Cefaclor Pharmacokinetic Parameters: Serum Concentrations Determined by a New High-Performance Liquid Chromatographic Technique

JOHN C. ROTSCHAFER,1,2* KENT B. CROSLEY,3,4 TIMOTHY S. LESAR,1,2 DARWIN ZASKE,1,2 AND KENNETH MILLER2,3

Section of Clinical Pharmacology1* and Department of Internal Medicine,3 St. Paul-Ramsey Medical Center, St. Paul, Minnesota 55101, and Clinical Pharmacokinetics Laboratory,4 College of Pharmacy,2 and Department of Medicine,4 University of Minnesota, Minneapolis, Minnesota 55455

Received 6 July 1981/Accepted 2 October 1981

Pharmacokinetic parameters of cefaclor were studied in eight patients after an oral dose of 250 mg. Serum samples were obtained before and on 19 occasions after oral administration. Cefaclor serum concentrations were determined by a new high-performance liquid chromatographic technique.

Cefaclor, a chlorinated modification of cephalixin, is a recently introduced oral cephalosporin antibiotic indicated for the treatment of urinary tract infection, otitis media, skin infections, and respiratory infections (9). In vitro studies have shown that this drug is highly active against Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, salmonellae, shigellae, Haemophilus influenzae, Citrobacter diversus, gonococci, meningococci, staphylococci, and group A beta-hemolytic streptococci (1, 3, 12–14, 17).

The study that we report here was designed to evaluate the pharmacokinetic parameters of this antibiotic with a new high-performance liquid chromatographic assay technique.

Eight patients (one male and seven females) being treated for urinary tract infection were enrolled in the study after giving informed consent. Patients ranged in age from 16 to 72 years and had serum creatinine levels ranging from 0.6 to 1.1 mg/dl. On the day of the study, patients fasted for at least 2 h before and at least 2 h after the oral administration of 250 mg of cefaclor.

Blood specimens were obtained just before and at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 75, 90, 105, 120, 150, 180, and 240 min after administration. Exact times of collection were recorded and used in the data analysis. Blood samples were immediately iced and centrifuged, and the serum was deproteinated within 3 h of collection to ensure maximum stability of the antibiotic (6).

The deproteinated supernatants were frozen until analysis.

**Cefaclor determination.** An analytical standard of cefaclor was supplied by Eli Lilly & Co. The internal standard, 8-chlorotheophylline, was obtained from the Aldrich Chemical Co. Methanol was purchased from Burdick and Jackson Laboratories. All other chemicals were reagent or analytical grade. Reference samples containing known amounts of cefaclor and an internal standard were prepared in blank serum obtained from the same patients.

**High-performance liquid chromatography.** High-performance liquid chromatographic analyses were performed with a Waters chromatograph equipped with dual M6000A pumps, a 660 solvent programmer, a U6K injector, and a variable-wavelength UV-VIS detector (Varian Varichrom) with the wavelength set at 266 nm. The flow rate was maintained at 1.0 ml/min, and the solvent composition was selected and maintained with the solvent programmer. The column was packed with a reverse phase (LiChrosorb C8, Altex), and the mobile phase was methanol and 0.01 M sodium acetate buffer (pH 5.2) in the ratio 30:70. All analyses were done at room temperature (22 to 24°C). A protein-free supernatant was injected directly onto the high-performance liquid chromatographic column, and drugs were quantitated by measuring peak height ratios of the drug to the internal standard. Cefaclor reference solution was prepared fresh each day. Analyses were done by dissolving the drug in 0.1 M, pH 4.5 monobasic potassium phosphate buffer. The coefficient of variation for the assay, including day-to-day variation, was less than 4% and independent of cefaclor concentration. The limit of sensitivity was approximately 0.2 µg/ml. No interference was seen with acetaminophen, salicylic acid, codeine, or caffeine with this method.

Cefaclor serum concentration time data were fitted to a biexponential equation by using computer-assisted (KINA, University of Minnesota) nonlinear regression analysis, which describes the standard open one-compartment model with first-order absorption for orally administered
drugs (16). Estimates of the absorption rate constant ($K_a$), elimination rate constant ($K_d$), lag time, half-life, and the area under the serum concentration time curve were determined by standard methods (7, 16). The peak serum concentration and the time to peak represent the largest measured serum concentration and the time elapsing between oral administration and the measurement of the highest serum concentration, respectively. Apparent total body clearance was calculated by dividing the dose by the area under the serum concentration time curve (19). The elimination phase was analyzed in seven of the eight patients because the concentration time data could not be fitted for patient no. 1. Creatinine clearance for each patient was determined by the method of Cockcroft and Gault (5).

Results of the pharmacokinetic analysis are presented in Table 1. Detectable serum concentrations of cefaclor were present by 40 min in all patients and were still present at the last sampling. Maximum serum concentrations were obtained at between 30 and 150 min, with a mean ($\pm$ standard deviation) of 8.9 ($\pm$ 5.5) $\mu$g/ml. The mean lag time for absorption was 23.4 ($\pm$10.9) min.

The pharmacokinetic variables of cefaclor exhibited large variation in these eight patients. Although all patients were fasting during the study period, $K_p$, the time to peak, and the peak serum concentration varied greatly. Variation in the rate of absorption and elimination affected the time to peak and maximum concentration attained. Other investigators, using healthy volunteers, have reported mean peak serum concentrations occurring at 30 to 75 min, with concentrations ranging from 5.2 to 8.6 $\mu$g/ml (8, 10, 11, 18). The average half-life reported in our patients is comparable to other reports of 35 to 60 min (8, 10, 11, 18). In patients with normal renal function, 85 to 90% of the administered dose is eliminated in 3 h.

Cefaclor, unlike the parent compound cephalixin, has a major nonrenal route of elimination (2, 14, 15). The half-life has been reported to increase by 50 to 100% as the creatinine clearance approaches zero (2, 4, 15). Although our patient population is relatively small, this relationship with creatinine clearance ($y = 130 + 3.4x; r = 0.90$) indicates a substantial amount of nonrenal cefaclor clearance, with a positive intercept of 130 ml/min. Cefaclor clearance, as expected, decreased with increasing age. This likely reflects decreasing renal function associated with increasing age.

The manufacturer currently recommends an 8-h dosage interval. Use of this relatively long dosage interval for an antimicrobial agent possessing a short serum half-life is likely to result in subtherapeutic antibiotic concentrations for a lengthy portion of the dosage interval. In situations where sustained high antibiotic concentrations are warranted, a shorter dosage interval could probably be used safely in patients with normal renal function. Further studies are required to document the potential safety and efficacy of shorter dosing intervals.

This work was supported in part by Eli Lilly & Co., the Medical Education and Research Foundation of St. Paul-Ramsey Medical Center, and College of Pharmacy Clinical Research Fund, University of Minnesota.

### LITERATURE CITED


