PHARMACOKINETICS OF CEFAMANDOLE IN RABBITS WITH EXPERIMENTALLY INDUCED RENAL IMPAIRMENT

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The pharmacokinetics of cefamandole have been studied in rabbits with normal renal function and varying degrees of renal impairment caused experimentally, by uranyl nitrate, after i.v. administration of a single dose of 30 mg/kg of the antibiotic. The plasma concentrations of cefamandole 80 minutes after administration were 3 μg/ml in normal rabbits reaching 90 μg/ml at 9 hours in the case of terminal renal impairment. With respect to the pharmacokinetic parameters established in rabbits with normal renal function, the following modifications may be observed in the case of rabbits with renal impairment: α, β, K_{12}, K_{21}, K_{13}, V_c and V_p are decreased, while there is an increase in $t_{\frac{1}{2}\alpha}$, $t_{\frac{1}{2}\beta}$ and $(AUC)_0^\infty$. Linear relationships have been established between log α and log β, respectively, and serum creatinine. Biliary excretion of cefamandole is increased parallel to the increase in the degree of renal impairment, there being a linear relationship between the percentage excreted of the antibiotic and serum creatinine. The values of K_B fall from 0.57 h^{-1} in rabbits with normal renal function, to 0.26 h^{-1} in rabbits with severe renal impairment.

Although the selection of a particular antimicrobial agent is usually based on microbiological criteria, the programming of the dosage regimen should be based on the pharmacokinetic parameters which define the incorporation and elimination of the drug from the distribution fluids. However, some pharmacokinetic properties (the degree of biotransformation, the access to peripheral tissues, dialysis capacity) may be criteria for their selection.

The pharmacokinetic parameters may be modified by various circumstances, in particular the effect produced by various pathological states. Among these, renal impairment is outstanding[1]. In patients with renal impairment, important modifications are produced, especially in the distribution and elimination processes, which makes it necessary to correct the dosage regimen in order to guarantee the efficiency and safety of the antiinfectious treatment[4]. Since it is possible to experimentally produce acute renal impairment in laboratory animals, it is possible to perfect our clinical studies on those aspects which are difficult to carry out.

The pharmacokinetic study has been carried out on a semisynthetic beta-lactam antibiotic: cefamandole. It is an antibiotic destined for parenteral use and has a high plasma protein binding capacity. It is eliminated in a principally unaltered state through the kidney[12,13].

Materials and Methods

Antibiotic

Cefamandole nafate (Eli Lilly & Co., Indiana, Ind., U.S.A.) in vials with the equivalent of 1 g of cefamandole activity was used.

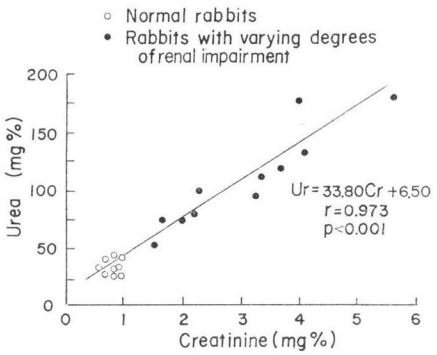
Animals

The animals used in the present survey were adult male New Zealand rabbits weighing 1.8 ~ 2.5

kg. The pharmacokinetic studies of cefamandole were carried out on two lots of animals: Lot 1 comprising of 9 animals with normal renal function, serum creatinine (Cr) = 0.96 ± 0.15 mg%; serum urea (Ur) = 38.74 ± 4.41 mg%. Lot 2 included 10 rabbits with varying degrees of renal impairment caused by the administration of a single i.v. dose of 2 mg/kg of $UO_2(NO_3)_2 \cdot 6H_2O$[2]. The pattern of acute renal impairment is characterized by progressive azotemia, creatininemia, declining urine osmolality and electrolyte excretion. The altered renal hemodynamics were responsible for diminished renal function after uranil nitrate administration. Studies carried out on rats show a progressive decrease in renal blood flow rate and whole kidney and single nephron glomerular filtration rates[6]. Renal hemodynamic alterations similar to those observed after uranil nitrate administration have been reported in human acute renal impairment of varied etiologies[9,10,14].

After administration of uranil nitrate, a daily monitoring of serum urea and creatinine was carried out until the desired degree of renal impairment was attained after which the cefamandole was administered. Since the relationship between the serum urea and creatinine, in both lots of rabbits used in the survey, was linear (Fig. 1), this permitted the indiscriminate use of both indices.

Fig. 1. Linear relationship between serum urea and serum creatinine.



It has not been observed that possible extrarenal effects caused by uranyl nitrate affect the disposition of cefamandole.

The groups of rabbits on which the various pharmacokinetic studies were carried out were different at all times and fasted for a period of 24 hours prior to beginning the experiment, though water was provided *ad libitum*.

Administration of the antibiotic

The cefamandole nafate was administered in a bolus type i.v. injection at a dose of 30 mg/kg dissolved in 1 ml of sterile water into the marginal ear vein. Heparinized blood samples were obtained from the animals while they were awake by means of permanent catheterization of the carotid artery at previously programmed times. The total amount of blood extracted from each animal during the course of the experiment never exceeded 3 ml.

Urine samples were collected directly from the bladders of the animals through a permanently fitted bladder catheter at intervals of 0~1, 1~2, 2~3, 3~4, 4~5, 5~6, 6~7, 7~8, and 8~9 hours.

Bile samples were collected from the catheterized bile duct of the animals under ether anesthesia at intervals: 0~0.083, 0.083~0.25, 0.25~0.5, 0.5~0.75, 0.75~1, 1~1.5, 1.5~2, 2~2.5, 2.5~3, 3~4, 4~5 and 5~6 hours and in rabbits with renal impairment, the intervals were extended up to 11 hours.

Microbiological assay

The concentration of the antibiotic was determined in each sample of the biological fluids with respect to standard curves derived from the same fluids, by a plate diffusion method[16] using *Bacillus subtilis* (ATCC No. 6633) as the test organism. It was ascertained that the administration of uranil nitrate does not interfere with the analytical technique used. All assays were repeated at least four times.

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated using a programmable Hewlett-Packard 67 calculator[7].

Results and Discussion

From the analysis of the average plasma levels curves of i.v. administered cefamandole to rabbits with normal renal function (Fig. 2) and to rabbits with varying degrees of renal function (Fig. 3), it may be seen that the antibiotic follows a two-compartment open kinetic model[15]. The pharmacokinetic parameters calculated from these plasma levels curves are shown in Table 1.

In rabbits with normal renal function the rapid disposition phase may be observed with a value of $\alpha = 4.46\ h^{-1}$; once equilibrium has been reached after 20 minutes, the slow disposition phase begins with a value of $\beta = 1.83\ h^{-1}$. The elimination of cefamandole is rapid; the value of $t_{\frac{1}{2}\beta}$ being 0.39 h, similar to that reported by CARBON *et al.*[3] for the same dose administered intramuscularly to rabbits. As a consequence of acute renal impairment, a significant modification may be observed in the following pharmacokinetic parameters: K_{12}, K_{21}, K_{13}, V_c and V_p are decreased, and $t_{\frac{1}{2}\alpha}$, $t_{\frac{1}{2}\beta}$ and $(AUC)_0^\infty$ are increased (Table 1).

Fig. 2. Average plasma level curve of cefamandole in rabbits with normal renal function.

The standard deviation (S. D.) of the mean is represented by the vertical strokes.

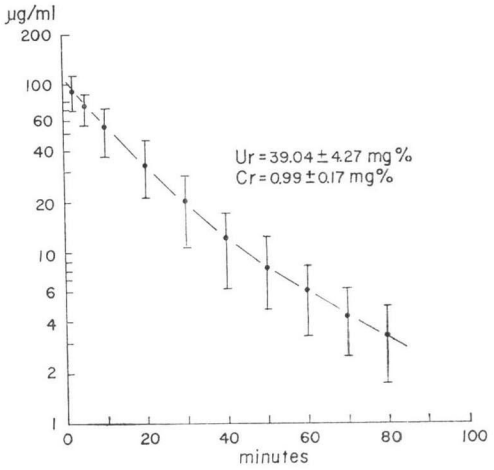
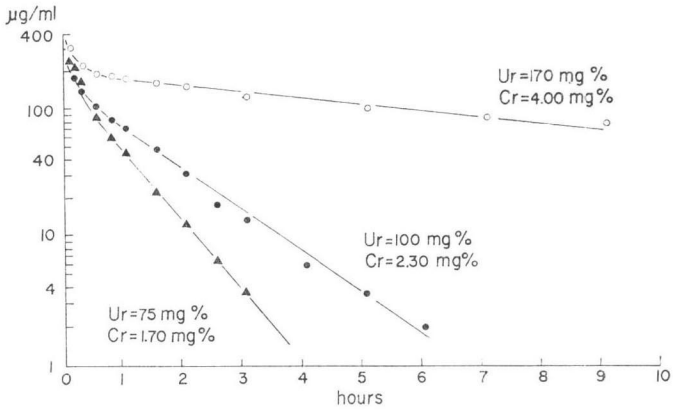


Fig. 3. Plasma levels curves of cefamandole in three rabbits with varying degrees of renal impairment.



The processes of distribution and elimination are clearly modified in renal impairment. A linear relationship is established between the logs of α and β and the serum creatinine values (Fig. 4). As a consequence of the decrease in the rapid disposition constant, a delay is caused in the distribution equilibrium of the antibiotic (Table 1). This is confirmed by a decrease in the distribution rate constants (K_{12} and K_{21}). A linear relationship is established between log t_{ss} and the value of serum creatinine (Fig. 5). The decrease in the hybrid constants α and β in renal impairment in clinical studies have also been reported in amikacin[11], cefoxitin[8] and cephacetrile[5].

In studies carried out in this laboratory, the results of which are still to be published, this delay in the access of various antibiotics to certain tissues has been confirmed in laboratory animals and in humans.

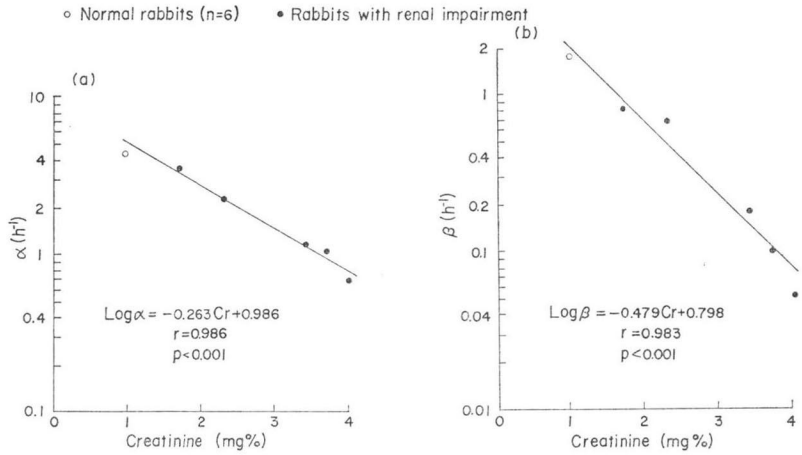
Table 2 shows the parameters defining the urinary excretion of cefamandole after i.v. administration. The high percentage excreted in urine in an unaltered form (78.88%) suggests that the principle

Table 1. Pharmacokinetic parameters of cefamandole in rabbits with normal renal function (n=6) and with acute renal impairment (n=5).

	(A) Normal renal function	(B) Acute renal impairment				
	Ur=39.04±4.27 Cr= 0.99±0.17	Ur=75.00 Cr= 1.70	Ur=100 Cr=2.3	Ur=125 Cr=3.40	Ur=140 Cr=3.70	Ur=170 Cr= 4
α (h^{-1})	4.46±1.16*	3.73	2.31	1.19	1.10	0.70
β (h^{-1})	1.84±0.30	0.84	0.70	0.18	0.11	0.05
$t_{\frac{1}{2}\alpha}$ (h)	0.17±0.05	0.19	0.30	0.52	0.63	0.99
$t_{\frac{1}{2}\beta}$ (h)	0.39±0.06	0.83	0.99	3.77	6.42	12.60
K_{12} (h^{-1})	0.51±0.29	0.99	0.42	0.32	0.39	0.24
K_{21} (h^{-1})	2.79±0.90	1.56	1.53	1.31	0.63	0.42
K_{13} (h^{-1})	2.93±0.61	2.00	1.05	0.29	0.19	0.09
V_c (l)	0.52±0.13	0.15	0.31	0.17	0.29	0.20
V_p (l)	0.09±0.05	0.09	0.08	0.04	0.18	0.12
$(AUC)_0^\infty$ (μg/ml.hr)	37.83±8.79	168.38	224.54	717.83	592.16	1829.03
t_{ss} (min)	20.00±6.52	30.98	44.48	111.48	140.40	237.85

* (M±SD) Mean arithmetic values and standard deviation; (α, β) hybridid rate constants; (K_{12}, K_{21}) distribution constants to and from the peripheric compartment; (K_{13}) elimination constant of the antibiotic; (V_c, V_p) apparent distribution volumes of the central and peripheric compartments; $(AUC)_0^\infty$ area under curve; (t_{ss}) steady-state time.

Fig. 4. Linear relationship between: (a) the logarithm of the rapid disposition constant (α) and (b) the logarithm of the slow disposition constant (β) with serum creatinine.



elimination route is the kidney, with a renal clearance of 20.63 ml/min. Fig. 6 shows the cummulative urinary excretion curve of the antibiotic. Since plasma clearance (Cl_p) is 26.16 ml/min, the quotient of Cl_r/Cl_p is slightly less than 1; this corroborates the aforementioned hypothesis. Given the fact that extra-renal clearance is 5.52 ml/min, it may be seen that there exist secondary elimination routes. The average parameters which define the biliary excretion of cefamandole calculated from a first order kinetic process are shown in Table 3.

In rabbits with normal renal function (Table 3), the total amount of cefamandole excreted in bile is 2.52% of the original dose administered, and the value of K_B calculated from the excretion

Fig. 5. Linear relationship between the logarithm of the time in which steady state is reached in min. (t_{ss}), and serum creatinine.

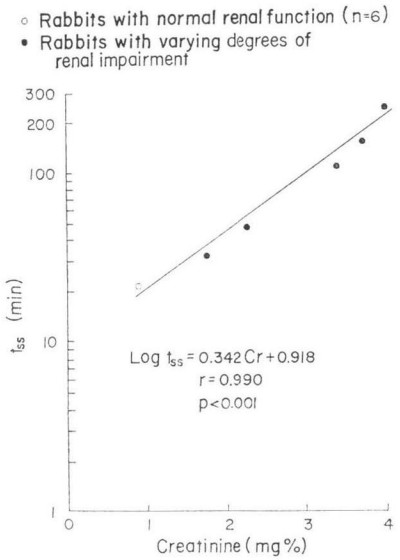


Table 2. Parameters of urinary excretion of cefamandole in rabbits with normal renal function.

		Mean±S.D.
K_u	(h^{-1})	1.05±0.099
$t_{\frac{1}{2}u}$	(h)	0.72±0.15
% of dose excreted		78.88±7.60
Cl_r	(ml/min)	20.63±1.98
Cl_{ex}	(ml/min)	5.52±1.99
Cl_p/Cl_r		1.27±0.11

(Mean±S.D.) Mean arithmetic values (n=6) and standard deviation; (K_u): urinary excretion constant; ($t_{\frac{1}{2}u}$): urinary excretion half-life; (Cl_r): renal clearance; (Cl_{ex}): extra-renal clearance; (Cl_p/Cl_r): quotient of plasma and renal clearance.

Fig. 6. Curve of accumulated urinary excretion of cefamandole.

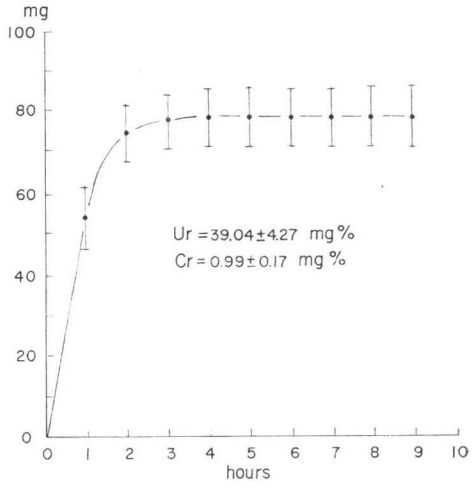


Fig. 7. Linear relationship between the percentage of the dose of cefamandole excreted in bile and serum creatinine.

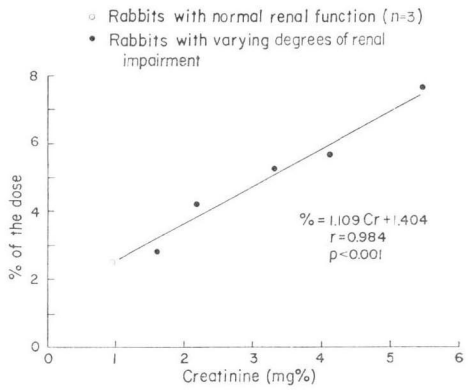


Table 3. Pharmacokinetic parameters defining biliary excretion of cefamandole in rabbits with normal renal function (n=3) and with acute renal impairment (n=5).

	(A) Normal renal function	(B) Acute renal impairment				
	Ur=38.44±4.54 Cr= 0.93±0.12	Ur=52.00 Cr= 1.60	Ur=74.00 Cr= 2.20	Ur=92.00 Cr= 3.33	Ur=130 Cr=4.1	Ur=188 Cr=5.5
K_B (h^{-1})	0.57±0.17*	0.42	0.30	0.45	0.34	0.26
$t_{\frac{1}{2}B}$ (h)	1.35±0.34	1.67	2.29	1.52	2.11	0.72
% of dose excreted	2.52±0.03	2.71	4.29	5.30	5.56	7.62
V_{max} (mg/h)	2.11±0.66	2.30	3.74	5.29	5.41	7.11

(K_B): biliary excretion constant; ($t_{\frac{1}{2}B}$): biliary excretion half-life; (V_{max}): maximum excretion rate.
* Mean ± S.D.

rate curves is that of 0.57 h^{-1}. Since the sum of K_B and K_u is 1.62 h^{-1}, close to that of the slow disposition phase, it would appear that the principle secondary elimination route of cefamandole is in bile. As a consequence of acute renal impairment (Table 3), the total amount of cefamandole excreted in bile is increased, there being a linear relationship between the percentage of the dose excreted and the serum creatinine (Fig. 7). As a consequence of the increase in biliary excretion, the maximum excretion of cefamandole (V_{max}) is also increased in renal impairment. Due to this pathological state, cefamandole is accumulated within the organism much longer than usual and the excretion process is thus prolonged. This is corroborated by the decrease which the biliary excretion constant (K_B) undergoes in proportion to the deterioration in the state of renal function (Table 3).

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