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Physiological pharmacokinetic model for ceftazidime disposition in the rat and its application to prediction of plasma concentrations in humans

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Abstract

A physiological pharmacokinetic model for the disposition of ceftazidime in the rat was developed. The model is composed of 10 compartments which represent most of the organs and tissues of the body. Ceftazidime concentration–time profiles in the organs and tissues represented in the model were simulated and compared with the observed concentration–time data after i.v. administration of 5 and 20 mg of antibiotic. The model gave an acceptable description of the observed data. The steady-state volume of distribution and total clearance of ceftazidime in healthy humans predicted from data obtained in the rat (0.21 l/kg and 113 ml/min, respectively) were similar to the values reported for these parameters by several authors. The model was scaled to humans by using the tissue volumes and plasma flow rates corresponding to a standard man, the tissue-to-plasma partition coefficients determined in rats, and the total plasma clearance of ceftazidime observed in humans. Good predictions of plasma concentrations of ceftazidime in normal subjects and patients with various degrees of impaired renal function were obtained.

Key words: Ceftazidime; Physiological pharmacokinetic model; Interspecies pharmacokinetic extrapolation; Rats.

Introduction

For several years scientist have been testing different approaches for extrapolating the pharmacokinetic data observed in laboratory animals to humans (Boxenbaum and D'Souza, 1988). The approach based on the development of physiological pharmacokinetic models is appealing in that the model has the potential to predict drug distribution in organs and tissues. A further advantage of these models is that the drug disposition in disease states may be simulated by altering estimates of physiological and pharmacokinetic parameters such as blood flow in the organs, clearance of the drug or plasma and tissue binding of the drug.

Ceftazidime is a third generation cephalosporin commonly used in clinical practice for the treatment of lower respiratory tract, skin, urinary tract and other tissue infections (AHFS, 1992). Ceftazidime pharmacokinetics in humans is characterized by a lack of metabolism, low degree of protein binding and renal excretion by glomerular filtration (Richards and Brogden, 1985). Like other β-lactam antibiotics, distribution of ceftazidime is presumably limited to the extracellular fluids (Schentag, 1989). All these characteristics make ceftazidime a drug that might be expected to follow principles of thermodynamic partitioning with relatively minor interspecies variation, and the tissue-to-plasma partition coefficients determined in a laboratory animal might then be useful for a model to be applied to humans.

The present investigation was undertaken to develop a physiological pharmacokinetic model for ceftazidime disposition in the rat and to scale the model to humans in an attempt to predict plasma and tissue concentration–time profiles of the drug in normal subjects and patients with altered renal function.

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Experimental procedures

Chemicals and animals

A commercially available preparation of ceftazidime (Fortam®, Glaxo Laboratories, Spain) was used in the experiments. Vials of ceftazidime were reconstituted with sterile water for injection according to the manufacturer's recommendations, and subsequent dilutions were made with sterile saline. All other chemicals used were of analytical grade or HPLC grade.

Male Wistar rats weighing 290–330 g were used throughout the study. All animals were subjected to cannulation of the right jugular vein with a medical grade silicone tubing (Silastic® 602–135, Dow Corning Co., Midlan, USA) under ether anaesthesia. Several animals were subjected to the additional cannulation of the carotid artery and others to the additional cannulation of the carotid artery and the urinary bladder. The carotid artery and the urinary bladder were cannulated with polyethylene tubing (0.3 mm i.d. × 0.7 mm o.d., Vygon, Spain) attached to silicone tubing. The free end of the venous, arterial and urinary cannulas were subcutaneously conducted to the rat's back, where they emerged. After surgery, animals were put in individual cages and they were fasted overnight, with free access to water, for 12–14 h prior to the experiments.

Clearance studies and determination of tissue-to-plasma partition coefficients of ceftazidime

Eight unanesthetized rats carrying venous, arterial and urinary cannulas were used. A loading dose of 7.5 mg of ceftazidime in 0.5 ml of normal saline, followed by a constant-rate infusion of 15 mg/h (from a solution of 15 mg/ml), was administered through the venous cannula. After 30 min, total urine was collected for three 20-min periods, and blood (0.3–0.4 ml) was collected with heparinized syringes via the arterial cannula at the midpoint of each urine collection period. Plasma was immediately separated from erythrocytes by centrifugation (1000 *g* for 5 min) and stored at −30°C until assayed. Total and renal clearances of ceftazidime were calculated as the ratio between the infusion rate and the steady-state plasma concentration of the antibiotic, and as the ratio between the renal excretion rate and the steady-state plasma concentration, respectively.

An additional arterial blood sample was drawn 90 min after the start of the infusion and the animal was sacrificed by an injection of 0.5 ml of KI solution (70%) into the jugular vein. Samples of lung, heart, skeletal muscle, duodenum, liver, kidney and adipose tissue were quickly excised, blotted to remove superficial blood content, weighed and homogenized with a 1.5-fold excess of cold saline in a Ultra-Turrax homogenizer. Sections of skin from the dorsal region were sampled and cut into small pieces, weighed and extracted with normal saline by shaking for 2.5 h in a 37°C tempered shaker bath. The homogenates (or skin extract) were then centrifuged at 2000 *g* for 10 min, and the supernatants were removed and frozen at −30°C until analysis. Corrections were made for blood volume included in lung and heart tissues (determined by comparing the absorbance at 542 nm of filtered supernatants with the absorbance of a standard of hemolyzed blood), and for ceftazidime contained in that blood. The remaining tissues had a negligible blood content, and no corrections were made. Tissue-to-plasma partition coefficients were calculated from ceftazidime concentration in the tissues and ceftazidime plasma concentration in the 90-min arterial blood sample, as described below.

Analytical method

All samples were analyzed for ceftazidime concentration by a reversed-phase HPLC method. Urine samples were diluted with water and a 20-μl aliquot was injected directly into the chromatographic system. Plasma samples and tissue homogenates (200 μl) were subjected to an extractive procedure (Jehl et al., 1987) prior to injection into the chromatograph.

The HPLC equipment used was a Perkin-Elmer chromatograph composed of a LC 250, LC 90 BIO and LCI 100 modules, and a Rheodyne injector (model 7125 with a 200 μl loop size). The mobile phase (acetonitrile: 0.1 M acetate buffer pH = 3, 10:90, v/v) was delivered at a flow of 1.5 ml/min through a μ-Bondapak C18 column (4.6 mm by 30 cm; Waters Associates, Inc.). Ceftazidime detection was performed at 254 nm. The coefficient of variation of the analytical method was less than 5% and the detection limit was about 0.3 μg/ml for plasma samples and 0.8 μg/g for tissue samples.

Model development

A blood flow rate-limited physiological pharmacokinetic model was developed to describe the disposition of ceftazidime in the rat (Fig. 1). The complete set of differential mass balance equations for the compartments represented in the model is given in the Appendix. Since in previous studies a negligible

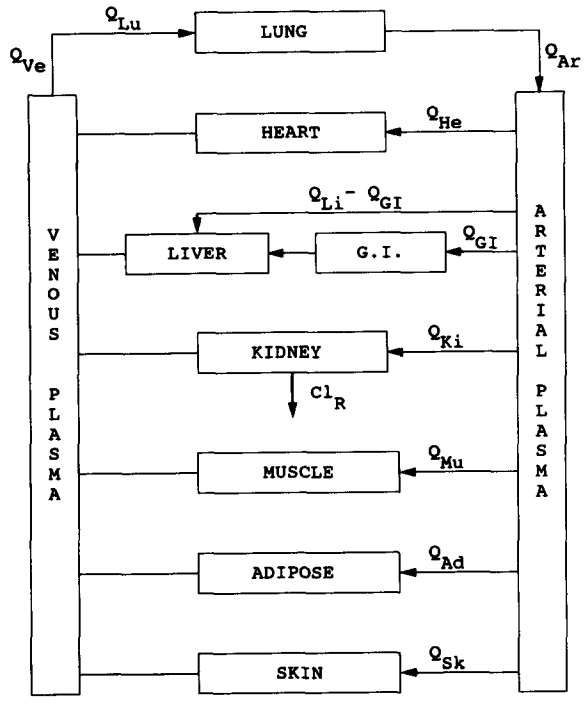

Fig. 1. Schematic diagram of physiological pharmacokinetic model for ceftazidime.

uptake of ceftazidime by rat erythrocytes was observed, plasma flow rates to tissues (Q), arterial and venous plasma volumes (V_{Ar}, V_{Ve}) and tissue-to-plasma partition coefficients (R) were used in the model instead of blood flow rates, blood volumes and tissue-to-blood partition coefficients. The kidney was considered the only eliminating organ for the antibiotic because clearance studies showed a renal clearance close to total clearance (see Results and Discussion).

Tissue volumes (V) except for adipose tissue and muscle were determined experimentally from the wet tissue weight by assuming a density of 1 g/ml for each tissue. The volumes of adipose tissue and muscle were obtained from the literature (Pierson et al., 1978). Total plasma volume was calculated according to an allometric equation for this parameter (Bischoff et al., 1971), and the arterial and venous plasma volumes were estimated by assuming that the ratio of arterial to venous plasma was 0.5 (Igari et al., 1982).

Plasma flow rates of tissues were obtained, except for the kidney, from the literature (Pierson et al., 1978). The plasma flow rate of the kidney was assumed to be equal to the renal clearance of *p*-aminohippuric acid at steady state (unpublished results).

Ceftazidime tissue-to-plasma partition coefficients for the noneliminating tissues were calculated by dividing the tissue concentration and the arterial plasma concentration of the antibiotic at steady-state. Since the kidney is an eliminating organ in the model, its partition coefficient was calculated by using the equation proposed by Lam et al. (1982).

Ceftazidime concentration–time profiles for the arterial and venous plasma and for the tissues of the rat were predicted by solving numerically by the Runge-Kutta method the set of differential equations in the Appendix.

Empirical validation

For model validation in the rat, plasma and tissue concentrations of ceftazidime were determined after i.v. bolus injection at two dose levels: 5 and 20 mg.

Arterial and venous plasma concentrations of ceftazidime were obtained in different groups of five rats each. The animals used to obtain venous plasma data were only cannulated in the jugular vein, and those used for arterial data were additionally cannulated in the carotid artery. After dosing, blood samples were drawn at 2, 5, 15, 30, 60, 90 and 120 min for the 5 mg dose, and at 2, 5, 15, 30, 75, 120 and 165 min for the 20 mg dose.

Data on ceftazidime tissue concentration were obtained by sacrificing groups of four rats at fixed times after the i.v. dosing. Sampling times were 2, 5, 10, 15, 20 and 30 min for the 5 mg dose, and 2, 5, 15, 30, 45, 60 and 90 min for the 20 mg dose. For kidney tissue, two additional groups of four animals were sacrificed at 60 min and 150 min after the 5 mg and 20 mg doses, respectively.

The model was validated empirically (Gabrielsson and Groth, 1988) by comparing the experimentally observed plasma and tissue concentrations of ceftazidime with the model-predicted concentration–time profiles. The physiological parameter values used for the simulation are given in Table 1.

Interspecies scaling

The apparent volume of distribution at steady state for ceftazidime in humans was predicted from tissue volumes (V) for a standard man (Table 1) and tissue-to-plasma partition coefficients determined in rats (R), by summing the total plasma volume and the products $V \times R$ for all tissues represented in the model (Benowitz et al., 1974).

Total clearance of ceftazidime calculated in the rat was extrapolated to humans by assuming that clearance of antibiotic is proportional to clearance of creatinine. The exponent of the allometric equation

Table 1
Physiological parameters and tissue-to-plasma partition coefficients used in the simulations[a]

Tissue	Rat (310 g)			Man (70 kg)	
	Volume (ml)	Plasma flow rate (ml/min)	Tissue-to-plasma partition coefficient	Volume (ml)	Plasma flow rate (ml/min)
G.I. tract	8.90 ± 1.68	8.22[b]	0.41 ± 0.08	2400[d]	670[d]
Heart	1.02 ± 0.14	0.67[b]	0.22 ± 0.08	300[d]	130[d]
Kidney	2.50 ± 0.16	5.89 ± 1.73	4.84 ± 1.02	300[d]	700[d]
Liver	14.10 ± 1.73	9.99[b]	0.25 ± 0.04	1500[d]	840[d]
Lung	1.74 ± 0.53	27.35[c]	0.44 ± 0.09	600[d]	2670[c]
Skin	40.50 ± 2.51	3.10[b]	0.39 ± 0.09	4000[f]	220[g]
Adipose tissue	21.70[b]	3.05[b]	0.16 ± 0.05	10000[d]	110[d]
Muscle	127.10[b]	4.65[b]	0.19 ± 0.05	30000[d]	670[d]
Arterial plasma	4.60[e]	27.35[c]		780[d]	2670[c]
Venous plasma	9.20[e]	27.35[c]		2200[d]	2670[c]

[a] Experimental values are given as mean ± s.d.
[b] Data from Pierson et al. (1978) and adapted to a 310 g rat.
[c] Total plasma flow rate.
[d] From data reported by Gibaldi and Perrier (1982).
[e] Calculated by using the equation of Bischoff et al. (1971) and assuming that $V_{Ar}/V_{Ve} = 0.5$ (Igari et al., 1982).
[f] Datum from Litter (1975).
[g] From Guyton (1981) and by assuming a hematocrit value of 0.44.

for creatinine clearance in several mammalian species is 0.69 (Adolph, 1949):

$$Cl_{cr} = 4.2B^{0.69} \quad (1)$$

where Cl_{cr} is creatinine clearance in ml/h and B is body weight expressed in g. Therefore, the same exponent was assumed in the allometric equation for ceftazidime clearance:

$$Cl_{cef} = aB^{0.69} \quad (2)$$

and, consequently:

$$Cl_{cef}(man) = Cl_{cef}(rat)\left(\frac{B(man)}{B(rat)}\right)^{0.69} \quad (3)$$

The physiologically based pharmacokinetic model developed for the rat was scaled to humans to predict ceftazidime plasma concentrations by using the tissue-to-plasma partition coefficients determined in rats, tissue volumes and plasma flow rates for a standard man (Table 1), and total clearance of ceftazidime in healthy volunteers and patients with renal insufficiency.

Results and discussion

Rat studies

Total and renal clearances of ceftazidime at steady-state were 2.68 ± 0.21 ml/min and 2.63 ± 0.20 ml/

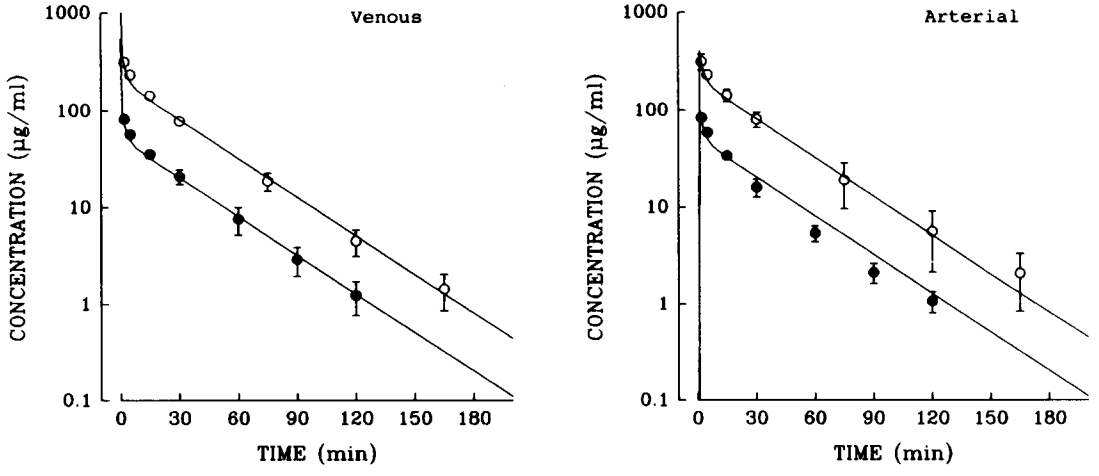

Fig. 2. Predicted (solid curves) and observed (symbols) plasma concentrations after i.v. bolus injection of 5 mg (●) and 20 mg (○) of ceftazidime in rats. Mean values ± s.d.

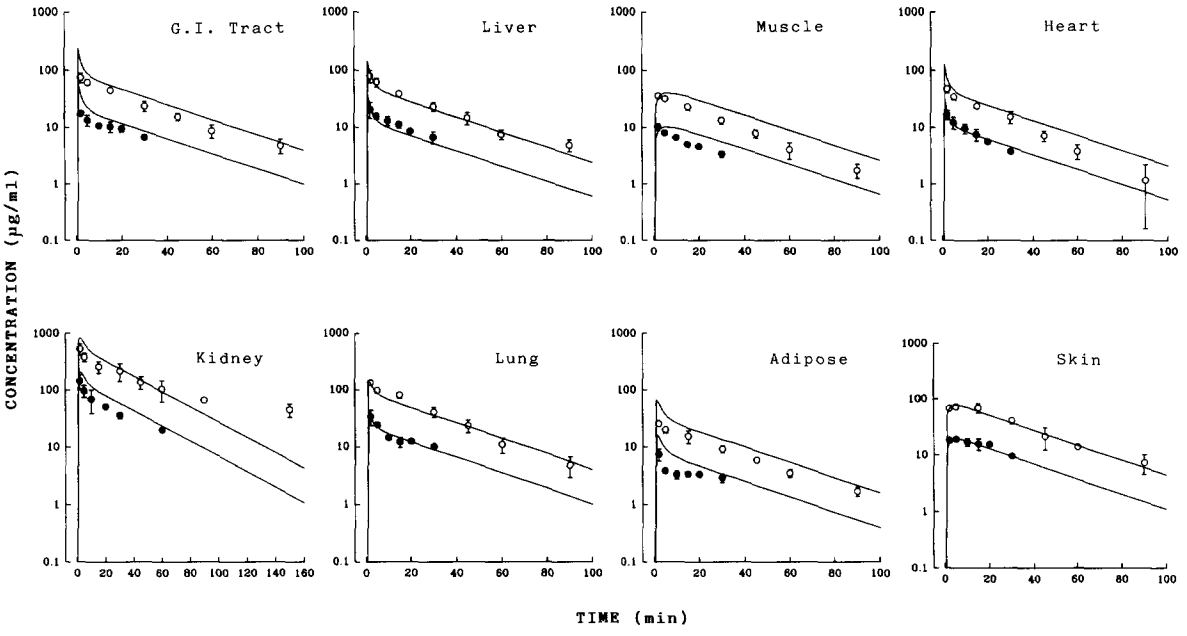

Fig. 3. Predicted and observed tissue concentrations of ceftazidime after i.v. bolus injection of 5 mg (●) and 20 mg (○). Mean values ± s.d.

min, respectively. These values indicate that ceftazidime is eliminated in the rat principally by renal excretion and, therefore, the kidney was considered the only eliminating organ in the physiological model.

Tissue-to-plasma partition coefficients (R) were, except for the kidney, smaller than 1 (Table 1). Since binding of ceftazidime to the rat plasma proteins is very low (less than 10%, unpublished results), these R values suggest that ceftazidime has a limited capacity to enter into the intracellular space, as in general occurs with β-lactam antibiotics (Tsuji et al., 1983; Schentag, 1989). The R value of kidney was extremely high because the antibiotic was highly concentrated in the kidney, which is the major eliminating organ. High values for this parameter were also obtained by Tsuji et al. (1983) using other β-lactam antibiotics.

Model predicted and experimentally observed ceftazidime plasma concentrations are shown in Fig. 2. As can be seen, the predicted arterial and venous plasma concentration–time profiles are in excellent agreement with the observed values for both doses assayed, 5 and 20 mg. The predicted arterial concentration–time curves showed an initial increase, reaching the maximum level in less than 1 min, and a subsequent decrease similar to the venous profile. Predicted ceftazidime concentrations in the arterial and the venous compartments practically coincided for times as early as 2 min after the i.v. administration, and this prediction was confirmed by the observed data: $C_{Ar} = 316 \pm 58$ μg/ml and $C_{Ve} = 318 \pm 23$ μg/ml for the 20 mg dose.

Fig. 3 illustrates the predicted and observed ceftazidime concentrations in tissues for the two doses assayed. Liver, skin and lung predictions were in very close agreement with the observed data, while the predicted ceftazidime concentrations in heart, gastrointestinal tract, muscle, kidney and adipose tissue showed some discrepancies with the observed concentrations. For the gastrointestinal tract, muscle and adipose tissue, the discrepancies could be due to an overestimation of the R value, and/or to an underestimation of the V values in the case of the muscle and the adipose tissue, which were taken from the literature and not actually measured in the present study. On the other hand, the initial decline in the predicted values for the gastrointestinal tract was larger than in the experimental values, which suggests that an overestimated plasma flow rate was used for the prediction. In contrast, for the muscle an underestimated plasma flow rate was probably used.

The predicted kidney concentration–time profile for the largest dose (20 mg) showed close coincidence with the observed drug levels at times ≤ 60 min. However, the observed tissue concentrations at 90 and 150 min were clearly higher than the predicted values and defined a terminal slope lower than that observed in the other compartments. At the moment, we have no satisfactory explanation for this phenomenon, although it could be due to an accumulation of the

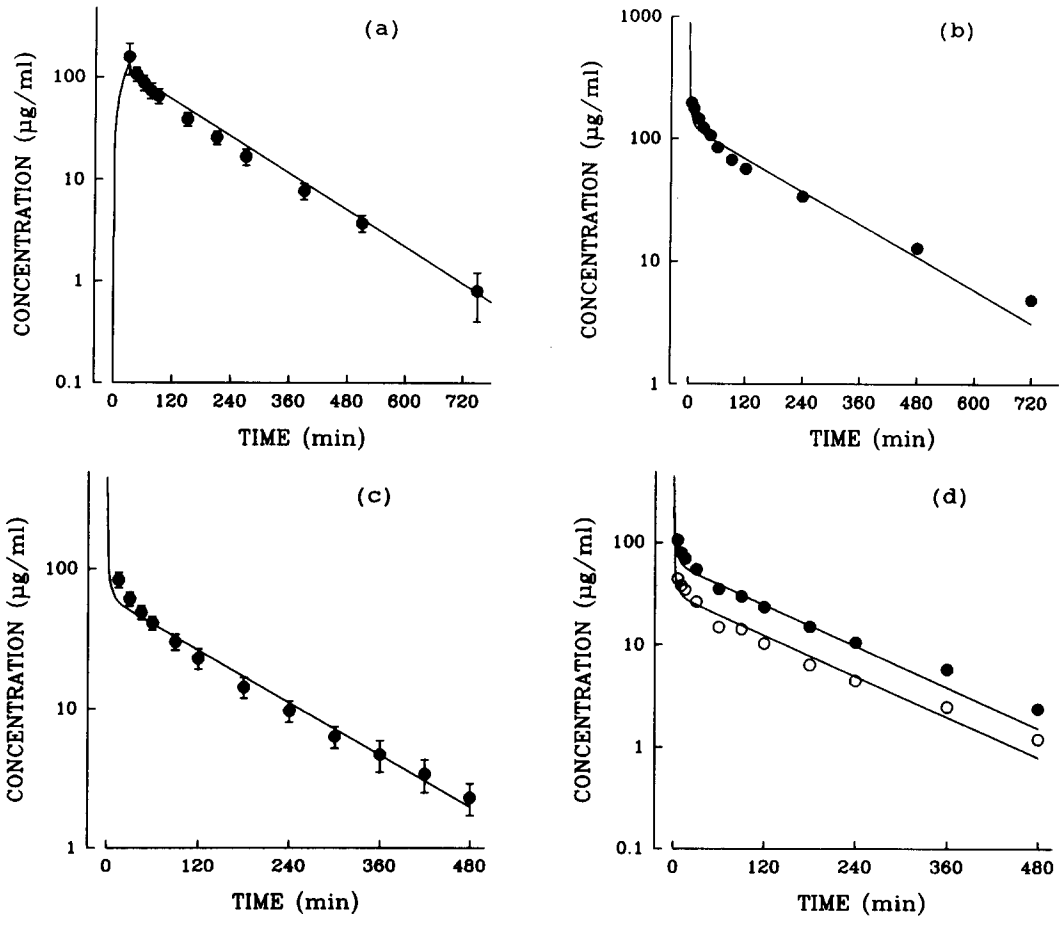

Fig. 4. Predicted (solid curves) and observed venous plasma concentrations of ceftazidime in healthy volunteers. (a) 30-min infusion of 2 g, Cl_{cef} = 107 ml/min (Drusano et al., 1984). (b) i.v. bolus injection of 2 g, Cl_{cef} = 78 ml/min (Wittmann et al., 1981). (c) i.v. bolus injection of 1 g, Cl_{cef} = 110.7 ml/min (Wise et al., 1981). (d) i.v. bolus injection of 0.5 g, Cl_{cef} = 118 ml/min, and 1 g, Cl_{cef} = 119 ml/min (Harding et al., 1981).

drug in the proximal tubular cells, as occurs with cephaloridine (Norrby, 1987).

In spite of the fact that predicted levels of ceftazidime in some tissues did not show complete coincidence with observed concentrations, it is the opinion of the authors that the model gives acceptable predictions of the experimental data.

Model scale-up

The steady-state volume of distribution of ceftazidime in humans predicted from R values determined in rats and tissue volumes for a standard man was 0.21 l/kg, which is in close agreement with the values reported for this parameter in healthy humans by several authors (0.22 l/kg, Tjandramaga et al., 1982; 0.21 l/kg, Drusano et al., 1984; 0.23 l/kg, Leroy et al., 1984). This suggests that the distribution of ceftazidime in rat and human tissues is similar and that a physiological pharmacokinetic model developed using the tissue-to-plasma partition coefficients determined in rats might correctly predict ceftazidime tissue concentrations in humans.

Total clearance of ceftazidime determined in rats was extrapolated to humans by using eq. 3, and a value of 113 ml/min was obtained, which is in good agreement with the average clearance reported for healthy adult humans (98–122 ml/min, AHFS, 1992).

The physiologically based pharmacokinetic model developed for the rat was scaled to application to healthy volunteers and to patients with renal insufficiency. Since the nonrenal clearance of ceftazidime in healthy humans represents about 2–20% of total clearance, depending on the authors (Harding et al., 1981; Wise et al., 1981; Drusano et al., 1984; Leroy et al., 1984), it was assumed that the kidney was the only eliminating organ for the antibiotic and the total clearance was assigned to this organ.

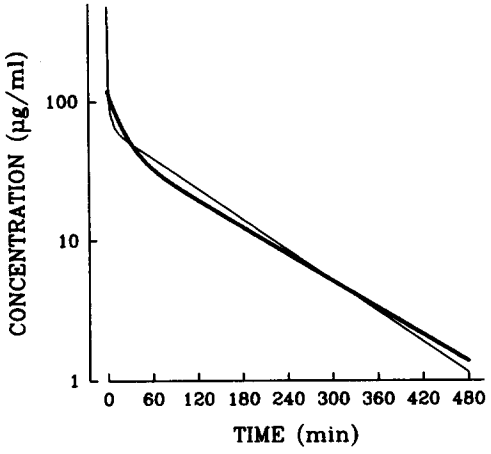

Fig. 5. Predicted concentrations (heavy line) obtained by fitting a two-compartment pharmacokinetic model to the data after administration of ceftazidime to subjects with normal renal function (Cl_{cr} > 80 ml/min). This curve is reproduced from pharmacokinetic parameters given by Leroy et al. (1984). Venous plasma concentrations of the antibiotic predicted by the proposed model (light line). Dose = 15 mg/kg given intravenously, Cl_{cef} = 130.0 ml/min.

The model was used to predict ceftazidime concentration–time curves in the ten compartments of the model and the simulated venous plasma levels were compared with the experimental concentrations obtained in humans by several authors. For each simulation, the total plasma clearance reported in the original paper was used.

Predicted and observed plasma ceftazidime concentrations in healthy humans are shown in Fig. 4. As can be seen, model predictions agree well with experimental plasma concentrations reported by Harding et al. (1981), Wise et al. (1981), Wittmann et al. (1981), and Drusano et al. (1984). Leroy et al. (1984) studied pharmacokinetics of ceftazidime in normal subjects and patients with various degrees of impaired renal function. Fig. 5 and Fig. 6 give the model predicted plasma levels and the theoretical concentrations reproduced from the pharmacokinetic parameters calculated by these authors (Leroy et al., 1984). Again, good

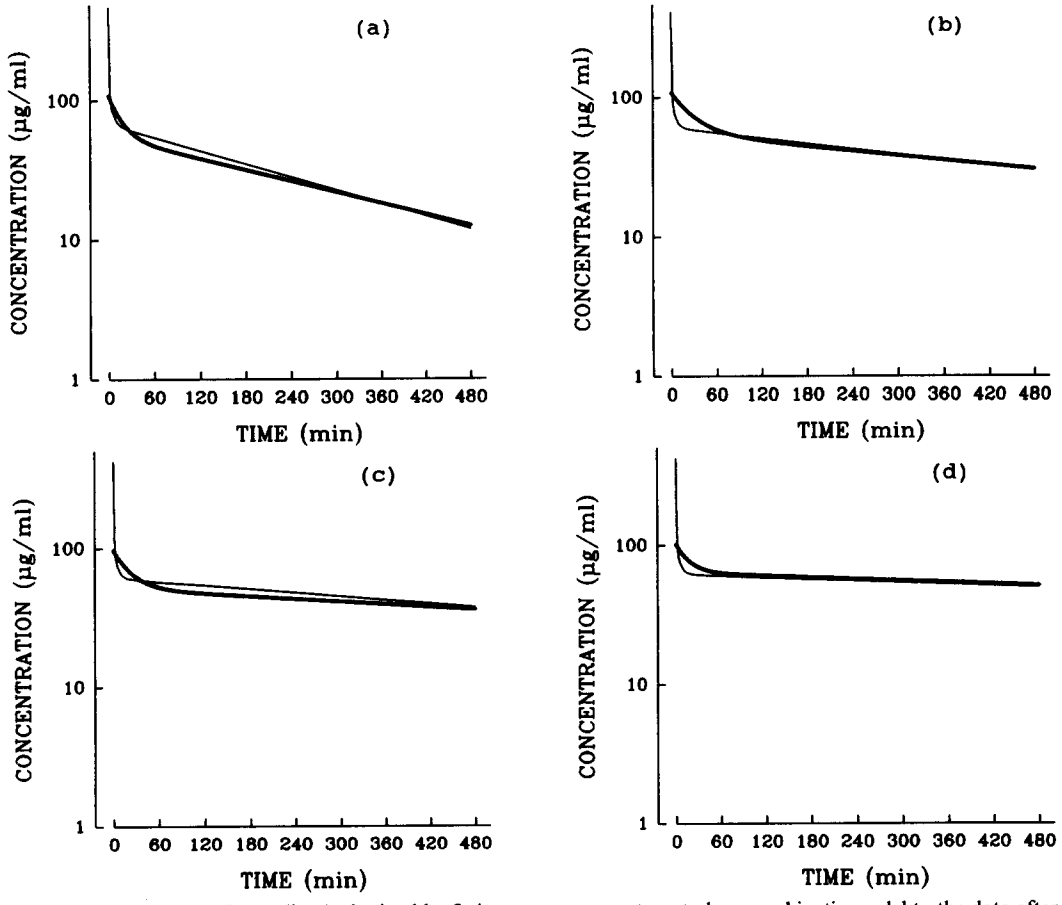

Fig. 6. Predicted concentrations (heavy lines) obtained by fitting a two-compartment pharmacokinetic model to the data after administration of ceftazidime to subjects with various degrees of impaired renal function. These curves are reproduced from pharmacokinetic parameters given by Leroy et al. (1984). Venous plasma concentrations of the antibiotic predicted by the proposed model (light lines). (a) Cl_{cr} = 30 to 80 ml/min, Cl_{cef} = 54.9 ml/min. (b) Cl_{cr} = 10 to 30 ml/min, Cl_{cef} = 21.8 ml/min. (c) Cl_{cr} = 2 to 10 ml/min, Cl_{cef} = 15.4 ml/min. (d) Anuric, Cl_{cef} = 6.8 ml/min. Dose = 15 mg/kg given intravenously.

predictions of ceftazidime plasma concentration–time profiles were obtained.

In conclusion, the proposed physiological pharmacokinetic model for ceftazidime disposition allows good predictions of antibiotic plasma levels in normal subjects and patients with impaired renal function when the clearance of ceftazidime observed in these subjects is used for the predictions. Nevertheless, the ultimate goal would be to achieve good predictions in humans using estimates of total clearance of ceftazidime obtained from creatinine clearance or another index of renal function. This would make it possible to predict plasma and tissue levels of ceftazidime in any given patient. These studies are currently being carried out.

Acknowledgments

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Appendix

Set of differential mass balance equations describing the concentration in each compartment of the model shown in Fig. 1:

$$V_{Ve}(dC_{Ve}/dt) = (Q_{He}C_{He}/R_{He}) + (Q_{Li}C_{Li}/R_{Li}) + (Q_{Ki}C_{Ki}/R_{Ki}) + (Q_{Mu}C_{Mu}/R_{Mu}) + (Q_{Ad}C_{Ad}/R_{Ad}) + (Q_{Sk}C_{Sk}/R_{Sk}) - (Q_{Ve}C_{Ve}) \quad \text{(A1)}$$

$$V_{Lu}(dC_{Lu}/dt) = (Q_{Lu}C_{Ve}) - (Q_{Ar}C_{Lu}/R_{Lu}) \quad \text{(A2)}$$

$$V_{Ar}(dC_{Ar}/dt) = Q_{Ar}(C_{Lu}/R_{Lu} - C_{Ar}) \quad (A3)$$

$$V_{He}(dC_{He}/dt) = Q_{He}(C_{Ar} - C_{He}/R_{He}) \quad (A4)$$

$$V_{GI}(dC_{GI}/dt) = Q_{GI}(C_{Ar} - C_{GI}/R_{GI}) \quad (A5)$$

$$V_{Li}(dC_{Li}/dt) = (Q_{Li} - Q_{GI})C_{Ar} + (Q_{GI}C_{GI}/R_{GI}) - (Q_{Li}C_{Li}/R_{Li}) \quad (A6)$$

$$V_{Ki}(dC_{Ki}/dt) = Q_{Ki}(C_{Ar} - C_{Ki}/R_{Ki}) - Cl_R C_{Ar} \quad (A7)$$

$$V_{Mu}(dC_{Mu}/dt) = Q_{Mu}(C_{Ar} - C_{Mu}/R_{Mu}) \quad (A8)$$

$$V_{Ad}(dC_{Ad}/dt) = Q_{Ad}(C_{Ar} - C_{Ad}/R_{Ad}) \quad (A9)$$

$$V_{Sk}(dC_{Sk}/dt) = Q_{Sk}(C_{Ar} - C_{Sk}/R_{Sk}) \quad (A10)$$

where Cl_R represents the antibiotic renal clearance, and the terms V, C, Q, and R represent tissue volumes, drug concentrations, plasma flow rates, and tissue-to-plasma partition coefficients, respectively. The subscripts of these terms are as follows:

Ve = venous plasma; GI = gastrointestinal tract; Lu = lung; Li = liver; Ar = arterial plasma; Ki = kidney; He = heart; Mu = skeletal muscle; Ad = adipose tissue; Sk = skin.

In the model $Q_{Ve} = Q_{Lu} = Q_{Ar} = (Q_{He} + Q_{Li} + Q_{Ki} + Q_{Mu} + Q_{Ad} + Q_{Sk})$.