ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1979, p. 1-6
0066-4804/79/07-0001/06$02.00/0

Vol. 16, No. 1

Comparative Pharmacokinetics of Cephalexin, Cefaclor, Cefadroxil, and CGP 9000

HARTMUT LODE,* RALF STAHLMANN, AND PETER KOEPPE

Department of Medicine, Klinikum Steglitz of the Free University Berlin, Hindenburgdamm 30, 1000 Berlin 45, West Germany

Received for publication 12 April 1979

In a randomized crossover study, the pharmacokinetics of three new cephalosporin antibiotics, cefaclor, cefadroxil, and CGP 9000, in comparison to cephalexin, were determined after oral administration, by capsules, of 1,000 mg on an empty stomach in 12 normal subjects. Serum concentrations were measured during a period of 8 h, and urine recovery was measured during 24 h. The significant parameters of bioavailability of an orally administered substance were determined. The maximal serum concentrations (y_{max}) for cephalexin, cefaclor, cefadroxil, and CGP 9000 (in milligrams per liter) were: 38.8 ± 8.1; 34.6 ± 7.8; 33.0 ± 5.4; and 23.3 ± 7.3, respectively. The areas under the curve (in hours × milligrams per liter) were: 93.0 ± 14.8; 74.5 ± 9.9; 70.1 ± 9.0; and 108.5 ± 18.4, respectively. In a further crossover study with six subjects, 1,000 mg of cephalexin and of cefadroxil were given during a standard breakfast. The y_{max} of cephalexin decreased to 23.1 ± 6.6 mg/liter, in contrast to cefadroxil, with an unchanged y_{max} of 32.7 ± 3.4 mg/liter.

The use of oral cephalosporins as alternative agents to penicillins for outpatient therapy has increased in recent years because of concern over allergic reactions to penicillins and because of the increased number of β-lactamase-producing staphylococci. Slight changes in the basic structure of the hitherto existing oral standard substances (cephalexin or cephradine) led to three new oral cephalosporins (Fig. 1).

According to investigations by various authors (4, 21, 24), cefaclor is more active than cephalexin against *Escherichia coli*, klebsiellae, *Proteus mirabilis*, salmonellae, shigellae, and *Haemophilus influenzae*. In experimental infections in animals, CGP 9000 proved to be superior to cephalexin (27). The bioavailability of cephadroxil administered orally is superior to that of cephalexin (10, 22). In the present study, the pharmacokinetic parameters of these three new substances and cephalexin were compared after oral administration to each of 12 fasting subjects. In addition, the influence of simultaneous food intake on the absorption of cephalexin and cefadroxil was examined in six test subjects.

(This paper was presented in part at the 18th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Ga., 1978.)

MATERIALS AND METHODS

Human volunteers. Twelve healthy test subjects (six females, six males) with no known allergies to cephalosporin antibiotics participated in the study after informed written consent was obtained. None was taking any other antimicrobial agents 14 days before and during the investigational period. Their ages ranged between 20 and 41 years, and their body weights between 52.5 and 76 kg (mean, 67.8 kg). Results of prestudy physical examinations and intensive pre- and poststudy laboratory investigations were normal.

Pharmaceutical preparations. Cefaclor (compound 99638), synthesized at Eli Lilly Research Laboratories, Indianapolis, Ind., was used as monohydrate capsules (batch no. CT-3348-7B). Cefadroxil (BLS 578), a product of Bristol-Myers Co., Syracuse, N.Y., was used as monohydrate capsules (batch no. 7 × 6 R 332). CGP 9000, synthesized at Ciba-Geigy Co., Basel, Switzerland, was used as monohydrate capsules (batch no. 04/585/4). Cephalexin substance was obtained from a commercially available capsule preparation, Oracef (batch no. EXF 4 AD 23; Lilly).

Dosage. The drugs were given in single equivalent (1,000-mg) doses: cefaclor, four 250-mg capsules; cefadroxil, two 500-mg capsules; CGP 900, four 250-mg capsules; and cephalexin, four 250-mg capsules. This amount provided a mean dosage of 15.2 mg/kg of body weight (range, 13.1 to 19.0 mg/kg). The capsules were taken under supervision at 8:00 a.m. on an empty stomach with 80 to 100 ml of water.

Experimental design. The study was carried out in a complete crossover fashion, i.e., all 12 subjects receiving all 4 preparations. Each subject received the drugs in a randomized order, implying that different preparations were given to the subjects on the same day. There was an 8-day washout period between crossover studies. All subjects were fasted overnight before each study. The drugs were always administered at 8:00 a.m., the fasting state being maintained for 2 h after dosage (study 1). In study 2, 6 of the 12

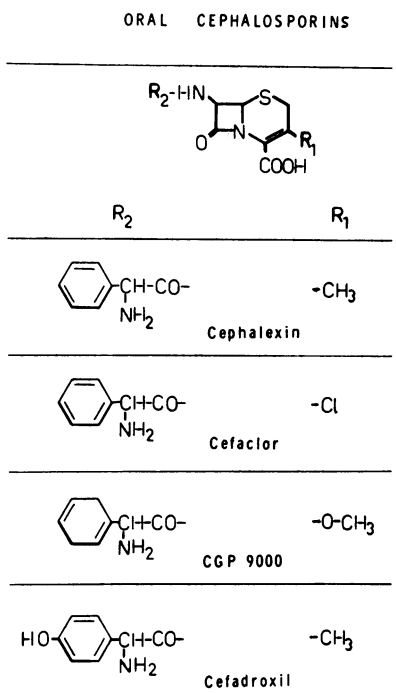

FIG. 1. *Four oral cephalosporins (cephalexin, cefaclor, cefadroxil, and CGP 9000).*

test persons of study 1 ingested a standard breakfast (two cups of coffee and two rolls) at 8:00 a.m. The 1,000-mg doses of cefadroxil or cephalexin were administered in random order between the first and second roll and cup of coffee.

Sampling. Blood samples (6 to 8 ml each) drawn from the antecubital vein before the first dose of each of the six dosing periods showed no detectable antibiotic activity. Venous blood samples for assay of plasma antibiotic concentrations were obtained at 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, and 8.0 h after drug administration. Since there was a loss of up to 50% of the cefaclor activity in serum samples that were left at room temperature for 3 to 8 h, all blood samples were cooled (4°C) immediately after collection, and the serum was separated in a refrigerated centrifuge. Thereafter followed the immediate assaying. Urine samples were collected before dosage (no activity during the investigation period) and during two 6-h periods and one 12-h period.

Microbiological assay. Microbiological assay was performed by means of the agar diffusion test (cup-plate method [2]) as modified by Reeves and Bywater (23). Serum assays were performed with antibiotic medium (Difco Laboratories, Detroit, Mich.), using *Sarcina lutea* ATCC 9341 as test organism; urine assays were performed by using *Bacillus subtilis* ATCC 6633. Pooled normal human serum (pH fixed on 7.4) was used as a diluent for serum specimens, and Sörensen phosphate buffer (cephalexin at pH 7.0, cefaclor at pH 4.5, cefadroxil at pH 7.0, CGP 9000 at pH 7.4) for urine samples and standards. For investigations of cefaclor, cefaclor-monohydrate (activity titer, 961 μg/mg, lot no. SI-100-6C; Eli Lilly) was used; for cefadroxil, cefadroxil-monohydrate (activity titer, 948 μg/mg; batch no. RR-109; Bristol-Meyers) was used; for CGP 9000, CGP 9000-monohydrate (activity titer, 861 μg/mg; batch no. 67/77 Kr III; Ciba-Geigy) was used; and for cephalexin, cephalexin-monohydrate (activity titer, 940 μg/mg; lot no. 8 HM 55; Lilly) was used. The plates were incubated at 37°C for 18 h. Zones of inhibition were measured by a zone reader, and antibiotic concentrations were computed by comparing the mean zone of inhibition of each sample with the curve constructed from the zone sizes of the standard solutions. The details of the bioassay were described previously (15, 16). With the given method, the lowest determinable levels (in milligrams per milliliter) were: for cefaclor, 0.30 in serum and buffer; for cephalexin, 0.39 in serum and 0.30 in buffer; for cefadroxil, 0.30 in serum and 0.30 in buffer; for CGP 9000, 0.30 in serum and 0.10 in buffer.

Pharmacokinetic calculations. In the present study, an open one-compartment model with first-order absorption lag was assumed (28). The model equation is: $y\ (t) = y_o[K_1/(K_1 - K_2)] \times [e^{-K_2}\ (t - t_o) - e^{-K_1}\ (t - t_o)]$, where $y(t)$ is the serum concentration (milligrams per milliliter) at time t (minutes), K_1 (per hour) is the first-order absorption rate constant, K_2 (per hour) is the overall first-order elimination rate constant, y_o is the fictive serum concentration (milligrams per liter) at time $t = 0$, and t_o is the lag time (minutes) between drug administration and the onset of absorption. The relevant pharmacokinetic parameters were determined by the Gauss-Newton iteration method (18); the fitting was performed via nonlinear regression analysis, using the digital computer Fortran and Asim II programs (15). Further parameters considered were: y_{max}, the maximal serum concentration (milligrams per liter); x_{max}, the time (minutes) after which y_{max} was reached; $t_{1/2A}$ (minutes), the absorption half-life; $t_{1/2E}$ (minutes), the elimination half-life; and the area under the curve (AUC; hours × milligrams per hour), calculated as area integral $y(dt)$ under the serum level curve (13, 16).

Bioavailability comparisons on a given antibiotic were performed by using K_1, x_{max}, and y_{max} to characterize rate of availability, and AUC to characterize total extent of availability once the statistical equivalence of K_2 values in the crossover had been established (28).

Statistical evaluation. The distribution being abnormal for some of the variables, the Wilcoxon signed rank test was used for the analysis of significance of differences, and all hypotheses were tested at the $P = 0.05$ level of significance.

RESULTS

Cephalexin. Figure 2 shows the cephalexin serum concentrations for each individual volunteer and the serum regression curve. This figure demonstrates the pharmacokinetic basis of the calculation in all investigated substances. The cephalexin curve was a typical serum concentration curve, with a rapid rise to a mean peak concentration of 38.8 ± 8.1 mg/liter (after an average of 55.5 ± 21.8 min) and a relatively

rapid decrease to only 1.2 mg/liter after 6 h, giving a biological half-life of 62.5 ± 5.5 min.

Cefaclor. Cefaclor exhibited a pharmacokinetic characteristic similar to that of cephalexin with equally rapid absorption (x_{max} = 65.2 ± 11.1 min) but a lower maximal serum level of (34.6 ± 7.8 mg/liter) than cephalexin. An average of only 0.5 mg/liter could still be measured 6 h after application.

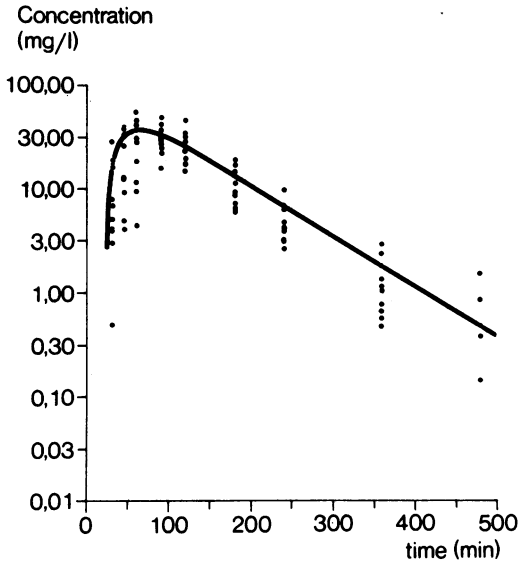

FIG. 2. *Regression curve and individual concentrations of cephalexin in sera of fasting volunteers after oral administration of 1,000 mg of cephalexin.*

CGP 9000. CGP 9000 basically resembles the aforementioned substances in its serum kinetics. However, after nearly the same absorption period (x_{max} = 69.3 ± 18.1 min), this antibiotic had an average maximal serum concentration of 23.3 ± 7.3 mg/liter, which was clearly lower than that of the other two drugs mentioned. After 6 h, an average of only 1.1 mg/liter could be determined.

Cefadroxil. Cefadroxil had a serum concentration course which differed from those of the other three cephalosporins. Both the absorption and the elimination velocities of this substance were lower; the mean maximal serum concentrations of 33.0 ± 5.4 mg/liter could be reached later, i.e., after 102.4 ± 27.3 min on the average; and high serum levels could be maintained over a longer period of time (6 h, 5.4 ± 2.2 mg/liter; 8 h, 2.1 ± 0.8 mg/liter).

This different kinetic behavior of cefadroxil is clearly indicated in Fig. 3, which shows mean value curves of the individual substances. The compilation of the pharmacokinetic parameters (Table 1) also substantiates these divergent serum kinetics. The AUC values show significant

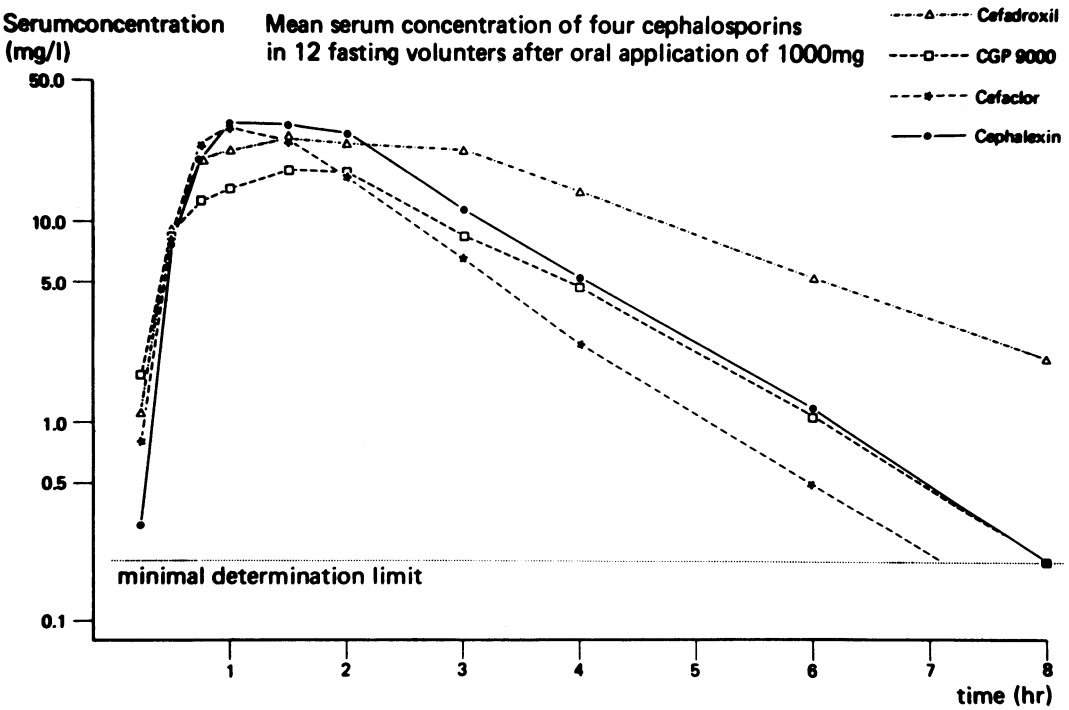

FIG. 3. *Mean serum concentrations of drug for 12 fasting volunteers after 1,000-mg oral doses of cefadroxil, CGP 9000, cefaclor, and cephalexin.*

differences ($2\alpha \leqq 0.05$) between cefadroxil and cephalexin on the one hand, and between cefadroxil and cephalexin and cefaclor and CGP 9000 on the other hand. The mean individual peak levels (milligrams per liter) of cephalexin (40.4 ± 8.4), cefaclor (35.7 ± 8.5), CGP 9000 (23.2 ± 7.5), and cefadroxil (32.1 ± 5.6) showed the significant superiority of cephalexin over CGP 9000 and cefadroxil, as well as of cefaclor over CGP 9000.

The low mean recovery rate within 24 h for cefaclor (52.7 ± 6.9%) could be explained by the hydrolysis of this substance in the urine or elsewhere (7). Within 24 h, a cefaclor inactivation of 50% could be measured in urine at 22°C, whereas the other three substances had an inactivation of 11% at a maximum.

In six test subjects each, the serum kinetics and urine elimination were determined for 1,000 mg of cephalexin or cefadroxil administered during a test breakfast. It is obvious (Fig. 4) that, although cephalexin absorption is slower (x_{max} = 112 ± 23.4 min) and also has a clearly lower y_{max} of 23.1 ± 6.6 mg/liter, the extent of absorption is, in the final analysis, of the same order of magnitude as after fasting administration (AUC, 70.0 ± 9.1 h · mg/liter; urine recovery, 83.2 ± 23.4%). After intake with food, cephadroxil shows no change in its absorption characteristic (Fig. 4). With 32. 1 ± 5.6 mg/liter (fasting) and 32.7 ± 3.9 mg/liter (nonfasting), the average individual serum peak concentrations are almost identical.

DISCUSSION

Criteria for assessing the bioavailability of orally administered substances are, in addition to the point of time and the level of maximal

TABLE 1. *Pharmacokinetic parameters in fasting volunteers given 1,000-mg doses of cephalexin, cefaclor, CGP 9000, and cefadroxil*[a]

Antibiotic	K_1 (h^{-1})	y_{max} (mg/liter)	x_{max} (min)	K_2 (h^{-1})	$t_{1/2K}$ (min)	AUC (h·mg/liter)	24-h urine recovery (% of doses)
Cephalexin	2.79 ± 1.31	38.8 ± 8.1	55.5 ± 21.8	0.67 ± 0.09	62.5 ± 5.4	93.0 ± 14.8	91.2 ± 18.5
Cefaclor	1.44 ± 0.87	34.6 ± 7.8	65.2 ± 11.1	0.98 ± 0.20	42.5 ± 8.3	74.5 ± 9.9	52.7 ± 6.9
Cefadroxil	1.37 ± 0.64	33.0 ± 5.4	102.4 ± 27.3	0.43 ± 0.05	97.6 ± 8.7	108.5 ± 18.4	89.6 ± 13.3
CGP 9000	1.55 ± 0.74	23.0 ± 7.3	69.3 ± 18.1	0.75 ± 0.12	55.5 ± 7.6	70.1 ± 9.0	79.8 ± 15.2

[a] Values represent mean ± standard deviation of results from 12 volunteers tested. Other definitions as described in the text.

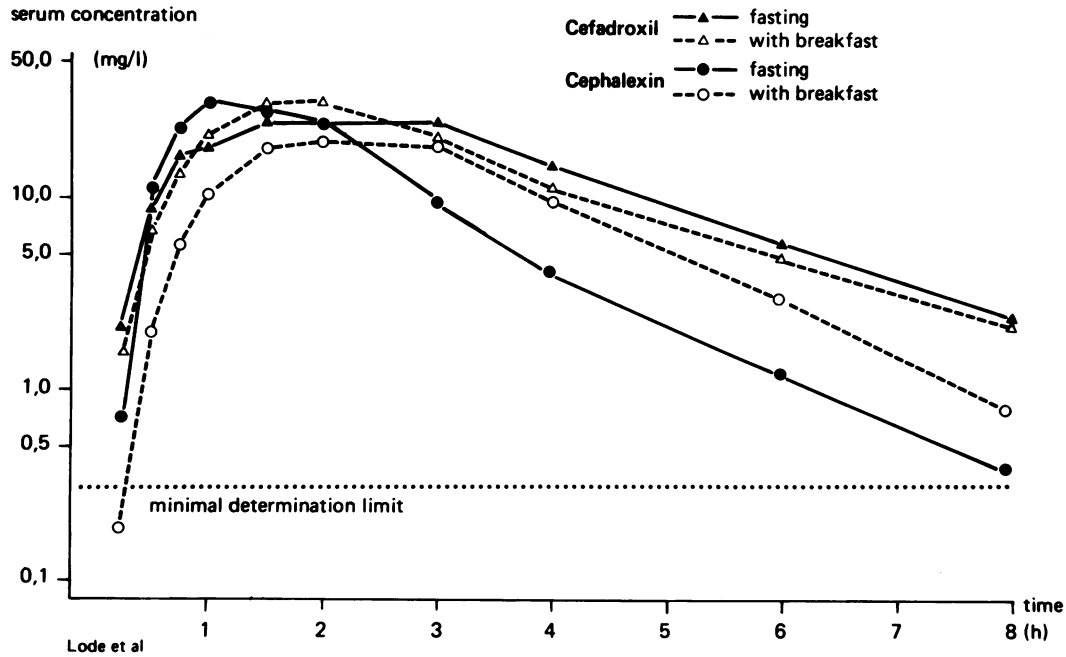

FIG. 4. *Mean serum concentrations of cephalexin and cefadroxil after oral administration of 1,000-mg doses in six volunteers (fasting and during breakfast).*

serum concentrations, the recovery rate in urine with largely renally eliminated substances and, above all, the area below the serum concentration curves (AUC, 28). With these parameters as criteria, cefadroxil evidenced the most favorable pharmacokinetic parameters in our investigations. Cephalexin effected the highest maximal serum concentrations, whereas cefaclor and CGP 9000 did not show any pharmacokinetic advantage over cephalexin.

Our results are in good agreement with the investigations of other authors (5, 6, 8, 9, 12). The cephalexin serum concentrations yielded by fasting and nonfasting application lie at the same order of magnitude specified by Griffith and Black (8) as well as by Speigt et al. (25). Administration with simultaneous food intake leads to a slower absorption, with a delayed and reduced maximal serum level; the area under the curve and the urine recovery are about 10 to 20% lower for nonfasting intake than for fasting intake.

Our pharmacokinetic cefaclor results largely agree with the data of Bloch et al. (5), Hodges et al. (11), Meyers et al. (20), Santoro et al. (24), as well as Spyker et al. (26). However, Korzeniowski et al. (14) found lower values with fasting subjects after a 250-mg dose, with a maximal concentration of 6.01 ± 0.55 mg/liter and a biological half-life of 0.58 ± 0.07 h. McCracken et al. (19) measured reduced cefaclor peak levels in children after nonfasting intake in comparison to fasting intake.

So far, Wirz et al. (30) and Holt et al. (12) have provided data on the pharmacokinetics of CGP that are largely in agreement with our own results. The bioavailability data of CGP 9000 are clearly below those of cephalexin for the 1,000-mg dosage.

Both Cutler et al. (6) and Pfeffer et al. (22) found the same kinetic results for cefadroxil, whereas Hartstein et al. (10) were the only authors to find concentrations of cefadroxil that were higher than those of cephalexin. Ginsburg et al. (9) did not observe any influence of food intake on cefadroxil absorption in children either.

From a purely theoretical point of view, cefadroxil evidences the most favorable pharmacokinetic data of the examined cephalosporins, particularly if the AUC is referred to in this connection. For antibiotic therapy, however, the peak serum level is clearly of greater significance, since this influences to a higher degree the interstitial concentrations at the infected area (1, 17, 29). Of course, Bergan (3) called attention to the fact that both high peak concentrations and a large AUC are necessary for effective antibiotic therapy. Even though at present this question has not yet been definitively clarified, the practical conclusion is clear: cephalexin and cefaclor should, if possible, be administered or taken on an empty stomach. These application restrictions do not apply to cefadroxil.

Surely the question as to whether or not the new oral cephalosporins represent a therapeutic improvement cannot be answered only on the basis of pharmacokinetic and microbiological data. Comparative clinical studies are necessary for conclusive assessment.

LITERATURE CITED

1. **Barza, M., and L. Weinstein.** 1974. Penetration of antibiotics into fibrin foci in vivo. I. Comparison of penetration of ampicillin into fibrin clots, abscesses, and interstitial fluid. J. Infect. Dis. **129**:59–65.
2. **Bennett, J. V., J. L. Brodie, E. J. Benner, and W. M. M. Kirby.** 1966. Simplified accurate method for antibiotic assay of clinical specimens. Appl. Microbiol. **14**: 170–178.
3. **Bergan, T.** 1978. Kinetics of tissue penetration. Scand. J. Infect. Dis. **14**(Suppl):36–46.
4. **Bill, N. J., and J. A. Washington.** 1977. Comparison of in vitro activity of cephalexin, cephradine, and cefaclor. Antimicrob. Agents Chemother. **11**:470–474.
5. **Bloch, R., J. J. Szwed, R. S. Sloan, and F. C. Luft.** 1977. Pharmacokinetics of cefaclor in normal subjects and patients with chronic renal failure. Antimicrob. Agents Chemother. **12**:730–731.
6. **Cutler, R. E., A. D. Blair, and M. R. Kelly.** 1978. Pharmacokinetics of oral cefadroxil in patients with renal insufficiency, p. 755–756. *In* W. Siegenthaler and R. Lüthy (ed.), Current chemotherapy. Proceedings of the 10th International Congress of Chemotherapy, vol II. American Society for Microbiology, Washington, D.C.
7. **Foglesong, M. A., J. W. Lamb, and J. V. Dietz.** 1978. Stability and blood level determinations of cefaclor, a new oral cephalosporin antibiotic. Antimicrob. Agents Chemother. **13**:49–52.
8. **Griffith, R. S., and H. R. Black.** 1970. Cephalexin. Med. Clin. North Am. **54**:1229–1244.
9. **Ginsburg, C. M., G. H. McCracken, J. C. Clahsen, and M. L. Thomas.** 1978. Clinical pharmacology of cefadroxil in infants and children. Antimicrob. Agents Chemother. **13**:845–848.
10. **Hartstein, A. I., K. E. Patrick, S. R. Jones, M. J. Miller, and R. E. Bryant.** 1977. Comparison of pharmacological and antimicrobial properties of cefadroxil and cephalexin. Antimicrob. Agents Chemother. **12**:93–97.
11. **Hodges, G. R., C. Liu, D. R. Hinthorn, J. L. Harms, and D. L. Worzak.** 1978. Pharmacological evaluation of cefaclor in volunteers. Antimicrob. Agents Chemother. **14**:454–456.
12. **Holt, H. A., J. M. Broughall, J. Füllhaas, A. J. Bint, and D. S. Reeves.** 1978. Multidose human pharmacology of CGP 9000 in volunteers, p. 829–830. *In* W. Siegenthaler and R. Lüthy (ed.), Current chemotherapy. Proceedings of the 10th International Congress of Chemotherapy, vol. II. American Society for Microbiology, Washington, D.C.
13. **Koeppe, P.** 1970. Effective serum concentration and action in pharmacokinetics. Pharmacol. Clin. **2**:201–203.
14. **Korzeniowski, O. M., W. M. Scheld, and M. A. Sande.** 1977. Comparative pharmacology of cefaclor and cephalexin. Antimicrob. Agents Chemother. **12**:157–162.
15. **Lode, H., B. Kemmerich, and P. Koeppe.** 1975. Comparative clinical pharmacology of gentamicin, sisomicin,

and tobramycin. Antimicrob. Agents Chemother. 8: 396–401.

16. **Lode, H., P. Janisch, G. Küpper, and H. Weuta.** 1974. Comparative clinical pharmacology of three ampicillins and amoxicillin administered orally. J. Infect. Dis. **129**(Suppl.):156–168.
17. **Mattie, H.** 1978. Pharmacokinetic aspects of tissue penetration. Scand. J. Infect. Dis. **14**(Suppl.):125–126.
18. **McCracken, D. D., and W. S. Dorn. (ed.).** 1966. Simultaneous linear algebraic equations, p. 226–283. Numerical methods and Fortran programming. John Wiley & Sons, Inc., New York.
19. **McCracken, G. H., C. M. Ginsburg, J. C. Clahsen, and M. L. Thomas.** 1978. Pharmacokinetics of cefaclor in infants and children. J. Antimicrob. Chemother. **4**:515–521.
20. **Meyers, B. R., S. Z. Hirschmann, G. Wormser, G. Gartenberg, and E. Srulevitch.** 1978. Pharmacological studies with cefaclor, a new oral cephalosporin. J. Clin. Pharmacol **18**:174–179.
21. **Neu, H. C., and K. P. Fu.** 1978. Cefaclor: in vitro spectrum of activity and beta-lactamase stability. Antimicrob. Agents Chemother. **13**:584–588.
22. **Pfeffer, M., A. Jackson, and J. Perche de Menezes.** 1977. Comparative human oral clinical pharmacology of cefadroxil, cephalexin, and cephradine. Antimicrob. Agents Chemother. **11**:331–338.
23. **Reeves, D. S., and M. J. Bywater.** 1976. Assay of antimicrobial agents, p. 21–78. *In* J. de Louvois (ed.), Selected topics in clinical bacteriology. Baillière Tindall, London.
24. **Santoro, J., B. N. Agarwal, R. Martinelli, N. Wenger, and M. E. Levison.** 1978. Pharmacology of cefaclor in normal volunteers and patients with renal failure. Antimicrob. Agents. Chemother. **13**:951–954.
25. **Speigt, T. M., R. N. Brogden, and G. S. Avery.** 1970. Cephalexin: a review of its antibacterial, pharmacological and therapeutic properties. Drugs **3**:9–78.
26. **Spyker, D. A., B. L. Thomas, M. A. Sande, and W. K. Bolton.** 1978. Pharmacokinetics of cefaclor and cephalexin: dosage normograms for impaired renal functions. Antimicrob. Agents Chemother. **14**:172–177.
27. **Vischer, W. A., O. Zak, E. A. Konopka, H. Fehlmann, J. Regös, and W. Tosch.** 1978. Experimental evaluation of CGP 9000, a new orally active cephalosporin, p. 825–827. *In* W. Siegenthaler and R. Lüthy (ed.), Current chemotherapy. Proceedings of the 10th International Congress of Chemotherapy, vol. II. American Society for Microbiology, Washington, D.C.
28. **Wagner, J. G.** 1972. An overview of the analysis and interpretation of bioavailability studies in man. Pharmacology **8**:102–117.
29. **Weinstein, L., G. K. Daikos, and T. S. Perrin.** 1951. Studies on the relationship of tissue fluid and blood levels of penicillin. J. Lab. Clin. Med. **38**:712–718.
30. **Wirz, H., W. A. Vischer, J. Füllhaas, and P. R. Imhof.** 1978. Pharmacokinetics of CGP 9000, a new orally active cephalosporin, in healthy volunteers, p. 827–829. *In* W. Siegenthaler and R. Lüthy (ed.), Current chemotherapy. Proceedings of the 10th International Congress of Chemotherapy, vol. II. American Society for Microbiology, Washington, D.C.