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Reduction in Biliary Excretion of Ceftriaxone by Diclofenac in Rabbits

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The effects of diclofenac, a nonsteroidal anti-inflammatory drug, on biliary excretion of ceftriaxone were evaluated in rabbits. In a previous study, we demonstrated that diclofenac increased the extravascular diffusion and antibacterial efficacy of ceftriaxone without any effect on serum protein binding and urinary excretion of this antibiotic. We perfected a surgical procedure that allowed the study of biliary secretion in conscious rabbits with a stable hemodynamic state. The kinetic study was carried out on the fourth day of treatment with ceftriaxone alone (30 mg/kg per day given intramuscularly; group 1) or combined with diclofenac (1.5 mg/kg per 12 h given intramuscularly; group 2). Cumulative biliary excretion of ceftriaxone over 6 h was significantly reduced in group 2 (5,291.6 ± 2,017.5 μg in group 1 versus 1,379.1 ± 567.1 μg in group 2). This phenomenon occurred without any change in biliary flow. Indocyanine green clearance (20 mg/kg) increased in animals treated with ceftriaxone alone compared with the saline-treated control group (55.04 ± 4.68 versus 33.29 ± 7.52 ml/min per kg, respectively). Diclofenac alone caused a significant decrease in indocyanine green clearance compared with clearance in controls (25.05 ± 4.74 versus 33.29 ± 7.52 ml/min per kg), and indocyanine green clearance appeared not significantly different from control values in animals receiving ceftriaxone plus diclofenac. These results suggest that (i) ceftriaxone could increase hepatic blood flow and (ii) reduction of the hepatic clearance of ceftriaxone by diclofenac may be due to hepatic hemodynamic variations involving diclofenac inhibition of prostaglandin synthesis, although an interaction of diclofenac with hepatic uptake of ceftriaxone cannot be ruled out.

The use of nonsteroidal anti-inflammatory drugs in the therapy of infectious diseases remains a subject for debate. Recent studies argue for a beneficial effect of cyclooxygenase inhibitors on gross pathology and levels of prostaglandin E2 in *Staphylococcus aureus*-induced experimental osteomyelitis (17) without any significant effect on the mean counts of *S. aureus*. Khurana and Deddish (C. M. Khurana and P. A. Deddish, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 544, 1986) reported that the administration of ibuprofen in conjunction with oxacillin or clindamycin increased the effectiveness of the antibiotic against an oxacillin-tolerant strain of *S. aureus* in an experimental model of osteomyelitis. These results suggest that prostaglandins may be involved in the pathogenesis of bone infection and that inhibition of their secretion may prevent deleterious lesions and help antibiotic efficacy. In the same respect, Tuomanen et al. (21) studied the effect of diclofenac on the inflammatory response in cerebrospinal fluid during *Streptococcus pneumoniae*-induced experimental meningitis in rabbits. The ability of the pneumococcal cell wall to cause death and to generate leukocytosis and an abnormal cerebrospinal fluid chemistry was prevented by the inhibition of the cyclooxygenase pathway of arachidonate metabolism.

In addition to these mechanisms of action, nonsteroidal anti-inflammatory drugs could improve the in vitro efficacy of antibiotics through pharmacokinetic interactions, increasing local concentrations of the antibacterial drugs. We have previously shown that phenylbutazone is able to increase the extravascular diffusion of cefazolin, a narrow-spectrum cephalosporin highly bound to serum proteins (3), through two different mechanisms, i.e., competition of drug binding and reduction of renal excretion. We have also demonstrated that indomethacin lowered the renal excretion of ceftazidime, a broad-spectrum cephalosporin, by reducing its glomerular filtered load without any effect on its protein binding (4). In another study (11), various effects of diclofenac on the kinetics of three different cephalosporins were observed. In this last study, diclofenac, chosen because of its lack of nephrotoxicity in rabbits (6), enhanced levels of cefotiam and ceftriaxone in serum without any effect on levels of cefmenoxime. This was due not to a modification of the protein binding of the cephalosporins but to a reduction of urinary excretion of cefotiam but not of ceftriaxone. In both cases, increased levels in serum enhanced extravascular diffusion as measured in tissue cage fluid and in cardiac vegetations in a rabbit model of *Escherichia coli* endocarditis. These increased levels were responsible for an increased antibacterial effect. The mechanisms by which diclofenac increased levels of ceftriaxone in serum and its elimination half-life remained unexplained. Since ceftriaxone is excreted via both urinary and biliary pathways (15), the hypothesis of an interaction of diclofenac in the biliary excretion of ceftriaxone was put forth.

The aims of the present study were (i) to perfect an experimental model for the study of the biliary elimination of drugs in conscious rabbits, (ii) to describe the effects of diclofenac on the excretion of ceftriaxone, and (iii) to attempt to identify the mechanisms by which such an interaction could occur.

This kinetic study was done on the fourth day of treatment with ceftriaxone alone or combined with diclofenac, in order to respect the conditions of previous works by Joly et al. (11, 12).

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MATERIALS AND METHODS

Animals. The investigations were done with male New Zealand rabbits (weight range, 1.9 to 3.3 kg). Each animal was maintained in an individual cage, was used only once, and had free access to food and water throughout the study.

Biliary fistula: experimental procedure. Twenty-four hours before surgery, the animal had free access only to water. On the fourth day of treatment (see below), surgery was performed 1.5 h before the last intramuscular (i.m.) injection. An ear vein was used to infuse isotonic saline (20 to 30 ml/min), allowing hydration of the animals and correction of fluid losses. Rabbits were anesthetized with ketamine hydrochloride administered by i.m. injection (20 mg/kg of body weight). A median laparotomy allowed access to the biliary duct. Dissection began over 1 cm from the duodenal termination of the duct. A polyethylene catheter (1.5-mm internal diameter) was inserted with the upper extremity below the confluent of the cystic duct, which remained patent. The wound was carefully closed around the catheter with surgical silk after local infiltration with lidocaine and then packed with gauze treated in saline. This allowed withdrawal of bile at the lower part of the incision. The total duration of the surgical procedure was around 20 min. Bile was collected in previously weighed tubes. The animals were completely awake when the pharmacokinetic study started. Before and at the end of the procedure, blood samples were taken for the determination of serum creatinine, alkaline phosphatases, transaminases (alanine aminotransferase and aspartate aminotransferase), and total bilirubin. Only animals with unchanged parameters were considered in the evaluation of the results of the experiments. Body temperature was not monitored during this brief anesthesia. Animals were operated on under the same conditions in any group and remained under the light of a warming lamp.

Drug administration. Animals were randomly divided into five groups. Group 1 (n = 5) rabbits received a single daily dose of ceftriaxone alone (30 mg/kg) for 4 days. Group 2 (n = 6) rabbits received ceftriaxone given as in group 1 plus diclofenac (1.5 mg/kg every 12 h) for 4 days. Both drugs were given i.m. at separate sites with different syringes and needles. In all cases, the pharmacokinetic studies were performed on the fourth day of treatment. Animals in these groups underwent surgery 1.5 h before the last i.m. injection. The last injection of ceftriaxone or ceftriaxone plus diclofenac indicated the beginning of the pharmacokinetic study, which lasted 6 h. Blood samples were collected at the times indicated in Fig. 1. Simultaneously, bile was collected during 12 30-min periods, allowing the determinations of bile output and ceftriaxone concentrations in bile.

Groups 3, 4, and 5 were used for the evaluation of the mechanisms of this interaction. Groups 3 and 4 (n = 6 and n = 5, respectively) were used for indocyanine green (ICG) test after treatment by ceftriaxone alone (group 3) or ceftriaxone plus diclofenac (group 4) as described for groups 1 and 2, respectively. The ICG test was performed after intravenous bolus injection of 2 mg/kg 15 min after the last i.m. injection of antibiotic with or without diclofenac. Blood samples were taken in heparinized tubes 30, 60, 90, 120, 180, and 240 s after the injection of ICG. Group 5 (n = 5) rabbits received diclofenac alone (1.5 mg/kg every 12 h) for 4 days and were used for the ICG test. One additional group (n = 6) was used as a control to study ICG pharmacokinetics. Animals of this group received isotonic saline (0.2 ml every 12 h) i.m. for 4 days.

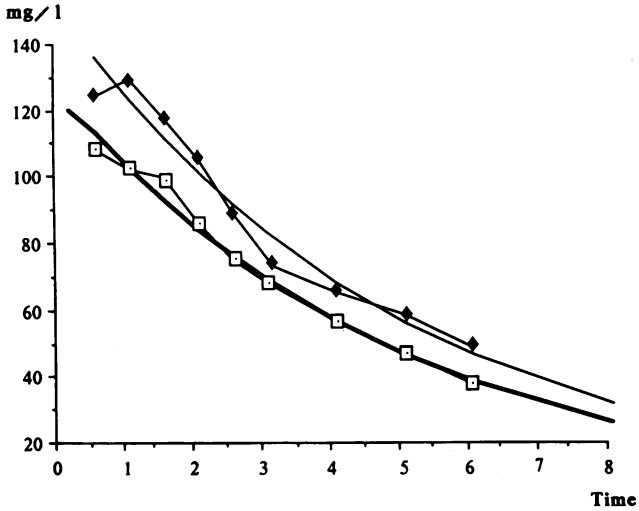

FIG. 1. Ceftriaxone concentrations measured on day 4 of therapy during the biliary excretion study. Values are means. Symbols: ⊡, ceftriaxone given alone (30 mg/kg) once daily for 4 days (five rabbits); ◆, ceftriaxone (30 mg/kg per 24 h) combined with diclofenac (1.5 mg/kg per 12 h) for 4 days (six rabbits); ⊡ and ◆, measured values; ■ and ——, computer-fit values.

Pharmacokinetic analysis. A single-compartment pharmacokinetic model was used for the determination of the kinetic parameters of ceftriaxone and ICG. For ceftriaxone, this model took into account only the elimination phase. The apparent elimination half-life was determined for each drug by linear regression analysis, using the least-squares method. Total body clearance (CL_B) was calculated from the formula $CL_B = D/AUC$, where D represents the injected dose and AUC represents the area under the serum concentration curve extrapolated from 0 h to infinity.

The volume of distribution (V) was calculated from the formula: $V = CL_B/\beta$, where β represents the elimination rate constant.

Assays. Blood samples were centrifuged, and plasma was kept at −20°C until ceftriaxone and antipyrine assays were performed. Plasma samples were stored at +4°C until the ICG assay was run.

(i) Antibiotic assay. Levels of ceftriaxone in serum and bile were measured by diffusion in nutrient agar by the method of Bennett et al. (1) with *E. coli* IP7624 as the test organism. The sensitivity limit of the test was 2.5 mg/liter. Standards for the assays of serum samples were prepared with normal rabbit serum. For determinations of levels in bile, standards were prepared with rabbit bile. The absence of diclofenac interference in the antibiotic assay was verified by comparison of two standards with and without diclofenac.

(ii) ICG assay. ICG values were measured spectrophotometrically at 800 nm (18) within 8 h of after sampling. The buffer used for dilution was isotonic saline supplemented with bovine serum albumin (0.1%). We previously verified that both ceftriaxone (100 mg/liter) and diclofenac (4 mg/liter) did not interfere in this assay by comparing standards with known concentrations of ICG with and without ceftriaxone, diclofenac, or both.

Statistical analysis. Student's t test was used for the comparison of ceftriaxone pharmacokinetic parameters and

TABLE 1. Ceftriaxone pharmacokinetic parameters[a]

Group	$t_{1/2}$ (h)	AUC (mg · h/liter)	CL_B (ml/min)	V (ml/kg)
1 (CTX)	3.13 ± 0.72	534.20 ± 111.60	2.60 ± 0.49	254.40 ± 23.07
2 (CTX + D)	3.58 ± 0.60	780.47 ± 128.34[b]	1.66 ± 0.51[b]	222.80 ± 12.88[b]

[a] Ceftriaxone (CTX) (30 mg/kg per 24 h) alone (group 1, $n = 5$) or combined with diclofenac (D) (1.5 mg/kg per 12 h) (group 2, $n = 6$) was injected i.m. for 4 days. Values represent means ± standard deviations. $t_{1/2}$, Elimination half-life; AUC, area under the serum concentration curve; CL_B, total body clearance; V, apparent volume of distribution.

[b] Significantly different from the value obtained with ceftriaxone alone ($P \leq 0.05$).

for the comparison of biliary excretion parameters in groups 1 and 2. Comparison of bile output as a function of time and treatment was done by variance analysis. The statistical significance of the ICG test and antipyrine clearance values was determined by variance analysis.

Further intergroup comparisons were made with Student's t test. When variance analysis was significant, the degree of significance between means was evaluated with Student's t test with the residual variance and its degree of freedom. In all cases, differences were considered significant for P values of ≤ 0.05.

RESULTS

Effects of diclofenac on biliary excretion of ceftriaxone. All of the animals studied were comparable as far as their serum creatinine and liver function tests at the end of the surgical procedure are concerned. Also, their weight variations during treatment were similar.

Levels of ceftriaxone measured in the serum of animals in groups 1 and 2 are presented in Fig. 1. Pharmacokinetic parameters of ceftriaxone measured in both groups are shown in Table 1. A significant increase of the area under the serum level curve was noted in group 2 as compared with that in group 1. Significant reductions of CL_B (around 36%) and of V (around 12%) were noted in group 2 as compared with those in group 1. The trough level (at 24 h) in group 1 was 1.6 ± 2.7 μg/ml, and that in group 2 was 1.5 ± 1.1 μg/ml; these values were similar.

The mean biliary flow remained unchanged in both groups, although a nonsignificant reduction was noted in group 2 beyond period 8 (Fig. 2). Biliary excretion of ceftriaxone was significantly reduced in group 2 (Fig. 3). In fact, at 6 h, the amount of ceftriaxone excreted through bile was 5,291.6 ± 2,017.5 μg in group 1 versus 1,372.1 ± 567.1 μg in group 2, a 72% reduction. The percentage of bile-excreted antibiotic was 6 ± 2% of the last dose in group 1 and 2 ± 1% in group 2 (67% reduction, $P < 0.01$) (Fig. 3).

ICG kinetic study. The pharmacokinetic parameters of ICG in the different groups studied are reported in Table 2. Ceftriaxone alone (group 3) induced a significant increase in the rate constant of ICG elimination as compared with controls ($P < 0.01$). The simultaneous administration of diclofenac (group 4) lowered this parameter to values comparable to those measured in control animals. A significant increase in the total clearance of ICG was also noted in group 3 as compared with group 4 (59.7%) and controls (65.3%). In group 4, no significant difference was observed for these parameters as compared with the control values. When diclofenac was administered alone (group 5), a significant reduction of all of the kinetic parameters except volume of distribution was noted as compared with controls. This latter parameter was similar in the different groups studied.

DISCUSSION

Nonsteroidal anti-inflammatory drugs can interfere with the pharmacokinetics of antibiotics through different mechanisms: modification of serum proteins and modification of urinary excretion, as previously described for the phenylbutazone effect on the behavior of cefazolin (3). In the same

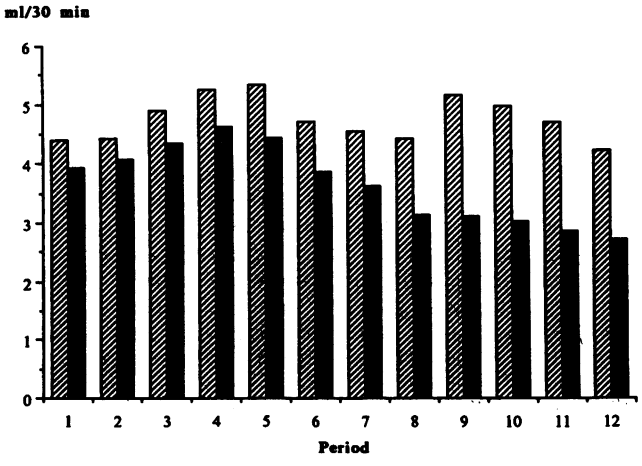

FIG. 2. Evolution of biliary flow (ml per 30 min) on the fourth day of treatment. Symbols: ▨, ceftriaxone alone (30 mg/kg) once daily for 4 days (five rabbits); ■, ceftriaxone (30 mg/kg per 24 h) combined with diclofenac (1.5 mg/kg per 12 h) for 4 days (six rabbits).

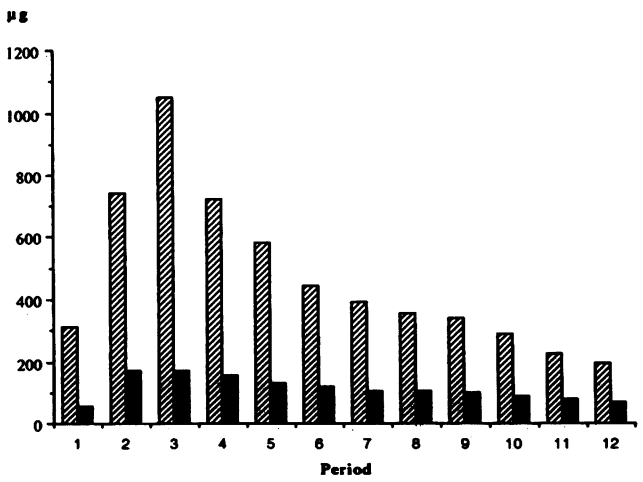

FIG. 3. Biliary excretion of ceftriaxone. Amounts of ceftriaxone excreted (in ordinate) over each 30-min period. Results are shown as the means for five rabbits in the ceftriaxone group (▨) and for six rabbits in the ceftriaxone-diclofenac group (■).

TABLE 2. ICG pharmacokinetic parameters after intravenous bolus injection of 2 mg/kg[a]

Group	n	$t_{1/2}$ (h)	AUC (mg · h/liter)	CL_B (ml/min)	V (ml/kg)
Controls	6	0.97 ± 0.08	62.85 ± 13.69	33.29 ± 7.52	45.88 ± 7.30
3 (CTX)	6	0.74 ± 0.03[b]	36.44 ± 3.05[b,c]	55.04 ± 4.68[c,d]	58.57 ± 7.48
4 (CTX +D)	5	1.22 ± 0.21	58.77 ± 7.41	34.46 ± 4.32	61.32 ± 15.77
5 (D)	5	1.60 ± 0.38[c,e,f]	81.94 ± 14.07[b,f,g]	25.05 ± 4.74[d,f,h]	57.48 ± 16.61

[a] The kinetic study was carried out on day 4 of treatment in saline-treated controls, in group 3 treated with ceftriaxone (CTX) (30 mg/kg per day) alone, in group 4 treated with ceftriaxone and diclofenac (D) (1.5 mg/kg per 12 h), and in group 5 treated with diclofenac alone. The control group (saline plus ICG test) underwent the ICG test followed by an antipyrine kinetic study. Values represent means ± standard deviations. See footnote *a* of Table 1 for an explanation of abbreviations.
[b] Significantly different from values obtained with group 4 ($P < 0.01$).
[c] Significantly different from values obtained with control group ($P < 0.001$).
[d] Significantly different from values obtained with group 4 ($P < 0.001$).
[e] Significantly different from values obtained with group 4 ($P < 0.02$).
[f] Significantly different from values obtained with group 3 ($P < 0.001$).
[g] Significantly different from values obtained with control group ($P < 0.01$).
[h] Significantly different from values obtained with control group ($P < 0.05$).

study, it was shown that the changes in the kinetics of the antibacterial agent were accompanied by alteration of the extravascular diffusion of the drug into the tissue cage fluid in an experimental model of noninfected extravascular fluid. We have also shown that diclofenac was able to interfere through different mechanisms with three closely related cephalosporins (12). More importantly, as a consequence of increased levels in blood, increased concentrations at the infected site and an increased antibacterial effect were noted in an animal model of bacterial endocarditis. Due to the absence of modification of the extent of ceftriaxone binding to serum proteins by diclofenac and to the absence of an effect of this latter drug on the urinary excretion of ceftriaxone, an interaction of diclofenac in the biliary excretion of ceftriaxone was postulated (11). In the present study, this hypothesis was verified.

Most experimental studies dealing with biliary elimination of antibiotics in rabbits have been performed on an in vitro model of isolated perfused liver (2). In the present investigation, we used a model allowing the study of biliary elimination of ceftriaxone in conscious animals. The following points are discussed: (i) the animal model, (ii) the results of the interaction of diclofenac in ceftriaxone kinetics and bile excretion, and (iii) the potential mechanisms through which such an interaction could occur in vivo.

Experimental model. In preliminary studies, we attempted to use the model of chronic biliary fistula described by Jimenez et al. (9). In this model, a double choledococholedocal fistula with a bypass on the main biliary duct was made, thus maintaining a continuous flow of bile into the duodenum. In our hands, this model appeared very complex, with a high rate of disturbances in renal and hepatic functions at the end of the procedure, which lasted several days. Thus, it was not possible to use this model in the perspective of pharmacokinetic studies. Under these conditions, we decided to use a model of acute fistula, performed on the day of the kinetic studies, in animals previously treated for 4 days with the test drugs. Only the animals with unchanged serum creatinine and hepatic tests were kept for analysis. We think that such a model used for a short period of time (up to 6 h) allowed us to compare, under highly reproducible conditions, the kinetics of ceftriaxone administered alone or combined with diclofenac, in spite of the interruption of the physiological bile flow into the digestive tract.

Ceftriaxone biliary excretion study. Our results confirmed the hypothesis put forth in light of our previous results. The main expressions of the interaction of diclofenac on the pharmacokinetics of ceftriaxone were the significant rise in the area under the serum level curves of ceftriaxone and the significant reduction in total body clearance of the antibiotic. However, the distribution volume of ceftriaxone was also significantly reduced by diclofenac. This could appear discrepant with previous results showing increased extravascular diffusion and efficacy of ceftriaxone due to diclofenac. In the absence of a significant variation of body weight during the experiment in both groups 1 and 2, a significant variation of plasma or extravascular volume is unlikely. The fact that serum creatinine was measured as normal on the fourth day of therapy both before and after the surgical procedure also argues for the absence of significant variation of the state of hydration throughout the study. Two mechanisms could explain our pharmacokinetic results. (i) There may be an increase in tissue levels of free antibiotic due to the effect of diclofenac. An indirect argument for this hypothesis could be the increased levels of antibiotic previously measured in cardiac vegetations. This hypothesis is very difficult to assess (20). (ii) There may be variations in the ratio of fatty body mass to lean body mass between groups 1 and 2. However, this hypothesis seems unlikely because of the short (4-day) duration of the experiments.

The reduction of ceftriaxone biliary excretion was blatant in the absence of a significant reduction in the biliary flow. Data on the kinetics of biliary excretion of antibiotics are still sparse in the literature. To the best of our knowledge, this is the first report of an interaction between a nonsteroidal anti-inflammatory drug and the biliary excretion of an antibiotic. Our results argue for an interaction of diclofenac in the hepatic clearance of ceftriaxone.

Hepatic clearance of a drug depends upon both hepatic blood flow and intrinsic hepatic clearance. Although significant hepatic metabolism of ceftriaxone was ruled out in rabbits in view of the fate of the ^{14}C-labeled compound (8), the hypothesis of an interaction of diclofenac, a drug metabolized in the liver through different hydroxylation pathways (16), was verified by antipyrine clearance determination an appropriate test for this purpose in rabbits (5) (unpublished results). The kinetic parameters of antipyrine were similar in all groups studied. Thus, the possibility of an interaction of diclofenac on hepatic microsomal metabolism in rabbits can be ruled out.

The hypothesis of some modifications of hepatic blood flow by diclofenac was investigated by using an indirect method, i.e., an ICG test that has been widely used in humans (14). The kinetics of ICG in rabbits have been detailed by Thiessen et al. (19). Thus, hepatic clearance of this indicator depends mainly upon hepatic blood flow when it is injected at low doses (less than 2.5 mg/kg). We used a 2-mg/kg dose to assure the accuracy of the spectrophotomet-

ric method used for the determination of ICG levels in blood. ICG plasma disappearance curves were monoexponential in the control group and three therapeutic groups. Thus, a competition for ICG binding sites on ligandin between the three drugs seems insufficient to explain the results of ICG kinetic study. We have shown that ceftriaxone induced a significant rise (60%) in the clearance of ICG, suggesting that the antibiotic increased the hepatic blood flow, as compared with controls. When diclofenac was administered concomitantly, the hepatic blood flow returned to values similar to those noted in control animals. Moreover, diclofenac given alone significantly reduced the hepatic blood flow, as compared with controls.

The mechanisms by which ceftriaxone could modify the hepatic blood flow remain unknown and deserve further study. The effects of diclofenac could suggest a role for prostaglandins. As suggested by Feely and Wood (7), direct determination of hepatic blood flow and precise studies of vasodilator prostaglandin pathways could help to identify the effects of prostaglandin synthesis inhibitors on hepatic drug clearance.

An interaction at the hepatic uptake level between ceftriaxone and diclofenac could not be ruled out in our study, but this hypothesis is not satisfactory to explain the reduction in biliary excretion of ceftriaxone. Diclofenac has a short half-life (below 1 h in animals [10]) and does not share any metabolic pathway with ceftriaxone; therefore, a saturation of ceftriaxone binding sites on ligandin by diclofenac is unlikely.

Our results help us to understand some of the pharmacokinetic mechanisms by which nonsteroidal anti-inflammatory drugs could increase in vivo activity of various antibacterial agents. These interactions may be clinically relevant. However, caution is warranted in extrapolation of animal data to humans, as recently emphasized by Korn et al. (13).

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