be solved by computationally intensive inversion of the Laplace solution to the model (Roberts et al., 1988).

It would be advantageous to find the middle ground between the computational simplicity but lower fidelity of a single-compartment model, and the opposite is true for stochastic dispersion-based models. The data suggest that a class of compartmental models known as “tank in series”
models (Beek and Muttzall, 1975; Roberts et al., 1988) may provide a means of doing this, as they can represent increased dispersion by increasing the number of compartments in series. However, these models can be written as differential equations in the time domain and, therefore, solved in the same manner as the traditional single-compartment organ models used in many physiological models.

The effect of adding extra compartments in these “in series” and “peripheral” configurations is not immediately obvious. However, the simulations shown in Fig. 6 illustrate the general principles. Note that each configuration has a characteristic effect on the venous concentrations emerging from the model. First, the single-compartment model is characterized by an exponential rise and fall of the venous concentrations when exposed to a “square wave” arterial concentration input. Importantly, the peak venous concentration always occurs at the point at which the venous concentrations cross the arterial concentrations—this is an embodiment of Zilversmit’s rule originally developed for the analysis of product-precursor relationships (Rescigno and Segre, 1966; Jones and Nicholas, 1984). This behavior is characteristic of systems in which there is only one compartment directly between arterial and venous blood. Second, it is clear that the principal advantage of the tank in series configuration is that it is possible to introduce a delay in the time of the peak venous concentration. The peak is also skewed to the right in a manner consistent with real data (Krejcie et al., 1996). Finally, note that the peripheral configuration of membrane-limited models also must obey Zilversmit’s rule by nature of the arrangement of their compartments, and the peak venous concentration will always occur when the venous concentrations cross the arterial, regardless of the number of additional peripheral compartments. Indeed, the principal effect of adding additional peripheral compartments is to prolong the elution process with only minor changes in the rate of uptake. The advantage of the compilation models is that both the delayed peak characteristic of dispersion and the prolonged elution characteristic of deep distribution can be accounted for to different extents as determined by the data.

An overall conclusion from this analysis is that arteriovenous concentration difference data across an organ can be used to differentiate between a variety of kinetic models. The

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**Fig. 5.** The best fit (solid line) of the observed coronary sinus concentration data (symbols) for the single flow-limited compartment model (model 1), a two tank in series model (model 2), a traditional membrane-limited model (model 3), and compilation model A, the optimal kinetic model (model 5). The latter model clearly has the least systematic deviation from the observed values. The dotted lines are the 95% confidence intervals of the observed data assuming a t distribution.

**Fig. 6.** A hypothetical simulation of the effect of adding extra compartments to a single flow-limited compartment in either a series configuration or as peripheral compartments. The input to the system (arterial concentration) is a pulse of 0.5-min duration and a height of 1 concentration unit. The mean transit time for each compartment in the system is 1 min. The curves shown are the venous concentrations emerging from the organ. Adding compartments in series increases dispersion, as shown by delayed peak concentration and a right-skewed curve. Adding extra peripheral compartments does not change the time of the peak concentration, but prolongs the washout from the organ.
redundancy of compartmental models when fitted to systemic blood concentration data, as pointed out by Wagner (1975), is not an issue in this quite different experimental paradigm. Overall, compilation model A was considered the optimal model (from those examined) for these data because it was the best fit to the kinetic data and one of the best for the kinetic-dynamic data without nonidentifiable parameters. This model is of a novel form because it incorporates both dispersion (two compartments in series) and deep distribution elements (a peripheral compartment). We currently are investigating the hypothesis that this relatively simple type of model may be of a sufficiently general form that it is suitable for describing regional kinetics for a wide range of organ and drug combinations.

**Appendix 1: The Equations of the Kinetic Models**

The volume of the compartment drained by coronary sinus blood (concentration given by $C_{cs}$) was designated as $V_h$. The volume of the additional compartments was designated $V_1$ and $V_2$, with concentrations $C_1$ and $C_2$, respectively. The apostrophe symbol (') after a variable indicates a derivative with time. The volumes of distribution are apparent volumes; thus, the concentrations in each volume will be numerically equivalent at steady state. The kinetic-dynamic models added the dynamic equation discussed in the text, with the effect linked to each concentration in the compartment ($C_{art}$, $C_1$, or $C_2$) in turn. The optimal model from these alternatives was chosen as the final kinetic-dynamic model.

**Model 1: Single Flow-Limited Compartment**

$$V_h \ast C_{cs}' = Qh \ast (C_{art} - C_{cs})$$

**Model 2: Two Tanks in Series**

$$V_1 \ast C_1' = Qh \ast (C_{art} - C_1)$$
$$V_h \ast C_{cs}' = Qh \ast (C_1 - C_{cs})$$

**Model 3: Traditional Membrane-Limited Model**

$$V_h \ast C_{cs}' = Qh \ast (C_{art} - C_{cs}) + PS1 \ast (C_1 - C_{cs})$$
$$V_1 \ast C_1' = PS1 \ast (C_1 - C_{cs})$$

**Model 4: Three Tanks in Series**

$$V_1 \ast C_1' = Qh \ast (C_{art} - C_1)$$
$$V_2 \ast C_2' = Qh \ast (C_1 - C_2)$$
$$V_h \ast C_{cs}' = Qh \ast (C_2 - C_{cs})$$

**Model 5: Compilation A**

$$V_1 \ast C_1' = Qh \ast (C_{art} - C_1)$$
$$V_h \ast C_{cs}' = Qh \ast (C_1 - C_{cs}) + PS2 \ast (C_2 - C_{cs})$$
$$V_2 \ast C_2' = PS2 \ast (C_2 - C_{cs})$$

**Model 6: Compilation B**

$$V_1 \ast C_1' = Qh \ast (C_{art} - C_1) + PS2 \ast (C_2 - C_1)$$
$$V_2 \ast C_2' = PS2 \ast (C_1 - C_2)$$
$$V_h \ast C_{cs}' = Qh \ast (C_1 - C_{cs})$$

**Model 7: Double Membrane-Limited A**

$$V_h \ast C_{cs}' = Qh \ast (C_{art} - C_{cs}) + PS1 \ast (C_1 - C_{cs})$$
$$V_1 \ast C_1' = PS1 \ast (C_1 - C_{cs}) + PS2 \ast (C_2 - C_1)$$

$$V_2 \ast C_2' = PS2 \ast (C_2 - C_{cs})$$

**Model 8: Triangular**

$$V_h \ast C_{cs}' = Qh \ast (C_{art} - C_{cs}) + PS1 \ast (C_1 - C_{cs}) + PS2 \ast (C_2 - C_{cs})$$

**Model 9: Double Membrane-Limited B**

$$V_h \ast C_{cs}' = Qh \ast (C_{art} - C_{cs}) + PS1 \ast (C_1 - C_{cs}) + PS2 \ast (C_2 - C_{cs})$$

**References**


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