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INFLUENCE OF EXPERIMENTAL RENAL IMPAIRMENT IN THE PHARMACOKINETICS OF CEFOXITIN AFTER INTRAVENOUS ADMINISTRATION TO RABBITS

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SUMMARY

The pharmacokinetics of cefoxitin have been studied in rabbit with normal renal function or with varying degress of renal impairment caused experimentally by uranyl nitrate, after i.v. administration of a single dose of 40 mg/kg. The plasma concentrations of cefoxitin 12 min after administration were 40 μg/ml in rabbits with normal renal function, and reached 36 μg/ml at 6 h in the case of terminal renal impairment. With respect to the pharmacokinetic parameters established in rabbits with normal renal function: K_{12}, K_{21}, K_e are decreased while there is an increase in $t_{1/2}\alpha$, $t_{1/2}\beta$, V_c, V_p and $(AUC)_0^\infty$ in rabbits with induced renal impairment. Linear relationships have been established between log K_e and serum creatinine. The dose percentage excreted through the kidney in normal rabbits was 85–90%. Biliary excretion of cefoxitin was increased in parallel to the increase in the degree of renal impairment, there being a linear relationship between the dose percentage excreted of the antibiotic and serum creatinine. The values of K_B fell from 1.62 h^{-1} to 0.84 h^{-1}, indicating that the duration of the biliary excretion process of cefoxitin is longer in the case of severe renal impairment.

INTRODUCTION

Studies on pharmacokinetics are of great auxiliary help in the rational use of drugs since the concentration levels which these reach in plasma or other body fluids are related to the activity or toxicity of the drug in question. The levels which a given drug may reach in the organism are governed by the processes of absorption, distribution, metabolism and excretion (Anderson et al., 1976; Dettli, 1977; Bennett et al., 1978), and these may be modified by various circumstances, principally the interaction which takes place in a combined therapeutic course and various pathological states.

Renal impairment is undoubtedly the pathological factor which causes the most important alterations in kinetic processes in those drugs which are metabolized to a very limited extent and whose elimination route is principally through the kidney.

Since antibiotics may be classed within the group of drugs which are eliminated in a principally unaltered form through the kidney, and which are normally administered in multiple doses, it is necessary to bear in mind the possible pharmacokinetic modifications which may occur in order to obtain a correct dosage regimen for a patient with renal impairment, and hence safe and efficient concentrations of the antibiotic. Cefoxitin is a semi-synthetic antibiotic belonging to a new family of beta-lactams: the cephamycins. Cefoxitin is active against the gram-negative germs: *Escherichia coli, Klebsiella, Enterobacter aerogenes, Proteus* indole positive, *Shigella, Salmonella, Serratia,* etc. (Wallick and Hendlin, 1973; Geddes et al., 1977).

The present study deals with the modifications produced in the pharmacokinetics of cefoxitin as a consequence of severe renal impairment in rabbits. There are few references in the literature to the use of animals for the study of the effects of renal impairment in the disposition of drugs. We have taken advantage of the analogy between renal impairment caused by uranyl nitrate and that caused by diverse pathological processes in order to improve our clinical studies.

MATERIALS AND METHODS

The pharmacokinetics of cefoxitin were studied in adult, male New Zealand rabbits weighing between 1.88 and 2.0 kg. The animals included in the study were divided into two groups. The first comprised 15 animals with normal renal function, serum urea 41.97 ± 8.98 mg%, and serum creatinine 0.85 ± 0.20 mg%. In 6 animals of this group the kinetics of the antibiotic in plasma were studied, in another 6, urinary excretion, and in the remaining 3, biliary excretion. The second group included 14 animals with varying degrees of renal impairment, serum urea from 49.25 mg% to 186.23 mg% and serum creatinine from 1.20 mg% to 3.88 mg%. Eight rabbits were used to study the kinetics of the antibiotic in plasma, and biliary excretion was studied in remaining 6. Administration was i.v. bolus-type injection at a dose of 40 mg/kg body weight.

Renal impairment was induced by i.v. administration of a single dose of 2 mg/kg of $UO_2(NO_3)_2 \cdot 6H_2O$ in an aqueous solution. 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 uranyl 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 (Flamenbaun et al., 1974). Renal haemodynamic alterations similar to those observed after uranyl nitrate administration have been reported in human acute renal impairment of varied etiologies (Hollenberg et al., 1968; Hollenberg et al., 1970; Reubi et al., 1973).

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

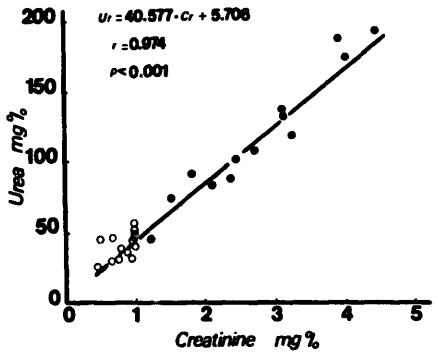


Fig. 1. Linear relationship between serum urea and serum creatinine in ○, normal rabbits and ●, rabbits with varying degrees of renal impairment.

indiscriminate use of both indices. The serum urea and creatinine concentrations remained stabilized throughout the duration of the experiments.

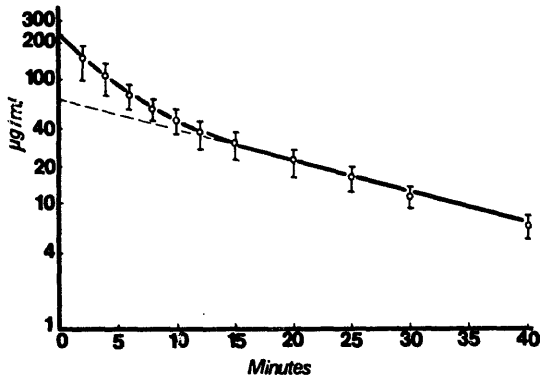
Blood samples were obtained from awake animals – at times previously programmed according to the degree of renal function – from the carotid artery which had previously been permanently cathetered. Urine samples were obtained at regular intervals from awake animals through a catheter permanently fixed into the bladder. Finally, bile samples were obtained from the animals under ether anesthesia from the biliary duct through a permanently fixed catheter.

The determinations of the concentrations of the antibiotic in plasma, urine and bile were carried out microbiologically using a plate diffusion method with *B. subtilis* (ATCC no. 6633) as the test organism. Standard curves were prepared with known concentrations of the antibiotic for each of the aforementioned biological fluids. Due to the stability of cefoxitin within the organism, which was confirmed by bioautography, in the determination, there were no interferences caused by the presence of active metabolites, such as occurs with other antibiotics; in particular with the acetylated cephalosporins.

The antibiotic, administered intravenously, followed an open two-compartment kinetic model according to the application of Saunders and Natunen's test (Saunders and Natunen, 1972).

RESULTS

Fig. 2 shows the average plasma level curve of cefoxitin obtained after the administration of a single i.v. dose of 40 mg/kg in 6 rabbits with normal renal function. The characteristic plot of a curve following an open two-comparment kinetic model may be observed. The plasma concentration of the antibiotic fell from 253.35 μg/ml (value of C_0 obtained by extrapolation) to 40 μg/ml 12 min after administration, the point at which the slow disposition phase begins. Table 1 shows the average pharmacokinetic parameters established from the experimental values of the plasma concentrations of the antibiotic.



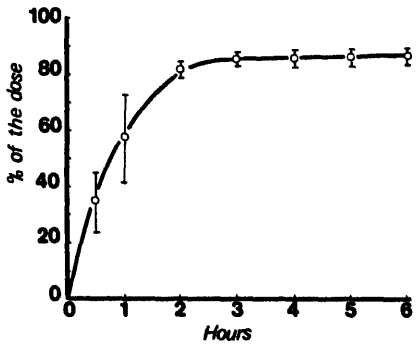


Fig. 2. Average plasma level curve of cefoxitin in rabbits with normal renal function (n = 6). (The standard deviation (S.D.) of the mean is represented by the vertical strokes.)

Fig. 3. Average curve of cumulative urinary excretion of cefoxitin.

Fig. 3 shows the average curve of cumulative urinary excretion of cefoxitin in 6 rabbits with normal renal function. The percentage of the antibiotic excreted in urine oscillates between 85 and 90% of the dose originally administered, the process being completed 360 min after administration. The urinary excretion constant has an average value of $K_u = 1.44 \pm 0.084\ h^{-1}$ (n = 6). Biliary excretion represents 0.51% ± 0.12 of the dose administered, the average value of the constant K_B being $1.62 \pm 0.32\ h^{-1}$ (n = 3).

Table 2 shows the pharmacokinetic parameters of cefoxitin established in rabbits with varying degrees of renal impairment. Fig. 4 shows the plasma levels curves obtained from 4 rabbits with varying renal function: serum creatinine values of 0.88, 2.38, 3.03 and 3.88 mg%. The elimination of the antibiotic from plasma decreased in parallel to the state of deterioration in renal function, although it is important to point out that the distribution processes are also significantly modified. This decreased elimination rate is of no great importance in individual administrations but it does cause a rapid accumulation to affect the circumstances of a multiple dosage regimen, indispensible in all anti-infectious therapeutics. This makes it necessary to introduce certain corrections in the dosage regimen due to the modifications observed in the pharmacokinetics of the antibiotic.

TABLE 1

AVERAGE PHARMACOKINETIC PARAMETERS OF CEFOXITIN IN PLASMA IN RABBITS WITH NORMAL RENAL FUNCTION (n = 6)

α	$= 21.34 \pm 4.36\ h^{-1}$	K_{21}	$= 8.48 \pm 1.31\ h^{-1}$
β	$= 3.80 \pm 0.19\ h^{-1}$	K_e	$= 9.64 \pm 1.76\ h^{-1}$
$t_{1/2}\alpha$	$= 0.032 \pm 0.006$ h	V_p	$= 0.28 \pm 0.09$ l
$t_{1/2}\beta$	$= 0.18 \pm 0.009$ h	V_c	$= 0.27 \pm 0.10$ l
K_{12}	$= 7.28 \pm 0.86\ h^{-1}$	Vd_{ss}	$= 0.55 \pm 0.18$ l
		$(AUC)_0^\infty$	$= 30.83 \pm 8.56$ (µl/ml) h

TABLE 2

PHARMACOKINETIC PARAMETERS OF CEFOXITIN IN PLASMA IN EIGHT RABBITS WITH VARYING DEGREES OF RENAL IMPAIRMENT

Creatinine (mg%)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	K_{12} (h^{-1})	K_{21} (h^{-1})	K_e (h^{-1})	V_c (liters)	V_p (liters)	$(AUC)_0^\infty$ (μg/ml)/h	Vd_{ss} (liters)
1.50	0.09	0.54	1.72	1.90	4.77	0.37	0.34	48.33	0.71
1.85	0.08	0.59	2.69	2.11	3.92	0.42	0.53	70.66	0.66
2.10	0.11	0.60	1.92	2.42	2.88	0.63	0.50	47.07	1.13
2.38	0.18	0.69	1.82	1.54	2.53	0.37	0.20	82.31	0.56
2.84	0.10	0.98	5.31	3.93	0.32	0.46	0.63	482.20	1.08
3.03	0.11	0.10	3.41	2.56	0.83	0.27	0.35	313.69	0.63
3.11	0.24	0.93	1.35	1.49	0.18	0.54	0.48	901.22	1.02
3.88	0.12	14.46	4.02	1.73	0.16	0.59	1.36	960.97	1.94

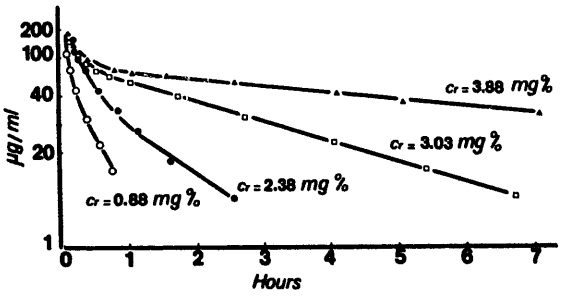


Fig. 4. Plasma level curves of cefoxitin in 4 rabbits with varying degrees of renal impairment.

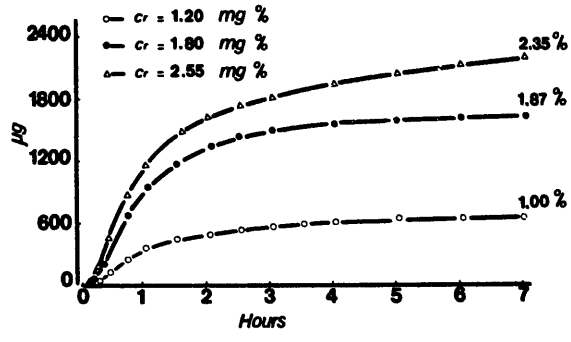


Fig. 5. Accumulated biliary excretion curves of cefoxitin in rabbits with varying degrees of renal function.

TABLE 3

BILIARY EXCRETION OF CEFOXITIN IN RABBITS WITH VARYING DEGREES OF RENAL IMPAIRMENT

creatinine (mg %)	% of dose excreted	K_B (h^{-1})
1.20	1.00	0.60
1.80	1.87	0.78
2.44	2.85	0.76
2.55	2.35	0.51
3.20	2.78	0.46
3.20	3.56	0.84

Biliary excretion of the antibiotic is also modified in the case of renal impairment. Parallel to the decrease in renal function, the amount of the original dose excreted in bile is increased. Table 3 shows the percentage of dose excreted in bile together with the biliary excretion constants (K_B) in 6 rabbits with varying degrees of renal function impairment. Fig. 5 shows the curves of the accumulated amounts of cefoxitin excreted in bile in 3 rabbits with varying degrees of renal function impairment.

DISCUSSION

According to the pharmacokinetic parameters established it may be said that cefoxitin disappears rapidly from the circulatory system through the distribution processes. Thus the α and β constants which define these processes have values of 21.34 h^{-1} and 3.80 h^{-1}, respectively. The relationship between both constants is similar to that established by us in patients with normal renal function (Garcia et al., 1979a). The relationship between the intercompartmental constants, K_{12}/K_{21}, has a value close to 1 which reflects a similar distribution between both compartments. The distribution volume has an average value of 0.55 liters, which is equivalent to 27% of body weight.

Cefoxitin is scarcely metabolized within the organism and is principally excreted through the kidney in an unaltered state. In this study, after i.v. administration of the antibiotic, 85–90% of the original dose is excreted in urine during the first 3 h after administration. The rapid urinary excretion is reflected by the value of the constant $K_u = 1.44 \pm 0.084\ h^{-1}$.

Bile is a lesser excretion route of cefoxitin in rabbits with normal renal function. This elimination route accounts for only 0.51 ± 0.12% of the original dose administered, the value of K_B being $1.62 \pm 0.32\ h^{-1}$ (n = 3). The sum of the biliary and urinary excretion constants is 3.06 h^{-1}; very close to the value established for the slow disposition constant.

In renal impairment it may be seen that there is a significant modification in those pharmacokinetic parameters which define the distribution and elimination processes (α, β, K_{21}, and K_e), together with the distribution volumes. The most outstanding modification is the decrease in the elimination rate. $t_{1/2}\beta$ increases from 0.8 h in rabbits with normal renal function to 6.0 h in rabbits with severe renal impairment. As a consequence, and at similar times, the plasma concentrations of cefoxitin are far greater in the case of renal impairment, thus causing an accumulation in the circumstance of a multiple dosage regimen. The distribution process is also modified in renal impairment. This is of great interest due to the fact that one of the principles of antiinfectious therapy is that of ensuring the access of the antimicrobial agent to the point of infection at a concentration sufficient to stop the pathological process.

After i.v. administration of the antibiotic, the time taken to reach steady-state in rabbits with normal renal fucntion increases from 12 min to 50 min in rabbits with severe renal impairment. This causes a delay in the access of the antibiotic to certain organs and tissues, as has been confirmed in our laboratory with various other antibiotics. (Garcia et al. 1979b; Cepeda et al., 1979). Thus renal impairment causes an accumulation of the antibiotic in the peripheral compartment. These modifications in the distribution process are the consequence of the superimposition of two circumstances: a decrease in the degree of plasma protein binding which has already been demonstrated in humans with

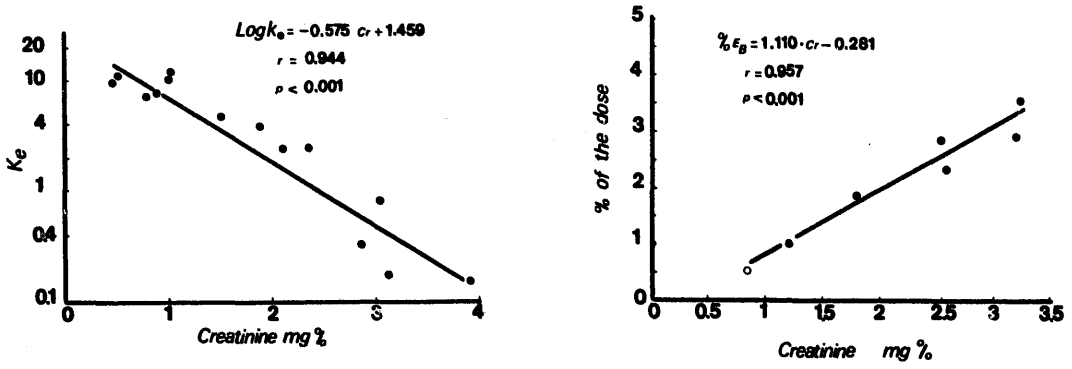


Fig. 6. Relationship between serum creatinine and the overall elimination constant K_e.

Fig. 7. Linear relationship between the percentage of the dose of cefoxitin excreted in bile and serum creatinine. ○, average normal rabbits; ●, rabbits with varying degrees of renal impairment.

cefoxitin (Garcia et al., 1979a) and the decrease in the elimination constant. The overall elimination constant shows a linear relationship with serum creatinine, used as the index of renal function, which maybe defined by the equation:

$\log K_e = -0.575\ Cr + 1.459$ (Fig. 6).

As the urinary excretion of cefoxitin is diminished, two important modifications in the pharmacokinetics of the antibiotic take place: a greater access to peripheral tissues (Garcia et al., 1979a) and an increase in the role of secondary excretion routes. Both modifications are a consequence of the prolonged time that the antibiotic remains within the systemic circulation. The elimination constant K_e will then be the result of the decrease in the urinary excretion constant and the increase in extrarenal excretion. In the case of drugs which are principally excreted extrarenally, there will be less effect on the elimination constant in states of renal impairment.

Biliary excretion of cefoxitin is increased in renal impairment. In rabbits with normal renal function, 0.51% of the original dose is excreted in bile and the process is completed in 3 h while in the case of rabbits with renal impairment (serum creatinine 3.20 mg%), 3.56% of the dose is excreted in bile and the process is completed in 8 h. Fig. 7 shows the relationship established between the percentage of the dose excreted in bile and the serum creatinine concentration used as the index of the degree of renal function.

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