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Physiological Pharmacokinetic Model of Ceftriaxone Disposition in the Rat and the Effect of Caffeine on the Model

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Abstract□A Physiologically based pharmacokinetic model was used to describe the distribution and elimination of ceftriaxone in the rat. To validate the practical application of the model, the effect of caffeine on the model was also examined. The model consisted of eleven compartments representing the major sites for ceftriaxone distribution including carcass which served as a residual compartment. Elimination was represented by renal and hepatic (metabolic biliary) excretion with GI secretion and re-absorption. The drug concentrations in most of the tissues were simulated using flow limited equations while brain levels were simulated using membrane limited passive diffusion distribution. The experimental data were obtained by averaging the concentration of drug in the plasma and tissues of five rats after i.v. injection of ceftriaxone 100 mg/kg without and with caffeine 20 mg/kg. The data for the amount of ceftriaxone excreted in urine and gut contents were used to apportion total body clearance. HPLC with UV detection was used for the assay with 0.1-0.2 μg/m*l* sensitivity. The great majority of drug concentrations with and without caffeine show reasonably good agreements to the simulation results within 20%. The effect of caffeine on renal and hepatic clearances was apparent with 18.8% and 18.6% increase in the model values, respectively.

Keywords□Ceftriaxone, caffeine, physiological pharmacokinetics

Physiological pharmacokinetics models are useful in understanding the drug disposition into the tissues and to estimate the inter-species relationship for drug kinetics[1]. As the physiological model of drug disposition should also prove useful as a predictive tool when drug is administered to patients or animals that are in altered biochemical or physiological state[2], the effect of caffeine on the model can validate this practical application of the model. Some of the pharmacological properties of caffeine including diuretic effects[3], effects on blood flow rate[4], drug metabolism in the liver[5,6] and fluid transport in the small intestine[7] can affect the parmacokinetics of drugs in the body which in turn is based on physiological and biochemical conditions.

This study describes a physiologically based pharmacokinetic model for ceftriaxone disposition and elimination in the rat and the effect of caffeine on the model.

EXPERIMENTAL METHODS

The experimental data, as previously reported[8], were obtained by averaging the concentration of the drug in the plasma and tissues of the five rats (male albino Wistar rats weighing 220-260g) euthanized at each time point after I. V. injection of ceftriaxone 100 mg/kg with and without caffeine 0 mg/kg. The amount of drug in gut wall and gut contents was measured separately for the estimation of bile clearance. From two other gruops of rats, urine was collected for 12 hours via a metabolism cage for the estimation of urinary clearance Ceftriaxone was extracted from tissue as previously described[9] and assayed by HPLC with UV detection with sensitivity of 0.1 μg/m*l* for plasma and 0.2 μg/m*l* for tissues.

The ceftriaxone transport into red blood cells were examined *in vitro*. after mixing ceftriaxone (100-200 μg/m*l*) with heparinized rat blood for 30 seconds by vortexing and 10 minutes by soft shaking, part of the blood was centrifuged and divided into plasma and blood cells. The ceftriaxone concentration in the plasma and the blood cells were determined by HPLC as mentioned above for tissue analysis.

Model development

A flow diagram delineating the compartmental interrelationships the model for ceftriaxone with and

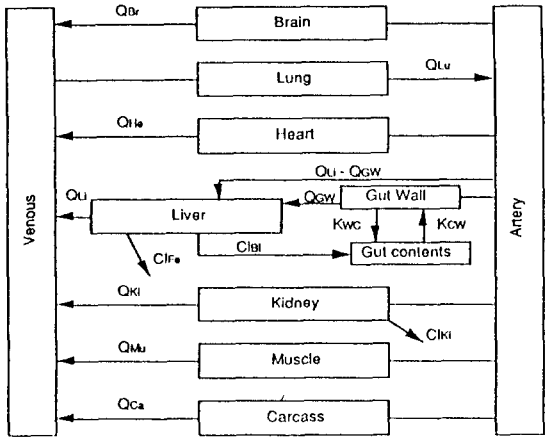

Fig. 1. Physiological pharmacokinetic model of ceftriaxone disposition in the rat.

without caffeine in the rat is shown in Fig. 1. Each of the eleven compartments represents a major site for ceftriaxone distribution and/or elimination.

The carcass serves as a residual compartment, and includes tissues and organs not otherwise incoporated into the model. The treatment of the data was based on the following assumptions: 1) each tissue acts as a well stirred compartment; 2) ceftriaxone distribution is limited by the blood flow rate, except brain; 3) the tissue-to-plasma partition coefficients are concentration and time independent; 4) caffeine dose not alter the organ volumes and the linear binding constants. The mass balance equations for the venous and artery plasma are given by

$$\frac{V_{Ve}\cdot dC_{Ve}}{dt} = \frac{Q_{Br}\cdot C_{Br}}{R_{Br}} + \frac{Q_{He}\cdot C_{He}}{R_{He}} + \frac{Q_{Li}\cdot C_{Li}}{R_{Li}} + \frac{Q_{Ki}\cdot C_{Ki}}{R_{Ki}} + \frac{Q_{Mu}\cdot C_{Mu}}{R_{Mu}} + \frac{Q_{Ca}\cdot C_{Ca}}{R_{Ca}} - Q_{Ve}\cdot C_{Ve}$$

$$\frac{V_{Ar}\cdot dC_{Ar}}{dt} = \frac{Q_{Lu}\cdot C_{Lu}}{R_{Lu}} - Q_{Ar}\cdot C_{Ar}$$

where Ve, Br, He, Li, Ki, Mu, Ca, Ar and Lu indicate venous plasma, brain, heart, liver, kidney, muscle, carcass, artery plasma and lung, respectively, C_i is the total ceftriaxone concentration bound and unbound to any protein. Q_i is the blood flow rate to tissue. R_i is the tissue-to-plasma partition coefficient and V_i is the volume of tissue. The mass balance equation for the liver is given by

$$\frac{V_{Li}\cdot dC_{Li}}{dt} = C_{Ar}\cdot(Q_{Li}-Q_{GW}) + \frac{Q_{GW}\cdot C_{GW}}{R_{GW}} - \frac{Q_{Li}\cdot C_{Li}}{R_{Li}} - Cl_{Li}\cdot C_{Ar}$$

where GW is gut wall and Cl_{Li} is hepatic clearance. The mass balance equation for the gut-wall and gut-contents are given by

$$\frac{V_{GW}\cdot dC_{GW}}{dt} = Q_{GW}\cdot\left(C_{Ar}-\frac{C_{GW}}{R_{GW}}\right) + K_{CW}\cdot V_{GC}\cdot C_{GC} - K_{WC}\cdot V_{GW}\cdot C_{GW}$$

$$\frac{V_{GC}\cdot dC_{GC}}{dt} = Cl_{Bi}\cdot C_{Ar} + K_{WC}\cdot V_{GW}\cdot C_{GW} - K_{CW}\cdot V_{GC}\cdot C_{GC} - Cl_{Fe}\cdot C_{GC}$$

where GC is gut-contents are K_{CW} and K_{WC} are the first order rate constants for gut absorption and secretion, respectively. Cl_{Bi} is the bile clearance into the gut contents. Cl_{Fe} is the fecal clearance but was neglected in this study as the sample of gut contents was taken within 6 hours which is not sufficient for fecal excretion. The general mass balance differential equations for the eliminating organ like kidney and the non-eliminating organs like brain, heart, muscle, and carcass are given as follows

$$\frac{V_i\cdot dC_i}{dt} = Q_i\cdot\left(C_{Ar}-\frac{C_i}{R_i}\right) - Cl_i\cdot C_{Ar}$$

where the clearance term Cl_i is zero for the non-eliminating organ and membrane diffusion rate constant (h_{Br}) was used instead of blood flow rate for brain. The equations for the drug concentration in lung and for the amount of drug excreted in urine are given by, respectively

$$\frac{V_{Lu}\cdot dC_{Lu}}{dt} = Q_{Ve}\cdot C_{Ve} - \frac{Q_{Lu}\cdot C_{Lu}}{R_{Lu}}$$

$$\frac{dC_{Ur}}{dt} = Cl_{Ki}\cdot C_{Ar}$$

Eleven differential equations were solved by a fourth order Runge-Kutta method using a digital computer, PDP-11.

Table I. Physiological and experimentally found constants used in the model for 240g rat

Organ	Organ volume[a], V (ml)	Plasma flow rate[c], Q (ml/hr)	Linear binding constant[f], R	Membrane diffusion rate constant[g], h (ml/hr)	Clearance[h] Cl (ml/hr)
Venous	6.95[b]	1218	–	–	–
Artery	3.48	1218	–	–	–
Brain	1.0[c]	27.4	0.022	0.028 (0.036)*	
Heart	1.0	46.2	0.11	–	–
Lung	1.6	1218	0.16	–	–
Liver	8.0	380[e]	0.30	–	35.0 (41.5)
Kidney	2.0	369	2.5	–	16.0 (19.0)
Gut Wall	10.3[d]	156	0.45	–	–
Gut contents	5.7[d]	–	–	–	–
Muscle	108	216	0.10	–	–
Carcass	92	178	0.12	–	–
Bile clearance (Cl_{Bi})					28.7 (34.0)
Gut absorptin rate constant (K_{CW})				0.005	
Gut excretion rate constant (K_{WC})				0.005	

[a] Reference 16, [b] Estimated from the volume of distribution, [c] Reference 17, [d] Experimental data, [e] Reference 18, [f] Calculated from data, [g] Estimated from data, [h] Calculated from data
*Number in parentheses are the parameters for the group with caffeine.

Determination of model parameters

The physiological parameters used in the model are summarized in Table I. Volume and plasma flow rates for most compartment were taken from literature values for the appropriate organs in the rat. When necessary, these values were scaled to a body weight of 240 g and a tissue density of 1g/ml was assumed. The volume of carcass was calculated by subtracting the sum of all other tissues and plasma from the total rat weight of 240g, and the plasma flow rate for carcass was calculated as a difference between the venous flow rate and all input plasma flow to venous. The diffusion parameter into brain (K_{CW}), and excretion (K_{WC}) rate constants were adjusted to obtain a reasonable simulation of the data. Tissue to plasma partition coefficients (R value) were determined by the equation of the Chen and Gross[10] by which R values were calculated after bolus injection.

$$R = \frac{(Q + Cl_i) \cdot C_i}{Q \cdot C_p + \beta \cdot V_i \cdot C_i}$$

where Q is the flow rate of plasma for in the tissue and Cl stands for the first order clearance for eliminating organs, and equal to zero for non-eliminating organs. C_i and C_p indicate the drug concentration in tissue and plasma at time zero extrapolated from the terminal phase. β is the terminal rate constant of tissue and V_i is the volume of the organ or tissue. The partition coeffifcients for the carcass (R_{Ca}) was calculated as a volume proportional mean of the non-eliminating organs as below

$$R_{Ca} = \frac{\Sigma(V_i \times R_i \text{ of non-eliminating organs})}{\Sigma(V_i \text{ of non-eliminating organs})}$$

The total body clearance and renal clearance (Cl_{Ki}) values were calculated from the data with and without caffeine as Dose/AUC and $k_u \cdot V_1$, respectively. Where dose is the initial dose and AUC is the area under the plasma drug concentration versus time curve, k_u is the renal excretion rate constant, and V_1 is the volume of distribution of central compartment for a two compartment pharmacokinetic model. The hepatic clearance term (Cl_{Li}) was calculated as the difference between the total clearance and renal clearance values. Bile clearance (Cl_{Bi}) was estimated from the amount of drug in gut contents.

RESULTS AND DISCUSSION

The physiological model developed herein simulates the disposition of ceftriaxone with and without caffeine in plasma, urine, gut contents and eight other tissue compartments of the male rat. Comparisons between the simulated results with experimentally deter-

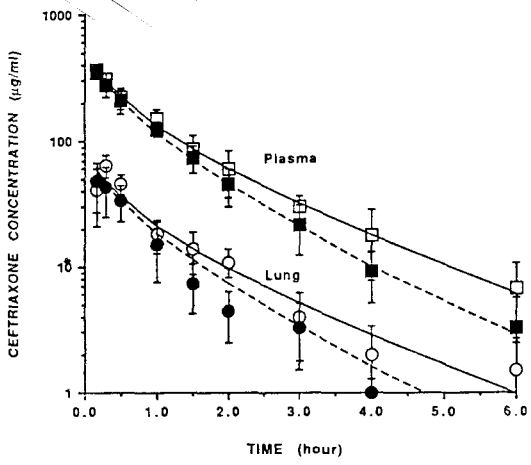

Fig. 2. Model predicted (lines) and observed (points) ceftriaxone concentrations in plasma and lung tissue after ceftriaxone 100 mg/kg I.V. with (filled symbol and dashed line) and without (open symbol and solid line) caffeine 20 mg/kg I.V. injection. Each point and vertical bar represents a mean and standard deviation of five subjects.

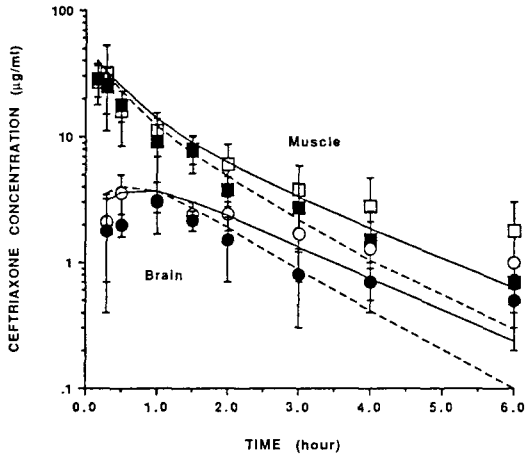

Fig. 4. Model predicted (lines) and observed (points) ceftriaxone concentrations in muscle and brain tissue after ceftriaxone 100 mg/kg I.V. with (filled symbol and dashed line) and without (open symbol and solid line) caffeine 20 mg/kg I.V. injection. Each point and vertical bar represents a mean and standard deviation of five subjects.

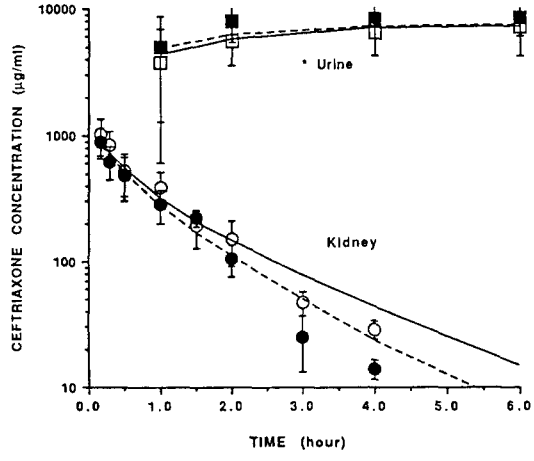

Fig. 3. Model predicted (lines) and observe (points) ceftriaxone amounts (μg) in (*) urine and kidney tissue concentrations after ceftriaxone 100 mg/kg I.V. with (filled symbol and dashed line) and without (open symbol and solid line) caffeine 20 mg/kg I.V. injection. Each point and vertical bar represents a mean and standard derivation of five subjects.

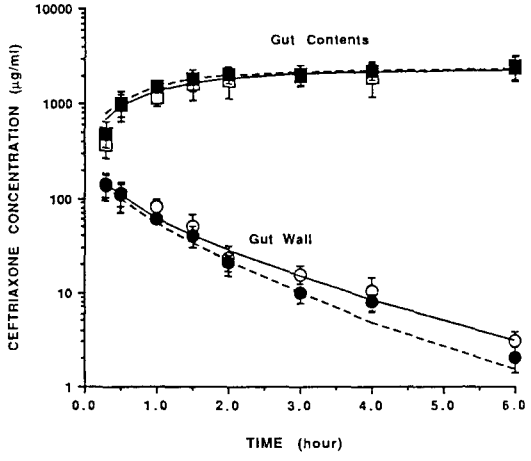

Fig. 5. Model predicted (lines) and observed (points) ceftriaxone concentrations in gut contents and gut wall tissue after ceftriaxone 100 mg/kg I.V. with (filled symbol and dashed line) and without (open symbol and solid line) caffeine 20 mg/kg I.V. injection. Each point and vertical bar represents a mean and standard deviation of five subjects.

mined ceftriaxone concentrations for nine compartments and amount excreted in urine are shown in Fig. 2-6. In each figure the points represent the mean ($\pm$S.D.) of the five experimentally determined ceftriaxone concentrations and the lines are model simulation results. All simulations with and without caffeine show reasonably good agreement to experimental data within about 20% in most of the data points. Some

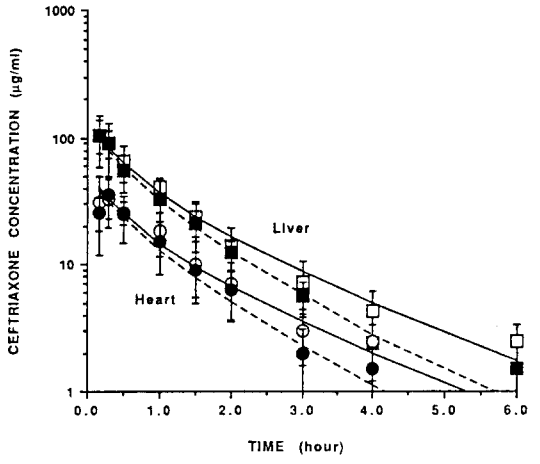

Fig. 6. Model predicted (lines) and observed (points) ceftriaxone concentrations in liver and heart tissue after ceftriaxone 100 mg/kg I.V. with (filled symbol and dashed line) and without (open symbol and solid line) caffeine 20 mg/kg I.V. injection. Each point and vertical bar represents a mean and standard deviation of five subjects.

scattered experimental data points in lung and kidney show over 30% deviation and some low drug concentrations in brain and muscle show around 100% deviation. Brain was assumed to have membrane limited passive diffusion transfusion because the data for brain were not parallel to plasma data and the ceftriaxone penetration was assumed to be controlled by the blood brain barrier. Still, the agreement between simulation and experimental data was not as good as with the other compartments suggesting the possible existence of other factors on effective ceftriaxone disposition into brain.

Model prediction of the ceftriaxone concentrations within a compartment are given by summing the concentrations of protein bound and free ceftriaxone. The protein binding rate of ceftriaxone to plasma protein *in vivo* was nonlinear and ranged from 5.6-32.8% of total ceftriaxone (3-347μg/m*l*) without caffeine and showed no alterations by caffeine[8]. The protein binding term of ceftriaxone in this model was neglected as the agreement between predicted and experimental data was good without the protein binding term. The blood to plasma concentration ratio of ceftriaxone was 0.72 ± 0.065 (mean $\pm$ S.D.). The equilibrium of ceftriaxone between plasma and red blood cells was achieved within 30 seconds.

Caffeine has a variety of pharmacological effects including diuresis[3], stimulation of cardiac muscle and relaxation of smooth muscle (increase of body blood flow)[4], free fatty acid elevation[11, 12] and stimulation of body metabolic rate[13] and drug metabolism[5] which can affect the pharmacokinetics of drug by altering the physiological or biochemical state. Among these, the effect of caffeine on free fatty acid elevation can cause a decrease in drug binding, however, it has been reported that caffeine does not alter the protein binding rate of ceftriaxone *in vitro* or *in vivo*[8, 14]. The effect on drug metabolism was not expected as single I.V. injection was given in this study and induction of hepatic enzymes was not possible[6]. The effects of caffeine related to drug absorption[15, 7] where also not applicable as I.V. administration was used in this study. There were no notable differences for the ceftriaxone concentration in plasma and tissues when the blood flow rate of caffeine group was increased by 10% in the model under the assumption that caffeine may alter the systemic blood flow rate of the rat. The difference between the groups with and without caffeine appears only as differences in renal and hepatic clearances which showed a 18.8% and 18.6% increase with caffeine, respectively. This result could be explained as an effect of caffeine on the kidney to produce diuresis[4] and on the body metabolic rate[13].

In conclusion, the present model contributes to a more complete understanding of ceftriaxone pharmacokinetics and the model should be readily applicable to estimate the inter-species relationship of the drug kinetics and should also prove useful as a predictive tool when drug is administered to patients or animals that are in altered abnormal physiological or biochemical condition.

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