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Pharmacokinetics of Cefuroxime Axetil and Cefaclor: Relationship of Concentrations in Serum to MICs for Common Respiratory Pathogens

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The pharmacokinetics of single doses of cefaclor at 250 and 375 mg and cefuroxime axetil at 250 mg administered under optimal conditions (i.e., cefuroxime axetil after food and cefaclor in the fasted state) were studied in 24 healthy male volunteers. Drug concentrations in serum were related to MICs for common respiratory tract pathogens by using data generated from a recently completed national survey. The time the concentrations in serum exceeded the MICs for *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella* (formerly *Branhamella*) *catarrhalis* were significantly greater ($P < 0.05$) for cefuroxime axetil at 250 mg than for cefaclor at 250 or 375 mg. With the recommended dosing regimens (cefuroxime axetil at 250 mg and cefaclor at 375 mg twice daily or cefaclor at 250 mg three times daily), cefuroxime concentrations exceed the MIC for 90% of the strains tested for a greater time period than cefaclor concentrations with either regimen. The reasons for this difference are (i) the greater potency and slower clearance of cefuroxime compared with those of cefaclor and (ii) the greater sensitivity of these pathogens to cefuroxime.

Cefuroxime axetil (Ceftin) and cefaclor (Ceclor) are both broad-spectrum oral cephalosporin antibiotics which are widely used for similar infections. Whereas cefuroxime axetil, the ester prodrug of the parenteral agent cefuroxime, is administered every 12 h, cefaclor may be given as the parent drug every 8 to 12 h for otitis media and pharyngitis and every 8 h for other infections (1, 6).

The primary differences between these drugs are in pharmacokinetics and in vitro activity. Both drugs are well absorbed, are not highly protein bound, and are primarily eliminated unchanged in the urine (1, 6). Whereas food increases cefuroxime absorption by 50% after dosing with cefuroxime axetil, food has no effect on cefaclor absorption (1, 6). Cefuroxime is eliminated from the body about half as rapidly as cefaclor, as indicated by the respective elimination half-lives of 1.2 h versus 0.6 h (1, 6, 21). While the in vitro antibacterial activity of these drugs against many bacteria (e.g., *Moraxella catarrhalis*) is similar, cefuroxime is more active than cefaclor against *Haemophilus influenzae* and *Streptococcus pneumoniae* (2, 3, 14).

Given the differences in pharmacokinetics and dynamics observed in separate studies (2, 3, 7, 12–14, 21), the present study was designed to compare the pharmacokinetic profiles of oral cefuroxime axetil and cefaclor in the same subjects and to relate these profiles to the antimicrobial activities of these two agents.

MATERIALS AND METHODS

Pilot study. The objective of this study was to compare the absorption and disposition of cefuroxime axetil tablets with those of cefaclor capsules and suspension in subjects who were fasted or were fed.

Subjects. Six healthy male volunteers were enrolled after informed consent was obtained. The ages of the study subjects ranged from 21 to 31 years (mean = 25). Exclusion criteria included a history of hypersensitivity to any drug, acute illness requiring treatment by a physician within 1 month prior to screening, clinically significant medical condition or laboratory test, and/or history or evidence of ethanol or drug abuse. The subjects did not consume foods or beverages containing caffeine or alcohol between 24 h prior to the first drug administration and 12 h after the last drug administration.

Protocol. This was a randomized, balanced, open, single-dose, six-period, six-treatment crossover pilot study. The study protocol and consent form were approved by an institutional review board. Subjects were randomized to receive one 250-mg cefuroxime axetil tablet (lot Z50087LR; Allen and Hanburys, Research Triangle Park, N.C.), one 250-mg cefaclor capsule (lot 2PH69B; Eli Lilly & Co., Indianapolis, Ind.), or 5 ml of cefaclor suspension (375 mg/5 ml, lot 2NR21A; Eli Lilly & Co.). Each of these treatments was administered following a 10-h fast or 15 min after ingestion of a standardized breakfast (corn flakes, milk, sugar, buttered roll with jam or marmalade, and decaffeinated tea or coffee with milk and sugar as needed). Each tablet and capsule was administered with 240 ml of water. The suspension was administered with 235 ml of water so that the total fluid volume for each treatment was 240 ml. No additional liquids or food was ingested for 4 and 5 h following dosing, respectively.

Blood samples (6 ml) for pharmacokinetic analysis were obtained by venipuncture prior to dosing and at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h following dosing. The samples were allowed to clot at room temperature, and the serum was separated by centrifugation and transferred into two polypropylene storage vials. All serum samples were stored at a minimum of −70°C until analysis.

Follow-up study. The objective of the follow-up study was to compare the pharmacokinetics of cefuroxime axetil and cefaclor by using their available oral dose forms with subjects who were fed or fasted, respectively.

Subjects. The ages of the 24 healthy male volunteers ranged from 21 to 34 years (mean = 26). Exclusion criteria,

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TABLE 1. Mean[a] pharmacokinetic parameters for cefuroxime and cefaclor

Treatment	Dose (mg)	Subject fed	C_{max} (μg/ml)	T_{max} (h)	AUC (μg · h/ml)	Half-life (h)
Pilot study (n = 6)						
Cefuroxime axetil tablet	250	No	4.19 (0.30)	1.38 (0.14)	12.66 (0.67)	1.39 (0.13)
Cefuroxime axetil tablet	250	Yes	4.63 (0.14)	2.33 (0.21)	16.80 (1.33)	1.08 (0.05)
Cefaclor capsule	250	No	9.30 (1.12)	0.67 (0.05)	9.84 (0.96)	0.45 (0.10)
Cefaclor capsule	250	Yes	5.33 (0.43)	1.50 (0.18)	9.47 (0.78)	0.63 (0.26)
Cefaclor suspension	375	No	14.12 (1.88)	0.67 (0.08)	14.55 (1.60)	0.59 (0.03)
Cefaclor suspension	375	Yes	9.04 (1.32)	1.10 (0.17)	15.88 (1.58)	0.50 (0.04)
Follow-up study (n = 24)						
Cefuroxime axetil tablet	250	Yes	4.29 (0.19)	2.26 (0.12)	14.21 (0.45)	1.09 (0.22)
Cefaclor capsule	250	No	8.81 (0.54)	0.69 (0.05)	9.04 (0.29)	0.53 (0.02)
Cefaclor suspension	375	No	12.08 (0.47)	0.55 (0.03)	11.51 (0.37)	0.55 (0.02)

[a] Values in parentheses are standard errors.

informed consent, and institutional review board procedures were identical to those in the pilot study.

Protocol. This was a randomized, balanced, open, single-dose, three-period, three-treatment crossover study. Subjects were randomized to receive one 250-mg cefuroxime axetil tablet (lot B1419GA; Allen and Hanburys) administered 15 min after the standardized breakfast, one 250-mg cefaclor capsule (lot 2MP24C; Eli Lilly & Co.) administered after a 10-h fast, or 15 ml of cefaclor suspension (125 mg/5 ml, lot 3AH59A; Eli Lilly & Co.) administered after a 10-h fast. The dosing procedure was identical to that used in the pilot study, except that the cefaclor suspension was administered with 225 ml of water so that the total fluid volume was 240 ml.

Blood samples (10 ml) were collected as described above but were allowed to clot at 4°C prior to centrifugation to prevent degradation. All other sample handling procedures were identical to those used in the pilot study.

Analyses. Cefuroxime and cefaclor analyses for the pilot study were conducted at Harris Laboratories, Inc. (Lincoln, Nebr.). Cefuroxime analysis for the follow-up study was conducted at Glaxo Inc. (Research Triangle Park, N.C.), and cefaclor analysis for the follow-up study was conducted at Phoenix International Life Sciences, Inc. (Montreal, Canada). A brief description of each validated analytical method follows.

Pilot study. Concentrations of cefuroxime in serum were determined by using a reverse-phase high-performance liquid chromatography (HPLC) method. Serum samples were prepared by using an acid-protein precipitation method. This internal standard assay was linear from 0.05 to 20 μg/ml ($r \geq 0.999$) with a coefficient of variation ranging from 2.2% at 20 μg/ml (n = 6) to 15.7% at 0.2 μg/ml (n = 6).

Concentrations of cefaclor in serum were determined by using a liquid-liquid extraction and reverse-phase HPLC method. This internal standard assay was linear from 0.05 to 25 μg/ml ($r \geq 0.990$) with a coefficient of variation ranging from 6.2% at 25 μg/ml (n = 36) to 11.7% at 0.5 μg/ml (n = 36).

Follow-up study. Concentrations of cefuroxime in serum were determined by using a reverse-phase HPLC method in conjunction with a cylindrical coordinate robot. Cefuroxime was isolated from serum by protein precipitation. This internal standard assay was linear from 0.1 to 20.0 μg/ml ($r \geq 0.997$) with a coefficient of variation of 3.5% at 20 μg/ml (n = 35) to 5.8% at 0.1 μg/ml (n = 35).

Concentrations of cefaclor in serum were determined by using a precolumn enrichment reverse-phase HPLC method. Cefaclor was isolated from serum by protein precipitation. This internal standard assay was linear from 0.2 to 25 μg/ml ($r \geq 0.996$) with a coefficient of variation ranging from 2.9% at 0.8 μg/ml (n = 27) to 6.5% at 0.2 μg/ml (n = 27).

Pharmacokinetic parameters. The maximum concentration of drug in serum (C_{max}) and time to the maximum concentration of drug in serum (T_{max}) were determined directly by observation of the data. The area under the concentration-time curve (AUC) from time 0 to the last measurable concentration was determined by the trapezoidal rule. The elimination rate constant was calculated by using weighted nonlinear least-squares regression of the concentration-versus-time curve. The AUC from time 0 to infinity was calculated by dividing the last measured concentration by the elimination rate constant and adding it to AUC from time 0 to the last measurable concentration. The half-life was calculated by dividing 0.693 by the elimination rate constant.

The time the concentration in serum exceeded the MIC for 90% of the strains tested (MIC_{90}) for common respiratory pathogens was calculated with the MIC data obtained in a recently completed national surveillance study (14). This study includes data collected at 15 U.S. medical centers from more than 300 isolates of each respiratory pathogen. The MICs reported in this latest survey are consistent with those reported in previous studies (2, 3).

Statistical analysis included analysis of variance, which tested for sequence, subject within sequence, period, and treatment (alpha = 0.05). Duncan's multiple-range test was performed to evaluate differences between treatments. A level of $P < 0.05$ was considered to be statistically significant.

RESULTS

The pharmacokinetic parameters determined in each study are presented in Table 1.

Pilot study. The C_{max} was higher for cefuroxime axetil administered to fed subjects compared with that administered to subjects who fasted, while the C_{max}s were greater for both cefaclor doses in subjects who fasted. The AUC for cefuroxime axetil was greater in subjects who were fed; there was little difference between the AUCs for cefaclor in subjects who fasted or were fed. These results suggest that the optimal condition for administration of cefuroxime axetil is after subjects have been fed and that for cefaclor is after subjects have fasted. These findings provided the basis for the selection of dosing procedures used in the follow-up study.

Follow-up study. Cefaclor was more rapidly absorbed than cefuroxime (T_{max} = 0.7 versus 2.3 h) and achieved higher

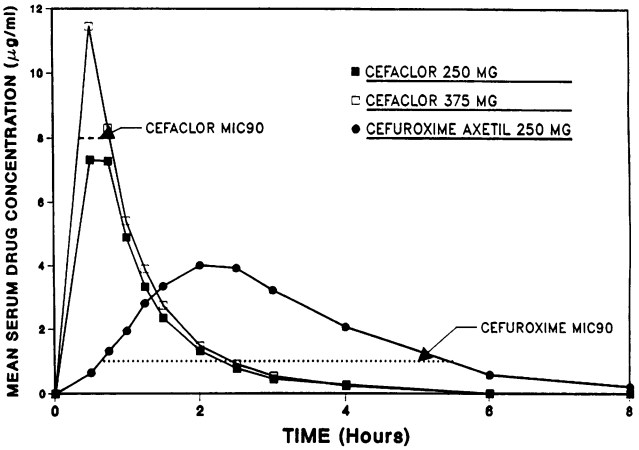

FIG. 1. Mean drug concentration in serum versus time. MIC_{90}s indicated are those for β-lactamase-positive *H. influenzae* (14).

peak concentrations in serum (8.81 μg/ml after 250 mg of cefaclor, 12.08 μg/ml after 375 mg of cefaclor versus 4.29 μg/ml after 250 mg of cefuroxime axetil). However, the half-life of cefaclor was much shorter than that of cefuroxime (0.5 versus 1.1 h).

The mean concentrations in serum versus time curves for the three treatments and their relationships to the MIC_{90}s for β-lactamase-positive *H. influenzae* (14) are shown in Fig. 1. The MICs of various antibiotics for respiratory pathogens were determined in a recent survey (14) and are presented for cefuroxime and cefaclor in Table 2. Table 3 summarizes the times the concentration in serum exceeded the MIC_{90} for each respiratory pathogen following a single dose of cefuroxime axetil or cefaclor in the follow-up study. Cefuroxime concentrations exceeded the MIC_{90}s for each respiratory pathogen significantly longer than cefaclor concentrations following a single cefaclor dose of either 250 or 375 mg. In addition, in order to approximate the actual clinical setting, the time the concentration in serum exceeded the MIC_{90} of a daily dosing regimen was calculated by using the recommended dosing regimens for cefuroxime axetil and cefaclor. Again, cefuroxime concentrations after a 250-mg dose of cefuroxime axetil tablets administered twice daily exceeded the MIC_{90} for each pathogen significantly longer than cefaclor concentrations following cefaclor tablets (250 mg) administered three times daily or the cefaclor suspension (375 mg) administered twice daily (data not shown). The

TABLE 2. MICs for respiratory pathogens (14)

Pathogen	MIC[a] (μg/ml) of drug			
	Cefaclor		Cefuroxime	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
H. influenzae (β-lactamase positive)	2	8	1	1
H. influenzae (β-lactamase negative)	2	4	1	1
S. pneumoniae	0.5	1	0.03	0.06
M. catarrhalis (β-lactamase positive)	0.5	1	1	1
M. catarrhalis (β-lactamase negative)	0.12	0.25	0.25	0.5

[a] MIC_{50}, MIC for 50% of the strains tested.

TABLE 3. Mean time that the concentration in serum exceeds MIC_{90} after a single dose

Organism	Time[a] (h)		
	Cefaclor (250 mg)	Cefaclor (375 mg)	Cefuroxime Axetil (250 mg)
H. influenzae (β-lactamase positive)	0.19 (0.04)	0.42 (0.03)[b]	4.59 (0.09)[b,c]
H. influenzae (β-lactamase negative)	0.78 (0.05)	1.03 (0.04)[b]	4.59 (0.09)[b,c]
S. pneumoniae	2.14 (0.06)	2.32 (0.06)	7.31 (0.27)[b,c]
M. catarrhalis (β-lactamase positive)	2.14 (0.06)	2.32 (0.06)	4.59 (0.09)[b,c]
M. catarrhalis (β-lactamase negative)	3.22 (0.08)	3.34 (0.10)[b]	5.76 (0.11)[b,c]

[a] Values in parentheses are standard errors.
[b] Significantly different from values for cefaclor at 250 mg ($P < 0.05$).
[c] Significantly different from values for cefaclor at 375 mg ($P < 0.05$).

results of the single-dose studies are presented in Fig. 2 as the ratio of serum drug concentration/MIC_{90} versus time for each treatment; this ratio was calculated with the MIC_{90} for β-lactamase-positive *H. influenzae* (14).

DISCUSSION

The results of the pilot pharmacokinetic study comparing cefuroxime axetil and cefaclor indicated that the C_{max} was higher and the T_{max} was earlier when cefaclor was administered to subjects who fasted. These findings are consistent with previous reports of cefaclor administration to adult volunteers and pediatric patients (9, 10, 16, 20). In contrast, the C_{max} was higher when cefuroxime axetil was administered to subjects who were fed while there was little difference in the T_{max}, results also consistent with previous findings (7, 22, 24).

The C_{max} observed following cefaclor administration in the follow-up study was higher than that reported in previous studies (13, 15, 21). This difference may be due to the use of an HPLC assay in the present study, rather than the microbiological assay used in the previous studies. In addition, the subjects fasted for 5 h following dosing in the present study, while most of the other studies used only a 2-h fast after drug

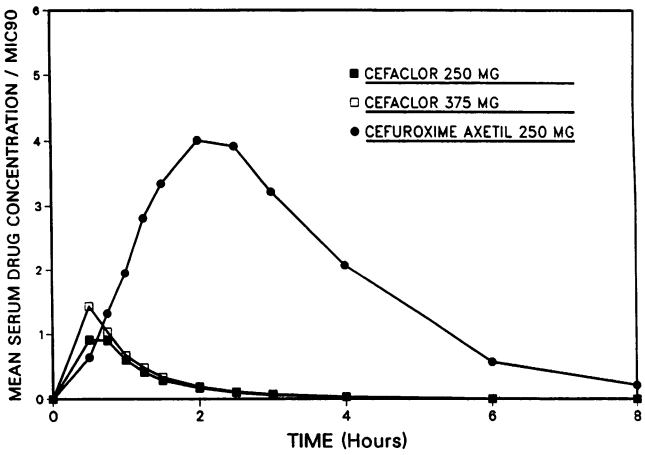

FIG. 2. Mean drug concentration in serum/MIC_{90} versus time. MIC_{90}s used for these calculations are those for β-lactamase-positive *H. influenzae* (14).

administration. It should be noted, however, that the cefaclor half-life observed in this study is very similar to that reported in other studies (11, 13, 15, 21). Similarly, the pharmacokinetic parameters determined after cefuroxime axetil administration agree with those reported previously (7, 12, 22, 24).

The data presented in this report characterize the single-dose pharmacokinetics of cefuroxime axetil and cefaclor. Although oral antibiotics are usually administered over a 5- to 10-day period, this single-dose study reflects the clinical setting since accumulation does not occur during multiple dosing in patients with normal renal function (11, 13, 15).

While there has been controversy about the correct interpretation of the relationship between pharmacokinetics and MIC data, several investigators have suggested that the time the concentration in serum exceeds an organism's MIC is important, especially for β-lactam antibiotics (4, 5, 19). It is thought that the time the concentration is below the MIC should not be excessive because it affords an opportunity for remaining organisms to proliferate (19).

Although a postantibiotic effect has recently been demonstrated against gram-positive organisms, including *S. pneumoniae*, with both cefuroxime and cefaclor, it was shown that at a range of drug concentrations corresponding to equivalent multiples of the MICs there was little difference between the two drugs (17). Thus, it does not appear that the less favorable pharmacokinetics seen in the present study with cefaclor compared with those of cefuroxime axetil would be offset in the clinical setting by a more pronounced postantibiotic effect with the former antibiotic.

Because one of the goals of antibiotic therapy is to eradicate organisms at the site of infection, the drug must diffuse into peripheral tissues. Given that only unbound drug is believed to penetrate into tissues, the degree of protein binding may be important in correctly interpreting pharmacokinetic data. However, because the binding of cefaclor and cefuroxime to serum proteins is similar (cefaclor, 20 to 50% [18, 23]; cefuroxime, 33 to 50% [1, 8]), this factor is insignificant in the comparison of these two antibiotics and should not alter the conclusions of the present study.

The difference in the time the drug concentration in serum exceeds the MIC of cefuroxime axetil versus cefaclor can be explained by several factors. The elimination half-life of cefuroxime is much longer than for cefaclor. Although the peak cefaclor concentration is greater than the peak cefuroxime concentration, the difference in half-lives more than compensates for this, allowing cefuroxime concentrations to remain above the MIC for a longer duration. In addition, the MIC_{90}s for the major respiratory pathogens, are, in general, the same or lower for cefuroxime compared with cefaclor (2, 3, 14), further contributing to the greater length of time that cefuroxime concentrations exceed the MIC_{90}. It should be noted that if cefaclor had been administered with food, it is likely that cefaclor concentrations in serum would not have exceeded the MIC_{90} for any length of time.

In summary, under optimal dosing conditions, concentrations of cefuroxime in serum following a 250-mg dose of cefuroxime axetil exceed the MICs for common respiratory pathogens for a significantly greater time than do cefaclor concentrations following a 250- or 375-mg dose of cefaclor. The reasons for this difference appear to be the slower clearance of cefuroxime compared with that of cefaclor, as well as the greater susceptibility of the pathogens to cefuroxime.

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