Pharmacology of Cefuroxime as the 1-Acetoxyethyl Ester in Volunteers

STUART M. HARDING,* PETER E. O. WILLIAMS, AND JOHN AYRTON

Glaxo Group Research Limited, Greenford, Middlesex, England UB6 0HE

Cefuroxime axetil is a new orally absorbed prodrug of the antibiotic cefuroxime. The results of pharmacological studies in 52 healthy volunteers are presented. Intact cefuroxime axetil was not detected in the systemic circulation, indicating that deesterification to yield cefuroxime occurs rapidly after absorption. The bioavailability as measured by urinary recovery of cefuroxime was 40 to 50% if the drug was taken after food and 30% if the drug was taken after overnight fasting. Absorption was similar for three different formulations at 500 mg and independent of dose over the range of 250 mg to 1 g. When the drug was taken after food, serum levels and urinary recoveries were significantly greater for cefuroxime than for ampicillin, but when the drug was taken after fasting the values were similar for the two drugs. The kinetic behavior of cefuroxime axetil and ampicillin was not influenced by repeated dosing at 250 mg. Cefuroxime axetil was well tolerated. Although changes in bowel flora and habit were noted during repeated dosing, these changes were no greater than with ampicillin.

Cefuroxime, with its relatively broad antibacterial spectrum and stability to many beta-lactamases, has an established place in antimicrobial therapy (12). However, like many cephalosporins, its application is handicapped by the need for parenteral delivery. Recent work has led to the development of cefuroxime axetil, the 1-acetoxyethyl ester of cefuroxime (Fig. 1), a derivative which is well absorbed from the gastrointestinal tract and promptly cleaved to cefuroxime thereafter. Preliminary research on cefuroxime axetil indicated that the compound was highly labile in blood and serum, enzymatic deesterification occurring in vitro to produce cefuroxime. To investigate the absorption and pharmacokinetics of cefuroxime axetil, it was necessary to develop an assay method which would extract the drug from blood while simultaneously preventing further enzymatic hydrolysis. The current report summarizes the results of studies designed to determine the concentrations of intact ester in peripheral venous blood, serum levels, and urinary recoveries after single oral doses of 250 mg, 500 mg, and 1 g given to male and female volunteers and the effect of food on absorption. Furthermore, tolerance was assessed during repeated doses of 250 mg given every 6 h in comparison with ampicillin, and the kinetics of cefuroxime and ampicillin were compared at the 250-mg dose level.

MATERIALS AND METHODS

Metabolism of cefuroxime axetil in vitro. The stability of cefuroxime axetil in blood was determined by adding a known amount of drug to fresh human blood and incubating the mixture for 15 min at 37°C. At 1.5-min intervals during the incubation a sample of blood (0.25 ml) was withdrawn, mixed with acetonitrile (0.5 ml) on a Vortex mixer for 5 s, and then centrifuged at 2,000 rpm for 5 min. The supernatant was assayed for cefuroxime axetil by using high-pressure liquid chromatography (HPLC), and then a sample (0.1 ml) was transferred to another tube, diluted with distilled water (0.4 ml), and assayed for cefuroxime by using a different HPLC method.

The effectiveness of acetonitrile for extracting cefuroxime axetil from blood and preventing its further deesterification was investigated by spiking identical volumes of blood and distilled water with known amounts of drug. The two samples were immediately mixed with twice their volume of acetonitrile and assayed for cefuroxime axetil at once and then 1, 6, and 24 h later.

Volunteer study designs. There were four studies involving a total of 38 male volunteers (average age, 32 years; range, 20 to 48 years; average weight, 75 kg; range, 60 to 101 kg) and 14 female volunteers (average age, 27 years; range, 22 to 37 years; average weight, 55 kg; range, 48 to 62 kg). Each volunteer was judged to be healthy on the basis of a medical examination, serum biochemistry, hematology, and urine testing. Written informed consent was obtained after ethical review committee approval had been given.

The four studies were as follows.

Study 1. Measurement of the concentrations of intact ester in the peripheral venous blood after single oral doses of 1.5 g given to 12 fasting male volunteers. Samples were taken 20, 90, and 150 min after the dose, and enzymatic activity in the blood was quenched by rapid mixing with 2 ml of acetonitrile within 20 s after sampling.

Study 2. An open investigation of the absorption of cefuroxime axetil taken in the fasting state and after food. Eight male and eight female volunteers were given single oral doses of 500 mg in two different tablet formulations and 500-mg and 1-g doses in aqueous suspension. This was an eight-part randomized cross-over study, with volunteers participating for 4 days in each of 2 consecutive weeks. Urine was collected for 0 to 6 and 6 to 12 h after each dose.

Study 3. An open comparison of serum levels and urinary recoveries of cefuroxime and ampicillin after a single oral dose of 250 mg given after food to six male and six female volunteers. The study was of randomized cross-over design with a 1-week interval between the doses. Blood samples were taken over 8 h via an indwelling winged needle at 20, 40, 60, 90, 120, 150, 180, and 210 min and 4, 5, 6, 7, and 8 h. The blood was allowed to clot, and the serum was separated by centrifugation at 3,000 rpm for 5 min. Serum samples were stored at −20°C until assay on the following day. Urine
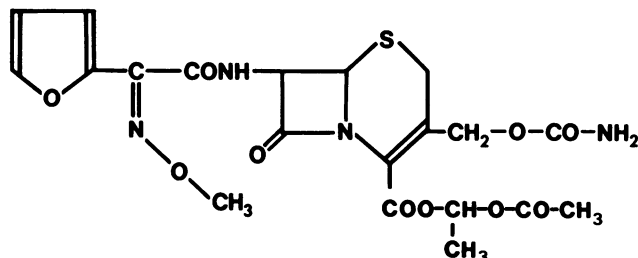
* Corresponding author.

FIG. 1. Structure of cefuroxime axetil.

collections were made over 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h. A sample from each collection to 12 h was stored at −20°C until assay on the following day; the sample from each 12- to 24-h collection was sent for assay directly.

For single dose studies 1 to 3, doses were taken with 50 ml of water after an overnight fast or, when specified, within 30 min of a standardized breakfast consisting of cornflakes, milk, sugar, two slices of toast, butter, marmalade, and two cups of tea or coffee.

Study 4. A comparison of pharmacokinetics and tolerance of cefuroxime and ampicillin given to 12 male volunteers in repeated doses of 250 mg every 6 h for 5 days. This was a randomized cross-over study carried out with an interval of 4 weeks between dosing periods. During each dosing period, doses were taken at strictly 6-h intervals, beginning at 10:00 a.m. on the first morning and at 4:00 p.m., 10:00 p.m., and 4:00 a.m. thereafter; doses were taken in the fasting state. Cefuroxime axetil was given as film-coated tablets containing 250 mg of cefuroxime as ester; ampicillin was presented in capsules. Dosing was blinded by the use of matching placebo tablets or capsules. Urine collections were made from 0 to 6 h after all 19 doses of both antibiotics. Tolerance was assessed by a screen of laboratory tests 4 days before and 4 days after each dosing week, a diary for bowel motions, and counts of total aerobic and anaerobic flora in fecal specimens before and during dosing. Fecal samples (three 0.5-g samples) were deep frozen in transport medium until assay at the Central Public Health Laboratory, Colindale, England. Selective conditions and media were used to measure total counts of aerobes, anaerobes, and yeasts. *Clostridium difficile* was identified by gas-liquid chromatography of envelope lipids. Clostridial toxins were assayed by cytotoxicity against human embryonic lung fibroblasts (5).

Blood samples were taken from six volunteers at 30, 60, 90, 120, and 150 min and 3, 4, 5, and 6 h after the first and 13th doses of each drug for kinetic analysis.

HPLC assay for cefuroxime axetil and cefuroxime. The HPLC equipment consisted of a Constametric III pump and a Spectromonitor III UV monitor set at 273 nm (Laboratory Data Control) connected to a Servogor 210 recorder and a Trivector integrator. Chromatography was performed on a stainless steel column 10 cm long and 5 mm in internal diameter packed with Hypersil ODS (Shandon Southern Ltd.) and fitted with a Rheodyne 7125 valve injector and a 0.02-ml-capacity loop. For the assay of cefuroxime axetil, the column was eluted with acetonitrile-water (50:50 [vol/vol]) at a flow rate of 1 ml/min; the ester retention time was 2 min, and the detection limit was 0.05 mg/liter. The cefuroxime assay was performed with a mobile phase of ammonium dihydrogen phosphate (0.05 M) containing 15% (vol/vol) acetonitrile at a flow rate of 1 ml/min; the retention time was about 3.5 min, and the sensitivity was 0.5 mg/liter. Quantitation of drug was achieved by assay against standards prepared by the addition of known amounts of either cefuroxime axetil or cefuroxime to blood which was immediately mixed with the appropriate volume of acetonitrile.

Microbiological assay for cefuroxime. Cefuroxime assay for all the volunteer studies was performed by using a large-plate agar-diffusion technique with *Bacillus subtilis* NCIB 3610 as the test organism for sera and *Staphylococcus aureus* NCTC 6571 as the test organism for urines. The lower limit of assay sensitivity was 0.08 mg/liter for cefuroxime in sera and 0.6 mg/liter for cefuroxime in urine. The ampicillin assay used the same technique with *B. subtilis* ATCC 6633 as the test organism for both sera and urines (lower limit of assay sensitivity, 0.15 mg/liter for both fluids). All samples were assayed in quadruplicate, and the reproducibility of the result was ±5%. Intact cefuroxime ester has no antimicrobial activity in common with other esterified cephalosporins (7). All nominal doses and assay concentrations refer to the content of cefuroxime or ampicillin as acids.

For kinetic analyses, peak serum levels and times to peak were recorded directly from the assay data. Areas under the serum level-time curves were calculated by the trapezoidal method. Serum elimination half-lives were calculated by computerized least-squares minimization after log transformation using values from 2.5 h onward.

Statistical comparisons to distinguish differences between treatments, volunteers, sexes, and treatment order were made by using analysis of variance. The kinetic data were compared by using Wilcoxon's signed ranks test. Comparisons were considered statistically significant if $P < 0.05$. The coefficient of variation was defined as the standard deviation divided by the mean.

RESULTS

The deesterification of cefuroxime axetil to yield cefuroxime in human blood in vitro was found to proceed with a half-life of 3.5 min. The effectiveness of acetonitrile at quenching the enzymatic hydrolysis of cefuroxime axetil was confirmed by the 24-h stability comparison of acetoni-

TABLE 1. Mean percentage urinary recoveries of cefuroxime after single oral doses of cefuroxime axetil given to 15 volunteers

Treatment (dose)	Mean (SE) of percentage urinary recoveries					
	After fasting			After food		
	0–6 h	6–12 h	0–12 h	0–6 h	6–12 h	0–12 h
Tablet 1 (500 mg)	27.7 (2.3)	2.5 (0.5)	30.2 (2.4)	42.0 (2.9)	3.5 (0.4)	45.5 (2.9)
Tablet 2 (500 mg)	28.8 (1.4)	2.3 (0.3)	31.1 (1.3)	37.8 (1.4)	3.9 (0.5)	41.7 (1.4)
Aqueous suspension (500 mg)	25.1 (2.3)	4.0 (1.8)	29.1 (1.4)	37.3 (2.3)	4.5 (0.7)	41.6 (2.3)
Aqueous suspension (1 g)	25.3 (1.2)	2.7 (0.7)	28.0 (1.6)	33.2 (2.2)	7.6 (1.1)	40.7 (1.8)
Overall	26.7 (0.9)	2.9 (0.5)	29.6 (0.9)	37.6 (1.2)	4.8 (0.4)	42.4 (1.1)

TABLE 2. Pharmacokinetic parameters of cefuroxime and ampicillin after single oral doses of 250 mg of cefuroxime axetil and 250 mg of ampicillin in 12 volunteers

Parameter (U)	Mean (range) and SE of each parameter after:	
	Cefuroxime axetil	Ampicillin
Peak serum level (mg/liter)	6.3 (4.8–9.1) 0.4	3.0 (2.1–4.6) 0.2
Time to peak (h)	1.9 (1.5–2.5) 0.1	1.8 (1.5–2.5) 0.1
Area under serum level-time curve (mg · h/liter)	18.2 (11.8–27.7) 1.2	7.5 (6.3–9.6) 0.3
Elimination half-life (h)	1.2 (0.9–1.8) 0.1	1.0 (0.8–1.5) 0.1
Urinary recovery, 0 to 4 h (%)	37.1 (16.8–44.4) 2.1	28.4 (17.0–39.0) 1.6
Urinary recovery, 4 to 8 h (%)	10.2 (4.2–29.5) 1.9	5.8 (1.7–8.2) 0.6
Urinary recovery, 8 to 12 h (%)	1.4 (0.2–6.0) 0.5	0.5 (0–1.0) 0.1
Urinary recovery, 12 to 24 h (%)	0.5 (0–3.4) 0.2	0.2 (0–0.3) 0.0
Total urinary recovery (%)	49.2 (40.2–57.6) 1.4	34.8 (22.4–47.9) 1.8

trile-treated samples; both water and blood samples showed only 6% reduction in cefuroxime axetil concentration during 24 h. A comparison of HPLC peak areas in the stability study also indicated that the extraction of cefuroxime axetil from blood by acetonitrile was about 90% efficient.

Study 1. Cefuroxime axetil was not detected in any of the 36 samples taken, despite attempts to maximize the likelihood of detection by using the large single dose of 1.5 g. The simultaneous mean cefuroxime concentrations (standard error) at the three sampling times were 3.1 (0.3), 9.8 (0.6), and 9.2 (0.7) mg/liter.

Study 2. One female volunteer withdrew from this trial because of diarrhea (more than four fluid motions per day) for 2 days after four doses. She recovered rapidly after symptomatic treatment. All her data have been excluded from the mean.

The mean urinary recoveries were 30% fasting and 42% after food (Table 1), an average increase of between one-third and one-half after food. For each dose the mean recovery was significantly higher after food than after fasting; this showed that the effect was independent of formulation and dose. There were no significant differences in urinary recoveries between male and female volunteers, values being, respectively, 30 and 29% after fasting and 41 and 44% after food.

Study 3. Mean urinary recoveries from 0 to 24 h after the dose were 49% for cefuroxime and 35% for ampicillin with ranges of 40 to 55 and 22 to 48% and coefficients of variation of 0.10 and 0.18, respectively. The mean 0- to 12-h urinary concentrations were 120 and 83 mg/liter for cefuroxime and ampicillin, respectively. These urine values were significantly different between the drugs. Data on fractional urinary recoveries and serum values are given in Table 2 and Fig. 2. Peak serum levels and areas under the serum level-time curve were significantly greater for cefuroxime than for ampicillin. Times to peak and elimination half-lives were not significantly different between the drugs.

Serum levels and urinary recoveries were similar in males and females on the two drugs. The mean peak serum levels (standard error) of cefuroxime were 5.6 (0.4) mg/liter in males and 7.0 (0.5) mg/liter in females. The corresponding figures for ampicillin were 3.1 (0.2) and 3.0 (0.4) mg/liter. The mean urinary recoveries of cefuroxime were 49% for males and 50% for females, with values for ampicillin of 33 and 37%.

In the three single-dose studies mean urinary recoveries of cefuroxime after food were 49% (250-mg dose), 43% (500-mg dose), and 41% (1-g dose). In the fasting state, recoveries averaged 32% (250-mg dose), 30% (500-mg dose), and 28% (1-g dose).

Study 4. The mean percentage urinary recoveries (standard error) from all 12 volunteers from 0 to 6 h after all doses
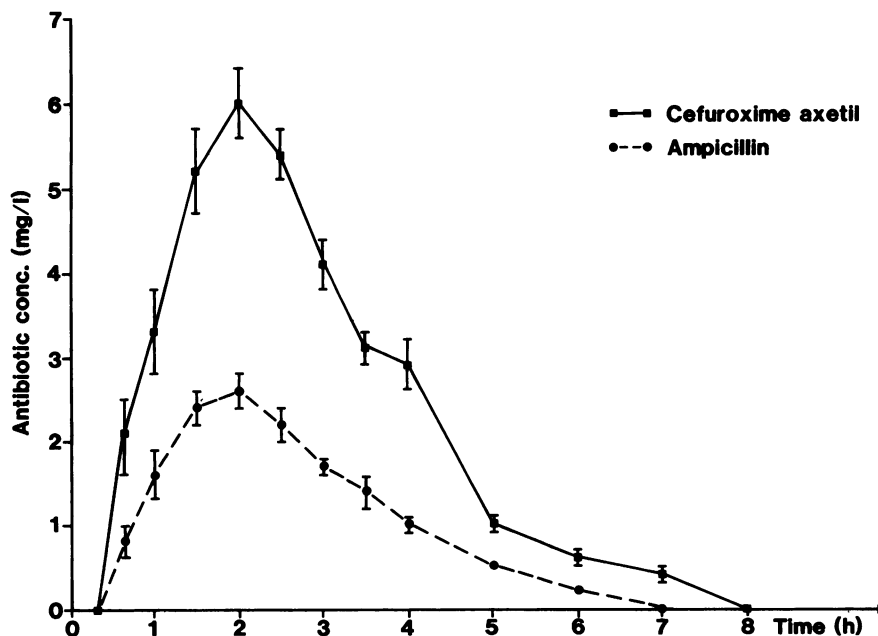

FIG. 2. Mean serum levels after a single oral dose of 250 mg of antibiotic in six male and six female volunteers. Vertical bars indicate means ± standard errors.
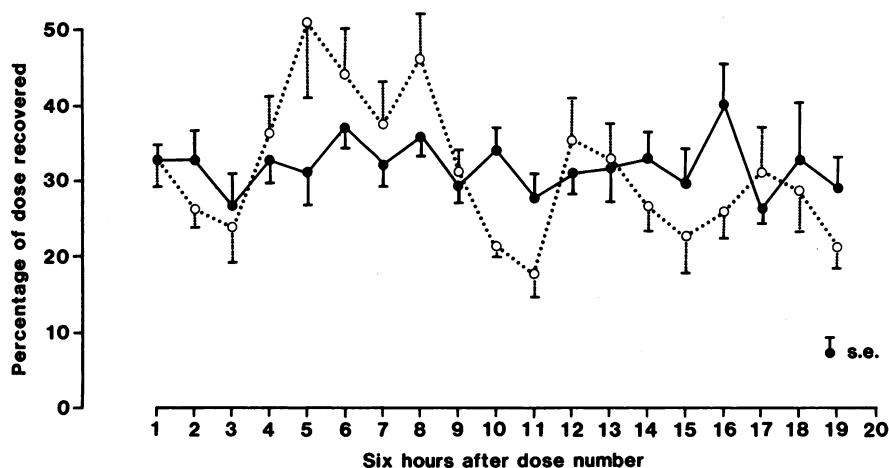
FIG. 3. Mean 6-h recoveries of cefuroxime and ampicillin in urine during repeated dosing with cefuroxime axetil (250 mg of cefuroxime as ester) (●) or ampicillin (250 mg) (○) in 12 volunteers. Vertical bars indicate standard error (s.e.).

were 31.8 (0.8)% for cefuroxime (220 values) and 31.6 (1.2)% for ampicillin (186 values). There appeared to be more variation in the recoveries of ampicillin, with a coefficient of variation of 0.54, than in the recoveries of cefuroxime, with a coefficient of 0.40. The average 6-h urinary recoveries for each dose are shown in Fig. 3.

The mean peak serum levels (standard error) of cefuroxime were 4.8 (0.3) and 4.5 (0.4) mg/liter after 1 and 13 doses of cefuroxime axetil. Corresponding values for ampicillin were 3.6 (0.5) and 4.9 (0.5) mg/liter. Serum level-time profiles are given in Table 3. Elimination half-lives could not be calculated because of limited data in the postabsorptive phase.

Seven volunteers experienced no side effects during the study on either drug. The other five volunteers had various degrees of bowel disturbance, four on cefuroxime axetil and five on ampicillin. An increase in bowel frequency to two or three soft stools per day for 2 days was recorded by three volunteers on cefuroxime axetil and two on ampicillin. Diarrhea, defined as four or more fluid stools per day, was reported by one volunteer for 2 days on cefuroxime axetil and by three volunteers on ampicillin. Two volunteers stopped dosing with ampicillin because of this diarrhea and one because of a marked maculopapular rash in addition to the diarrhea. The diarrhea in the volunteer on cefuroxime axetil did not necessitate stopping dosing.

Of the laboratory tests, only one possible drug-related abnormality was identified: a rise in eosinophil count (from 70×10^6/liter to 690×10^6/liter) in one volunteer 4 days after dosing with cefuroxime axetil; the count 2 weeks later was 300×10^6/liter. Stool culture showed changes in both aerobic and anaerobic bacterial counts which were not consistently correlated with the severity of side effects. There was

essentially no net change in aerobic or anaerobic count on either cefuroxime axetil or ampicillin in the majority of volunteers. The aerobic flora was replaced by yeasts in three volunteers receiving cefuroxime axetil and one receiving ampicillin. One volunteer receiving cefuroxime axetil produced a stool sample containing a toxigenic strain of C. difficile. He reported a mild bowel disturbance only, and the organism disappeared by the time interdose stool samples were collected.

DISCUSSION

Currently available oral beta-lactam antibiotics have either a moderate spectrum of activity or gaps in their spectra because of instability to bacterial enzymes. Cefuroxime axetil overcomes most of these deficiencies in a single drug. The studies described in this report indicate that the pharmacokinetics and tolerance of this drug are such as to provide a useful extension of oral beta-lactam therapy.

The esterification of the carboxyl C-4 group of cefuroxime renders the molecule more lipophilic and therefore more readily absorbed. In these studies the urinary recovery of cefuroxime after cefuroxime axetil was over 40%, compared with only 1% obtained after oral cefuroxime sodium (2). The detection of cefuroxime only in the systemic circulation after oral cefuroxime axetil, as demonstrated in study 1, indicates that absorbed ester is hydrolyzed more rapidly than the 3.5-min half-life determined in the in vitro stability study. The ester is presumably absorbed intact and then rapidly hydrolyzed in the intestinal mucosa and portal blood. Such a theory is supported by the work of Shindo et al. (10), who, using radiolabeled pivampicillin, demonstrated that the epithelial cells of the intestinal villi are the main site of pivampicillin hydrolysis in rats and monkeys. Deesterifica-

TABLE 3. Mean serum profiles of cefuroxime and ampicillin after 1 and 13 oral doses of 250 mg of cefuroxime axetil and 250 mg of ampicillin in six volunteers

Drug and dose	Mean (SE) antibiotic concentration (mg/liter) at time after dose:								
	30 min	60 min	90 min	120 min	150 min	180 min	4 h	5 h	6 h
Cefuroxime axetil dose 1	1.9 (0.5)	3.3 (0.7)	4.0 (0.5)	3.8 (0.4)	3.2 (0.4)	2.1 (0.4)	1.2 (0.2)	0.7 (0.1)	0.5 (0.1)
Cefuroxime axetil dose 13	2.6 (0.4)	3.5 (0.5)	3.9 (0.5)	2.9 (0.3)	2.3 (0.4)	1.7 (0.4)	1.2 (0.2)	0.7 (0.1)	0.7 (0.2)
Ampicillin dose 1	0.7 (0.2)	1.8 (0.6)	2.6 (0.6)	3.2 (0.5)	2.4 (0.2)	1.7 (0.1)	1.2 (0.2)	0.7 (0.2)	0.4 (0.1)
Ampicillin dose 13	1.8 (1.1)	3.4 (0.8)	3.8 (0.8)	3.7 (0.5)	3.7 (0.5)	2.4 (0.4)	2.3 (0.9)	1.1 (0.3)	0.6 (0.2)

tion after absorption is probably the reason for the increased bioavailability of mecillinam after oral pivmecillinam (3) and of ampicillin after administration of esters such as talampicillin (4) and pivampicillin (1).

Since cefuroxime is excreted almost entirely in the urine, measurement of urinary cefuroxime output will reflect gastrointestinal absorption of cefuroxime axetil. The mean urinary recovery of cefuroxime was significantly increased by taking food before a dose in the range of 250 to 1,000 mg. This may have been due to the effects of food on drug absorption, gastric emptying, gut motility, neutralization of gastric acidity, inhibition of luminal esterases, or the surfactant properties of the food itself or of bile salts. An investigation of these factors is currently under way, but study 2 showed that the effect was independent of formulation and dosage, suggesting that the dispersion of these formulations was not critical.

After an oral dose of 250 mg of cefuroxime axetil after food, the mean area under the cefuroxime serum level-time curve was 56% of the value of 32.6 mg · h/liter given by Foord (2) after 250 mg of cefuroxime sodium intravenously. When the serum profiles obtained by oral and intravenous administration are compared, the mean levels after oral dosing are higher from 2 h to 8 h, indicating that absorption continues for at least 2 h after dosing. Likewise, comparison of urinary recoveries suggests an oral bioavailability of 49% if the recovery after intravenous doses is assumed to be a maximum of 100% of the dose. As expected, the mean elimination half-life of cefuroxime was the same (1.2 h) after oral cefuroxime axetil and parenteral cefuroxime sodium.

Ampicillin was used a comparator drug in studies 3 and 4 because it is an oral beta-lactam which is clinically effective and extensively used (6). When the drug was taken after food in study 3, the serum levels and urinary recoveries were significantly higher for cefuroxime than for ampicillin. These differences were probably due to greater absorption of cefuroxime axetil, since the longer half-life of cefuroxime (1.2 verus 1.0 h) could not solely account for the larger area under the serum level-time curve (18.2 versus 7.5 mg · h/liter). Although the serum levels we obtained after ampicillin were higher than those reported by others, these levels can be reduced by food (11).

In single-dose studies 2 and 3, the absorption of cefuroxime axetil was similar in men and women. Sex differences have not been counted among the factors affecting drug absorption from the gastrointestinal tract (8).

When ampicillin was compared with cefuroxime axetil in fasting volunteers (study 4), the serum levels and urinary recoveries were similar, again illustrating the effect of food on cefuroxime axetil absorption. There were no changes in the kinetic behavior of either drug during repeated dosing. No significant accumulation occurred, and the small increase in peak level which would be expected for both drugs

may have been masked by the variation of the figures in the case of cefuroxime axetil. With both cefuroxime axetil and ampicillin there was some variation in absorption, measured by urinary recovery, from dose to dose. In study 3, in which dosing was supervised, the coefficient of variation in urinary recovery was smaller for cefuroxime axetil than for ampicillin. The same was true in study 4, in which doses and urine collections were mostly unsupervised, although coefficients of variation were higher in this study. These findings reinforce the apparently greater variation in urinary recovery of ampicillin depicted in Fig. 3. The variation in recovery for ampicillin shown in this diagram indicates peaks of absorption in the morning and regular troughs in the evening. Such dependence upon time of dosing has been reported previously for ampicillin (9), but cefuroxime axetil does not appear to be subject to this effect.

In conclusion, cefuroxime axetil possesses more favorable pharmacological properties than ampicillin. Since ampicillin is of proven clinical efficacy, cefuroxime axetil should also be effective. The broader antibacterial spectrum of cefuroxime, together with these favorable properties, renders cefuroxime axetil a promising new oral antibiotic.

LITERATURE CITED

1. Foltz, E. L., J. W. West, J. H. Breslow, and H. Wallick. 1971. Clinical pharmacology of pivampicillin. Antimicrob. Agents Chemother. p. 442–454, 1970.
2. Foord, R. D. 1976. Cefuroxime: human pharmacokinetics. Antimicrob. Agents Chemother. 9:741–747.
3. Godtfredsen, W. O. 1977. An introduction to mecillinam. J. Antimicrob. Chemother. 3(Suppl. B):1–4.
4. Jones, K. H., P. F. Langley, and L. J. Lees. 1978. Bioavailability and metabolism of talampicillin. Chemotherapy 24:217–226.
5. Larson, H. E., J. V. Parry, A. B. Price, D. R. Davies, J. Dolby, and D. A. J. Tyrell. 1977. Undescribed toxin in pseudomembranous colitis. Br. Med. J. 1:1246–1248.
6. Leigh, D. A. 1982. Antimicrobial usage in forty-three hospitals in England. J. Antimicrob. Chemother. 9:75–84.
7. Murphy, C. F., and A. J. Webber. 1972. Alteration of the dihydrothiazine ring moeity, p. 134–182. In E. H. Flynn (ed.), Cephalosporins and penicillins: chemistry and biology. Academic Press, Inc., New York.
8. Prescott, L. F. 1974. Gastrointestinal absorption of drugs. Med. Clin. North Am. 58:907–916.
9. Sharma, S. D., V. A. Deshpande, M. R. Samuel, and B. J. Vakil. 1979. Chronobioavailability of ampicillin. Chronobiologia 6:156.
10. Shindo, H., K. Fukuda, K. Kawai, and K. Tanaka. 1978. Studies on intestinal absorption of pivampicillin and species difference in the intestinal esterase activity. J. Pharmacobio-Dyn. 1:310–323.
11. Welling, P. G., H. Huang, P. A. Koch, W. A. Craig, and P. O. Madsen. 1977. Bioavailability of ampicillin and amoxycillin in fasted and non-fasted subjects. J. Pharm. Sci. 66:549–552.
12. Wood, C., and Y. Rue (ed.). 1981. Cefuroxime update. R. Soc. Med. Int. Congr. Symp. Ser. 38:1–191.