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An Extended Physiological Pharmacokinetic Model of Methadone Disposition in the Rat: Validation and Sensitivity Analysis

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An extended physiological model of methadone disposition in the rat was constructed and evaluated in various tests of model validity. A separate circulation model of the fetus was included due to the large tissue concentration differences obtained after a constant rate infusion but also to propose the use of this type of model for optimization of toxicological tests. Simulations were performed with the animal model and scaled-up models of humans to elucidate the determinants of methadone dispostion. The rationale of the use of an extended model for methadone was also discussed.

KEY WORDS: physiological model; methadone; simulations; rat; pregnancy; model validation; sensitivity analysis.

INTRODUCTION

Although several of the basic pharmacokinetic principles were outlined by Teorell (1) in the mid-1930s, their utility was not at first generally recognized. Systematic application of these principles to practical problems was then undertaken during the 1960s primarily by pharmacists and pharmacologists, who began to realize the potential usefulness of kinetic models in integrating observed plasma and urine concentration into a coherent picture of drug disposition and action (2). So far, compartmental and empirical models have dominated the literature as they meet the needs of

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most pharmacokinetic studies. However, they generally lack physiological meaning. For instance, a kinetic compartment may or may not correspond to a physiological tissue or fluid volume; it is in fact an abstraction that may include functionally disparate tissues.

The earliest concepts of physiological modeling evolved from the work of anesthesiologists who were interested in the exchange of inhaled gases between the lung and body tissues and in the distribution of parenterally administered anesthetics (3–5). The modern era of physiological flow models can probably be traced back to the work of Bischoff and Dedrick (6) in which they presented a mathematical model of thiopental kinetics. To date a large number of drugs and other compounds have been analyzed by means of flow models (7). This approach allows us to formulate in mathematical terms a proposed mechanism of drug transport and to test the hypothesis by comparing simulations with experimental data. The physiological approach also renders possible extrapolation outside the range of existing data—even to other species—with some confidence, if the dominant mechanisms of transport and biochemical transformation are sufficiently well represented.

On the other hand, physiological models tend to become very complex and difficult to validate. These models should therefore be carefully designed—they should be kept as simple as possible and still describe the behaviour of the system to be represented. An organ or compartment should be included in the model if it is a substantial depot for drug distribution, excretion, or metabolism, or if it is of special interest, such as the fetus in the case of the present study.

The main objective in modeling the disposition of methadone in pregnant rats was to obtain a computational tool for simulation of the major determinants of methadone kinetics. The approach was to construct a physiological pharmacokinetic model that was sufficiently detailed and comprehensive for the study of the turnover of methadone in the rat, and then to use this model in studying the overall effects of physiological changes on the circulating drug.

The ultimate goal of the modeling work presented herein was to scale-up the animal model to man in an attempt to describe and predict the disposition of methadone in tissues where the drug is either harmful or is known to have harmful effects, and therefore maternal cardiac and adipose tissues were also represented, as well as fetal cerebral-, hepatic-, and miscellaneous tissues.

Since a model required for predictive purposes is mainly subjected to empirical and pragmatic validation, whereas an explanatory model of a complex system also has to be validated from a theoretical and heuristic point of view, methods of systems and sensitivity analysis were applied here as the most powerful methods of choice.

MATERIALS AND METHODS

The Model

The model in Fig. 1 is based on relevant physiological and anatomical parameters such as blood flows (Q_i), organ or tissue volumes (V_i), and tissue-to-blood partition coefficients (K_{Pi}). The volumes of various tissues and blood flows have been compiled for the rat and are readily available in the literature (8–10).

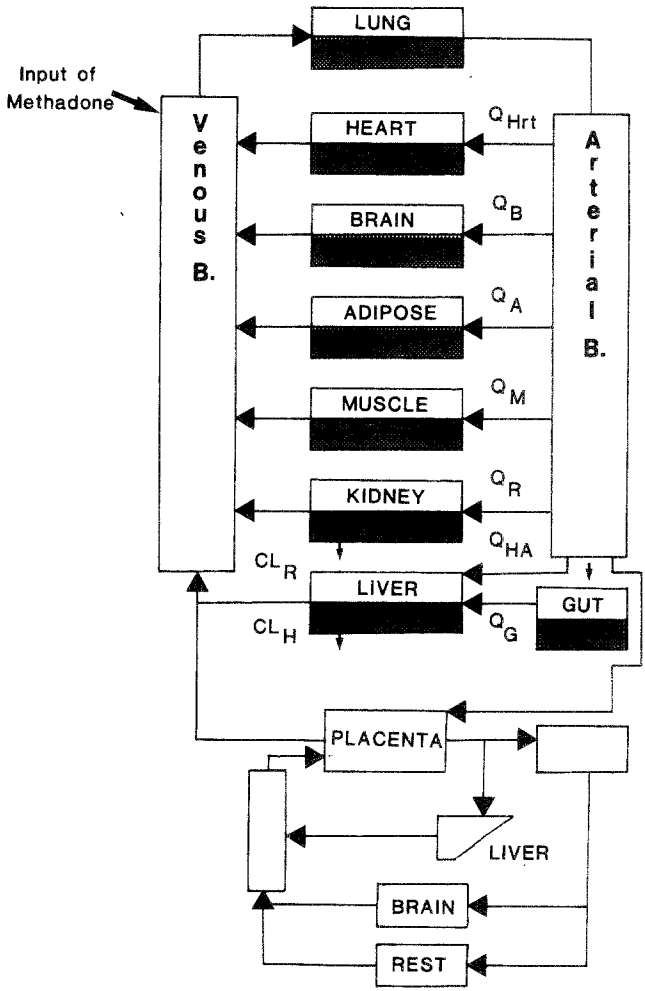

Fig. 1. The proposed extended physiological model for methadone disposition.

In applying the model to methadone, the following assumptions are made: (i) That there is instantaneous mixing of the drug in venous blood after intravenous (iv) injection; (ii) that all drug transport is perfusion-limited except across the placental membrane and into intestinal tissues, where membrane restriction is assumed to be important; (iii) that all tissue-to-blood partition coefficients of methadone are concentration-independent within the observed concentration range; (iv) that all clearance factors are also concentration- and time-independent.

Based on these assumptions a set of mass-balance equations are derived in order to describe the model mathematically

$$V_i \cdot dC_i/dt = Q_i(C_A - C_i/K_{Pi}) - Cl_i C_i/K_{Pi} \quad (1)$$

where subscript i refers to the ith body compartment (i = M for muscle; i = H for liver, A for arterial blood, etc). For the case of membrane-limited uptake, the following equation for the vascular tissue compartment is proposed

$$V_{Bi} \cdot dC_{Bi}/dt = Q_{Di}(C_A - C_{Bi}) - D_i(C_{Bi} - C_{Ti}/K_{Pi}) \quad (2)$$

and for the corresponding tissue compartment the equation

$$V_{Ti} \cdot dC_{Ti}/dt = D_i(C_{Bi} - C_{Ti}/K_{Pi}) \quad (3)$$

V_{Bi} and V_{Ti} are the volumes (ml) for the vascular and tissue spaces, respectively in compartment i; C_{Bi} and C_{Ti} are the concentrations (ng/ml) in the vascular and tissue spaces, respectively; Q_i is the blood perfusion rate (ml/min); Cl_i is the intrinsic clearance (ml/min) from compartment i; D_i is the diffusion parameter (ml/min) across the tissue membranes—in this particular case intestinal or placental membrane; and K_{Pi} is the tissue-to-blood partition coefficient.

The various tissues were included for the following reasons: Adipose and muscular tissues because of their large capacity to store and retain methadone; renal tissues and the liver because of their eliminating capacity; pulmonary tissue because of the high tissue-to-blood partition coefficient; heart muscle since it exhibits a three times larger affinity for methadone than skeletal muscle tissue; intestinal tissue since it runs in series with the liver and may partly protect the liver from high concentration fluctuations and contains opiate receptors, and because clinically methadone is administered orally; brain tissues because of the analgesic activity of methadone; and fetal brain, liver, and eviscerated carcass because of the embryotoxic effects of methadone that have been reported to occur in rodents.

Experimental Design and Methods

Details concerning the animals, chemicals, experimental design, and analytical methods have been described in previous reports from our laboratory (11).

Model Parameters

The partition coefficients were determined after an iv infusion lasting for 5–9 hr aiming at an arterial blood concentration of approximately 200 ng/ml. The mean partition coefficients are given in Table I.

Some tissues, even though they have morphological similarities, such as skeletal and heart muscle tissues, or physicochemical similarities, such as adipose and brain tissues with regard to their fat content, exhibit large differences in their affinity for methadone, which means that they differ kinetically. It was therefore of interest to include these tissues as separate compartments in the present modeling study.

Table I. Physiological and Experimentally Observed Values for Different Variables in the Pregnant Rat Used in the Present Model

Organ or tissue	Blood flow Q (ml/min)[a]	Organ volume V (ml)[a]	K_{Pi} (mean ± SD)[b]	Clearance (ml/min)[c]
Blood	74.0	20.0	—	22.0
Adipose tissue	2.6	20.0	43.9 ± 9.4	—
Brain	5.0	1.5	6.3 ± 2.4	—
Heart muscle	6.0	3.0	39 ± 19	—
Intestines	14.0	20.0	39 ± 19	10.0 (diffusion)
Kidney	17.0	3.0	75 ± 27	1.5
Liver	25.0	15.0	120 ± 15[d]	17.5
Lung	74.2	2.0	185 ± 56	—
Skeletal muscle	20.0	120.0	15 ± 4.9	—
Placenta	7.2	10.0	—	1.00 (diffusion)
Whole fetus	—	25.0	8.8 ± 2.6	—
Fetal brain	2.0	5.0	12 ± 3.9	—
Fetal liver	2.3	2.0	15 ± 5.9	—
Fetal eviscerated carcass	4.0	11.0	5.5 ± 2.3	—
$\Sigma K_P * V_T$			12.0 L/kg (based on a 400 g rat)	

[a] Values from refs 8, 9, and 15 and adapted to a 400 g pregnant rat.
[b] Experimentally found tissue-to-blood coefficients from ref. 11.
[c] Experimentally found clearance and diffusion values from ref. 11. The diffusion parameters were derived after several simulations.
[d] Corrected for extraction.

The total body clearance was calculated by dividing the dosing rate by the arterial blood concentration at steady state. The renal clearance of methadone was assumed to be 10% of the total body clearance (12).

The independent volume of distribution for methadone was estimated by summing up the products of the partition coefficients and their corresponding physiological tissue volumes [12.0 L/kg (11)]. This indicated a substantial distribution to certain tissues.

Computer Simuation-Procedure

Once values of the model parameters have been substituted, the mass-balance equations are solved simultaneously by computer, using the DARE-P simuation program (13).

Sensitivity Analysis

Our mathematical model involves a number of parameters which have to be known to a certain degree of accuracy. If the model is adequately robust, minor variations in the parameters should not alter the results to any great extent. In addition to the knowledge of the robustness of the model, it is also necessary to know which parameters should be changed in order to reach agreement between predicted and experimentally observed variables. The physiological values listed in Table I are statistical average values that may be regarded as realisitic (9,10).

The parameter sensitivity of the model was tested by comparing various variables calculated on the basis of standard values for all parameters, with corresponding values calculated after variation of the standard values for each of the following parameters: (i) the volume of any body region (±20%); (ii) the blood flow through any body region (±20%); (iii) the tissue-to-blood partition coefficient of any tissue (±20%); (iv) the intrinsic clearance factors (±20%).

Validation

Theoretical vaidity means that the model should be consistent with accepted theories and models (see model assumptions above). An example of theoretical validation is to check whether our model is circulatorily consistent or whether the way of modeling drug uptake into tissues is consistent with the literature.

The model was validated *empirically* by using experimentally found parameter values and comparing the calculated concentration time profiles with experimentally observed blood and tissue concentrations after iv bolus injection into rats.

The final *pragmatic* validation of the model for application on humans has to be done by comparing model predictions for the purpose in question with experimental data, and considering questions such as: Does the model respond realistically to conventional dosing in humans? Is it possible to optimize the dosing schedule by model based simulations? Is the model practically useful in clinical work?

Simulations were also performed with a scaled-up version of the proposed physiological model with the aim of predicting the disposition of methadone in obesity, malnutrition, and during late pregnancy and at delivery in humans. This kind of "what if" calculation is potentially very useful for generating hypotheses and designing new experiments and thus for heuristic validation of a model (14).

Interspecies Scaling

Some questions that may be asked in the testing of a new agent concerning its therapeutic potential in humans include: What is the time course of drug concentration as a function of dose and schedule? What is the exposure of an organ or the fetus to unbound drug? What pharmacological or toxicological effects may we anticipate from this exposure? Is it possible to construct a quantiative model for the human system? In order to describe and predict the turnover of methadone in humans, we scaled up the animal model to a human by using human organ volumes and blood flows and clearance factors. In order to estimate the human placental and gastrointestinal diffusion parameters, we scaled these according to Eq. 4 (15).

$$(Parameter)_{\text{man}} = (Parameter)_{\text{rat}} * ((Body\ mass)_{man}/(Body\ mass)_{\text{rat}})^{b} \qquad (4)$$

where $b = \frac{3}{4}$. The tissue-to-blood partition coefficients were assumed to be the same in rat and man, except for noneliminating organs for which a correction had to be done. The paramters for the proposed human model are given in Table II. The theories of interspecies scaling have been thoroughly discussed by Adolph (16), Lindstedt and Calder (17) and Yates and Kugler (18).

RESULTS

Empirical Validation

In general, the simulated concentration-time curves were consistent with the observed data (Fig. 2). However, the values for the initial phase of the simulated time course of the concentration in pumonary and renal tissues were constantly higher than the corresponding experimental values. Further experimentation is therefore needed to elucidate the complexity of the initial disposition of methadone in these tissues.

Table II. Physiological and Experimentally Observed Values for Different Variables in the Scaled-Up Model of a 70 kg Pregant woman.

Organ	Blood flow Q (L/min)[a]	Organ volume V (L)[a]	K_{Pi}[b]	Clerance (L/min)
Blood	5.4	5.0	—	0.33
Adipose tissue		10.0	44	—
Brain	0.8	3.5	6.3	0.0078 (diffusion)
Heart muscle	0.2	0.3	39	—
Intestines	1.1	2.4	39	0.25 (diffusion)
Kidney	1.2	0.3	75	0.03
Liver	1.5	1.5	—[b]	0.30
Skeletal muscle	1.5	30	13	—
Lung	5.4	0.8	185	—
Placenta	0.5	0.5	—	0.047 (diffusion)
Fetal brain	—	0.5	12	—
Fetal liver	—	0.5	15	—
Fetal carcass	—	2.5	5.5	—

[a] Values from refs. 18 and 19 and adapted to a pregnant woman.
[b] Derived from the rat study and corrected for extraction (11).

Flow-limited uptake was previously assumed for intestinal and fetal tissues, but the present model, which includes membrane restriction and diffusion-limited uptake of methadone, gave better agreement than the flow-limited approach for the description of the early time points (11). It is also logical to assume that diffusional processes take place across the placenta.

The fractional uptake of methadone into various tissues is presented in Fig. 3. Skeletal muscle and adipose tissue are responsible for the storage of methadone at the intermediate and terminal points of time. The data in Fig. 4 suggest that the adipose compartment governs the terminal phase of the drug disposition owing to the large fraction of the drug residing within these tissues.

Sensitivity Analysis

Of all model parameters, we have chosen to vary the values of the following: the intrinsic heptaic clearance ($Cl_{int,H}$), the hepatic blood flow (Q_H), the muscular tissue-to-blood partition coefficient (K_{PM}), and the adipose ($V_{Adipose}$) and muscular (V_M) tissue volumes. In the sensitivity analysis, these were the most critical parameters governing the turnover of the studied drug. As seen in Figs. 5 and 6, variation of these parameter values by ±20% from the standard values does not dramatically change either the typical time course or the numerical levels of important state

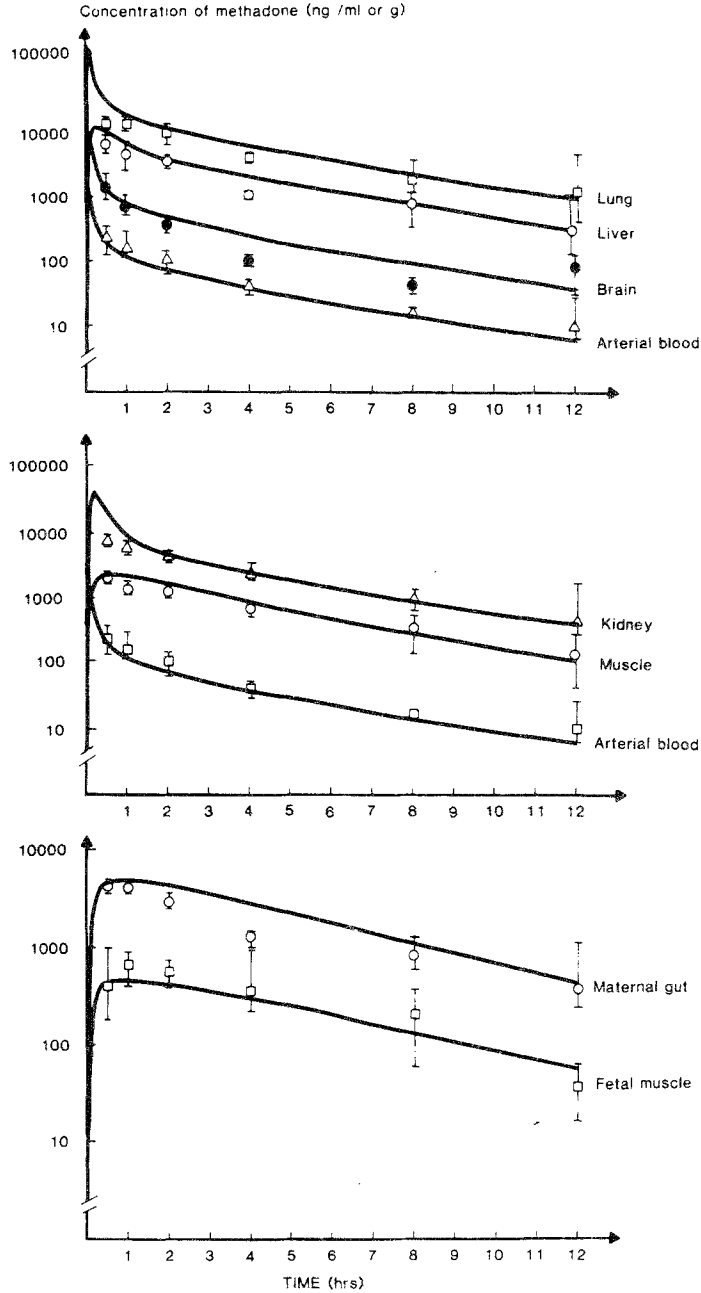

Fig. 2. Blood and tissue concentrations vs. time for methadone in the pregnant rat following a single iv dose of 2 mg/kg body mass. The points represent experimental data and the bars indicate the highest and lowest observed concentrations. Solid lines represent concentrations with use of the model in Fig. 1.

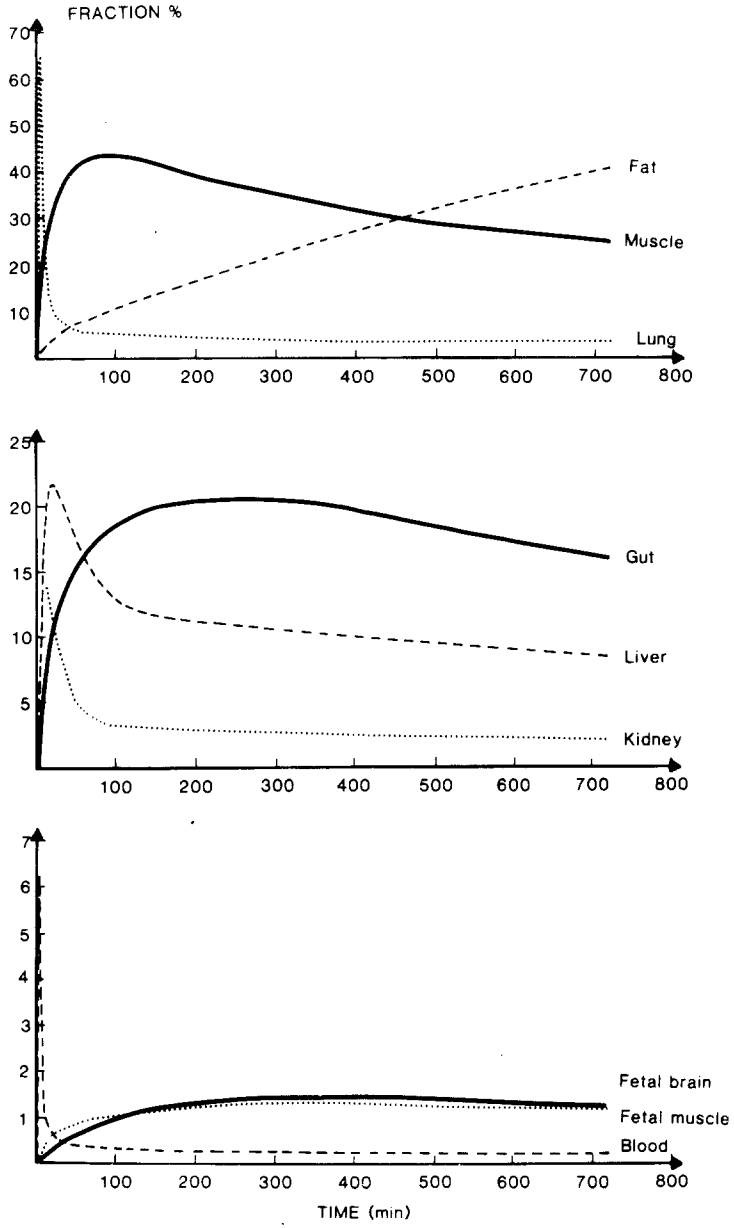

Fig. 3. The fractional uptake of methadone into various tissues and blood relative to the total amount of methadone in the body.

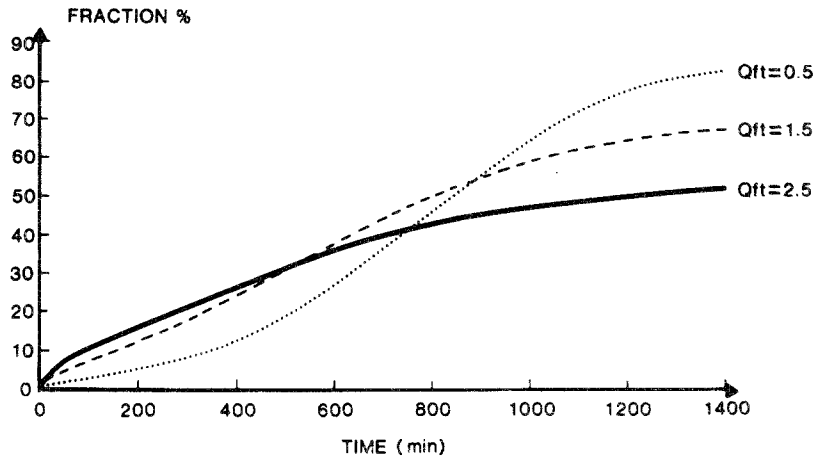

Fig. 4. The impact of a change in the perfusion through the adipose tissue on the time taken to reach pseudo-equilibrium in the organism, represented in terms of fractional uptake of methadone into adipose tissues ($Q_{fat} = 2.5$ ml/min is the normal state).

variables (blood, muscle tissue, etc.). The intrinsic hepatic clearance, $Cl_{int,H}$ and the hepatic blood flow, Q_H, have a similar impact on the arterial concentration-time profile, whereas an alteration of the skeletal muscle volume, V_M, or partition coefficient, K_{PM}, gives rise to a different concentration-time pattern, as seen in Figs 5 and 6.

Another way to illustrate the impact of a change in blood flow (±20%) on the rate processes is by plotting the derivative of the concentration-time course as seen in Fig. 7. By increasing the flow the amplitude of the derivative is increased, indicating a faster transport of the drug and a shorter time to reach concentration maximum within the organ or tissue.

To elucidate the physiological characteristics of the model on the turnover of the drug in the rat, the following physiological states were considered and displayed in Figs. 8 and 9.

Extreme underweight was simulated, since it is a situation that may be common among drug abusers (Fig. 8). Obesity was also simulated, but did not show any pronounced effects on the methadone concentration-time course and is therefore not represented. As shown in Fig. 9, a change of ±50% in intrinsic hepatic clearance had an impact on the arterial blood concentration as well as the terminal half-life, since methadone behaves as a highly cleared drug in the rat.

First Step Towards Pragmatic and Heuristic Validation

The time courses of methadone in human maternal blood, brain, and fetal brain following a daily maintenance dose of 30 mg are illustrated in

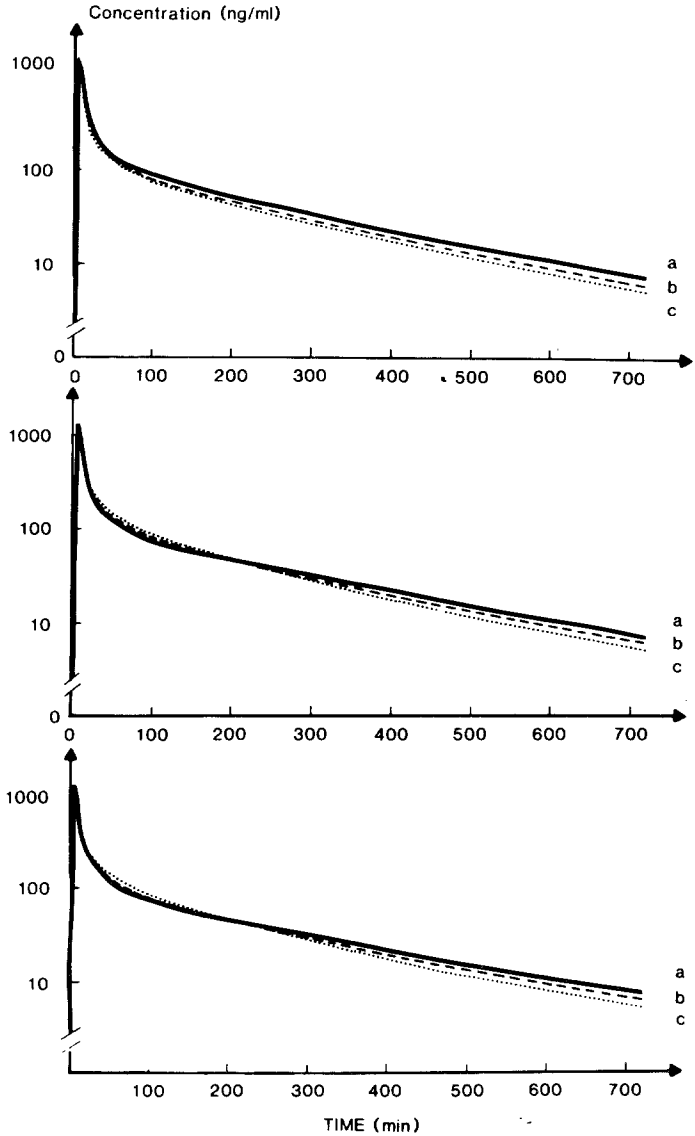

Fig. 5. Results of the sensitivity analysis; A ± 20% change in Q_H (upper figure, a is decrease, b is standard, and c increase), $K_{P,M}$ (middle figure, a is increase, b is standard, and c is decrease), and V_M (bottom figure, a is increase, b is standard, and c is decrease).

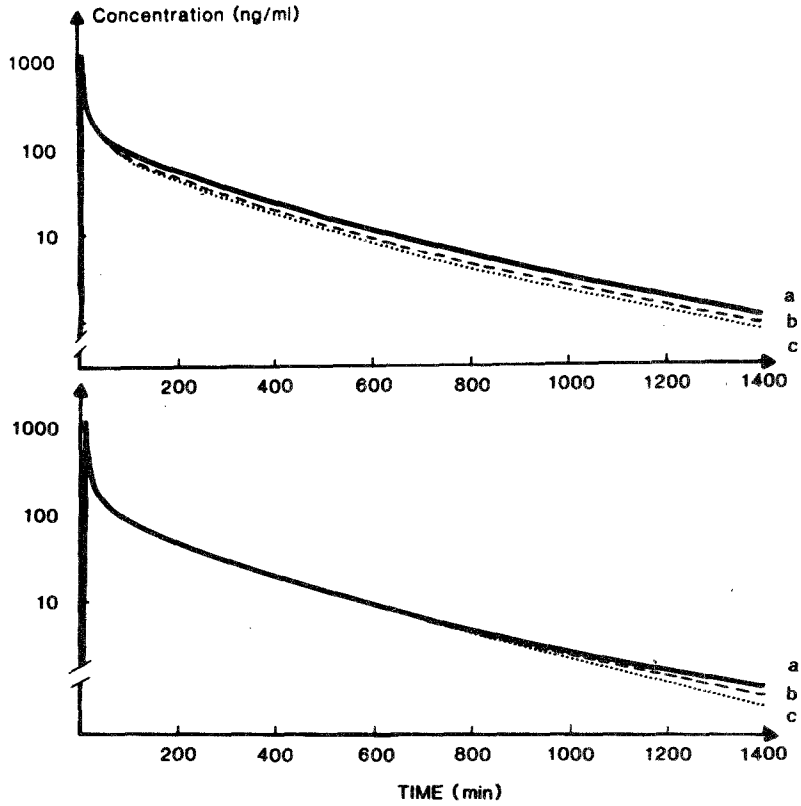

Fig. 6. Results of the sensitivity analysis; A±20% change in CL_{int} (upper figure, a is a decrease, b is the standard value, and c is an increase) and $V_{adipose}$ (bottom figure).

Fig. 10. Note especially the large differences in the time taken to reach steady state in maternal blood and fetal and maternal brain tissues. Even though steady state is reached within 2 or 3 days in maternal blood, there is a pronounced time lag before equilibrium in fetal brain.

DISCUSSION

Rationale for Use of the Extended Model

The main advantage of physiological models relative to traditional compartmental models is the possibility of predicting the concentration–time profile in practically and ethically inaccessible organs. These models also reveal characteristics of the system, e.g., large concentration differences between organs and blood, that may be disguised in compartmental analysis.

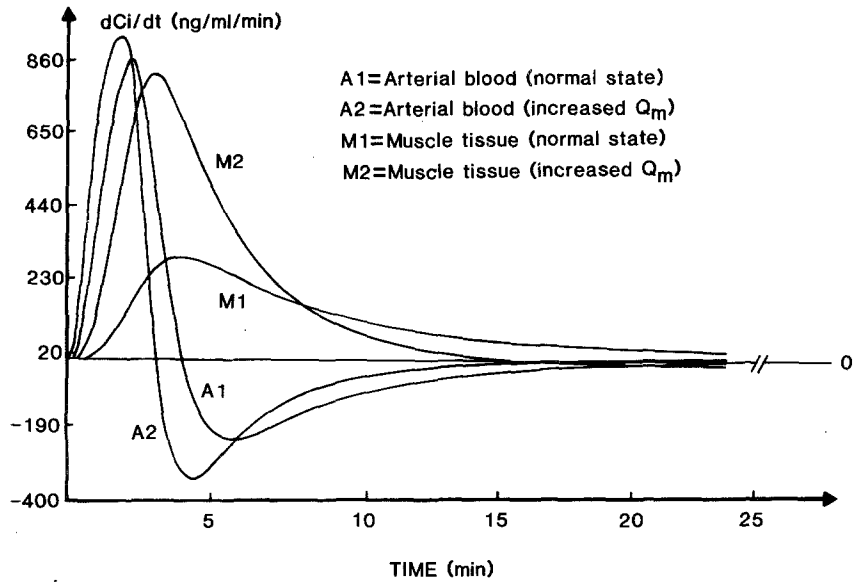

Fig. 7. The effect of a change in muscular blood flow (Q_M) on the derivative of the concentration-time profiles of arterial blood and muscular tissue.

We recently reported on a less complex model of methadone kinetics in the pregnant rat (11). In the present study we also included adipose tissue, since this tissue has a considerable uptake of methadone and is poorly perfused, a combination that enables adipose tissue to become a deep compartment that governs the concentration-time course during the terminal phase.

There were other reasons for extending the model and for not lumping organs in this study:

First, methadone behaves kinetically differently in the various organs. The partition coefficients may differ significantly in tissues with similar morphological properties; for example, in skeletal and heart muscle tissues we found a threefold difference in the tissue-to-blood partition coefficients (13.1 and 38.6, respectively). This may be important to consider from a toxicological point of view. Some organs serve as eliminating organs, e.g., the kidneys and the liver, and between other organs the perfusion varies and consequently they become kinetically different.

Second, the fetus is interesting to study from a toxicological point of view as a target organ for methadone. Animal studies have revealed embryotoxicity to methadone in rodents (18). A detailed fetal physiological model is therefore more attractive than a lumped fetal compartment model, in

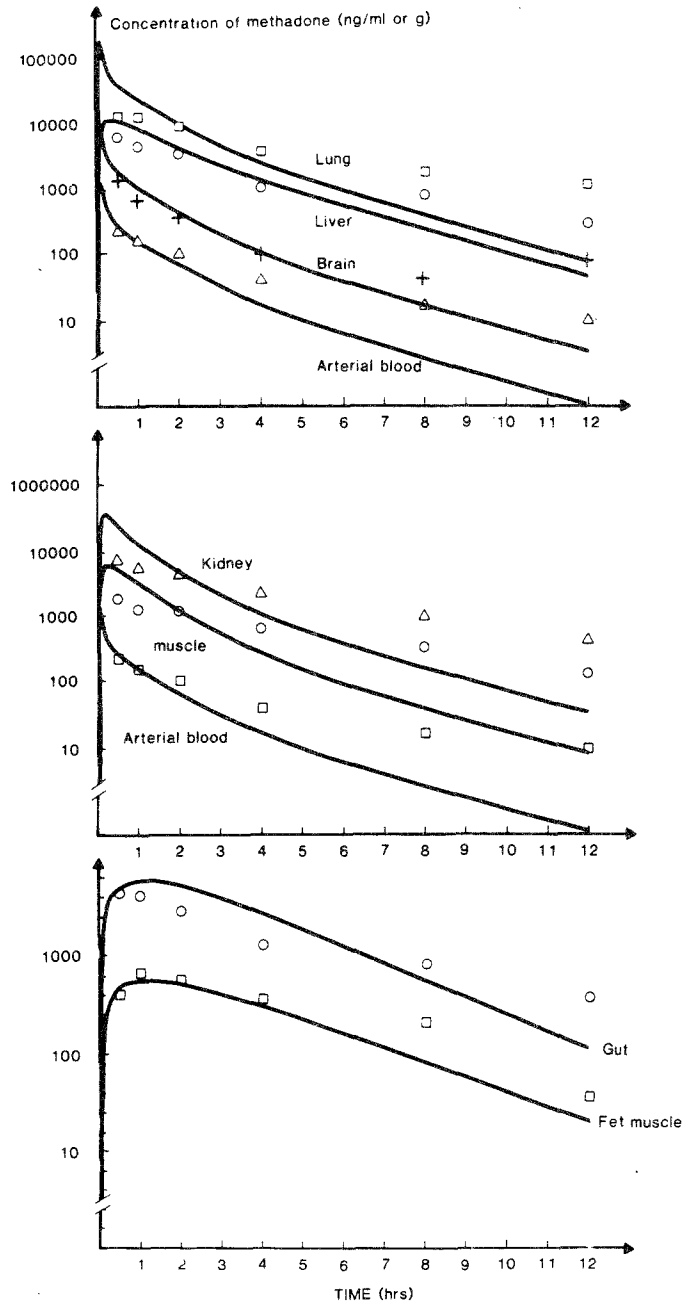

Fig. 8. Figure to elucidate the overal effects of a simulated decrease in body mass on methadone kinetics in rats. The symbols are observed values and the solid lines are simulated concentrations.

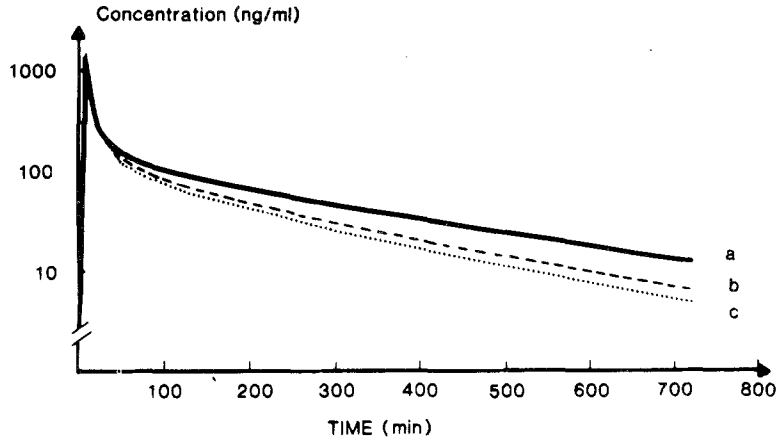

Fig. 9. The impact of a ±50% change in the intrinsic hepatic clearance on the time course of the methadone concentration in arterial blood (a is decrease, b is the standard value, and c is an increase in CL_{int}).

view of the significant concentration differences in, for example, fetal brain, liver, and eviscerated carcass.

Third, physiological and biochemical deviations are likely to occur among drug abusers, in that they show a reduced body mass, impaired hepatic or renal function, and are subject to drug interactions.

Comments on the Validation and Scaled-Up Model

For most tissues the model-predicted concentrations after iv bolus administration were consistent with the observed data. For pulmonary

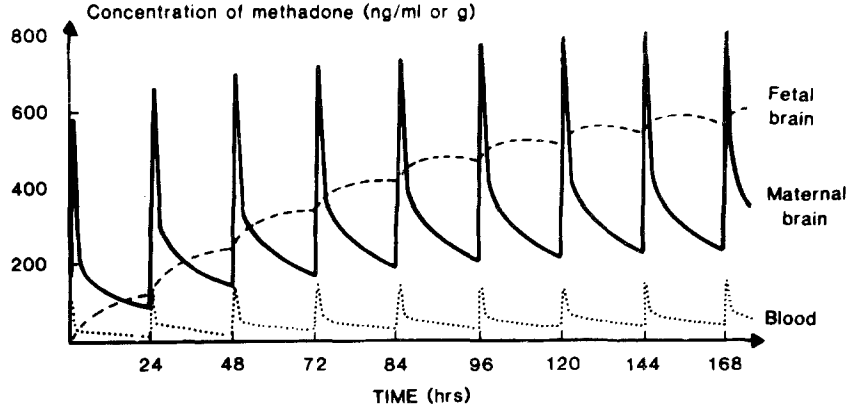

Fig. 10. The effect of a daily 30-mg maintenance dose of methadone in a pregnant patient was simulated, and the maternal and fetal brain and maternal blood are shown.

tissues significant deviations were found in the early observations ($t <$ 60 min) and we have not been able to remove this discrepancy in the present model. However, for our present purpose this is not critical.

The simulation also predicts three kinetic phases, two of which were observed in a previous investigation, where the methadone concentration declined bi-exponentially in blood and various tissues (11). The third terminal phase is an effect of the extended model, which also includes adipose tissues. At the terminal time points, during pseudo-equilibrium, the majority of the drug resides within adipose tissues. The uptake or release of the drug from a certain tissue will then also be related to the local blood perfusion.

Further simulations and experiments are required in order to assess more thoroughly the heuristic validity of the present model.

In view of the fact that the main part of the drug is sequestered into pulmonary, muscular, and adipose tissues during the initial, intermediate, and terminal time points, respectively, these tissues are of particular interest during the corresponding periods. It is evident that a major change in the adipose and muscular tissue volume have a bearing upon the terminal half-life.

The kinetics of methadone in blood was altered very little by changing the local tissue perfusion, unless it was related to an eliminating organ, e.g., the liver or the kidneys. The time taken to reach equilibrium within a particular organ was determined by the perfusion, as seen in Fig. 7. When the rate of drug transfer is equal to zero, equilibrium is attained. The rate then approaches zero at infinite time.

To judge the impact of a change in a certain parameter on the time course of the drug, one should know how much it contributes either to the clearance or to the volume of distribution. A 20–30% increase or decrease in the volume of the muscular compartment or in any other of the model parameters did not markedly affect the concentration–time courses of the drug. However, a reduction, in terms of underweight, in both the muscle and adipose tissue volumes, decreased the total volume of distribution, leading to a reduction in the half-life.

Since methadone exhibits a large tissue distribution, the impact of a decrease in the adipose and muscular tissue volume, which may be the case in chronic addicts or in malnutrition, is obvious from the simulation with the rat model illustrated in Fig. 8. One may of course speculate on the fact that the metabolic capacity may also decrease, leading to status quo with regard to the terminal half-life.

An important goal in the development of physiologically based models in animals is the potential application to humans by upscaling of the model parameters. To gain an impression of how a real time course of methadone might appear in the human, a simulation was performed with the proposed

model for treatment of the mother with 30 mg of methadone hydrochloride given orally once a day over a period of 8 days (Fig. 10). Such a simulation illustrates the completely different time course of drug in maternal blood and fetal tissues. This indicates that the maternal blood concentration is a rather poor measure of the ongoing processes in deep compartments such as the fetal brain. It is also interesting to note that the time taken to attain steady state in maternal blood and, for example, fetal brain differs vastly. The pronounced time lag between maternal blood and fetal brain concentrations might explain the clinical observations of delayed withdrawal symptoms in newborn infants of mothers undergoing methadone maintenance treatment (20).

Conclusions

The aim of physiological modeling is to represent the actual anatomy and physiology as closely as possible and to analyze the time course of the drug concentration in each tissue. It may therefore be possible to predict more accurately the concentration-time course in the maternal and fetal tissues of interest. However, before extrapolation outside the animal range is performed, a thorough systems analysis is required in terms of empirical, theoretical, and pragmatic validation, and also a sensitivity analysis, in order to elucidate the impact of various pharmacokinetic and physiological parameters and variables on the overall time course of the drug.

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