Prediction of the volume of distribution of a drug: which tissue–plasma partition coefficients are needed?

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Abstract

The aim of this study was to identify the tissue–plasma partition coefficients (K_p) needed for an initial prediction of the volume of distribution at steady state (Vd_{ss}) of a drug in humans. Values of K_p were collected from the literature. Only K_p values plausibly representing true steady state distribution were accepted, and data had to be available for muscle, fat, skin and at least five other organs. The apparent volume of distribution of a drug in an organ/tissue (V_{app}) was calculated as K_p multiplied by the volume of the organ/tissue, and the Vd_{ss} as the sum of all available V_{app} values. The percentage contribution of each V_{app} to the Vd_{ss} was estimated. In addition, linear regressions were calculated between K_p values of all drugs in a specific organ/tissue and K_p in muscle or fat. Finally, the Vd_{ss} was re-calculated using (for basic drugs) the K_p in fat to calculate V_{app} in fat and lungs and the K_p in muscle for the V_{app} of all other organs/tissues. The two sets of estimates of Vd_{ss} were compared by linear regression. The same calculations were performed for acidic drugs, except that muscle K_p was used also for the lungs. Distribution to fat and muscle accounted for 84 % (61–91 %) (median and range) of the total estimated Vd_{ss} of the basic drugs (n = 17). The regressions between K_p in organs/tissues and muscle K_p were statistically significant except in the case of liver. For acidic drugs (n = 18), distribution to fat and muscle accounted for 65 % (42–92 %) of Vd_{ss}, and the regressions of K_p were significant for all organs/tissues except kidney and bone. For both types of drugs, correlations between organ/tissue K_p values and K_p in fat were generally worse. There were excellent linear correlations between Vd_{ss} calculated by means of only two K_p values and the originally calculated Vd_{ss} ($r^2 \geqslant 0.99$ for both basic and acidic drugs; slopes were not significantly different from unity). Thus, initial estimation of the Vd_{ss} of a new drug can normally be based on only two K_p values, those of muscle and fat. The muscle K_p can be used to represent all lean tissues, including the residual ''carcass'', with the exception that fat K_p can be used for distribution of basic drugs to lungs.

Introduction

Physiologically based pharmacokinetic (PBPK) models can be used as a tool in drug development (Charnick et al 1995; Iwatsubo et al 1996; Leahy et al 1997; Poulin & Theil 2000, 2002). One such use can be to get initial estimates of the disposition of a drug candidate from limited data on tissue distribution and hepatic or renal clearance. For PBPK modelling, the tissue–plasma partition coefficients (K_p) of the drug in various organs and tissues need to be known.

Determination of K_p values by drug infusion to animals and assay of blood and tissues is quite laborious, and therefore various methods have been proposed to predict K_p from the physicochemical characteristics of the drug and the physiological composition of the tissue (Davis & Mapleson 1993; El-Masri & Portier 1998; Poulin & Theil 2000, 2002; Poulin et al 2001). It has also been proposed, and in part demonstrated, that the K_p of a drug in various tissues can be predicted from that in muscle (Poulin & Theil 2000).

The number of organ/tissue compartments that are used in a PBPK model may vary from four to six in many early models to 15 or more in the most sophisticated models (Gerlowski & Jain 1983; Björkman et al 1994; Nestorov et al 1998a), and the choice of tissues to model sometimes seems more or less arbitrary. It has been shown that very complex PBPK models can be considerably reduced by lumping of compartments,

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without much loss of power to predict plasma concentrations (Nestorov et al 1998a; Weiss 1998). Therefore, determination of only the essential K_p values, and not those of organs/tissues that do not appreciably contribute to the in-vivo distribution of the drug (unless they are of interest for pharmacodynamic or toxicological reasons) might represent an important saving in time and work.

In spite of the extensive literature on physiological pharmacokinetics, the question of which tissue compartments that are actually needed for initial PBPK modelling seems to have been largely ignored. To cite a very recent example, Poulin & Theil (2002) predicted the volume of distribution at steady state (Vd_{ss}) of 123 drugs by calculating K_p in 11 tissues (plus erythrocytes), accounting for at least 80% of the bodyweight. Thus, spleen and heart, assumed to represent 0.26% and 0.47% of the bodyweight, were included in the calculations, whereas other organs and tissues that constitute up to 20% of the bodyweight were left out.

The aim of this study was to identify the K_p values needed for an initial prediction of the Vd_{ss} of a drug in humans. For this purpose, the relative contributions of drug distribution in various organs and tissues to the total Vd_{ss} of a number of basic and acidic drugs were calculated. The possibility of predicting the K_p of a drug in any organ or tissue from either the K_p in muscle or the K_p in fat was then explored. Finally, the relative error introduced by calculating Vd_{ss} using only two K_p values (muscle and fat) instead of all available values was estimated.

Materials and Methods

Data collection

Values of K_p were collected from the literature, using several MEDLINE searches and checking the lists of references in the publications. Criteria for inclusion of data into the study were: (i) specific assay of the drug in plasma or blood and organs/tissues; (ii) reported K_p values plausibly representing true steady state distribution, either after infusion of drug to steady state or after correction of non-steady state data, for example by the method of Chen & Gross (1979); (iii) appropriate calculation of K_p in eliminating organs; and (iv) data being available for muscle, fat, skin and at least five other organs. Findings from toxicological studies on, for example, neutral organic chemicals were not included.

Estimation of relative contributions of organs/tissues to Vd_{ss} in humans

The apparent volume of distribution of a drug in an organ/tissue (V_{app}) was calculated as:

$$V_{app} = K_p \times V_{tissue} \tag{1}$$

where V_{tissue} is the physical volume of an organ/tissue in a "standard" human, which is the mean value of the organ/

tissue volume in a "standard" man and in a "standard" woman (Wada et al 1997; Björkman et al 1998). The K_p obtained in an animal study was used without modification (Ichimura et al 1984; Björkman et al 1990, 1994, 1998; Wada et al 1997). The predicted Vd_{ss} was then calculated as:

$$Vd_{ss} = V_{blood} \times \lambda + \sum_{i=1}^{n} \equiv V_{app} \tag{2}$$

where V_{blood} is the volume of blood in the arteries and veins of the "standard" human (capillary blood is included in the V_{tissue} of the respective organ/tissue) and λ is the blood–plasma concentration ratio. Finally, the percentage contribution of each V_{app} to the Vd_{ss} was calculated. The tissue volumes and an example of the calculations are shown in Table 1.

Correlations between K_p values

Linear regressions were calculated on K_p values of all drugs in a specific organ/tissue as a function of K_p in muscle and also as a function of K_p in fat. The calculations were performed separately for basic and acidic drugs. For this purpose, literature data fulfilling the quality criteria were included even if less than eight organs/tissues had been studied.

Use of muscle K_p to represent all "lean" organs/tissues

For each drug, the K_p value in muscle was substituted for all K_p values, except that of fat, and the Vd_{ss} was re-calculated. For basic drugs only, replacement of the lung K_p by the fat instead of the muscle K_p was also investigated (see Table 1). The two sets of estimates of Vd_{ss} were compared by linear regression.

Results

A total of 126 published works containing K_p values of 115 drugs were scrutinized. Data satisfying all criteria for inclusion into the study were found in 18 of them, and supplementary data that could be used for correlations between K_p values were found in another seven. In a few studies, K_p values were found to be concentration-dependent or to represent irreversible tissue binding, and these were excluded. The K_p values of the included drugs are listed in Table 2. The K_p values of the basic drugs invariably exceeded those of inulin, while for some of the acidic drugs, some or most of the K_p values were similar to those of inulin.

The relative contributions of various organs and tissues to the calculated Vd_{ss} of the drugs in a "standard" human are shown in Table 3. As regards basic drugs, distribution

Table 1 Organ/tissue volumes in a "standard" human, and an example of the calculations, as applied to lidocaine.

Organ/tissue	Tissue volume (L)	All measured K_p values			Two K_p values		
		K_p	V_{app} (L)	% of total	K_p	V_{app} (L)	% of total
Blood	2.44	(1.6)[a]	3.9	6.0	(1.6)[a]	3.9	6.1
Brain	1.34	1.2	1.6	2.5	0.65	0.9	1.4
Heart	0.41	0.96	0.4	0.6	0.65	0.3	0.4
Lungs	0.87	3.1	2.7	4.2	2.0	1.7	2.7
Gut	1.21	1.6	1.9	3.0	0.65	0.8	1.2
Liver	2.19	0.61	1.3	2.1	0.65	1.4	2.2
Kidneys	0.34	2.8	1.0	1.5	0.65	0.2	0.3
Bone	9.50	0.39	3.7	5.7	0.65	6.2	9.7
Skin	2.85	0.57	1.6	2.5	0.65	1.9	2.9
Muscle	24.6	0.65	16.0	24.7	0.65	16.0	25.1
Fat	15.3	2.0	30.6	47.3	2.0	30.6	47.9
Carcass	5.46[b]						
Total	66.5		64.7	100.0		63.8	100.0

V_{app}, apparent volume of distribution in the tissue; K_p, tissue–plasma partition coefficient as determined in the monkey (see Table 2). [a]The blood–plasma concentration ratio (λ). [b]The portion of the body not accounted for, or "carcass", represents 8.2% of the bodyweight.

to fat predominated, followed by distribution to muscle. Together, fat and muscle accounted for a median of 84% (range 61–91%) of the total estimated Vd_{ss}.

In the case of the acidic drugs whose K_p values exceeded those of inulin, distribution to fat generally equalled or exceeded distribution to muscle. The median sum of distribution to these two tissues was 65% (range 42–92%) of the total Vd_{ss}. The proportions, however, varied markedly. For the drugs with at least some K_p values similar to those of inulin (e.g. ceftazidime, nalidixic acid and tolbutamide), distribution to muscle predominated. This was, however, observed also for some of the barbituric acids.

The equations for all the regressions between K_p in an organ/tissue and K_p in either muscle or fat are given in Table 4. As regards basic drugs, significant correlations with muscle K_p were obtained for all organs/tissues except liver. This also applied to regressions between organ/tissue K_p and fat K_p; however, many of these were characterized by low slopes and significant y-axis intercepts. In the case of acidic drugs, significant correlations with muscle K_p were seen for all organs except kidneys and bone. Significant y-axis intercepts were, however, found in four of the nine regressions. Correlations with fat K_p were generally weaker (lower r^2 and higher P values) and failed to reach significance for lungs, liver, kidneys and bone. All regressions with fat K_p showed significant y-axis intercepts.

Some of the regressions (those of brain, heart, lungs, gut, kidneys and fat) with muscle K_p showed much lower slopes for acidic than for basic drugs. This was particularly the case for lungs, where a 12-fold difference was observed. The partitioning of basic drugs to lungs was also much more similar to partitioning to fat (slope = 1.1) than to muscle (slope = 9.5). For acidic drugs, it was the other way around (Table 4).

For basic drugs, the correlation between the Vd_{ss} calculated using the K_p of muscle for all tissues except fat and the Vd_{ss} calculated using all original K_p values was $y = 0.954x - 5.07$; $r^2 = 0.997$. The deviation of the slope from unity was statistically significant ($P < 0.001$). However, when the K_p of fat was used for the lungs, the slope was no longer significantly different from unity (Figure 1). The deviation between the two estimates of Vd_{ss} was: median −1.8%, range −23–+9.1%. For acidic drugs, replacing the K_p of all tissues, except fat, with that of muscle gave the correlation shown in Figure 2. The deviation between the two estimates of Vd_{ss} was: median −6.9%, range −37–+12%.

Discussion

Application of the seemingly reasonable quality criteria outlined above resulted in more literature data being excluded than included. In the cases of biperiden, pentazocine and valproic acid, data from two species (rats and rabbits) were markedly different, presumably owing to differences in plasma protein binding. The rat and rabbit findings were therefore treated as independent data. The calculations on the acidic drugs depended rather heavily on the homologous series of nine 5-n-alkyl-5-ethyl barbituric acids investigated by Blakey et al (1997). The 19 basic and 24 acidic drugs that were finally included may, however, be regarded as representative for the major classes of low molecular weight drugs.

Some of the acidic drugs had K_p values in at least some organs/tissues that were similar to those of inulin. Inulin is a polysaccharide that distributes only to the interstitial spaces (i.e. not into the cells) of the organs/tissues and is

Table 2 Tissue–plasma partition coefficients of 43 drugs, as compiled from the literature.

Drug	Species	Brain	Heart	Lungs	Gut	Liver	Kidney	Bone	Skin	Muscle	Fat	Source
Bases												
Data used in all calculations												
Alfentanil	Rat	0.13	0.55	0.78	0.66	1.0	0.82		0.18	0.31	1.7	Björkman et al (1990, 1993)
Biperiden	Rabbit	26	34	131	23		31	5.2	9.9	8.5	120	Nakashima et al (1987)
Biperiden	Rat	7.0	7.0	61	11		11	2.0	4.0	3.1	58	Nakashima et al (1987)
Chlorpromazine	Rabbit	9.3	14	64	11			4.3	5.4	5.2	41	Yokogawa et al (1990)
Clomipramine	Rabbit	11	41	144	29			5.7	5.6	6.2	86	Yokogawa et al (1990)
Clotiazepam	Rabbit	3.2	2.6	11	3.6			1.0	1.4	1.6	5.9	Yokogawa et al (1990)
Diazepam	Rabbit	3.2	6.0	8.4	6.7			1.0	1.6	3.5	12	Yokogawa et al (1990)
Fentanyl	Rat	3.6	4.5	14	8.0	3.8	12		2.1	3.1	27	Björkman et al (1990, 1993)
Haloperidol	Rabbit	8.2	14	54	11			5.4	6.2	7.2	28	Yokogawa et al (1990)
Inaperisone	Rat	12	7.4	33		34	58		6.3	4.1	16	Nagata et al (1990)
Lidocaine	Monkey	1.2	0.96	3.1	1.6	0.61	2.8	0.39	0.57	0.65	2.0	Benowitz et al (1974)
Midazolam	Rat	3.3	4.2	4.5	4.8	8.8	4.6		1.4	1.3	9.0	Björkman et al (1996)
Nitrazepam	Rabbit	2.1	1.4	1.8	2.2			1.2	1.6	1.7	2.3	Yokogawa et al (1990)
Pentazocine	Rat	4.3	5.4	27	4.7	2.3	20	5.4	4.7	5.9	2.5	Ichimura et al (1983)
Pentazocine	Rabbit	5.1	6.4	32	4.3	3.3	18	4.5	5.1	6.4	2.5	Ichimura et al (1984)
Promethazine	Rabbit	20	35	151	33			9.5	14	15	133	Yokogawa et al (1990)
Trihexyphenidyl	Rabbit	21	23	74	22			7.9	8.1	13	76	Yokogawa et al (1990)
Data used only for the regressions of K_p values												
Morphine	Rat					1.2	9.5			2.5		Gabrielsson & Paalzow (1983)
Procainamide	Rat		2.5			3.2	6.4			3.1	0.13	Gole & Nagwekar (1991)
R-Carvedilol	Rat		3.5			4.4	2.7			0.79		Fujimaki (1992)
S-Carvedilol	Rat		7.4			12	7.0			1.6		Fujimaki (1992)
Acids												
Data used in all calculations												
Ceftazidime	Rat		0.22	0.44	0.41	0.25	4.8		0.39	0.19	0.16	Granero et al (1998)
Ethyl barbitones	Rat											Blakey et al (1997)
5-Methyl-		0.60	0.55	0.61	0.60	2.8	1.3	0.98	1.1	0.60	0.35	
5-Ethyl-		0.73	0.69	1.0	0.69	3.7	1.8	0.63	1.2	0.82	0.72	
5-Propyl-		1.2	1.1	1.5	1.0	2.9	3.9	1.3	1.6	1.4	1.3	
5-Butyl-		1.5	1.9	1.5	1.9	3.0	4.4	0.98	1.4	1.3	1.8	
5-Pentyl-		1.2	2.4	1.7	1.9	3.2	2.9	0.49	1.1	2.0	3.5	
5-Hexyl-		2.3	2.3	1.2	2.2	2.8	2.1		2.6	2.0	12	
5-Heptyl-		1.0	1.6	1.3	1.4	1.4	2.1		1.1	1.5	8.7	
5-Octyl-		1.7	1.6	3.1	0.98	1.6	2.5		1.2	0.82	4.6	
5-Nonyl-			3.9	2.2	1.7	2.1	8.5		2.1	1.3	5.0	
Hexobarbitone	Rat		1.1	3.3	1.3	6.0	1.5		0.91	0.63	1.6	Igari et al (1982)
Nalidixic acid	Rat	0.22	0.49	0.33	0.49	0.58	0.54	0.29	0.35	0.36	0.10	Okezaki et al (1988)
Phenobarbitone	Rat		0.91	0.77	1.6	1.8	0.73		1.2	0.99	0.30	Igari et al (1982)
Phenytoin	Rat	0.91	1.2	0.95	2.5	2.3	1.6		1.7	1.1	1.8	Itoh et al (1988)
Thiopentone	Rat	0.7	1.1	1.1	1.3	2.3	3.1		0.8	0.5	7.8	Ebling et al (1994)
Tolbutamide	Rat	0.097	0.27	0.25	0.12	0.30	0.22		0.22	0.13	0.13	Sugita et al (1982)
Valproic acid	Rabbit	0.23	0.52	0.28	0.55	0.52	2.0	0.20	0.55	0.22	0.61	Ichimura et al (1985)
Valproic acid	Rat	0.07	0.43	0.42	0.45	1.8	1.5		0.47	0.16	0.15	Kobayashi et al (1990)
Data used only for the regressions of K_p values												
Cefazolin	Rat		0.10	0.15	0.11	0.79	2.8	0.11	0.30	0.077		Tsuji et al (1983)
Dicloxacillin	Rat		0.074	0.12	1.4	0.43	1.3			0.051		Tsuji et al (1983)
R-Etodolac	Rat	0.031	0.18			0.12	0.12				0.068	Brocks & Jamali (1991)
S-Etodolac	Rat	0.046	0.45			0.43	0.39				0.17	Brocks & Jamali (1991)
Penicillin V	Rat		0.095	0.16	0.97	0.25	3.7			0.062		Tsuji et al (1983)
p-Phenylbenzoic acid	Rat	0.055	0.23	0.28	0.15	0.35	0.30		0.15	0.08	0.059	Kawahara et al (1998)
Salicylic acid	Rat	0.060	0.19	0.19	0.21	0.23	0.44	0.14	0.24	0.12		Yoshikawa et al (1984)
Included for comparison												
Inulin	Rat		0.12	0.20	0.096	0.17		0.15	0.30	0.12		Tsuji et al (1983)

Table 3 Calculated percent distribution of the drugs to different organs/tissues in humans, with percentage of total bodyweight accounted for in the calculation of volume of distribution at steady state (Vd_{ss}).

Drug	Percentage of Vd_{ss}					Percentage of bodyweight
	Organs[a]	Bone	Skin	Muscle	Fat	
Bases						
Alfentanil	10.8		1.3	18.9	64.8	78
Biperiden (rabbit K_p)	8.6	2.1	1.2	9.0	78.9	89
Biperiden (rat K_p)	7.6	1.8	1.1	7.1	82.2	89
Chlorpromazine	9.7	4.6	1.7	14.2	69.8	84
Clomipramine	11.1	3.1	0.9	8.8	76.1	84
Clotiazepam	11.9	5.9	2.5	24.2	55.6	84
Diazepam	7.2	3.1	1.5	28.1	60.0	84
Fentanyl	7.6		1.1	14.2	76.7	78
Haloperidol	10.6	4.0	2.4	24.3	58.7	84
Inaperisone	27.8		3.5	19.8	48.0	76
Lidocaine	13.8	5.7	2.5	24.7	47.3	92
Midazolam	17.2		1.9	15.0	64.7	78
Nitrazepam	7.6	11.3	4.5	41.6	35.0	84
Pentazocine (rabbit K_p)	17.9	13.7	4.7	50.6	12.3	92
Pentazocine (rat K_p)	16.3	17.1	4.5	48.2	12.7	92
Promethazine	7.7	3.3	1.4	13.8	73.9	84
Trihexyphenidyl	7.5	4.4	1.4	18.9	67.8	84
Median	10.6	4.4	1.7	18.9	64.7	84
Min	7.2	1.8	0.9	7.1	12.3	76
Max	27.8	17.1	4.7	50.6	82.2	92
Acids						
Ceftazidime	27.7		9.8	41.1	21.5	72
Ethyl barbitones						
5-Methyl-	20.0	21.3	7.3	33.7	12.2	92
5-Ethyl-	21.4	10.9	6.3	36.8	20.2	92
5-Propyl-	14.4	14.3	5.2	39.7	23.6	92
5-Butyl-	16.0	10.4	4.3	36.1	30.5	92
5-Pentyl-	11.4	3.7	2.5	38.1	42.4	92
5-Hexyl-	5.6		2.9	19.5	71.0	78
5-Heptyl-	4.8		1.7	19.6	72.6	78
5-Octyl-	10.4		3.3	18.8	65.3	78
5-Nonyl-	10.2		4.6	24.1	59.3	76
Hexobarbitone	29.2		4.1	24.4	38.5	76
Nalidixic acid	16.7	16.2	5.9	52.2	9.0	88
Phenobarbitone	17.1		8.2	58.2	11.0	76
Phenytoin	15.3		6.6	37.1	37.7	78
Thiopentone	6.8		1.6	8.4	81.6	78
Tolbutamide	14.9		7.0	35.6	22.2	78
Valproic acid (rabbit K_p)	14.0	8.2	6.8	23.4	40.3	92
Valproic acid (rat K_p)	38.3		9.1	26.8	15.6	78
Median	15.1	10.9	5.5	34.7	34.1	78
Min	4.8	3.7	1.6	8.4	9.0	72
Max	38.3	21.3	9.8	58.2	81.6	92

[a]Brain, heart, lungs, gut, liver and kidneys.

not bound to plasma proteins. Thus, the K_p of inulin in an organ/tissue represents that of a drug with these characteristics (Tsuji et al 1983). Distribution of such drugs into adipose tissue, of which approximately 85% is fat cells (Rosell & Belfrage 1979), can be expected to be low. In principle, K_p values of these drugs can be predicted from the known fractional volumes of the interstitial spaces of the various organs/tissues (Tsuji et al 1983; Poulin & Theil 2000). However, since it is not known *a priori* whether a drug candidate does or does not distribute to the cells of representative organs/tissues, no distinction has been made between these and other drugs in the present work. Drugs of this type were also included in the regressions of K_p values reported by Poulin & Theil (2000).

Table 4 Correlations of tissue–plasma partition coefficients of the drugs in all organs/tissues with those in muscle or fat, respectively.

Organ/tissue	Correlation with muscle					Correlation with fat				
	n	Slope	Intercept	r^2	P	n	Slope	Intercept	r^2	P
Bases										
Brain	17	1.53	$(0.46)^a$	0.697	0.00003	17	0.16	2.57	0.780	0.000003
Heart	20	2.37	(0.11)	0.591	0.00007	18	0.28	(2.09)	0.841	0.0000001
Lungs	17	9.50	(−0.55)	0.597	0.0003	17	1.11	(7.09)	0.891	0.00000001
Gut	16	1.97	(0.85)	0.680	0.0001	16	0.22	2.68	0.910	0.00000001
Liver	11	(0.74)	(4.78)	0.025	0.64	8	(0.50)	(3.35)	0.177	0.30
Kidneys[b]	12	3.33	(0.16)	0.951	0.0000001	9	0.17	7.71	0.483	0.04
Bone	13	0.64	(0.31)	0.916	0.0000003	13	0.04	2.25	0.497	0.007
Skin	17	0.83	(0.36)	0.864	0.0000001	17	0.07	1.94	0.713	0.00002
Muscle						18	0.07	2.44	0.606	0.0001
Fat	18	8.22	(−6.40)	0.606	0.0001					
Acids										
Brain	16	0.90	(0.07)	0.747	0.00002	17	0.14	0.40	0.512	0.001
Heart	23	1.21	(0.14)	0.652	0.000003	21	0.17	0.67	0.409	0.002
Lungs	23	0.80	(0.43)	0.304	0.006	19	(0.09)	0.93	0.123	0.14
Gut	23	0.87	0.42	0.599	0.00001	19	0.11	0.81	0.313	0.01
Liver	23	1.32	0.86	0.324	0.005	21	(0.10)	1.67	0.054	0.31
Kidneys	23	(0.95)	1.67	0.101	0.14	21	(0.18)	1.75	0.098	0.17
Bone	9	(0.41)	(0.26)	0.389	0.07	7	(0.04)	0.65	0.010	0.83
Skin	21	0.90	0.29	0.726	0.000001	19	0.12	0.75	0.378	0.005
Muscle						19	0.11	0.55	0.391	0.004
Fat	19	3.55	(−0.33)	0.391	0.004					

[a]Values in parentheses are not significantly ($P > 0.05$) different from 0. [b]Inaperisone excluded as an obvious outlier (see Table 2).
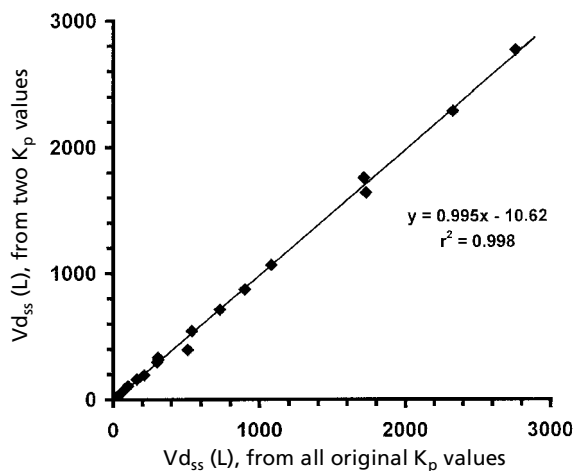
Figure 1 Basic drugs (n = 17). The correlation of Vd_{ss} in a "standard" human calculated by the use of two K_p values (that of muscle for all organs/tissues, except lungs and fat, and lung K_p = fat K_p) with the Vd_{ss} calculated from all available K_p values. The 95% confidence intervals of the slope and intercept were 0.97–1.02 and −40–+19, respectively.
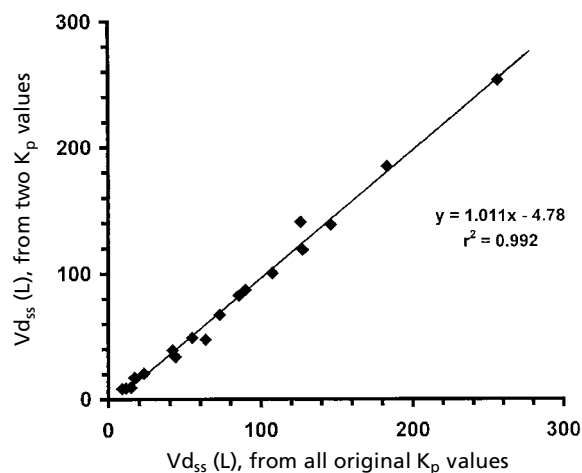
Figure 2 Acidic drugs (n = 18). The correlation of Vd_{ss} in a "standard" human calculated by the use of two K_p values (that of muscle representing all organs/tissues, except fat), with the Vd_{ss} calculated from all available K_p values. The 95% confidence intervals of the slope and intercept were 0.96–1.06 and −9.9–+0.3, respectively.

Correction of calculated V_{app} and Vd_{ss} values for differences in plasma protein binding between animals and humans was not necessary for the purpose of this investi-gation (and data on unbound fraction in humans were missing for some of the drugs). The percentages of Vd_{ss} accounted for by the various organs/tissues would not

change if all K_p values were multiplied by the same conversion factor. Not all the predicted Vd_{ss} values in Figures 1 and 2 may correspond to reality. However, the aim of these predictions was to calculate the relative errors introduced by substituting muscle K_p for all "lean" K_p values (and in the case of basic drugs also fat K_p for lung K_p). With the simple tissue modelling used here, these errors would not be influenced by correction for plasma protein binding.

The mean residence time (MRT) of a drug in a tissue equals V_{app} divided by the systemic clearance of the drug (Weiss 1998), and the MRT in all organs/tissues add up to the total MRT in the body. Therefore, the percentages calculated for V_{app} also apply to MRT in the respective organs/tissues.

Fat followed by muscle were identified as the most important distribution spaces of basic drugs. For acidic drugs, fat and muscle together accounted for a major part of the Vd_{ss}, but in varying proportions for different drugs. These findings are of course expected because of the large volume and high drug binding capacity of these tissues, however systematic calculations on a number of representative drugs have not been reported previously. More importantly, the implications for PBPK modelling do not seem to have been fully appreciated. One may conclude that the K_p values of a drug in fat and muscle should be determined (or calculated). There then remains the question of how to deal with the other organs/tissues.

Poulin & Theil (2000) suggested that the K_p of muscle should be used as a predictor of the K_p of other organs/tissues. In keeping with this, they demonstrated linear relationships between the logarithms of bone, brain, heart, skin, intestine and lung K_p, respectively, and the logarithm of K_p in muscle for a large number of drugs with varying physicochemical characteristics. The work presented here differs from that of Poulin & Theil (2000) in several respects. First, quality control criteria were applied to the literature data in order to include only K_p values that plausibly represent steady state distribution. In contrast, Poulin & Theil (2000) concede that some of the K_p values used in their study probably had not been determined at steady state. Second, as many organs/tissues as possible were included in the calculations (eight instead of six, apart from muscle and fat). Third, linear instead of double-logarithmic regressions were used between K_p values. Fourth, basic and acidic drugs were dealt with separately. Even early in development it is known whether a drug candidate is an acid or a base, and it therefore seems better to utilize this knowledge than to find relationships that can be applied to both types of compound. This separation also led to some different conclusions from those of Poulin & Theil (2000). The difference in slopes between regression lines obtained with basic and acidic drugs makes the suggestion to combine the two types of drugs in the same calculations rather questionable.

The original intention of this work was to calculate the Vd_{ss} of a number of drugs using the K_p in muscle as a predictor of K_p in all organs/tissues except fat, and then to compare these Vd_{ss} values with those calculated from all actually measured K_p values. This, however, did not prove

feasible since a linear correlation with muscle K_p could not be found for K_p of basic drugs in liver, or for K_p of acidic drugs in kidneys or bone. Changing from muscle K_p to fat K_p as the independent variable did not improve the situation. The lack of correlation observed for liver with basic drugs may reflect the presence of active transport mechanisms or the problems of determining the K_p of a drug in an eliminating organ (all basic drugs in the present work are extensively metabolized in the liver). A similar problem applies to acidic drugs in the kidneys. Some of these are excreted and in the process accumulated in the kidney, leading to very high K_p values (in comparison with other organs/tissues), as observed for instance with the β-lactam antibiotics ceftazidime, cefazolin, dicloxacillin and penicillin V (Table 2).

Since the K_p of a drug in the various organs/tissues could not always be predicted from the K_p in muscle, an even simpler solution was explored, namely to use the muscle K_p as it is to represent all "lean" organs/tissues. Theoretically, this seems less appealing than using a function, since for some organs/tissues the slopes of the obtained regressions differed markedly from unity. In one case, that of basic drugs in lungs, comparison of the slopes clearly indicated that use of the fat K_p was more logical than use of the muscle K_p. Apart from this, however, the predictions of total Vd_{ss} were generally very little affected by the substitution of muscle K_p for all "lean" K_p values.

One limitation in the interpretation of the present findings, which applies to PBPK modelling in general, is that K_p values were known only for selected parts of the body. The data in Tables 2 and 3 demonstrate that not all the major organs/tissues may be investigated even in studies of good quality. Many of the rejected studies involved even fewer organs/tissues. There are, in principle, three ways reported in the literature to handle residual organs/tissues. In their work on β-lactam antibiotics, which are distributed only to the interstitial spaces of most organs/tissues, Tsuji et al (1983) estimated the characteristics of the "carcass" compartment from assumed values of the interstitial space and tissue–plasma albumin ratio. For drugs that are distributed also to cells, one way is to include a "dummy" compartment into the PBPK model and estimate its characteristics by fitting the model to plasma concentration data (Gabrielsson & Paalzow 1983; Blakey et al 1997; Nestorov et al 1998a, b). This, of course, can only be done if suitable plasma concentration data are available. The other way is to arbitrarily use skin K_p for the "carcass" compartment (Björkman et al 1994, 1998, 2001). The rationale for this was that the "carcass" to a large extent would consist of connective tissue, with physiological characteristics not unlike skin. As shown in the respective references, this method worked well for predicting the disposition of alfentanil, fentanyl and midazolam in humans from rat data. In retrospect, it could also be calculated that the use of muscle K_p instead of skin K_p for "carcass" would change the average estimated Vd_{ss} in humans by -1.5%, -0.99% and 2.2%, respectively, for these three drugs. Based on these limited findings, it may be suggested that the K_p of muscle should be used also for the "carcass" compartment.

In conclusion, initial estimation of the Vd_{ss} of a new drug can normally be based on only two K_p values, those of fat and muscle. The muscle K_p can be used to represent all lean tissues, including "carcass". The fat K_p could be used for basic compounds in lungs.

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