ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1984, p. 373-377
0066-4804/84/090373-05$02.00/0

Vol. 26, No. 3

Renal Disposition of Ceftazidime Illustrated by Interferences by Probenecid, Furosemide, and Indomethacin in Rabbits

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Received 26 March 1984/Accepted 25 June 1984

Excretion of ceftazidime (C), a new cephalosporin antibiotic, has been reported to occur unexpectedly through glomerular filtration only, without being significantly affected by probenecid. We investigated renal tubular disposition of C in rabbits by calculating its rates of fractional excretion, net tubular secretion, and absolute excretion. During continuous intravenous infusion of C, 3 mg of furosemide (F), 15 mg of probenecid (P), or 2 mg of indomethacin (I) per kg was injected intravenously as a bolus. Equilibrium dialysis showed that the percentage of C bound to serum proteins (14 ± 5%) was not altered by F, P, or I. Fractional excretion of C was 94 ± 22, 65 ± 21, 182 ± 36, and 98 ± 3% for the drug given alone and after injection of F, P, and I, respectively. For 15 min after P injection, we observed net tubular secretion of C (404 ± 276 μg/min). The C absolute excretion rate was significantly reduced by I compared with the absolute excretion rate for the control (405 ± 104 versus 696 ± 157 μg/min). We conclude that (i) C undergoes bidirectional transport in the nephron, revealed by the effects of F and P, with a nil net C balance; (ii) F and P have opposite unexpected effects on tubular handling of C, possibly due to competition for C secretion processes; (iii) I reduces C excretion solely by decreasing its glomerular-filtered load; and (iv) tubular handling of C differs from that of previously studied cephalosporins.

The finding that probenecid did not affect ceftazidime serum levels, serum half-life, or renal excretion suggests that glomerular filtration is the main route for renal elimination of this drug (11). Luthy and co-workers (14) noted substantial differences in the pharmacokinetic behaviors of ceftazidime, cefotaxime, and moxalactam in humans. According to these authors, cefotaxime is secreted by the renal tubules, and the addition of probenecid significantly reduces this tubular secretion. Ceftazidime appears to be reabsorbed (ceftazidime renal clearance to creatinine clearance, 0.58 ± 0.09) without interference by probenecid, and the same results can be applied to moxalactam (ceftazidime renal clearance to creatinine clearance, 0.46 ± 0.06). As regards ceftazidime, this pattern of renal disposition was somewhat unexpected for the cephalosporin antibiotics, which ususally exhibit tubular secretion, although some exceptions have been reported for moxalactam (10, 14) and ceforanide (13).

The purpose of the present study was to clarify the renal disposition of ceftazidime in rabbits, using the interfering agents furosemide, probenecid, and indomethacin. In a previous study (6), we demonstrated that furosemide significantly increased, by different mechanisms, urinary excretion of cefazolin, suggesting bidirectional tubular transport of the antibiotic. In the present study, probenecid was chosen in an attempt to elucidate the mechanisms of the interaction of this drug with cephalosporins (1, 17). The effect of indomethacin was also studied because a previous report on indomethacin-probenecid or indomethacin-furosemide interactions (12) suggested that they might have common elimination pathways.

(This work was presented in part at the Second World Conference on Clinical Pharmacology and Therapeutics, Washington, D.C., 1983, abstr. no. 630, p. 110).

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MATERIALS AND METHODS

Animal model. The investigations were carried out in 36 male rabbits (Fauve de Bourgogne; weight range, 1.9 to 2.4 kg). Extravascular tissue cage fluid was obtained from subcutaneous tissue cages as previously described (6). Each animal was used once only.

Protein binding. Protein binding was investigated by equilibrium dialysis for 6 h at 37°C in 0.15 M phosphate buffer, pH 7.4, by using a Dianorm System (Diachema A. G., Rüchlikon, Switzerland) with 2 ml of cells and cellulose dialysis membranes (Union Carbide Corp., Chicago, Ill.). Antibiotic concentrations were measured on each side of the dialysis membrane. To reach equilibrium, 6 h of dialysis was enough. The stability of the ceftazidime molecule was verified after a 6-h incubation at 37°C in buffer and serum.

Extravascular diffusion study. A single intramuscular (i.m.) injection of ceftazidime (30 mg/kg) was administered to six rabbits, alone or combined with 3 mg of furosemide, 2 mg of indomethacin, or 15 mg of probenecid per kg. Blood and tissue cage fluid samples were collected for antibiotic assays at the times indicated in Fig. 1 and 2.

Urinary excretion. Renal disposition of ceftazidime and the effects of furosemide, probenecid, and indomethacin on the urinary excretion of ceftazidime were studied in three groups of four rabbits. Animals were anesthetized with ketamine hydrochloride administered by i.m. injection (10 mg/kg). Two catheters were inserted into femoral veins for infusion and sampling. For urine collection, both ureters were catheterized through a suprapubic incision. The wounds were carefully closed around the catheters with surgical silk after local infiltration with lidocaine and then packed with gauze treated in saline. Continuous isotonic saline infusion was started at 0.5 ml/kg per min 2 h after ketamine injection. Ceftazidime was infused at 30 mg/kg per h concomitantly with [^{3}H]inulin (0.1 μCi/min) (Amersham Corp., Les Ulis,

France) in saline (0.5 ml/kg per min) over a period of 2 h for equilibration. After two control periods of 15 min each, 3 mg of furosemide, 15 mg of probenecid, or 2 mg of indomethacin per kg was injected intravenously as a bolus, followed by two experimental periods of 15 min each. At the end of each control and experimental period, blood samples for antibiotic and inulin assays were collected; urine was obtained throughout the four periods. No attempt was made to replace precisely the fluid and electrolyte losses. For each period, we calculated (i) the ceftazidime-filtered load, (ii) the ceftazidime absolute excretion rate, and (iii) the absolute rate of net ceftazidime tubular secretion, taken as the rate of urinary excretion of ceftazidime minus its rate of glomerular filtration; the latter was calculated as the product of the unbound ceftazidime serum concentration and the glomerular filtration rate (GFR), which was [^{3}H]inulin renal clearance. The ceftazidime, sodium, and potassium fractional excretions were also determined, as well as urinary pH. Control values, for each parameter reported, represent means of the two control periods.

Assays. Blood samples were centrifuged at 1,200 × *g* for 15 min, and serum, tissue cage fluid, and urine were stored at −30°C.

Antibiotic assays. Standards for the assays of serum samples were prepared with normal rabbit serum. Standards for the assays of tissue cage fluid samples were prepared with rabbit serum diluted threefold in 0.15 M phosphate buffer, pH 7.4, to reduce the level of total protein to that observed in tissue cage fluid (4). The standard curves obtained under these conditions correlated well with those for tissue cage fluid. Standards for the assays of urine samples were prepared in 0.15 M phosphate buffer, pH 7.4. All serum, tissue cage fluid, and urine samples were studied in duplicate. Antibiotic concentrations were determined by diffusion in nutrient agar by the method of Bennett et al. (3) with *Escherichia coli* LM 83156 as the test organism. Results were within 10% of the known value for concentrations less than 25 μg/ml and were reproducible between 0.5 and 25 μg/ml, with a sensitivity limit of 0.4 μg/ml. Samples for ceftazidime determinations were diluted when necessary. The absence of furosemide, probenecid, or indomethacin interference in the antibiotic assays was verified by comparison of standards with or without furosemide, probenecid, or indomethacin and in vivo by using serum from an animal given furosemide, probenecid, or indomethacin but no antibiotic, to exclude the potential role of interfering metabolites.

Scintillation counting of [^{3}H]inulin was performed on an SL 30 CK scintillation counter (Intertechnique Instrument Corp., Orsay, France) with Aquasol (New England Nuclear Corp., Boston, Mass.) as a scintillation solution.

Sodium and potassium concentrations were measured by flame photometry.

Statistical analysis was carried out by variance analysis. The degree of significance between means was evaluated by the Student's *t* test with the residual variance and its degree of freedom.

RESULTS

Protein binding. At concentrations of 5, 20, or 60 μg/ml, the percentage of serum protein binding of ceftazidime was 14 ± 5% (range, 8 to 22%) when this drug was studied alone. This percentage was not modified when ceftazidime was associated with furosemide (5 μg/ml), probenecid (20 μg/ml), or indomethacin (5 μg/ml) (four determinations in each case).

Extravascular diffusion. Serum levels obtained after i.m. administration of ceftazidime alone or combined with furosemide, probenecid, or indomethacin are given in Fig. 1. These serum concentration curves were similar. At 2 h, ceftazidime concentrations were significantly higher when the drug was administered with one of the three interfering agents than when it was administered alone. At 4 h, ceftazidime concentrations were higher when this antibiotic was administered with furosemide or probenecid than when it was given alone (3.7 ± 1.1 and 3.2 ± 0.3 versus 2.2 ± 0.6 μg/ml, respectively).

The extravascular fluid concentrations of ceftazidime measured after injection of ceftazidime alone or combined with an interfering agent are given in Fig. 2. Ceftazidime extravascular levels remained unchanged after probenecid injection but were significantly raised by indomethacin at 1, 2, 4, and 8 h (1.4 ± 0.1, 2.6 ± 0.6, 3.7 ± 1.1, and 2.5 ± 0.5 μg/ml versus 1.0 ± 0.2, 1.9 ± 0.3, 2.4 ± 0.6, and 1.8 ± 0.6 μg/ml for the antibiotic alone) and by furosemide at 4 and 8 h (3.5 ± 0.4 and 2.7 ± 0.2 versus 2.4 ± 0.6 and 1.8 ± 0.6 μg/ml, respectively). At 1 and 2 h, indomethacin enhanced extravascular ceftazidime levels more than did furosemide (1.4 ± 0.1 and 2.6 ± 0.6 versus 1.0 ± 0.2 and 1.7 ± 0.6 μg/ml, respectively).

Urinary excretion. The results obtained for urinary excretion appear in Table 1. The control value for ceftazidime fractional excretion was not significantly different from 100%. No significant net tubular secretion was noted.

Furosemide significantly increased the urinary flow rate, as well as sodium and potassium fractional excretion, during both experimental periods. A significantly brief (15 min) rise in the GFR was noted. A reduction of ceftazidime fractional excretion was observed with furosemide during both experimental periods, with a significant decrease in the absolute excretion rate during the second experimental period. Probenecid significantly reduced the GFR and raised the absolute rate of net tubular ceftazidime secretion as well as its fractional excretion during both experimental periods. The antibiotic absolute excretion rate only rose during the first experimental period. Probenecid significantly increased sodium and potassium fractional excretion. Indomethacin significantly reduced the urinary flow rate, GFR, ceftazidime-filtered load, and absolute rate of excretion of ceftazidime during the first experimental period. Indomethacin did not significantly modify sodium and potassium fractional excretion. The mean value of urinary pH was 6.29 ± 0.65 during the control period. No significant change was observed during any of the experimental periods.

DISCUSSION

We shall consider first the data obtained with ceftazidime alone and second the effect of each interfering agent on the extravascular diffusion and renal excretion of this antibiotic.

Ceftazidime data. Ceftazidime displayed a low level of binding to serum proteins in rabbits. The mean value we measured was similar to the values reported in humans, as measured by the ultracentrifugation technique (11). Peak extravascular levels of about 2.4 μg/ml were obtained 4 h after a single i.m. injection of 30 mg of ceftazidime per kg. These levels were about twice those we previously noted for cefamandole in the same animal model (4). Wise et al. (18) reported a similar relation between the maximum extravascular concentration of each drug, in blister fluid withdrawn from humans. The antibiotic levels obtained with the cantharides blister technique were much higher than those we noted in our model, in which the extravascular fluid exhibit-

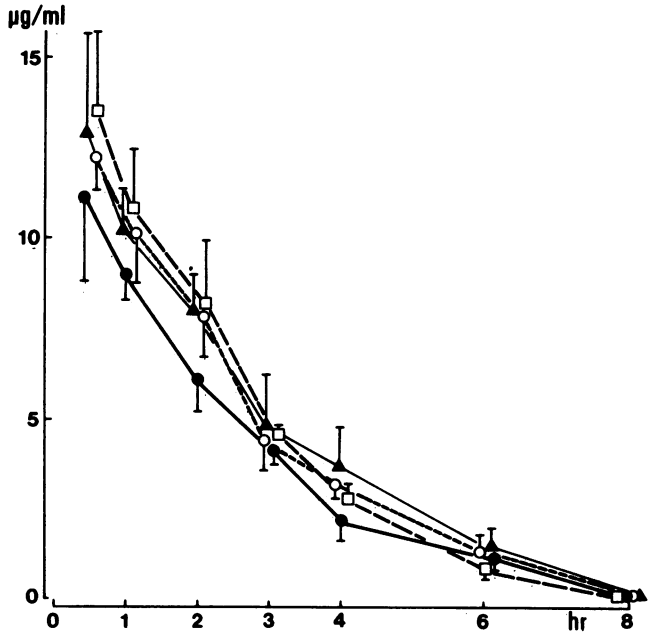

FIG. 1. Serum total ceftazidime levels obtained after a single i.m. injection of 30 mg of ceftazidime per kg alone or combined with a simultaneous injection of 15 mg of probenecid, 3 mg of furosemide, or 2 mg of indomethacin per kg. Values are means of six experiments, and vertical bars represent plus or minus the standard deviation. Significant differences are described in the text. Symbols: ●, ceftazidime alone; ○, ceftazidime plus probenecid; ▲, ceftazidime plus furosemide; □, ceftazidime plus indomethacin.

ed lower protein levels. In our study, ceftazidime fractional excretion was not significantly different from 100%. A similar pattern has been reported in humans (11, 14). This pattern suggests that renal excretion of ceftazidime occurs either through exclusive glomerular filtration or through glomerular filtration combined with nil net tubular bidirectional transport. The main cause of the difference between the ceftazidime kinetic values in humans and rabbits appears to be the higher GFR in rabbits. However, these data must be interpreted in light of decreases in physiological function per unit of animal weight with increases in size as reported previously (9). In previous studies, we stressed the interest of the "s.c. tissue-cage" animal model for studies of drug interferences (5, 6). The results we obtained with furosemide or phenylbutazone for cefazolin kinetics and renal excretion allowed us to demonstrate the competitive inhibition of cefazolin serum protein binding. We also found that cefazolin undergoes bidirectional tubular transport in rabbits. This prompted us to use drugs that are apt to modify renal disposition of ceftazidime, to elucidate the precise mechanisms of its excretion. However, with ceftazidime, we were not able to demonstrate competitive inhibition of its binding to serum proteins by any of the interfering agents we studied. This result was probably due to the small amount of this antibiotic bound to serum proteins.

No major alteration of renal hemodynamics was observed during our studies. GFR remained constant during the two experimental periods and similar from one group to another.

Interaction with furosemide. Furosemide administered i.m. raised serum levels of concomitantly i.m. injected ceftazidime but did not significantly modify the early extravascular levels of ceftazidime. This was mainly due to the unchanged amount of ceftazidime bound to serum proteins and is in agreement with our previous report (6). Conversely, furosemide significantly enhanced peak extravascular levels of ceftazidime. This new pattern of ceftazidime diffusion suggested that furosemide possibly reduced its excretion. In the urinary excretion study, we noted a significant decrease in ceftazidime fractional excretion combined with a reduction in the absolute excretion rate of ceftazidime during the second experimental period. This suggested either augmented reabsorption or diminished secretion of the antibiotic. The data we obtained from the cefazolin-furosemide interaction study were exactly the opposite (6). In this study, we postulated that the increased renal cefazolin excretion

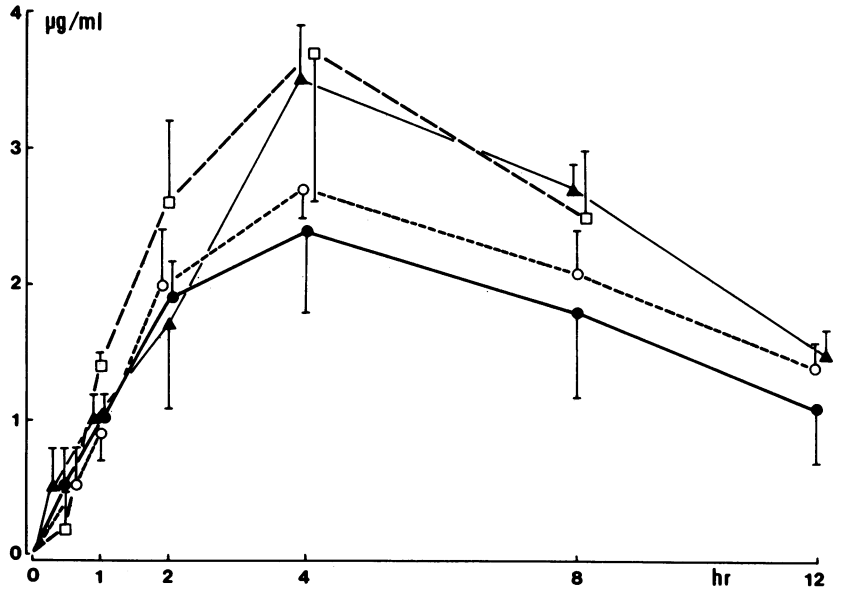

FIG. 2. Extravascular ceftazidime levels after a single i.m. injection of 30 mg of ceftazidime per kg alone or combined with 15 mg of probenecid, 3 mg of furosemide, or 2 mg of indomethacin per kg. Values are means of six experiments, and vertical bars represent plus or minus the standard deviation. Significant differences are described in the text. For symbols, see the legend to Fig. 1.

TABLE 1. Urinary excretion of ceftazidime and effects of interfering agents[a]

Treatment	Effect[b]								
	UFR (ml/min)	GFR (ml/kg per min)	Fractional excretion (%)			Total serum C level (μg/min)	C-filtered load (μg/min)	Net tubular C secretion (μg/min)	C absolute excretion rate (μg/min)
			Na	K	C				
Ceftazidime (control)	0.40 ± 0.21	7.1 ± 2.0	2 ± 1	17 ± 6	94 ± 22	40 ± 7	783 ± 396	24 ± 53	696 ± 157
Ceftazidime + furosemide									
Period 1	4.28 ± 0.91[c]	9.8 ± 2.5[c]	16 ± 5[c]	40 ± 7	65 ± 21[c]	38 ± 7	803 ± 185	0	527 ± 255
Period 2	2.65 ± 0.42[c]	6.5 ± 0.6	13 ± 5[c]	33 ± 12	73 ± 18[c]	39 ± 6	544 ± 101	0	384 ± 69[c]
Ceftazidime + probenecid									
Period 1	0.58 ± 0.18	4.3 ± 1.1[c]	4 ± 1[c]	27 ± 4	182 ± 36[c]	48 ± 4	611 ± 220	404 ± 267[c]	1,015 ± 197[c]
Period 2	0.53 ± 0.32	3.6 ± 1.2[c]	5 ± 1[c]	31 ± 2	161 ± 86[c]	49 ± 4	506 ± 201	248 ± 337[c]	753 ± 309
Ceftazidime + indomethacin									
Period 1	0.21 ± 0.08[c]	4.0 ± 1.2[c]	3 ± 1	19 ± 1	98 ± 3	35 ± 4	414 ± 104[c]	2 ± 4	405 ± 104[c]
Period 2	0.32 ± 0.17	7.4 ± 2.1	2 ± 1	18 ± 1	89 ± 13	36 ± 4	765 ± 148	3 ± 7	670 ± 132

[a] Control period values (row 1) represent means plus or minus the standard deviation for two control periods in which ceftazidime was continuously infused with [^{3}H]inulin for use as described in the text. Experimental period values represent means plus or minus the standard deviation for two periods per treatment in which ceftazidime and each of the interfering agents were combined for use as described in the text.
[b] UFR, Urinary flow rate; C, ceftazidime.
[c] Significantly different from the control value ($P < 0.05$).

caused by furosemide was due to a reduction in tubular reabsorption after an increase in the urinary flow rate. A similar pattern for the effects of furosemide was described for vancomycin in rabbits (15). Because of these results and the significant increase in net ceftazidime reabsorption by furosemide, it seems that furosemide reduced tubular secretion of ceftazidime, possibly by a competition effect, despite the rise in the urinary flow rate.

Interaction with probenecid. Probenecid injection did not significantly modify the serum and extravascular levels of ceftazidime. This was quite unexpected in view of the interactions previously described between probenecid and β-lactam antibiotics (7). Probenecid also induced changes in ceftazidime renal excretion that were opposite to those induced by furosemide. Probenecid caused a significant decrease in GFR. This fact appeared in the study by Shimada et al. (16) although it was not extensively discussed and was not previously noted in humans. In our study, this reduction of GFR caused an insignificant decrease in the ceftazidime-filtered load. Probenecid also caused a significant rise of the ceftazidime fractional excretion, which was concomitant with the onset of net tubular secretion. This resulted in a transient significant increase (15 min) in the absolute excretion rate of ceftazidime. These results differ from those obtained by Shimada et al. (16) in their study of renal disposition of moxalactam. These authors reported that probenecid reduced tubular secretion of moxalactam in rabbits and suggested that this observation, which differed from that noted in dogs and monkeys, might be because rabbits are considered to excrete alkaline urine. In fact, in our experiments we collected ureteral urine which appeared to be acidic (pH 6.29 ± 0.65). In acidic urine, probenecid has been demonstrated to undergo net tubular reabsorption (8). Therefore, our data on the effects of probenecid on the urinary excretion of ceftazidime could suggest a mutually competitive effect of these drugs on their tubular reabsorption. The increase of probenecid dosage could possibly modify this pattern of interaction as noted with uric acid transport. The significant increase in sodium and potassium fractional excretion after probenecid injection should be stressed. However, our data do not show whether this increase is related to the urinary ceftazidime excretion.

Interaction with indomethacin. Indomethacin did not affect ceftazidime binding to serum proteins. The significant augmentation in ceftazidime serum and extravascular levels observed after i.m. injection of both ceftazidime and indomethacin suggested that indomethacin reduced renal excretion of the antibiotic. In the urinary excretion study, we noted that indomethacin lowered the GFR and, consequently, the ceftazidime-filtered load. This effect was significant during the first experimental period only, with a return to the control value within 15 min. Baylis and Brenner (2) observed that administration of indomethacin to rats was followed by a reduction in glomerular plasma flow and GFR. In our study, this transient diminution in GFR was not accompanied by significant variations in sodium or potassium excretion. Fractional excretion of ceftazidime was not changed by indomethacin. Thus, the reduction in the absolute excretion rate of ceftazidime noted during the first experimental period appeared to be related to the decrease in the filtered load. The existence of a common tubular secretion pathway for ceftazidime and indomethacin or its metabolites seemed unlikely.

In this study, ceftazidime appeared to exhibit—at least in rabbits—unique renal disposition, different from that described for other cephalosporins. Our data suggest that ceftazidime undergoes a bidirectional tubular transport, which can be modified by probenecid and furosemide. The effect of indomethacin, which reduced renal ceftazidime excretion, was simply to reduce the GFR. Our results were obtained in rabbits that each received a single injection of ceftazidime and of one interfering drug, and these methods did not allow extrapolation of the results to humans, who are usually given repeated doses and who could exhibit a different pattern of tubular disposition of ceftazidime.

ACKNOWLEDGMENTS

We thank Y. Boussougant, who kindly provided the *E. coli* strain for the ceftazidime assays, R. M. Dreyfus for her review of the English text, and Nadine Muller and Nicole De Launay for secretarial asistance.

This work was supported by a grant from the Conseil Scientifique U.E.R. Xavier Bichat. F. D. was recipient of a grant from the Foundation pour la Recherche Médicale.

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