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Prediction of ftorafur disposition in rats and man by a physiologically based pharmacokinetic model

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Summary

A physiologically based pharmacokinetic model including fourteen compartments (artery, vein, and twelve tissues) was used to predict plasma and tissue ftorafur concentrations in rats after a 100 mg/kg i.v. dose. Fairly good agreement was obtained between the predicted and observed time courses of ftorafur concentrations in plasma and tissues. This model was also used to predict plasma ftorafur concentrations for man. Fairly good agreement was again obtained between the predicted and observed plasma ftorafur concentrations. Additionally, it was ascertained that the ratio of body weight (kg) to distribution volume (liter) of ftorafur was approximately 1 : 1 in man, rat, monkey, dog and rabbit, and the ratio of body weight (kg) to total body clearance (ml/min) was the same in all cases except rabbit.

Introduction

Ftorafur (FT) is used as an anticancer agent, particularly against gastrointestinal and breast cancers (Karev et al., 1972). Many studies on the pharmacokinetics of FT have been reported in animal and man, e.g. Choen (1974) and Kozhukhov et al. (1977) found that plasma radioactivity declined exponentially with a half-life of 5 h and triexponentially with a terminal half-life of 13.6 h after i.v. administration of [2-^{14}C]FT to rats, respectively. Also Benvenuto et al. (1978) and Au et al. (1979)

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reported that plasma FT disposition in cancer patients followed one-compartment kinetics, with a half-life of 8.8 h and two-compartment kinetics, with the β-elimination half-life ranged from 6 to 16 h after i.v. dose, respectively. However, prediction of the time courses of FT in blood and organs, and extrapolation from animals to man have not been investigated yet. The recent development of anatomically and physiologically realistic pharmacokinetic models for drug disposition based on actual organ blood or plasma flows and physiological volume has made it possible to predict, in principle, the drug concentration in any tissue at any time and thus to obtain considerable insight into the drug dynamics (Bischoff et al., 1971; Benowitz et al., 1974; Sugita et al., 1982; Ichimura et al., 1984). The purpose of this study was to predict the time courses of FT concentrations in plasma and tissues of rats by using a physiologically based pharmacokinetic model, and to predict the plasma time course of FT in man by using the model and data obtained from in vivo and in vitro studies in rats. In addition, the extrapolation from animals to man in total body clearance and distribution volume of FT was attempted.

Materials and Methods

Materials and analytical method

FT, 5-fluorouracil (5-FU), [1,3-$^{15}N_2$]5-FU, and all organic solvents used for the determination of FT and 5-FU were the same as those described in a previous report (Marunaka et al., 1980). All other reagents were commercial products of analytical grade. The determination methods for FT and 5-FU in plasma and tissues were the same as those described in a previous paper (Marunaka et al., 1980), i.e. FT and 5-FU were determined by HPLC and GLC-mass spectrometric methods, respectively.

Animal experiment

Adult male Wistar rats weighing 250 ± 5 g were used. The body temperature was kept at 37°C by means of a heat pump. Under light ether anesthesia, the femoral artery was cannulated with PE-50 polyethylene tubing. Cannulated rats were given a bolus injection of FT at a dose of 100 mg/kg into the femoral vein or portal vein. Blood samples were collected in heparinized tubes through the cannula at appropriate time intervals up to 5 h after FT injection. Samples were immediately centrifuged and resultant plasma was separated, and stored at −20°C until analysis. After removal of blood samples, the animals were sacrified at appropriate time intervals after a bolus i.v. administration of FT at a dose of 100 mg/kg by an injection of saturated KCl solution into the carotid artery. The desired organs and tissues were quickly excised, rinsed well with cold saline, blotted and weighed. All tissues were stored at −20°C until required. A plasma sample (100 μl) was diluted to 2.0 ml with distilled water. A samples of tissue was homogenized in an ice bath with 2 vols. of physiological saline and then 200–300 μl of the homogenate was diluted to 2.0 ml with distilled water. The samples of plasma and tissue homogenates were used for determination of FT.

Plasma-to-blood concentration ratio (C_p / C_b) of FT in rat

Blood was collected from several rats and mixed in a heparinized container. One ml of the blood containing 10–200 μg of FT was shaken at 37°C for 20 min. Then, 100 μl of blood was taken into another container and the remainder was centrifuged at 3000 rpm for 20 min. The blood and plasma samples (100 μl in each case) were assayed for FT. No hemolysis was apparent in the plasma samples.

Unbound fraction of FT in rat plasma (f_p)

Plasma protein binding was determined by an ultrafiltration method using a membrane cone (Amicon Centriflo ultrafiltration membrane filter cone, type CF-25). Two ml of plasma (obtained from several rats) containing 40–400 μg of FT was applied to the membrane cone after incubation at 37°C for 5 min. The plasma and filtrate (100 μl each) were analyzed for FT. The absorption of FT to the membrane and the leakage of macromolecular plasma components into the filtrate were negligible.

Tissue-to-plasma partition coefficient (K_p) and distribution volume (V_d) of FT in rat

The apparent K_p value at the terminal phase (90 min) after a bolus i.v. injection of FT (100 mg/kg) was corrected by the method of Chen and Gross (1979). V_d was calculated by multiplying K_p by tissue volume (V_T).

Intrinsic clearance (CL_{int}) in rat

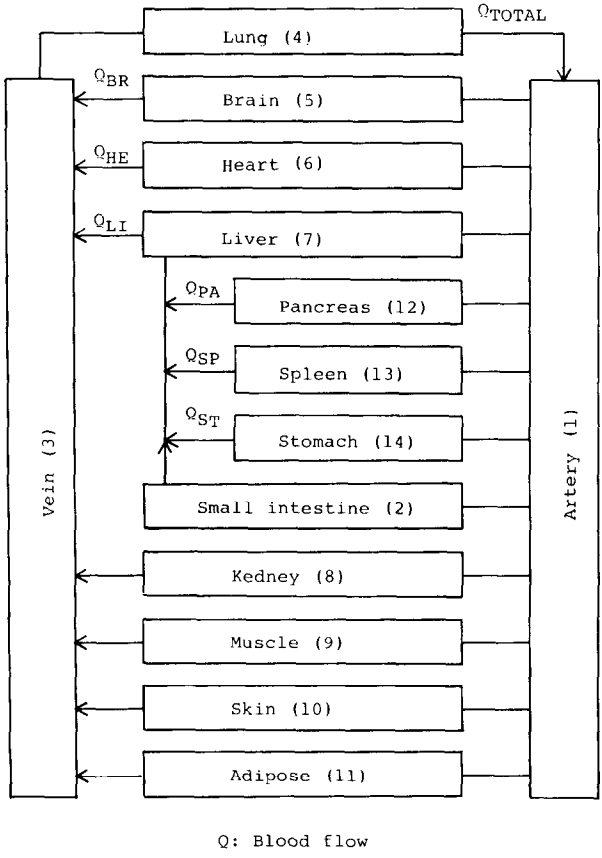
The elimination rate constant (k) of FT in vitro was measured by assaying 5-FU formed from FT in blood, liver microsomes, and other tissue homogenates. Blood and blood-free tissue samples were prepared by the same method as described above without FT administration. The tissue, except liver, was homogenized in physiological saline (2, 4 or 9 ml/g of wet weight) in an ice bath. The reaction mixture of blood (0.1 ml) or tissue homogenate (1.0 ml), contained 0.2 mg of FT and 0.1 μg of [1,3-$^{15}N_2$]5-FU, which as well as 5 mM $MgCl_2$ and 1 mM NADPH in the case of lung and kidney homogenates, was shaken at 37°C for 5, 10, 20 or 30 min. The reaction was started by addition of chemicals after a 2 min preincubation and stopped by freezing immediately the mixture in an ice–acetone bath. The homogenate (0.3 ml) and blood (0.1 ml) were used for the determination of 5-FU. The blood-free liver was homogenized with nine volumes of 0.25M sucrose solution in 0.05M Tris-HCl buffer (pH 7.4) in an ice bath. And then, the microsomal pellets were prepared by the same method of Sugita et al. (1981). The microsomal pellets were suspended in a sufficient volume of ice-cold 0.05 M Tris-HCl buffer to make a concentration of 80 mg/ml. The final reaction mixture, which contained 1.4 ml of microsomal suspension and 0.2 mg of FT, 0.1 μg of [1,3-$^{15}N_2$]-5-FU, 5 mM $MgCl_2$, and 1 mM NADPH in 0.6 ml of 0.05M Tris-HCl buffer, was shaken at 37°C for 5, 10, 20 or 30 min. The reaction was started by addition of NADPH after a 2-min preincubation and stopped by the same method as described above. The reaction mixture (0.3 ml) was assayed for 5-FU. Since the time course of 5-FU formation from FT was linear in each case, the slope was calculated by the least-squares method, and k was calculated as follows:

$$k(\text{min}^{-1} \cdot \text{g}^{-1}) = \frac{1}{f} \times \frac{\text{slope}\ (\mu\text{g} \cdot \text{min}^{-1})}{0.649 \times \text{FT}\ (\mu\text{g})}$$

where 0.649 is the molecular weight ratio of 5-FU to FT and f is the amount (g or ml) of blood, tissue or liver microsomes used. K was represented as the mean value of k obtained from each case. In the case of liver, the amount of microsomal protein was determined by the biuret method and the protein content per g of liver was calculated by the method of Sugita et al. (1981). Intrinsic clearance was calculated as $k \cdot V_T$.

Pharmacokinetic model for FT

A physiologically based pharmacokinetic model for FT disposition is shown in Scheme 1. The model consists of twelve tissues and blood compartments, in which FT is eliminated. This model assumes that: (a) each tissue acts as a well-stirred compartment; (b) intercompartmental transport occurs by blood flow; (c) distribu-



Scheme 1. Pharmacokinetic model for the disposition of ftorafur.

tion of FT is a blood flow-limited and linear process; (d) only free FT is available for tissue distribution; (e) elimination and metabolism occur only with free FT; and (f) excretion into hepatic bile is negligible (Matsuno et al., 1982). Mass balance–blood flow equations were written for the concentration in each compartment shown in Scheme 1. The complete set of differential equations is given in the Appendix and solved numerically by the Runge-Kutta-Marson method using a Hitachi M 180-H digital computer (Hanano, 1980).

Prediction of FT disposition

(1) Study in rats

Physiological constants used in the simulation for 250 g rat are listed in Table 1.

TABLE 1
PHYSIOLOGICAL PARAMETERS FOR MODELING IN RAT AND MAN

Tissue	Parameter			
	Rat [a]		Man [b]	
	Volume [c] (ml)	Blood flow [d] (ml/min)	Volume (ml)	Blood flow (ml/min)
Artery	6.3 [e]	51.9	1700 [f]	4620 [l]
Vein	12.6 [f]	51.9	3390 [f]	4620 [l]
Lung	1.3	51.9	600 [j]	4620 [m]
Brain	1.3	3.2	1400 [k]	700 [k]
Heart	1.1	6.4	300 [j]	240 [j]
Liver	12.3	16.5	3900 [j]	1580 [j]
Kidney	2.2	12.8	300 [j]	1240 [j]
Spleen	0.5	1.0	200 [k]	200 [k]
Pancreas	0.9	1.0	200 [f]	200 [f]
Stomach	1.3	1.1	270 [f]	280 [f]
Small intestine	12.4	12.3	500 [f]	780 [f]
Adipose tissue	10.0 [g]	0.4	10,000 [j]	200 [j]
Skin	43.8 [h]	5.0	3000 [j]	60 [j]
Muscle	125.0 [i]	7.6	30,000 [j]	600 [j]

[a] Based on a 250 g rat.
[b] Based on a 70 kg man.
[c] Determined experimentally from the wet tissue weight by assuming a density of 1.0 for each tissue (lung, brain, heart, liver, kidney, stomach, small intestine, pancreas, and spleen).
[d] From Sugita et al., 1982.
[e] Bischoff et al., 1971.
[f] Benowitz et al., 1974.
[g] Lutz et al., 1977.
[h] Dedrick et al., 1973.
[i] Dedrick, 1973.
[j] Mapleson, 1963.
[k] Smith et al., 1972.
[l] $Q_{BR} + Q_{HE} + Q_{LI} + Q_{KI} + Q_{SK} + Q_{AD} + Q_{MU}$; for keys, see Scheme 1.
[m] Assumed to be the same as those of artery and vein.

TABLE 2
PHARMACOKINETIC PARAMETERS OF FTORAFUR IN RATS

Parameter	Dose and route	
	100 mg/kg	
	Femoral vein	Portal vein
A ($\mu g \cdot ml^{-1}$)	78.232 ± 9.270	92.961 ± 8.616
α (min^{-1})	0.250 ± 0.056	0.143 ± 0.022
B ($\mu g \cdot ml^{-1}$)	187.137 ± 4.540	189.141 ± 10.928
$\beta \times 10^3$ (min^{-1})	1.181 ± 0.121	1.399 ± 0.193
$t_{0.5}^{\beta}$ [b] (min)	655.300 ± 61.880	532.480 ± 112.885 [f]
AUC [c] ($min \cdot \mu g \cdot ml^{-1}$)	197.420 ± 12.390	144.875 ± 19.144 [f]
$V_{d\beta}$ [d] (ml)	124.349 ± 8.682	135.127 ± 9.265 [f]
CL_{tot} [e] ($ml \cdot min^{-1}$)	0.132 ± 0.008	0.185 ± 0.020 [f]

[a] Results are given as the means ± S.E. of 5 rats.
[b] Biological half-life = $0.693/\beta$.
[c] Area under plasma concentration curve = $A/\alpha + B/\beta$.
[d] Distribution volume = CL_{tot}/β.
[e] Total body clearance = Dose/AUC.
[f] No significant difference ($P < 0.05$) from the value in the case of femoral vein.

Tissue volumes except for muscle, skin, adipose tissue, and blood were determined experimentally from the wet weight by assuming a density of 1.0 for each tissue. The muscle volume was assumed to be half of the body weight (Dedrick, 1973). The skin

TABLE 3
MEAN VALUES OF ELIMINATION RATE CONSTANT (K), INTRINSIC CLEARANCE (CL_{int}), TISSUE-TO-PLASMA PARTITION COEFFICIENT (K_p), AND DISTRIBUTION VOLUME (V_d) OF FTORAFUR IN RATS

	$K \times 10^3$ (min^{-1})	$CL_{int} \times 10^3$ [a] ($ml \cdot min^{-1}$)	K_p	V_d [b] (ml)
Lung	0.39	0.51	0.26	0.34
Brain	0.55	0.72	0.41	0.53
Heart	0.63	0.69	0.38	0.42
Liver	6.40	78.72	0.39	4.80
Kidney	0.49	1.08	0.68	1.50
Spleen	0.51	0.26	0.42	0.21
Pancreas	0.32	0.29	0.20	0.18
Stomach	0.52	0.68	0.28	0.36
Small intestine	0.39	4.84	0.44	5.46
Adipose tissue	0.42	4.20	0.17	1.70
Skin	0.37	16.21	0.40	17.52
Muscle	0.25	31.25	0.50	62.50
Blood	0.29	5.48		
Plasma			1.00	11.14

Results are the means of 5 rats. Distribution volume for erythrocytes is 7.75 ml as calculated from the hematocrit value (0.41) and C_p/C_b value (1.262, Table 4).
[a] $CL_{int} = K \times$ tissue volume.
[b] $V_d = K_p \times$ tissue volume.

and adipose tissue volumes were obtained from the literatures, respectively (Dedrick et al., 1973; Lutz et al., 1977). The blood volume was calculated by the method of Bischoff et al. (1971). The volume ratio of arterial-to-venous blood was assumed to be 0.5 (Benowitz et al., 1974). The blood flow rate in the lung was assumed to be the same as that in an artery or vein. Blood flow rates of other tissues or organs were obtained from the literature (Sugita et al., 1982). Various parameters used for simulation, C_p/C_b, f_p, K_p and CL_{int}, were given the mean values shown in Tables 2 and 3.

(2) Scale-up from rats to man

Physiological constants used in the simulation for man are listed in Table 1. These values (Mapleson, 1963; Smith et al., 1972, Benowitz et al., 1974), plasma FT concentrations in man (Au et al., 1979), and free fraction of FT in human plasma, 0.6, (Benvenuto et al., 1978) were taken from the literature. The C_p/C_b, K_p and CL_{int} values and model were the same as those used for the simulation in the case of rat.

Statistical analysis

All means are presented with their standard error (mean $\pm$ S.E.). Statistical analysis was performed by the use of Student's t-test with $p = 0.05$ as the minimal level of significance.

Results and discussion

Plasma FT disposition in rats

Fig. 1 shows the time courses of plasma FT concentrations following a bolus femoral or portal vein administration of FT at dose of 100 mg/kg. Plasma FT concentration declined biexponentially, indicating a two-compartment disposition in two cases. Pharmacokinetic parameters (A, α, B, β) were computed by a non-linear iterative least-squares method (Nakagawa et al., 1979) and are listed in Table 2. Biological half-life ($t_{0.5}^{\beta}$), the area under plasma concentration curve (AUC), distribution volume ($V_{d\beta}$), and total clearance (CL_{tot}) were calculated from these parameters (Table 2). The two-compartment kinetics resulted is consistent with the finding in cancer patients following i.v. administration at 2 g/m^2 dose of FT (Au et al., 1979). The terminal elimination half-life of FT was approximately 10 h. This value is consistent with the finding in man (Benvenuto et al., 1978), but is considerably different from the reported values of 5 h and 13.6 h in rats as described already. There was no significant difference between the $t_{0.5}^{\beta}$ values in different administration routes. Similar results were obtained for the AUC, $V_{d\beta}$ and CL_{int} values (no significant difference between routes). These results show that the elimination process and distribution were linear in the dose used, and the hepatic first-pass effect for FT is small, indicating that FT was metabolized in other tissues besides the liver.

CL_{int} of FT in rats

The mean values of k and CL_{int} in blood and tissues are shown in Table 3.

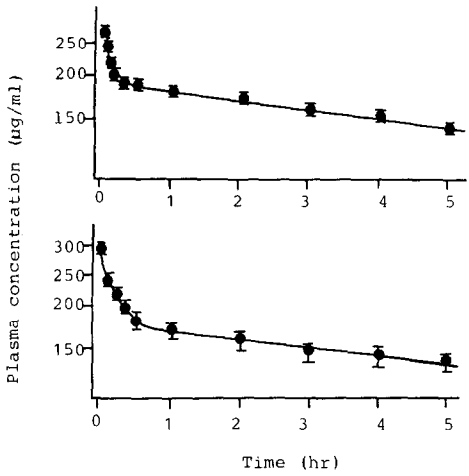


Fig. 1. Plasma concentrations of ftorafur after femoral and portal vein administration of ftorafur at dose of 100 mg/kg in rats. Key: a, femoral vein; b, portal vein. Each point and vertical bar represent the mean ± S.E. of 5 rats.

Hepatic CL_{int} estimated was only 54.3% of the total CL_{int}. Total CL_{int} was 0.145 ml/min, corresponding well to CL_{tot}, i.e. 0.145 ml/min (Table 2).

K_p and V_d in rats

The K_p and V_d mean values are also shown in Table 3. The K_p values in the tissues were less than 1.0, indicating that FT was distributed into tissues at lower concentrations than in plasma. The sum of the V_d values was 114 ml, corresponding to the value of 124 ml of $V_{d\beta}$ (Table 2).

C_p/C_b and f_p of FT in rats

As shown in Table 4, the C_p/C_b value of FT seems to be constant over the dose range studied, and f_p was also apparently dose-dependent. These values show that

TABLE 4
PLASMA-TO-BLOOD CONCENTRATION RATIO (C_p/C_b) AND UNBOUND FRACTION OF FTORAFUR IN PLASMA IN RATS

Ftorafur concentration (μg/ml)	C_p/C_b	Unbound fraction (%)
300	1.263 ± 0.059	76.57 ± 2.87
150	1.243 ± 0.005	76.54 ± 0.01
50	1.270 ± 0.003	76.48 ± 0.24
20	1.259 ± 0.020	82.28 ± 1.72
10	1.277 ± 0.047	79.98 ± 0.76

Results in each concentration are given as the mean ± S.E. of 3 experiments. The mean values of C_p/C_b and unbound fraction (%) are 1.262 ± 0.027 and 78.34 ± 1.12, respectively.

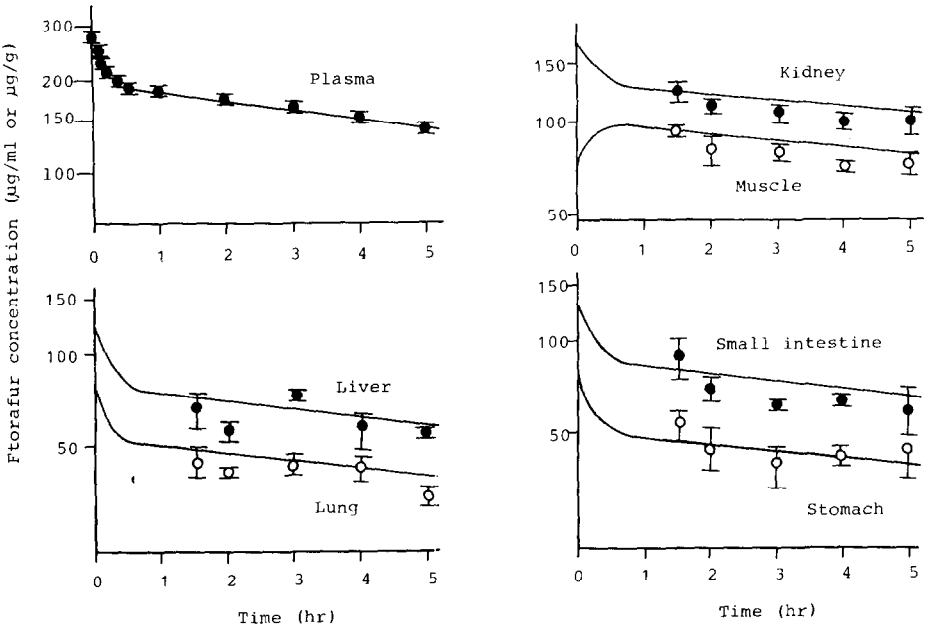


Fig. 2. Predicted and observed log concentrations of ftorafur in plasma and tissues following intravenous administration of 100 mg/kg of ftorafur in rats. The smooth lines are predicted concentrations of ftorafur. Each point and vertical bar represent the means ± S.E.

FT is not well taken up by hematocytes and binds only weakly to plasma protein (about 22%). The binding of FT to rat plasma protein was lower than that to human plasma protein, 30–50% (Benvenuto et al., 1978).

Simulation in rat

Significant antitumor activity of FT against gastrointestinal and breast cancers has been reported (Karev et al., 1972). Thus, stomach, small intestine, and lung were selected as target tissues. Kidney and muscle which showed high FT concentration at the terminal phase (90 min) after an i.v. administration of FT, and the liver as the main site of FT metabolism (Fujita et al., 1976; Ohira et al., 1976) were also selected. Fig. 2 shows the predicted and observed FT concentrations in plasma and target tissues after a 100 mg/kg i.v. dose of FT. Fairly good agreements were obtained between the predicted and observed time courses of FT concentrations in plasma and tissues.

Simulation in man

Prediction of the plasma FT concentration in man was attempted using the present physiological model and the mean values of C_p/C_b, K_p and CL_{int} in rats, and the mean value of f_p in human plasma and plasma FT concentrations in five subjects with cancer. Fig. 3 shows the predicted and observed plasma FT concentrations. The predicted FT plasma disposition in man was in reasonably good agree-

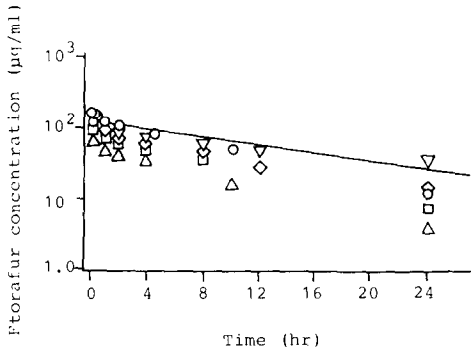


Fig. 3. Predicted and observed plasma ftorafur concentrations in 5 subjects following intravenous administration of ftorafur at 2 g/m^2 dose. Key: ○, △, ▽, □ and ◇ represent 5 subjects, respectively, and they were taken from the literature (Au et al., 1979). The line is the predicted level (for detail, see text).

ment with the observed values, though the predicted levels were slighly higher than the observed ones. This deviation may be related to the application of parameters obtained from healthy rats for scaling up to cancer patients. Further work is necessary on this problem.

Relationships of body weight to distribution volume and total clearance of FT in several animals

Lower clearance in man than in other animals has been reported for many drugs that are oxidatively metabolized in the liver (Boxenbaum, 1980). FT is metabolized oxidatively in other tissues and organs besides the liver, and it is of interest to know whether or not animal data on tissue and organ clearance of such drugs can be

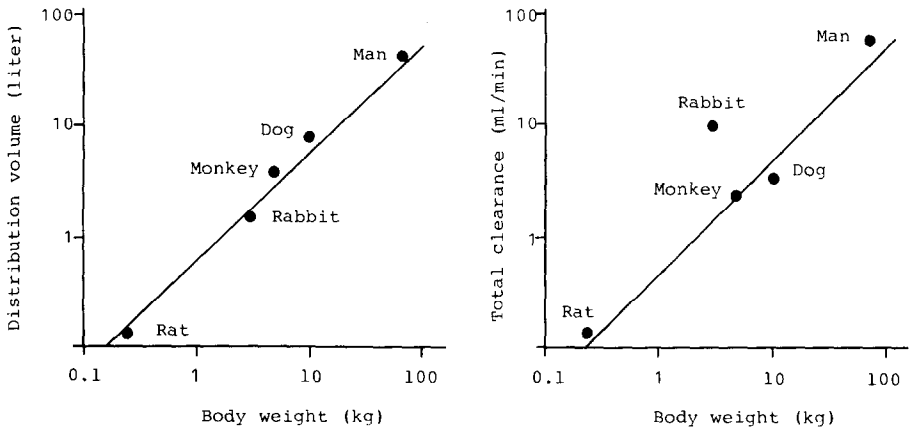


Fig. 4. Relationships between body weight and distribution volume and between body weight and total body clearance in various animals. Except for rat, the data were taken from the cited references (man, Au et al., 1979; dog and monkey, Freudenthal et al., 1977; rabbit, Wu et al., 1978).

directly extrapolated to humans. Fig. 4 shows the relationships of body weight to distribution volume and total clearance in rat, man (Au et al., 1979), dog (Freudenthal et al., 1977), monkey (Freudenthal et al., 1977), and rabbit (Wu and Sadée, 1978). Except for the rat, the data were taken from the cited references. The former relationship showed an approximately 1 : 1 ratio with little difference among the five animals. The latter also showed a ratio of 1 : 1, except in rabbit. The findings showed that such extrapolation is possible from rat, monkey and dog to man as regards total body clearance and from rabbit as well in the case of distribution volume.

Appendix

Model equations

The following mass balance–blood flow equations describe the concentrations in each compartment of the pharmacokinetic model shown in Scheme 1.

Artery (1)

$$V_1 \cdot dC_3/dt = (C_4/K_{p4} - C_1)Q_1 - FR_1 \cdot C_1 \cdot CL_1$$

Vein (3)

$$V_3 \cdot dC_3/dt = (C_5 \cdot Q_5/K_{p5} + C_6 \cdot Q_6/K_{p6} + C_7 \cdot Q_7/K_{p7} + C_8 \cdot Q_8/K_{p8} + C_9 \cdot Q_9/K_{p9} + C_{10} \cdot Q_{10}/K_{p10} + C_{11} \cdot Q_{11}/K_{p11}) - C_3 \cdot Q_3 - FR_3 \cdot C_3 \cdot CL_3$$

Lung (4)

$$V_4 \cdot dC_4/dt = (C_3 - C_4/K_{p4})Q_4 - FR_4 \cdot C_4 \cdot CL_4$$

Liver (7)

$$V_7 \cdot dC_7/dt = (Q_7 - Q_2 - Q_{12} - Q_{13} - Q_{14})C_1 + Q_2 \cdot C_2/K_{p2} + Q_{12} \cdot C_{12}/K_{p12} + Q_{13} \cdot C_{13}/K_{p13} + Q_{14} \cdot C_{14}/K_{p14} - Q_7 \cdot C_7/K_{p7} - FR \cdot C_7 \cdot CL_7$$

Other organs; small intestine (2), brain (5), heart (6), kidney (8), muscle (9), skin (10), adipose (11), pancreas (12), spleen (13), and stomach (14).

$$V_j \cdot dC_j/dt = (C_1 - C_j/K_{pj})Q_j - FR_j C_j CL_j$$

J is the tissue number.

General: V = volume of tissue (ml); Q = blood flow rate through tissue (ml/min); C = tissue or blood concentration of ftorafur (μg/ml); K_p = tissue-to-plasma partition coefficient of ftorafur; FR = plasma free fraction of ftorafur; CL = tissue clearance (ml/min).

Subscripts

BR brain	SP spleen
PA pancreas	MU muscle
KI kidney	LI liver
AD adipose	ST stomach
HE heart	SK skin

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