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ORIGINAL ARTICLES

A PHYSIOLOGICAL MODEL FOR THE DISTRIBUTION OF INJECTED AGENTS, WITH SPECIAL REFERENCE TO PETHIDINE†

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SUMMARY

The model is based on Mapleson's Model P for inhaled anaesthetics, but has compartments for lungs, peripheral shunt, kidneys, portal bed, liver, other viscera, muscle, other lean, fat, brain, i.m. injection site and for various blood "pools". Intracellular and extracellular fluids are represented separately in each compartment and in blood. In each fluid, four forms of the agent are distinguished: unionized dissolved in water ("standard" form), ionized dissolved in water, unionized dissolved in lipid, and bound to protein. Equations define the equilibrium between these four forms in any one fluid and between blood and tissue. After changing two of the more uncertain numbers in the quantification for pethidine, good agreement was obtained between computed and published venous concentrations after single i.v. and i.m. injections, continuous i.v. infusions and repeated i.m. injections. The model can be used to make a wide variety of "what if" predictions. (Br. J. Anaesth. 1993; **70**: 248–258)

KEY WORDS

Analgesics: pethidine. Pharmacokinetics physiological model

There are broadly two ways of modelling the distribution of anaesthetic and other agents in the body. In one, an empirical compartmental model is fitted to experimental data for the change in plasma concentration over time, as measured in several subjects; the resulting equations provide a good description of the mean response of that group of subjects, but cannot give much information about how other, different, groups of patients may respond. In the other method, a compartmental model is defined and quantified on the basis of known anatomy and physiology of the species, or even the individual, and of known physicochemical properties of the agent being modelled. The difficulty with these models lies in obtaining the necessary quantification data.

Traditionally, injected agents have mostly been modelled by the empirical approach, perhaps because of the difficulty of quantifying physiological models; inhaled agents have mostly been modelled by the physiological approach, no doubt partly because of the greater ease of obtaining the necessary quantifying information, but probably largely because of the pioneering work of Kety [1].

This Department has considerable experience in the physiological modelling of inhaled anaesthetics, so extending the technique to injected agents presented an interesting challenge. The model was designed to be general, but quantification has been attempted only for pethidine. As in the models of inhaled agents [2], it is assumed that diffusion is fast enough for equilibrium between blood and tissue to be complete within the time it takes the blood to flow through a capillary, but slow enough for there to be negligible direct diffusion of drug between compartments. Thus the distribution of the drug is perfusion-limited.

STRUCTURE OF THE MODEL

Anatomy and physiology

The structure of the model is based on Mapleson's Model P [3], in which circulation delays are taken into account by "storing" blood in a series of "pools" (fig. 1). This has been shown [3] to give almost as detailed an indication of circulation delays for inhaled anaesthetics as more complex models. It has also been shown [2] that, for predictions of the arterial concentrations of inhaled anaesthetics, the tissues of the body, other than the lungs, may be grouped into only three compartments but that, for the prediction of concentration in specific tissues, or even in parts of tissues with specific perfusion characteristics, it is necessary to represent each of those tissues as an independent compartment. Accordingly, in addition to the compartments in the original Model P, separate compartments are now included for the kidneys (for the sake of modelling renal excretion), the portal bed and the liver (for the sake of modelling metabolism), a "sample" brain compartment (only 10 g, but with a perfusion corresponding to that estimated to apply to the site of action of inhaled anaesthetics [4], or to the

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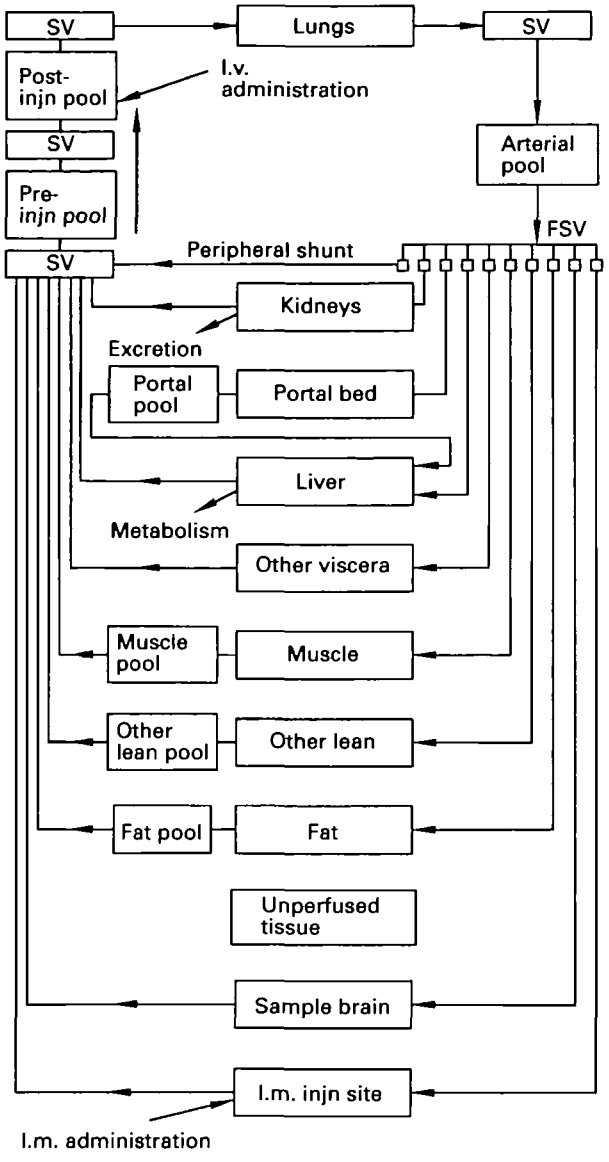

FIG. 1. Diagram of the model. SV = Stroke volume; FSV = fractional stroke volume; injn = injection.

medullary chemoreceptors [5]), and an i.m. injection site (10 g). In addition, because of the very different protein binding characteristics of muscle (see below) the customary "lean" compartment has been split into "muscle" and "other lean" compartments. "Unperfused" tissue is shown in figure 1 for the sake of completeness; it represents those tissues in which the perfusion is so small that exchange of agent between blood and tissue may be neglected without causing appreciable error in the rest of the model. Ventilation of the lungs is not represented because of the negligible vapour pressure of most injected agents.

Unlike model P, in this model *all* the blood is placed in pools, including a portal pool to obtain the appropriate circulation delay for blood reaching the liver from the portal bed.

Distribution of the injected agent is brought about as follows. A stroke volume of blood is removed from the post-injection pool and equilibrated with the tissue in the lung compartment; a stroke volume is removed from the arterial pool, divided into fractions according to the relative perfusion of the different compartments, and the fractions (together with a fractional stroke volume from the portal pool in the case of the liver) are equilibrated with the corresponding tissue; fractional stroke volumes are removed from the muscle, other lean, and fat pools; a stroke volume is removed from the pre-injection pool; any injection of drug is added to the appropriate site (i.v. post-injection pool, or i.m. injection site); all stroke volumes and fractional stroke volumes are added to the next "downstream" pool. The whole cycle of calculations is then repeated as often as necessary to follow the distribution process for the required period of time. Note that the "post-injection" pool is so called because, even though i.v. injections are added to it, it corresponds to the volume of blood which separates the point of injection (and corresponding points in all other peripheral veins) from the lungs.

The "stroke volume" is not necessarily of a physiological size; it is rather the volume of blood pumped by the heart in the period represented by one calculation cycle. For economy of computation time, this cycle period should be longer rather than shorter, but it cannot be longer than about 6 s in a standard 70-kg man because that gives a stroke volume of about 650 ml, and the volumes of the pre-injection, post-injection and arterial pools are each about 675 ml.

Physical chemistry

With inhaled anaesthetics, it is generally safe to work with the total concentration in blood (arterial or venous) or any tissue and to make two assumptions: first, that, in the clinical range, the total concentration at any site is proportional to the partial pressure at that site; second, that the constant of proportionality (the solubility) does not change appreciably in the course of anaesthesia. With injected agents it seems necessary, until proved otherwise, to distinguish the concentrations of four different forms of the drug: unionized, dissolved in water; ionized, dissolved in water; unionized dissolved in lipid; bound to protein. It is also necessary to distinguish between plasma and erythrocytes, and between interstitial fluid (ISF) and tissue cells. This is because of their different compositions, different values of pH (leading to different ionized:unionized ratios) and different proteins.

In general, only the unionized form of a drug can diffuse freely through cell membranes. Therefore, when two domains, for example plasma and erythrocytes, are in equilibrium, the unionized, dissolved in water, concentration is the same in both. This we have termed the "concentration in standard form" and given it the symbol *Cs* (mol drug per kg water). It is equivalent to the partial pressure or tension of an inhaled agent because, in the absence of elimination and metabolism, all parts of the body tend towards the same tension, or the same *Cs*.

The other concentrations are related to *Cs* as follows. The ionized, dissolved in water, concentration (mol drug per kg water) (*Ci*) is given by:

$$Ci = Cs \times 10^{b(pK_a - pH)} \qquad (1)$$

where $b = 1$ for a basic drug (such as pethidine), and -1 for an acidic drug; $pK_a = pK_a$ of the drug (strictly pK_a' as the equation is in terms of concentration and not activity); pH = pH of the medium.

The unionized (ui), dissolved in lipid (l), concentration (mol drug per kg lipid) is given by:

$$Cui_l = Cs \times \lambda l/s \quad (2)$$

where $\lambda l/s$ = lipid/water partition coefficient as defined by Kaufman, Senco and Koski [6] for the unionized form of the drug. (Beware confusion with reported coefficients, sometimes termed "distribution coefficients", but sometimes also termed partition coefficients, which relate the concentration dissolved in lipid to the *total* concentration in water.)

The following equation was used for the concentration bound to protein (mol drug per kg protein):

$$Cb = \frac{n}{m} \times \frac{k.Cs}{1+k.Cs} \quad (3)$$

where n = number of binding sites on the protein molecule (maximum mol drug per mol protein); m = molar mass of the protein (kg mol^{-1}); k = "Scatchard association constant" [7] (kg water per mol drug). This is essentially the Scatchard equation and is the simplest one to represent non-linear, saturable binding. Thus when Cs is large ($k.Cs \gg 1$), $Cb = n/m$; therefore n/m is the maximum (saturated) concentration. When $Cs = 1/k$, $Cb = (n/m)/2$; therefore k is most usefully thought of as the reciprocal of the concentration in standard form (Cs_{50}) at which Cb is half maximum. Equation (3) is used to represent the net effect of all the proteins in any given "domain" (plasma, erythrocytes, ISF, tissue cells). Provided that the necessary quantification data are available, the equation can be reformulated by substituting Ci for Cs, to represent binding of only the ionized form of the drug to the protein, and by substituting Cdw, the total, dissolved in water, concentration ($Cdw = Cs + Ci$), to represent binding of both forms of the drug equally.

The above concentrations are multiplied by the mass fractions (kg medium per kg domain) of water (F_w), lipid (F_l) and protein (F_{pr}) to obtain concentration (B) in mol drug per kg domain:

$$\begin{aligned} Bs &= Cs \times F_w \\ Bi &= Ci \times F_w \\ B_l &= C_l \times F_l \\ Bb &= Cb \times F_{pr} \end{aligned}$$

These are then added to give the total concentration (mol drug per kg domain) in all forms:

$$\begin{aligned} Ba &= Bs + Bi + B_l + Bb \\ &= [\{1 + 10^{b(pK_a - pH)}\} \times F_w \\ &\quad + \lambda l/s \times F_l \\ &\quad + \frac{n}{m} \times \frac{k}{1+k.Cs} \times F_{pr}] \times Cs \end{aligned} \quad (4)$$

Note that this equation is of the form $Ba = [K] \times Cs$, so that K (which represents the terms within the square brackets) is equivalent to a solubility coefficient for an inhaled anaesthetic. However, K depends, not only on the drug (via b, pK_a, $\lambda l/s$, n, m, k) and domain (via F_w, F_l, F_{pr}, n, k), but also on pH and Cs. Therefore, unlike inhaled agents, the solubility is concentration dependent (unless $k.Cs \ll 1$; that is, $Cs \ll Cs_{50}$) and may vary during anaesthesia because of changes of pH.

The total concentration of drug in all forms in blood is then given by:

$$Ba_{bl} = Ba_r \times F_r + Ba_P \times (1 - F_r) \quad (5)$$

where Ba_r and Ba_P = concentrations in all forms in erythrocytes (red cells) and plasma, respectively; F_r = the mass fraction of erythrocytes in the blood. (PCV is the *volume* fraction of all cells in the blood.)

Similarly, the total concentration of drug in tissue is given by:

$$Ba_{tl} = Ba_c \times F_c + Ba_{ISF} \times (1 - F_c) \quad (6)$$

where Ba_c and Ba_{ISF} = concentrations in all forms in tissue cells and ISF; F_c = mass fraction of cells in the tissue.

Finally, the total amounts (A) (in mol) of drug in all forms in a bolus or pool of blood, or in a tissue compartment, are given respectively by:

$$Aa_{bl} = M_{bl} \times (Ba_r \times F_r + Ba_P \times (1 - F_r)), \quad (7)$$

$$Aa_{tl} = M_{tl} \times (Ba_c \times F_c + Ba_{ISF} \times (1 - F_c)) \quad (8)$$

where M_{bl} and M_{tl} = mass of blood and tissue, respectively.

Erythrocytes and plasma in a bolus or pool of blood are assumed always to be in equilibrium (both at the same Cs), as are the cells and ISF in a tissue compartment. Therefore, if Cs is known, Ba_r, Ba_c, etc., can be calculated from appropriately quantified versions of equation (4) and substituted in (7) and (8) to give Aa_{bl} or Aa_{tl}.

In contrast, when a bolus of blood is equilibrated with a tissue compartment (both are brought to the same Cs), equations (7), (8) and (4) have first to be used in reverse to determine the common Cs. Thus, at the start of a simulation, all tissue compartments and blood pools contain no drug. For an i.v. injection, a known amount of drug is put into the post-injection pool. A known fraction of this blood (a stroke volume), containing an equal fraction of the contained drug, is drawn from this pool. Therefore the amount of drug in this bolus is known. Since it is to be equilibrated with the lung compartment, call the amount $Aa_{bl,L}$. Also, the amount of drug in the lung-compartment tissue, $Aa_{tl,L}$, is known: it is zero. Equilibrium is then brought about by setting the sum of $Aa_{bl,L}$ and $Aa_{tl,L}$ to $Aa_{bl+tl,L}$ and solving equations (7) and (8) (in versions specific to the lung compartment) iteratively for Cs. Then the amount in the lung compartment can be calculated from equations (4) and (8) ready for the next equilibration; and the amount in the bolus can be calculated from equations (4) and (7) for addition to the arterial pool. (In practice, to avoid the accumulation of rounding errors, the amount in the compartment is determined by subtracting the calculated amount in the bolus from the total amount present before equilibration.) In turn, boluses of blood from the arterial pool, containing known amounts of drug, are similarly equilibrated with tissue compartments containing known amounts of drug (initially zero). Thus the

distribution of the drug around the body may be followed indefinitely: at every equilibration, the amounts of drug in blood bolus and tissue before equilibration are known, so the equilibrium Cs can be calculated, and hence the amounts in tissue and bolus after equilibration. Thus the representation of equilibration is quite elaborate.

By contrast, the representation of metabolism and renal excretion is relatively simple: this is primarily because of the lack of data to quantify anything better—although Higgins [8] has presented some ingenious ideas for improvement. For hepatic metabolism in the present model, a fixed extraction fraction is used: after equilibration of each bolus of blood with the tissue of the liver (H), the amount of drug in all forms in blood bolus plus tissue after metabolism, $Aa_{bl+tl,H}{}^{a}$, is calculated from the amount before metabolism, $Aa_{bl+tl,H}{}^{b}$, from:

$$Aa_{bl+tl,H}{}^{a} = Aa_{bl+tl,H}{}^{b} \times (1 - F\text{met}) \quad (9)$$

where Fmet is the fraction metabolized. A similar approach is used for renal (R) excretion except that the excretion fraction is made pH-dependent:

$$Aa_{bl+tl,R}{}^{a} = Aa_{bl+tl,R}{}^{b} \times (1 - F\text{exc}) \quad (10)$$

where

$$F\text{exc} = 10^{(a_U + b_U \times \text{pH}_U)} \quad (11)$$

where pH_U = pH of the urine, and a_U and b_U are constants, estimated empirically from the literature (see below).

The model exists as a computer program written in strict Fortran IV for the sake of "portability". During its lifetime, it has been run on an ICL System-4 mainframe computer, a Data General Nova 2 mini computer, a Honeywell mainframe, an IBM 3084, and under Unix on a DEC mainframe. On the DEC mainframe, an 8-h simulation took about 7 s. When the program was run on an IBM-compatible personal computer, with a full 80386 processor and 80387 maths co-processor, it took 14 min; on an Acorn Archimedes personal computer, with an ARM3 processor but no maths co-processor, it took 13 min.

QUANTIFICATION OF THE MODEL

Anatomy and physiology

Body mass was normally taken as 70 kg and cardiac output as 6.48 litre min^{-1} [9]. The division of the total body mass into compartments and the sharing of the cardiac output between them (table I) was as previously specified [9], except as follows. The lean compartment was split into skeletal muscle and "other lean" (on the basis of the report of the International Commission on Radiological Protection (ICRP) [10]). Also, some trivial rounding errors were corrected.

The water, lipid and protein content of the tissue in each compartment, and of the plasma and erythrocytes (table I), was derived, as previously [9], from the ICRP report [10]. Here, however, the values have been corrected to those which are applicable when the "residual blood" (25% of the total blood volume) [10], and its contained water, lipid and protein, are mathematically removed from the tissues in each compartment. Also, in those few instances in which the sum of the masses of water, lipid, protein and ash for a tissue exceeded the (no-doubt rounded) total mass for a tissue [10], the amounts were expressed as a fraction of the sum of those components. ICRP values [10] were used for the densities of body tissues and fluids including, in particular, 1.10 g ml^{-1} for erythrocytes, 1.03 g ml^{-1}

TABLE I. *Main characteristics of compartments for standard man. "Net mass" of tissue excludes "residual blood" [10]*

Compartment	Net mass (% whole body)	Net tissue mass (%)				Arterial perfusion (% of cardiac output)	Blood pool (% of total blood)	a_c in eq. (12) for cell pH
		Water	Fat	Protein	Cells			
Lung parenchyma	0.66	74.4	1.4	17.4	80	100.0	—	−0.40
Peripheral shunt	0.00	—	—	—	—	15.1	0.0	—
Renal	0.41	76.4	5.5	16.8	80	18.8	0.0	−0.30
Portal bed	1.99	78.3	6.1	13.8	80	17.1	17.1	−0.60
Hepatic	2.46	71.9	6.9	17.8	80	6.9	0.0	−0.30
Other viscera	2.69	77.2	10.9	9.4	73	19.1	0.0	−0.60
Skeletal muscle	39.62	78.6	2.2	17.1	80	9.1	17.3	−0.46
Other lean	12.83	54.4	15.7	28.4	80	8.6	16.5	−0.40
Fat	19.56	13.4	81.8	4.6	92.5	5.3	10.1	−0.20
Unperfused tissue	11.92	—	—	—	—	0.0	0.0	—
Sample brain	0.0143	78.5	11.2	7.4	70	0.150	0.0	−0.30
I.m. injection site	0.0143	78.6	2.2	17.1	80	0.0033	0.0	−0.46
Blood	7.86	—	—	—	—	—	—	—
Arterial pool	—	—	—	—	—	—	13.0	—
Venous pools								
Pre-injection	—	—	—	—	—	—	13.0	—
Post-injection	—	—	—	—	—	—	13.0	—
Plasma	—	91.7	0.7	6.6	—	—	—	—
Erythrocytes	—	62.5	0.5	32.5	—	—	—	−0.20
ISF in:								
Other viscera	—	98.3	0.0	1.7	—	—	—	—
Sample brain	—	99.0	0.0	1.0	—	—	—	—
Other compartments	—	96.5	0.0	3.5	—	—	—	—

for plasma, and 1.06 g ml^{-1} for whole blood. The results differ little from the previous values, except for the marked differences between skeletal muscle and "other lean". Water, lipid and protein content of ISF in various compartments was estimated [11] from data in the literature.

Values for the mass fraction of cells in each tissue (table I) were derived from the literature [11]. The volume of erythrocytes was set at 0.435 litre per litre of blood [12] = 0.45 kg per kg. The pH values of plasma and ISF were taken usually as 7.4; the intracellular pH values for erythrocytes and for each compartment were calculated according to:

$$pH_c = pH_e + a_c + b_c(pH_e - 7.4) \qquad (12)$$

where pH_c = pH in the cell; pH_e = pH of extracellular fluid (plasma, or ISF); a_c and b_c = constants. Values of a_c (table I) were derived from the literature where possible [11]; elsewhere Stewart's [13] values, derived from chemical equilibrium theory, were used: −0.2 for erythrocytes and −0.4 for tissue cells. For b_c, theoretical values, derived [11] from Stewart's [13] equation for uncompensated respiratory acidosis, were used exclusively: −0.4 for erythrocytes and −0.8 for tissue cells.

Physical chemistry

The molar mass of pethidine is 0.2473 kg for the base and 0.2838 kg for the hydrochloride [14]. Throughout the remainder of this paper, doses are reported in mg of pethidine hydrochloride because that is the common practice, and doses reported in the literature are assumed to be in terms of the hydrochloride unless there is evidence to the contrary. There is fairly close agreement on the pK_a' of pethidine and, after careful consideration and correction for activity coefficients [11], the value of 8.62 was adopted as relevant to a clinical concentration of 0.165 mol litre^{-1} at 37 °C. Information on the lipid/water partition coefficient is surprisingly meagre and indirect. Davis [11] concluded that the most likely value was 5, but that it might be as large as 50 or even 500.

The characteristics of the binding of pethidine to protein were determined experimentally for plasma, erythrocytes and muscle cells [11]. The resulting values of n and k in equation (3) are given in table II on the basis of two different hypotheses: that only unionized pethidine binds to protein; and that all pethidine binds, irrespective of whether it is ionized or unionized. (The experiments were unable to discriminate between the two hypotheses.) The fractional values for n (the number of binding sites on the protein) arise because the equation is being used empirically to fit the experimental data on the assumption of a hypothetical "average protein". The mean molar masses of the proteins concerned (table II) were derived from the literature [11].

To complete the gaps in the quantification of protein binding, the values of n and k for plasma have been assumed to apply to interstitial fluid and most other cells. The one exception was cells in the lung parenchyma, because Roerig and others [15] have shown a large first-pass uptake of pethidine by the lungs and Persson and colleagues [16] have reported a steady-state tissue/blood partition coefficient of 30 for the lungs. Therefore, for these cells, n was increased to a value such that, at small values of Cs ($k.Cs \ll 1$), $Ba_{tI,L}/Ba_{bI,L}$ (from versions of (5) and (6) specific to the lung compartment) was equal to 30—rather than the 1.5 obtained by using the values of n and k for plasma protein.

On the basis of a detailed study of the literature [11], the extraction fraction of the liver, Fmet, was set at 0.535 while, for renal elimination, a_U and b_U in equation (11) were set at 0.2955 and −0.2914 respectively. Urine pH was taken as 6.2.

TESTING OF THE MODEL

General

The purely computational validity of the Fortran program was tested in a way that is not often practical. Dr M. J. Higgins wished to develop a similar model for fentanyl [8]. He was provided with a copy of the original program [11] which he first translated into the Basic language. Before adapting the result to fentanyl, he corrected errors in his first Basic version, and detected and corrected a number of errors in Davis's original Fortran program. The version of the Fortran program used in preparing this paper has been shown to give the same results as Higgins' Basic program for pethidine when they are quantified in the same way. The net effect of the corrections, however, is small—as comparison with Davis's thesis [11] will show.

The biological validity of the model was tested by

TABLE II. *Protein binding characteristics—*n *and* k *as in equation (3). Data based on work by Davis [11], but see text for values for lung parenchymal cells*

Location of protein	Mean molar mass (kg)	Binding of unionized pethidine		Binding of all pethidine	
		n (mol peth/ mol protein)	k (kg water/ μmol peth)	n (mol peth/ mol protein)	k (kg water/ μmol peth)
Erythrocytes	65	0.0293	0.12287	0.0277	0.01697
Muscle and i.m. injection site	76	0.8547	0.08013	1.4286	0.00159
Lung parenchymal cells	91	13.9600	0.03197	3.9000	0.00566
Plasma, ISF and all other cells	91	0.2584	0.03197	0.3268	0.00566

quantifying it to match the circumstances of published experimental studies and then comparing predicted and measured concentrations. Only those studies which report their circumstances and results in the necessary detail could be used. Also, since the model was quantified on the basis of healthy conscious volunteers, comparison was confined mainly to studies involving such volunteers.

Composition of peripheral venous blood

Almost all experimental studies report concentrations in *peripheral* venous plasma or blood. The composition of this is some unknown mixture of venous blood from the peripheral shunt, muscle, fat and, perhaps, other lean compartments. The contribution from the other lean compartment was neglected because the majority of its venous drainage comes from non-peripheral tissues. In the absence of firm information about the relative contributions from the other compartments, the most "neutral" assumption is that of equal fractions from all three (shunt, muscle and fat). However, six other assumptions were also tried: 20% from any one compartment with 40% each from the other two; and 50% from any one compartment with 25% each from the other two—a total of seven different mixtures.

The largest differences can be expected shortly after an i.v. injection because then the arterial, and hence peripheral shunt, concentration is very large, while the concentrations from the muscle and fat compartments are almost zero. Therefore the injection of pethidine hydrochloride 50 mg i.v. to a standard man was simulated and the computed peripheral venous plasma concentrations for each of the seven different mixtures were plotted against time. As expected, there were substantial differences initially, but these diminished rapidly (fig. 2): after 5 min the maximum deviation, from the equal-fractions mixture, of any of the other mixtures was

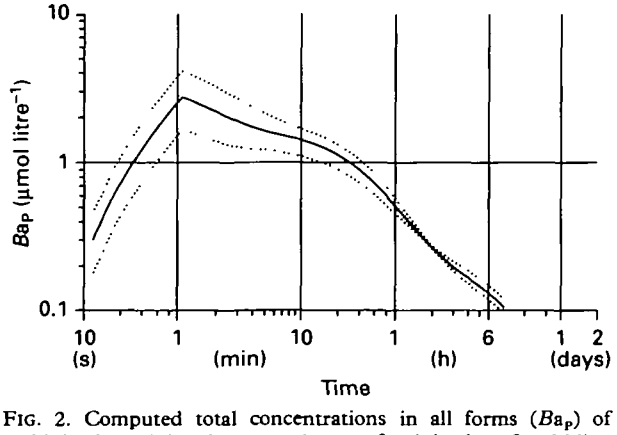

FIG. 2. Computed total concentrations in all forms (Ba_P) of pethidine in peripheral venous plasma, after injection of pethidine hydrochloride 50 mg i.v. over 60 s, to a 70-kg standard man (table I), using a lipid/water partition coefficient, λl/s, of 5 and assuming binding of only the unionized form of the drug to protein (table II). The continuous line was obtained by assuming that the blood was composed of equal flows from the three compartments: peripheral shunt, muscle and fat. The dotted lines indicate the "envelope" or range of the curves obtained by assuming the following compositions. Each compartment in turn was set to contribute: first, 20% (with 40% from each of the other two); then 50% (with 25% from each of the other two).

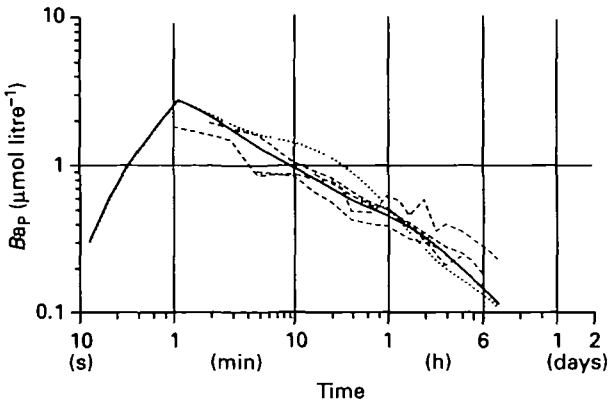

FIG. 3. Comparison of computed and measured total concentrations of pethidine in peripheral venous plasma (Ba_P) following an injection of 50 mg i.v., normally over 60 s. The broken lines refer to four experimental studies and represent means of from four to six patients with durations of injection of 60 s [17, 18], 120 s [20] and unspecified [19]. The smoothly curving dotted line (after 66 s) is that generated by the model when quantified as in figure 2 (equal flows of venous blood from the peripheral shunt, muscle and fat compartments; λl/s = 5; duration of injection = 60 s); the smooth continuous line is that produced when λl/s was set to 50.

±30%. Therefore all the following comparisons with experimental studies used the equal fractions composition of peripheral venous blood.

Single i.v. injection

Four experimental studies [17–20] were found which gave sufficient information about single i.v. injections of pethidine hydrochloride 50 mg. They are compared with two versions of the model in figure 3. The jagged broken lines represent the means of the four to six patients in each study; the smooth dotted and continuous lines represent the results of the model using lipid/water partition coefficients (λl/s) of 5 and 50, respectively. It can be seen that the original "most probable" value of 5 results in a systematic deviation of shape (dotted curve) from the experimental data. On the other hand, a value of 50 gives a curve (continuous) which lies almost entirely within the range of the four experimental means. Using a coefficient of 500 changed the shape of the computed curve further in the same direction and worsened the fit. Therefore, a coefficient of 50 was adopted for all further simulations.

Single i.m. injection

Three suitable experimental studies [19–21] were found for 50-mg injections i.m., one of which [20] included injection into two different muscles (gluteus and deltoid) in the same five volunteers on different occasions. The four experimental plots are compared with the model in figure 4. The dotted line represents the model as described so far (with λl/s = 50) and is not consistent with the experimental data. Changing the size of the i.m. injection site (the amount of tissue over which the injection is presumed to be distributed—10 g in the model) has little effect: doubling the size of the site doubles the blood flow, but halves the concentration. However, increasing the specific perfusion (g min^{-1}/g tissue) of the site, to

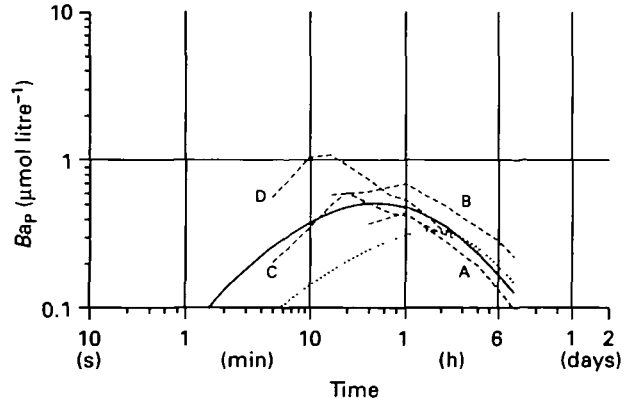

FIG. 4. As figure 3, but for pethidine 50 mg *i.m.* The broken lines represent the mean measured concentrations from: A 24 patients, muscle unspecified [21]; B six patients, muscle unspecified [19]; C five patients, gluteus muscle [20]; D the same five patients, deltoid muscle [20]. The dotted line is that produced with the model quantified as in figure 3 (with λl/s = 50); the continuous line results from increasing the perfusion of the i.m. injection site to three times that of the main muscle compartment.

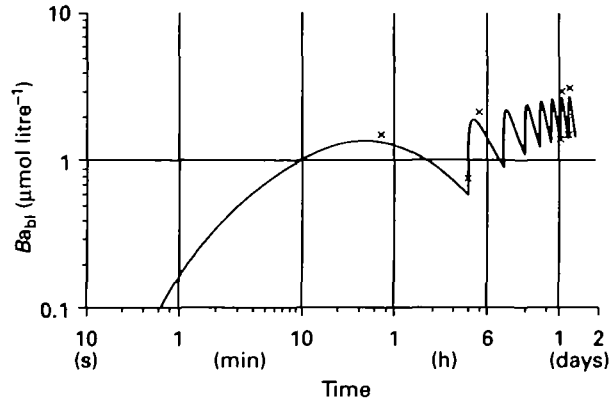

FIG. 6. As for figure 4 (with tripled perfusion of i.m. injection site), but in terms of whole blood concentration, and for eight successive, 4-hourly, i.m. injections of pethidine into the right buttock of patients after hysterectomy or cholecystectomy [24]. The measured values (x) are means for the five patients for whom complete data were reported.

three times that of muscle in general, placed the computed curve (continuous) within the range of the experimental means, except those for the first 1 h after injection into the deltoid muscle. To match those data would require about a nine-fold increase in perfusion. One study with a 100-mg injection into the gluteal muscle of four volunteers [22] was almost perfectly fitted with the three-fold increase in specific perfusion.

Continuous i.v. infusion

One study [23] reported measurements of *blood* concentration during continuous i.v. infusion of pethidine, at three different rates, to 10 patients, for 32 h after abdominal hysterectomy. The predictions of the model matched the trend of the measurements (fig. 5), but were less than the measured concentrations to a remarkably consistent degree: mean concentration 32% less than measured (SD 6%).

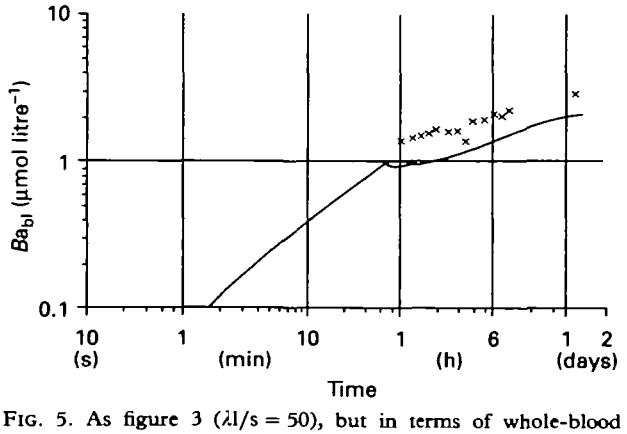

FIG. 5. As figure 3 (λl/s = 50), but in terms of whole-blood concentration (Ba_{bl}) and for three successive i.v. infusions of pethidine to patients after hysterectomy [23]: 1.0 mg min^{-1} for 45 min, 0.53 mg min^{-1} for 28 min, and 0.4 mg min^{-1} for the remainder of 32 h. The measured values (x) are means for 10 patients.

Repeated i.m. injections

One study [24] reported some mean peak and mean trough blood concentrations during a series of regular, 4-hourly injections of pethidine 100 mg i.m. (right buttock) to patients after hysterectomy or cholecystectomy. When this study was simulated, with the normal muscle perfusion applied to the i.m. injection site, the experimental trough concentrations were quite well matched, but the trough-to-peak amplitude was only 50% that in the experimental data. However, when the perfusion of the i.m. injection site was increased three-fold (as in matching most single i.m. injections) the match was good (fig. 6) except that, again, the simulated values were systematically a little smaller: mean concentration 11% less than measured (SD 8%).

Blood : plasma concentration ratios

In the simulations, this was almost always 1.26—within the very wide range of published experimental values: 0.68 [25], 0.98–1.04 [26] and 1.20–1.43 [17].

Alternative protein binding characteristics

Simulations were also run on the assumption that all forms of pethidine bound to plasma (rather than only the ionized form) and using the corresponding n and k values from table II. This had a relatively small effect on the results: the new curves of simulated concentration gave slightly better fits to the experimental data at some times and slightly worse at others.

Simulation of very rapid injections

The model failed to match the data of Roerig and others [15]. They measured the concentration of pethidine at 1-s intervals in the radial artery for 45 s after injecting 25 mg in 2 s into a central venous catheter. The measured concentration increased and decreased much more rapidly than predicted by the model, even when the duration of the calculation cycle was reduced from 6 s to 1 s.

APPLICATION OF THE MODEL

The above comparisons give confidence in the broad validity of the model and encouraged us to make some predictions from it.

Change in cardiac output

When the cardiac output was reduced to 50% of standard, peripheral venous plasma concentrations were slower to increase and reached a marginally greater peak (because of the slower distribution to the tissues). However, after the first few minutes, the change was simply that the concentration decreased more slowly: the two curves could be made to coincide on the log (time) scale of figures 2–6 by shifting the halved cardiac output curve by log (0.5) to the left.

Change in plasma pH

Figure 7 shows that, in severe respiratory acidosis (plasma pH 6.9 instead of 7.4), the plasma concentration after injection of pethidine 50 mg i.v. is doubled initially and remains greater than normal throughout the 8 h plotted. By contrast, the concentration in standard form in the brain (which is what is likely to be most important in terms of determining effect) is almost halved from 5 min onwards (fig. 8).

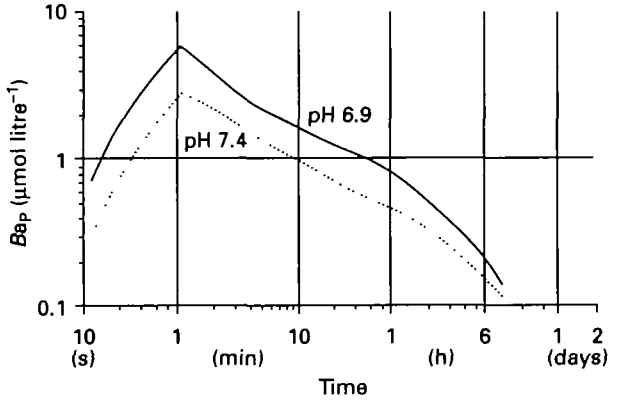

FIG. 7. Computed effect of respiratory acidosis (pH 6.9) on total peripheral venous plasma concentration (Ba_P) after pethidine 50 mg i.v. Model as in figure 3 (λ1/s = 50).

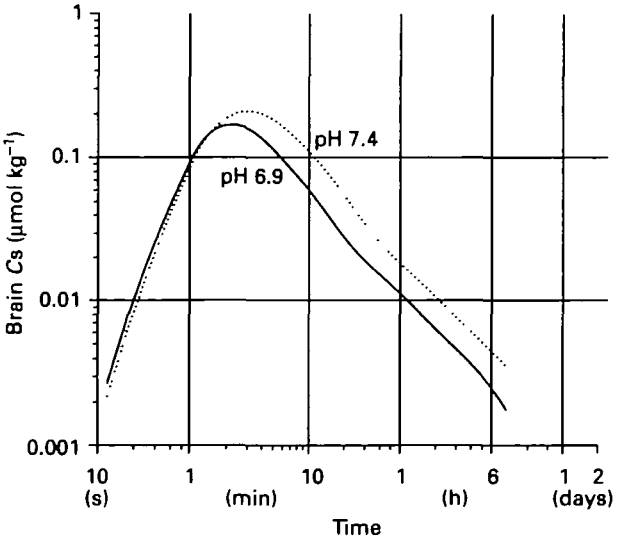

FIG. 8. As figure 7, but showing the computed effect of respiratory acidosis on the concentration in standard form (unionized, dissolved in water (*Cs*)) in the sample brain compartment.

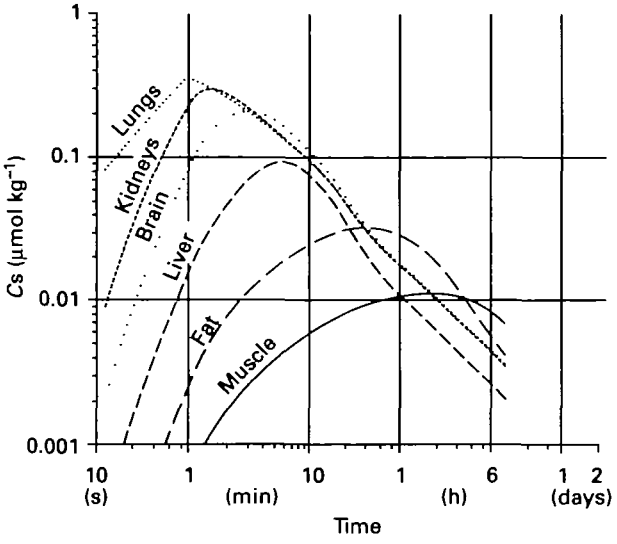

FIG. 9. Computed concentrations in standard form (*Cs*) in various compartments (the continuous line is for arterial blood) following pethidine 50 mg i.v. Model as in figure 3 (λ1/s = 50).

Concentrations in standard form (Cs) in various compartments

These are shown in figure 9, again after 50 mg i.v. Note that the peak concentration for each compartment, signifying no uptake or release of pethidine from the tissue, occurs as its curve intersects the curve for the arterial concentration. This is because, at that instant, blood and tissue are in equilibrium (at the same *Cs*). However, in the case of liver, the peak concentration is less than the arterial and occurs when the rate of uptake is equal to the rate of metabolism. Note also that, unlike all volatile agents, muscle is slower to equilibrate than fat. This is because, for pethidine, it has a larger tissue/blood partition coefficient than fat (see below).

Tissue/blood partition coefficients

Because the model includes saturable binding to protein (equations (3) and (4)), tissue/blood partition coefficients can be expected to be concentration-dependent. However, it transpires that, with the current quantification of the model and for clinical doses of pethidine, the concentrations are never (with one exception) great enough for this to be apparent. Consequently, fixed computed partition coefficients can be reported: table III shows that, with λ1/s = 50, these are mostly between 1.5 and 2, and the largest coefficient is not for fat (1.7) but for muscle (6.44). This is because of the large protein binding capacity found experimentally [11] for muscle. The one exception to constant coefficients is the i.m. injection site. Here, the initial total concentrations are so large (17400 μmol kg^{-1} after 50 mg i.m.) that protein binding approaches saturation, leading to extra large *Cs* values (460 μmol kg^{-1}) and hence large blood concentrations (8000 μmol kg^{-1}).

TABLE III. *Computed tissue/blood partition coefficients for pethidine at small concentrations in standard form* (k.Cs ≪ *1*) *and for* $\lambda l/s = 50$

Compartment	Coefficient
Lung	1.54
Renal	1.45
Portal bed	2.07
Hepatic	1.45
Other viscera	1.86
Skeletal muscle	6.44
Other lean	1.84
Fat	1.70
Sample brain	1.21

As a consequence, the initial injection site/blood partition coefficient is only 2.17, gradually increasing towards the 6.44 of the remainder of muscle as the pethidine is absorbed. The large concentration in the blood draining the i.m. injection site reduces the local blood/plasma coefficient from the normal 1.26 to 1.02.

Effects of speed of injection

Peacock and others [27] have reported the effects on induction time of three different rates of injection of propofol: "normal" (20 ml min^{-1}), half-normal and quarter-normal. The model was used to simulate a corresponding experiment for pethidine, with injection rates of 50 (normal), 25 and 12.5 mg min^{-1}; "induction time" was taken to be the time at which the computed concentration in the brain compartment reached some specified threshold. This threshold ($Cs = 0.061$ μmol kg^{-1}) was chosen so as to force the induction time for pethidine at the normal rate to match the experimental value for propofol at its normal rate (51.1 s). A precisely similar experiment, with 2.5% thiopentone [28], using the same three rates of infusion, was matched in the same way, except that the threshold concentration in the pethidine model was set to 0.040 μmol kg^{-1}. This forced the simulated induction time with pethidine at the normal rate to equal 40.8 s, as in the experimental study with thiopentone. Table IV shows that the ratio of simulated to measured induction times (fixed at 1.0 for the normal speed of injection in each comparison) remained within −4% to +11% of 1.0 for the other conditions for both agents.

TABLE IV. *Effect of speed of injection on induction time (s): mean measured values for propofol [27] and 2.5% thiopentone [28] ("normal" injection rate 20 ml* min^{-1}*); simulated "induction times" (see text) for pethidine (normal rate 50 mg* min^{-1}*), matched in turn to those for propofol and thiopentone at the "normal" injection rate*

	Speed of injection		
	"Normal"	Half-normal	Quarter-normal
Measured for propofol	51.1	67.6	103.5
Simulated for pethidine	51.1	74.9	113.9
Simulated/measured	1.0	1.11	1.10
Measured for thiopentone	40.8	57.4	90.8
Simulated for pethidine	40.8	58.7	87.1
Simulated/measured	1.0	1.02	0.96

Peacock and others [27] also report the mean peripheral plasma concentration at the moment of induction with propofol. With the slowest injection rate, this was only 0.50 of that for the normal rate; in each of the simulations of pethidine, the corresponding fraction was 0.52. These authors further report that, at the moment of induction, there was less hypotension with the slowest injection rate. This could be explained by following Chilcoat, Lunn and Mapleson [29] in assuming that the "blood-pressure control centre" is better perfused than the "induction-of-anaesthesia control centre": the simulation showed that, in a compartment with four times the specific perfusion of the sample brain compartment (actually the kidney), *Cs* at the moment of induction with the slowest injection rate was 70% of that with the normal rate.

DISCUSSION

The quality of fit of the model to the experimental data is encouraging. Using the most "neutral" mixture, of equal fractions of flow from the peripheral shunt, muscle and fat compartments, to form the peripheral venous blood, and adopting the second most likely value of the lipid/water partition coefficient ($\lambda l/s = 50$ instead of 5), makes the predictions of peripheral venous plasma concentration lie within the range of experimental data for four studies of 50-mg i.v. injections to volunteers (fig. 3). It can be seen that discrepancies between different experimental studies were greater than those between the model and any one experiment.

Increasing the perfusion of the i.m. injection site to three times that of resting muscle (which might perhaps be attributed to reactive hyperaemia) produced a similar fit to data from three experimental studies of pethidine 50 mg i.m. (fig. 4) and one of pethidine 100 mg i.m. to volunteers. To fit the data after injection into the deltoid muscle [20] (fig. 4) required about a nine-fold increase in perfusion. To attribute this further three-fold increase to hyperaemia seems unjustified. However, two points should be noted. First, the experimental data after the deltoid injections came from the same study [20] and the same five individuals as that for the gluteal injections. Therefore, clearly, there is a more rapid absorption from the deltoid muscle than from the gluteus. Second, although there is little information about perfusion of different muscles in humans, wide variations, from 33 to 252 ml min^{-1} kg^{-1}, have been reported in sheep [30].

An alternative to increased perfusion, as a means of fitting the experimental data, would be a normal perfusion rate but a three- and a nine-fold increase in the concentration in the blood leaving the injection site. This would require a corresponding increase in the concentration in standard form, *Cs*, at the injection site for the same total concentration—the same dose. Equation (4) shows that this would require a reduction in protein binding or in solution in lipid, or an increase in pH. However, protein binding at the injection site is already saturated and it was found that reducing both local protein binding and solution in lipid to zero produced only a trivial

increase in the initial blood concentration. The pH of the local ISF needed to be increased to about 10 to match the gluteal injections, and about 14 to match those into the deltoid muscle. Pending reliable measurements, we think that increased perfusion is a more likely explanation.

No further adjustments were required to make the model match experimental data for one study of continuous i.v. infusion (fig. 5) and one of repeat i.m. injections (fig. 6), both in patients after operation. In both cases there was some systematic difference: the predicted concentrations were 32% and 11% less, respectively, than the measured ones. This is within the range of variation between different studies of single i.v. and i.m. injections. However, some systematic difference of this kind is to be expected because, when patients and volunteers have been included in the same study, concentrations of pethidine in the plasma of patients have been larger than in that of volunteers, after both i.v. [17] and i.m. [22] injections. The difference might be attributed to the patients having a reduced cardiac output and, under the prolonged effects of pethidine, a degree of respiratory acidosis, both of which have been shown here to increase the computed plasma concentration of pethidine.

The smallness of the effect of changing the assumption about the form of pethidine which binds to protein (from the unionized form only to all forms) is not surprising: the alternative values of n and k (table II) were obtained [11] by fitting the alternative binding equation to the same experimental data.

The failure to match the rapid changes of arterial concentration after a rapid central venous injection [15] was initially surprising—the Model P [3] used here had given such a good fit to the breath-by-breath uptake of nitrous oxide [4]. On reflection, however, it is clear that modelling the administration of a small fraction (one tidal volume) of the total dose of an inhaled anaesthetic, once every 4 s or so, and diluting it in the storage capacity of the lungs, is one requirement; modelling the first 1 min after the administration of a complete dose of an injected agent, directly into the blood stream, in 2 s, is a much more demanding requirement. In particular, the large post-injection and arterial pools in model P can be expected to dilute the injected pethidine much more than the longitudinal mixing that actually occurs in the blood vessels. Therefore, as Higgins has suggested [7], the more detailed representation of circulation delay provided by Model F or Model M [3] would be required—probably Model M, since that does incorporate longitudinal mixing.

Several aspects of the studies of the effect of injection rate on induction time with propofol [27] and thiopentone [28] could be matched by predictions of the model for corresponding effect with pethidine. This suggests that these effects are not specific to propofol and thiopentone, nor to the elderly patients in whom the effects were observed, but a fundamental pharmacokinetic characteristic of i.v. induction. The fact that the effect of the injection rate on induction time could be so well matched also provides further support for the choice [4, 5] of 1 ml min^{-1} ml^{-1} for the perfusion of the sample brain compartment.

In a conventional two- or three-compartment empirical model, four (or six) constants are chosen to give a (close) fit to the mean results for one experiment. Here, by adjusting two uncertain parameters, λl/s and the perfusion of the i.m. injection site, a good fit has been obtained to the mean results of a wide variety of experimental studies. This implies that the basic design and physiological quantification does most of the matching; it does not prove that λl/s is equal to the 50 that we have adopted, that perfusion of the i.m. site is as we have assumed, that the protein binding parameters of cells other than erythrocytes and muscle cells are as we have assumed (equal to those for plasma)—or even that the protein binding parameters (n and k) taken from Davis [11] are accurate. Adjusting the binding characteristics of some compartments, rather than changing λl/s, could probably produce an equally good fit to the experimental i.v. data—although, as we have found, not to the i.m. data. However, these findings do point to what experimental work needs to be done in order to permit the type of searching test that has been applied [31] to the modelling of the uptake and distribution of halothane. Also, the discrepancy in the matter of very rapid injections shows the way the model needs to be elaborated to match such procedures.

We conclude that physiological or "perfusion based" models of injected agents have great potential value: they can be used to predict likely effects of changes of circumstance which have not been studied experimentally (changes in cardiac output and in plasma pH have been simulated here); they could also be used to make tentative predictions of how the distribution of a drug might be affected in individual patients with known, quantified abnormalities. There remains the problem of quantifying the model, particularly in respect of the physicochemical characteristics of the agents—even for the standard man. However, with improvements in analytical technology, this information will no doubt gradually become available. Modelling of injected agents is now in about the state that modelling of inhaled anaesthetics was in the 1960s: then, many tissue/blood coefficients were assumed [2] to be unity for lack of other information. In that sense, the present model is but a step in the right direction; but, now, comprehensive measurements of the partition coefficients of new volatile anaesthetics become available within a few years of the agent being developed. Therefore we think that physiological modelling is well worth developing.

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