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Pharmacokinetics and Tolerance of Cefuroxime Axetil in Volunteers During Repeated Dosing

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A total of 158 volunteers each received 21 repeated oral doses of 500 mg of cefuroxime axetil (CAE) during four comparative cross-over trials. Pharmacokinetics were studied in 8 volunteers (CAE versus ampicillin), relative bioavailability and tolerance were studied in 100 volunteers (CAE versus pivmecillinam and CAE versus pivampicillin), and tolerance alone was studied in 50 volunteers (CAE versus ampicillin). Overall, urinary recoveries of the active antibiotics ranked absorption of the drugs in the order least to greatest: pivmecillinam, ampicillin, CAE, and pivampicillin. The pharmacokinetics of CAE and ampicillin did not change after repeated dosing. Peak serum levels of cefuroxime were significantly higher than those of ampicillin after doses 1 and 21 but the urinary recoveries of both antibiotics were around 35% of the dose. CAE was as well tolerated as ampicillin but there were smaller numbers of episodes of fluid bowel motions on pivmecillinam and pivampicillin than on CAE, which may have been due to the smaller amounts of active antibiotic in the doses of the pivaloyloxymethyl esters.

Cefuroxime is established as a safe, effective antibiotic for the treatment of infections caused by a wide range of bacterial species. Cefuroxime axetil (CAE; cefuroxime as the 1-acetoxyethyl ester) (Fig. 1) is a prodrug of cefuroxime and makes oral rather than parenteral administration of this β-lactamase-stable cephalosporin possible.

The ester moiety is rapidly cleaved by nonspecific esterase enzymes to yield cefuroxime:

cefuroxime acetoxyethyl ester → cefuroxime + acetaldehyde + acetic acid

This de-esterification probably occurs in the intestinal mucosa and the blood, since no intact ester could be detected in the blood of volunteers after oral doses of CAE when the simultaneous cefuroxime concentration was up to 16 mg/liter (7).

Our investigations were designed both to detect changes in the pharmacokinetics or relative bioavailability which might have been induced by repeated dosing and to assess the tolerance of CAE in comparison with other oral antibiotics.

MATERIALS AND METHODS

Four human volunteer studies are described. One study (A) was of pharmacokinetics only, two (B and C) were of relative bioavailability and tolerance, and one (D) was of tolerance only. Studies A, B, and C were performed at the Glaxo Institute of Clinical Pharmacology, University of Pretoria, Republic of South Africa. Study D was performed at Glaxo Group Research Limited, Greenford, United Kingdom. All the studies were randomized, cross-over comparisons; those involving tolerance assessment were performed double-blind. Ethical review committee approval and written consent were obtained for all studies.

In all, 137 male and 21 female volunteers participated. For the men, mean (and range) of ages, weights, and heights were 25 (18 to 52) years, 75 (49 to 97) kg, and 180 (155 to 196) cm, respectively. For the women, the corresponding figures were 20 (19 to 26) years, 55 (46 to 65) kg, and 164 (152 to 177) cm.

Study A. Eight male volunteers each received 21 repeated oral doses of 500 mg of cefuroxime as the acetoxyethyl ester during one of two dosing periods. The study was a cross-over comparison with 500 mg of ampicillin in the same dosage regimen during the other period. There was an interval of 3 weeks between dosing periods.

The pharmacokinetics of cefuroxime and ampicillin were studied after doses 1 and 21 of each antibiotic. On day 1 of each dosing period, the first dose was taken after breakfast, and the second dose was taken 8 h later. Then dosing was three times daily at 0700, 1300, and 1900 after meals for 6 days in each dosing period. On day 8, the last dose was taken just after breakfast.

Blood samples were taken to provide serum for antibiotic assay at the following times after dosing: 0, 30, 60, 90, 120, 150, 180, and 210 min and 4, 5, 6, 7, and 8 h. After allowing the blood to clot for 30 min, the serum was separated by centrifugation at 3,000 rpm for 5 min and stored at −18°C until assay. Four timed urine collections were made from 0 to 2, 2 to 4, 4 to 6, and 6 to 8 h after dosing. The total volume of urine in each collection was measured, and a sample was stored until assay to calculate urinary recovery.

From each serum level-time curve, the peak serum level and the time to peak were recorded, and the area under the curve was calculated by the trapezoidal method. Serum and renal clearances were derived from dose and urinary recovery in milligrams, respectively, divided by the area up to 8 h. Clearances were probably overestimated by this method but serum profiles could not be adequately described by a compartmental model, and so areas to infinity could not be estimated.

Study B. The same scheme of dosing as in study A was used to compare repeated oral doses of 500 mg of cefuroxime as acetoxyethyl ester with 400 mg of pivmecillinam (Selexid; Leo Laboratories). Each dose of pivmecillinam was equiva-

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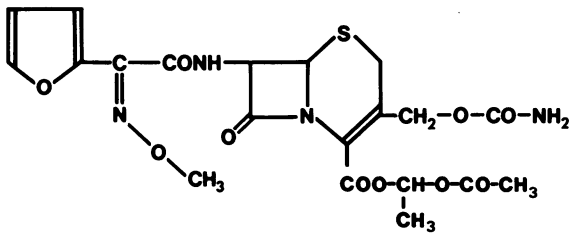

FIG. 1. CAE (cefuroxime as the 1-acetoxyethyl ester).

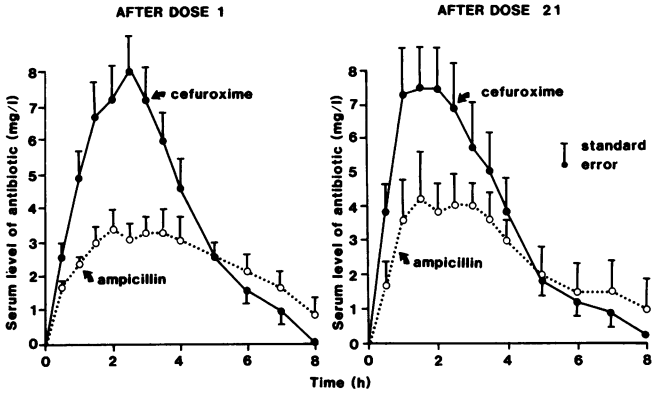

FIG. 2. Serum level-time curves for cefuroxime and ampicillin after 1 and 21 oral doses of CAE and ampicillin given to eight male volunteers.

lent to 272 mg of mecillinam as the pivaloyloxymethyl ester. Fifty volunteers (39 males and 11 females) participated.

The only samples assayed were single portions from urine collections (0 to 8 h postdose) after doses 1 and 21 of each drug. The total volume of each collection was measured, and so four urinary recoveries were derived per volunteer.

Study C. The same scheme of dosing and sampling as in study B was used to compare repeated oral doses of 500 mg of cefuroxime as acetoxyethyl ester with 500 mg of pivampicillin (Pondocillin; E. Burgess Ltd.). Each dose of pivampicillin was equivalent to 375 mg of ampicillin as the pivaloyloxymethyl ester. Fifty volunteers (40 male and 10 female) participated in this study.

Study D. This was a similar study to B and C, except that urine assays were not performed. Fifty male volunteers each received 21 repeated oral doses of 500 mg of cefuroxime as acetoxyethyl ester during one of two dosing periods. The study was a cross-over comparison with 500 mg of ampicillin in the other dosing period.

Assays. All assays were performed by high-pressure liquid chromatography on Hypersil octadecylsilane columns. For cefuroxime assays, the mobile phase was 9% acetonitrile with 0.05 M ammonium dihydrogen orthophosphate; the flow rate was 1 ml/min (serum) or 1.6 ml/min (urine). For ampicillin assays, the mobile phase was modified to 6% acetonitrile with 0.05 M ammonium dihydrogen orthophosphate and 0.01% formic acid; the flow rate was 1 ml/min (serum) and 2 ml/min (urine). For mecillinam assays, the conditions were the same as for the cefuroxime assays.

The internal standards used for quantitation were cephaloridine for cefuroxime assays, cephalexin for ampicillin assays, and cefuroxime for mecillinam assays. The respective detection wavelengths were 273, 230, and 230 nm. Cefuroxime in serum was assayed with a susceptibility of 0.1 mg/liter, and ampicillin was assayed in serum with a susceptibility of 0.2 mg/liter. The assay susceptibility for cefuroxime, ampicillin, and mecillinam in urine was about 5 mg/liter, and the reproducibility of each assay was within 10%.

Assessment of tolerance. Studies B, C, and D involved assessments of tolerance by means of laboratory safety tests. Samples were taken for standard serum biochemistry and urinalysis before, during, and after each dosing period, and in study D, full blood counts and measurements of clotting factors were performed. In all three studies of tolerance, any values outside the reference ranges were coded according to the probable reason for the abnormality.

At the end of studies B, C, and D, each volunteer was asked whether he had had any side effects, specifically softening of stools, abdominal pains, extra flatus or flatulence, perianal itching, bitter aftertaste, nausea, and smelly urine. In addition, volunteers were each given a diary in which they recorded all bowel motions from one week before the start through to one week after the end of all dosing. Each motion was given a time on a 24-h clock and an overall rating: 1 = firm, 2 = soft, and 3 = fluid.

Statistical methods. Pharmacokinetic parameters were compared between doses and between drugs by Student's t tests, except for maximum concentration in serum over time, which was compared by Wilcoxon's matched pairs test (T). Chi-squared (χ^2) tests were used to examine differences between the two drugs in the incidence of fluid motions, gastrointestinal side effects, and codes for abnormal laboratory values. Values of t, T, and χ^2 were only regarded as significant if they had probabilities of less than 5% ($P < 0.05$).

TABLE 1. Pharmacokinetic parameters of cefuroxime and ampicillin after administration of 1 and 21 oral doses of 500 mg of CAE and 500 mg of ampicillin to eight male volunteers (study A)

Parameters (units)	Mean (range) of each parameter			
	CAE		Ampicillin	
	Dose 1	Dose 21	Dose 1	Dose 21
Urinary recovery 0–8 h (%)	36.1 (30.0–42.9)	36.5 (24.6–59.2)	33.3 (17.5–52.8)	33.2 (15.5–57.2)
Peak serum level (mg/liter)	8.6 (4.5–12.8)	9.0 (2.3–15.0)	4.4 (1.5–6.9)	5.2 (1.8–11.5)
Time to peak level (h)	2.4 (1.5–3.0)	1.8 (1.0–3.0)	3.0 (1.5–5.0)	2.4 (1.5–3.5)
Area under serum level-time curve (mg · h/liter)	30.3 (18.3–44.3)	28.6 (7.8–46.4)	19.3 (2.7–27.2)	20.3 (5.3–55.4)
Serum clearance (liters/h)	18.1 (11.3–27.3)	23.9 (10.7–64.1)	44.5 (15.9–185.2)	42.3 (9.0–94.3)
Renal clearance (liters/h)	6.4 (4.2–8.3)	7.7 (3.1–15.8)	13.4 (4.0–47.2)	12.6 (1.8–32.8)

RESULTS

Pharmacokinetics. Study A. None of the pharmacokinetic parameters changed significantly between doses 1 and 21 of either CAE or ampicillin. The only pharmacokinetic parameters which were significantly different between the drugs were the peak serum levels after doses 1 and 21, and the areas under the curve after dose 1, which were greater after CAE than after ampicillin (Table 1 and Fig. 2).

Studies B and C. Only those volunteers who completed all four urine collections (study B, $n = 46$; study C, $n = 47$) have been included in the analysis (Table 2). In study B, the mean recovery of cefuroxime was significantly greater after dose 21 than after dose 1. Recoveries of cefuroxime were significantly greater than mecillinam in study B after dose 21 only and significantly less than ampicillin in study C after both doses.

Tolerance. All eight volunteers completed both parts of study A without the occurrence of adverse events. One volunteer withdrew from study B because of persistent diarrhea (defined as four or more fluid motions per day) on CAE. Two volunteers withdrew from study C after failing to comply with the protocol. One volunteer in study D had diarrhea and nausea after 14 doses of CAE (during his second dosing period). A cytotoxin which could be neutralized by antibodies raised against clostridial toxin was detected in his stool samples. Symptoms lasted for 2 weeks and were cleared by oral vancomycin; they were probably caused by an antibiotic-induced overgrowth of *Clostridium* sp. in the large bowel.

In the analysis of the diaries for bowel motions, more fluid stools were noted after CAE than after pivmecillinam (40 versus 22%) and pivampicillin (36 versus 14%) but not after ampicillin (24 versus 28%). Most episodes were short lived and subsided despite continued dosing. As mentioned above, two volunteers stopped dosing whilst on CAE due to persistent symptoms.

Volunteers who did not complete both dosing periods were excluded from the analysis of laboratory safety monitoring (Table 3). More samples were taken in study D than in studies B and C, and occasional missing samples within each study mean that the total number of tests on each drug was not identical. Most of the abnormal findings were clinically insignificant deviations from normality. Some volunteers had persistently abnormal findings with no overt disease. There were seven volunteers who showed increases in serum transaminase levels (Table 4), which are recognized side effects of β-lactam antibiotics (2).

The only significant differences between drugs in the answers to the questionnaires were in the reporting of bitter aftertaste on CAE in studies B and C (62 to 65% compared with 12 to 15%). However, in these studies the tablets of CAE were not film coated, unlike the tablets of the comparator drugs. A film-coated tablet of CAE has now been formulated which avoids this aftertaste. Softening of the stools was the most frequently recorded item and ranged from 39 to 58% for CAE in the three studies and from 29 to 46% for the comparator drugs.

TABLE 2. Summary of urinary recoveries of active antibiotic after 1 and 21 oral doses of 500 mg of CAE and 400 mg of pivmecillinam or 500 mg of pivampicillin

Dose	Mean urinary recoveries (SE) after oral doses of:			
	Study B		Study C	
	CAE	Pivmecillinam	CAE	Pivampicillin
1	32.5 (1.8)	26.4 (1.5)	33.8 (1.6)	45.0 (2.6)
21	38.4 (2.1)	23.7 (1.4)	35.9 (2.1)	46.2 (2.2)

TABLE 3. Summary of abnormal laboratory findings after 21 oral doses of 500 mg of CAE and 500 mg of ampicillin or 400 mg of pivmecillinam or 500 mg of pivampicillin in groups of 50 volunteers

Parameters	Study B		Study C		Study D	
	CAE	Pivmecillinam	CAE	Pivampicillin	CAE	Ampicillin
No. of volunteers	49	49	48	48	48	48
No. of tests	2,755	2,723	2,699	2,723	8,230	8,106
Incidence of abnormal finding (%)	4.2	5.2	4.4	4.6	3.2	3.2
No. of drug-related changes	0	3	1	0	1	2

DISCUSSION

The pharmacokinetics of β-lactam antibiotics are not usually altered by repeated dosing (4, 6). Induction of nonspecific esterase activity in the gut lumen could reduce the oral bioavailability of esterified prodrugs such as CAE during a treatment course. In study A, the pharmacokinetics of CAE and ampicillin did not change between doses 1 and 21. Also from the data in Table 2, there was no evidence for esterase induction by repeated doses of CAE, pivmecillinam, or pivampicillin because urinary recoveries remained unaltered. This result confirms the findings of Foltz et al. (5) with repeated doses of pivampicillin. The same conclusion was reached by Jones et al. (8) during their studies of another esterified β-lactam, talampicillin.

Overall, the urinary recoveries of cefuroxime, ampicillin, and especially mecillinam in studies B, C, and D were lower than reported elsewhere (7, 10, 11). Some degradation of the antibiotics may have occurred during storage before assay, and this problem would have been more likely with mecillinam.

The incidences of abnormal laboratory findings were around 5% on all drugs, which is the expected figure from a healthy population. The method of calculation of the reference ranges involves the exclusion of 2.5% of the highest and lowest values from the ranges obtained during routine biochemical screens of volunteers.

All four drugs involved in the cross-over comparisons were well tolerated with no cases of hypersensitivity. There was only one systemic disturbance, which was probably due to overgrowth of a toxigenic clostridial strain in the large bowel of a volunteer on CAE. This was the only instance of this side effect in 158 different volunteers who received repeated oral doses of the drug, and the incidence (0.7%) is similar to that reported for other antimicrobial agents (1). The greater occurrence of fluid stools with CAE than with the pivaloyloxymethyl esters may have been due to the difference in dose of active antibiotic: 500 mg with CAE, 375 mg with pivampicillin, and 272 mg with pivmecillinam. In contrast, the incidence after CAE and ampicillin (500-mg doses) was almost identical.

It is concluded that CAE is as well tolerated as ampicillin. However, minor bowel disturbances are frequently seen, and these appear related to dose. The relationship between intestinal tolerance and dose should be investigated in the clinic.

TABLE 4. Changes in laboratory findings which were probably drug related

Volunteer (study)	Drug	Biochemical test	Value (IU/liter)			Normal range (IU/liter)
			Before	During	After	
6 (B)	Pivmecillinam	Aspartate transaminase	17	13	211	6–30
24 (B)	Pivmecillinam	Aspartate transaminase	10	10	218	6–30
37 (B)	Pivmecillinam	Aspartate transaminase	15	37	37	6–30
40 (C)	CAE	Alanine transaminase	36	40	49	8–40
2 (D)	Ampicillin	Aspartate transaminase	28	52	30	14–36
2 (D)	CAE	Aspartate transaminase	29	46	45	14–36
47 (D)	Ampicillin	Aspartate transaminase	22	44	23	14–36

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