ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1982, p. 248–253
0066-4804/82/020248-06$02.00/0

Vol. 21, No. 2

Single-Dose Pharmacokinetics of Ceftriaxone in Infants and Young Children

URS B. SCHAAD[1] AND KLAUS STOECKEL[2]*

Department of Pediatrics, University of Berne, CH-3010 Berne,[1] and Pharmaceutical Research Department, F. Hoffmann-La Roche & Co. Ltd., CH-4002 Basel,[2] Switzerland

Received 21 July 1981/Accepted 29 October 1981

The pharmacokinetics of ceftriaxone were studied in five infants (7 to 15 months old) and five young children (24 to 70 months old). Both groups received a single 50-mg/kg dose in an intravenous infusion over 5 min. No major pharmacokinetic differences were observed between the two populations. The total (bound plus unbound) plasma concentration-versus-time data could be described in each case by a biexponential equation. Changes in renal clearance indicated time- and dose-dependent pharmacokinetic behavior. The fraction excreted unchanged in the urine (f_u) and the biological half-life ($t_{1/2(\beta)}$) were, however, dose independent. The average values were 47% for f_u (0 to 12 h) and 6.5 h for $t_{1/2(\beta)}$. Weight-corrected total systemic clearance was Cl_S^T = 0.71 ml/min per kg; volume of distribution was $V_{D(\beta)}$ = 394 ml/kg. The data support intravenous administration of 50 mg of ceftriaxone per kg of body weight every 12 h in assessing its activity against *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* in postneonatal-stage pediatric patients.

Standard antimicrobial regimens for childhood bacterial meningitis consist of ampicillin, chloramphenicol, or penicillin G. The therapeutic dilemma of physicians who manage pediatric patients with bacterial meningitis includes: an increasing percentage of ampicillin-resistant *Haemophilus influenzae* type b strains (13, 24); potential toxicity and wide variability in the pharmacokinetics of chloramphenicol (11, 18); recent reports of clinical isolates of *H. influenzae* type b that are resistant to chloramphenicol (9, 27); experimental evidence of the antagonistic action of ampicillin plus chloramphenicol against some strains of pneumococci or meningococci (5); and the emergence of pneumococcal strains that are "insensitive" (minimal inhibitory concentration, 0.1 to 1.0 μg/ml) or resistant (minimal inhibitory concentration, 1.0 μg/ml) to penicillin G (1, 2).

Ceftriaxone with its excellent in vitro activity against the three major etiological agents of childhood bacterial meningitis, *H. influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* (4, 14, 22, 28), has the potential to be an alternative therapy of this disease. A considerable penetration of ceftriaxone into cerebrospinal fluid (CSF) of infected rabbits and dogs (10, 19) and preliminary clinical experience in children and young adults with bacterial meningitis (3; P. Narciso, R. Giannuzzi, G. Tocci, P. DeMori, and G. Visco, 12th Int. Cong. Chemother., Florence, Italy, 1981, abstr. no. 993, p. 222) support the potential usefulness of this compound in meningitis therapy.

Recent pharmacokinetic studies have shown that the elimination of ceftriaxone is about two-thirds renal and one-third nonrenal. The nonrenal clearance appears to be predominantly biliary (23). The plasma concentration-time data of ceftriaxone can be described in healthy adult volunteers by a bi-exponential equation (21, 23). However, a pharmacokinetic analysis of the data by a compartmental model was of limited value since areas under the total (bound plus unbound) drug concentration-time curves ($AUC_{0-\infty}$) did not increase in proportion to increased doses (23). As a consequence, pharmacokinetic parameters such as total body clearance (Cl_S^T) and volume of distribution [$V_{D(\beta)}$] were not constant but increased with increasing doses. The deviation from linear pharmacokinetics was, however, relatively small for intravenous doses up to 1,500 mg (e.g., Cl_S^T increased by 28% between a 500-mg and a 1,500-mg dose). The observed non-linearity could be explained by the concentration-dependent plasma protein binding of the drug. The pharmacokinetics of free (unbound) ceftriaxone were linear and dose independent. The two important pharmacokinetic parameters, half-life [$t_{1/2(\beta)}$ = 8 h] and fraction excreted unchanged in the urine (f_u = 0.65), were found to be independent of dose.

The purpose of this study was to compare the

pharmacokinetics of ceftriaxone in infants and young children with those previously obtained in adults (23). Such pharmacokinetic information should facilitate identification of a suitable dosage regimen of this investigational antibiotic for therapy in invasive bacterial diseases such as meningitis in pediatric patients.

MATERIALS AND METHODS

Study patients. Pharmacokinetic studies following the administration of a single intravenous dose of ceftriaxone were performed in 10 pediatric patients treated at the Department of Pediatrics, University of Berne, for viral infections (six patients) or epilepsy (four patients). They were divided into two categories according to age: (i) five infants between 7 and 15 months (mean, 12 months) of age, and (ii) five children between 24 and 70 months (mean, 41 months) of age. The study participants included nine males and one female. Patient characteristics and coadministered drugs are listed in Table 1.

At the time of the trial the study patients had received no antimicrobial therapy for at least 48 h and their hydration status was clinically judged as being normal. They had no medical history of previous allergy to beta-lactam compounds, nor of renal or hepatic diseases. Laboratory studies before the trial (urine analysis; blood urea nitrogen or serum creatinine or both; liver enzymes) revealed normal renal and hepatic functions in all subjects. Informed parental consent was obtained for all patients in accordance with the guidelines of the local Institutional Committee on Human Investigation.

Drug administration. Drug vials contained an equivalent of 1,000 mg of ceftriaxone (free acid) as the lyophilized disodium salt. The contents of the vials were dissolved in sterile water to a concentration of 50 mg/ml (free acid). Ceftriaxone (50 mg/kg) was infused over 5 min via an indwelling catheter into a peripheral vein. Adverse reactions (local or systemic) to ceftriaxone were assessed by clinical observation.

Collection of specimens. Blood samples for drug assay were collected from an intravenous catheter or heparin lock before the administration of ceftriaxone (predose sample) and at 0.25, 0.5, 1.5, 4, 8, 16, 24, 32, and 34 h after the termination of the infusion. The blood was immediately mixed with sodium citrate and centrifuged within 1 h at 1,000 × *g* for 10 min. Plasma samples, stored at −20°C, were assayed within 2 weeks of collection.

The total urine was collected from 8 of the 10 study patients at the following time intervals: −2 to 0, 0 to 3, 3 to 6, 6 to 9, and 9 to 12 h after the dose. Urine was sampled from either sterile receptacles (five patients) or urinary catheters (three patients). Volumes and pH values of voided urine were measured, and the samples were stored at −20°C until assayed within 2 weeks of collection.

Plasma protein binding. Plasma for the protein binding analysis was obtained by pooling all remaining plasma samples from each patient after completion of the high-pressure liquid chromatographic assay. To achieve similar total plasma concentrations among the plasma pools, small volumes (<10%, vol/vol) of an isotonic phosphate buffer solution of ceftriaxone (5

TABLE 1. Subject characteristics and total plasma concentrations of ceftriaxone after a 50-mg/kg intravenous dose

Patients		Dose (mg)	Age (mos)	Wt (kg)	Ht (cm)	Body surface area (m^2)	Comedication	Ceftriaxone concn (μg/ml of plasma) obtained at time (h) after dose:							
Category	No.							0.25	0.5	1.5	4	8	16	24	32	34
Infants	1	405	7	8.1	67	0.39	None	236	196	135	83.9	58.9	22.7	13.0[a]	5.3	4.5
	2	425	11	8.5	76	0.43	None	202	184	125	99.2	54.8	27.8	14.8	8.4	6.2
	3	505	13	10.1	72	0.46	None	236	189	149	78.6	35.5	NA[b]	2.4	0.85	NA
	4	460	13	9.2	77	0.45	None	179	139	114	66.6	31.3	NA	5.0	1.8	NA
	5	515	15	10.3	83	0.48	None	244	197	139	84.0	50.0	24.8	12.6	6.3	NA
Young children	6	560	24	11.2	88	0.52	Noramidopyridine	241	209	173	108	70.2	30.5	16.1	7.3	NA
	7	550	27	11.0	86	0.52	Clonazepam, ACTH[c]	NA	180	128	74.4	32.5	NA	5.1	2.4	1.8
	8	465	29	9.3	74	0.44	Diphenylhydantoin	226	190	134	81.7	35.8	13.0	6.3	2.9	2.1
	9	940	54	18.8	107	0.75	None	NA	188	128	76.1	38.3	15.0	5.6	2.9	2.2
	10	980	70	19.6	126	0.80	None	250	186	138	90.2	51.8	22.0	10.5	4.6	3.4

[a] 26-h value.
[b] NA, Not available.
[c] ACTH, Adrenocorticotropin.

mg/ml) were added to each pool. The ceftriaxone concentrations of the individual pools ranged between 135 and 250 μg/ml. A plasma pool from six healthy adults with a total ceftriaxone concentration of 180 μg/ml was used as a reference standard.

Plasma protein binding was determined by equilibrium dialysis using Teflon dialysis cells (Dianorm) and Spectrapor-2 dialysis tubing (presoaked in buffer) with a molecular weight cut-off of 12,000 to 14,000. One milliliter of plasma was dialyzed against an equal volume of isotonic phosphate buffer (pH 7.4). The cells were rotated at 37°C for 4 h. Aliquots from both sides of the membrane were removed and assayed for the free acid of ceftriaxone.

Ceftriaxone assay. Plasma, urine, and buffer samples were analyzed for free acid of ceftriaxone by a specific high-pressure liquid chromatographic assay (26). Basically the method utilized ion-pair reversed-phase chromatography with a Lichrosorb RP-18 column and three mobile phases differing in counter ion, acetonitrile, and phosphate buffer concentration. With a variable-wavelength detector at 287 nm, the detection limit for ceftriaxone was 3 μg/ml in urine, 0.4 μg/ml in plasma, and 0.1 μg/ml in isotonic sodium phosphate buffer. The accuracy of the single measurements was within ±3% of the actual values. The mean ± standard deviation recovery of ceftriaxone was 93.4 ± 2.5% from plasma and 100% from urine and phosphate buffer.

Estimation of pharmacokinetic parameters. Plasma concentration-time data after single intravenous doses were fitted individually to equation 1 using the nonlinear least-squares program NONLIN (12). In all cases a weighting factor of 1/observed concentrations was applied.

$$C = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \quad (1)$$

A and B are the coefficients of the biexponential equation, and α and β are the disposition constants. In the pharmacokinetic analysis the short infusion of ceftriaxone (approximately 5 min) was considered analogous to a bolus injection.

The total area under the drug concentration time curve ($AUC^{T}_{0-\infty}$) was calculated from the coefficients A and B and the exponents α and β of equation 1 as follows:

$$AUC^{T}_{0-\infty} = \frac{A}{\alpha} + \frac{B}{\beta} \quad (2)$$

The total systemic clearance (Cl^{T}_{S}) and apparent volume of distribution [$V_{D(\beta)}$] corrected by weight were calculated from the relationships:

$$Cl^{T}_{S} = \frac{D_{iv}}{AUC^{T}_{0-\infty} \cdot BW} \quad (3)$$

and

$$V_{D(\beta)} = \frac{D_{iv}}{\beta \cdot AUC^{T}_{0-\infty} \cdot BW} \quad (4)$$

where D_{iv} is the dose administered intravenously and BW is the total body weight of the subjects.

The renal clearance during the 3-h collecting intervals was calculated from the following equation:

$$Cl^{T}_{R} = \frac{\Delta X_u / \Delta t}{Cp_{mid}} \quad (5)$$

where $\Delta X_u/\Delta t$ approximates the urinary excretion rates and Cp_{mid} represents the total (bound plus unbound) plasma concentrations determined at the midpoint of each urine collection period.

A mean renal clearance during the time interval 0 to 12 h after administration was calculated from equation 6:

$$Cl^{T}_{R} = \frac{X_{u\ 0-12}}{AUC^{T}_{0-12}} \quad (6)$$

where X_u represents the amount of ceftriaxone excreted during the 12-h collection interval and AUC^{T}_{0-12} is the area under the total drug concentration time curve for the same time interval.

The area was determined by the trapezoidal rule.

RESULTS

Plasma concentrations. The total (bound plus unbound) plasma concentration-versus-time data achieved in infants and children after a 50-mg/kg dose could be described by a biexponential equation. The correlation between the calculated and observed plasma data was in all cases equal to or greater than 0.993. No distinct differences were observed in the profile of the total plasma concentration time data between infants and young children.

Table 1 shows the measured total plasma concentrations of ceftriaxone in the individual patients. The mean total plasma concentrations achieved 15 min after dosing were 219 μg/ml in infants and 239 μg/ml in children. After 32 h the mean plasma levels had fallen to 4.5 and 4.0 μg/ml, respectively. All of the predose samples were free of any ceftriaxone concentration.

The mean pharmacokinetic parameters calculated for total drug in infants and young children are listed in Table 2. There was no significant difference ($P > 0.5$) between infants and young children. The mean terminal half-life was 6.5 h. Total systemic clearance, corrected for body weight and based on total ceftriaxone concentrations (Cl^{T}_{S}), averaged 0.71 ml/min per kg. The mean volume of distribution [$V_{D(\beta)}$], corrected for body weight and with reference to total drug, was 394 ml/kg.

Protein binding. The extent of binding of ceftriaxone to plasma proteins in infants and young children at similar total plasma concentrations is presented in Table 3. The mean free fraction (ratio of unbound to total drug concentrations) of ceftriaxone was 0.158 ± 0.03% in infants (concentration range, 147 to 161 μg/ml) and 0.164 ± 0.03 in young children (118 to 202 μg/

TABLE 2. Comparison of mean pharmacokinetic parameters[a] in infants and young children

Category	$t_{1/2(\beta)}$ (h)	$V_{D(\beta)}$ (ml/kg)	Cl_S^T (ml/min per kg)	Cl_R^T (avg. 0 to 12 h) (ml/min per kg)	$AUC_{0-\infty}^T$ (μg.h/ml)
Infants (n = 5)	6.5 ± 1.5 (4.1–7.7)	386 ± 67 (302–488)	0.71 ± 0.18 (0.56–0.95)	0.38 ± 0.1 (0.26–0.52)	1,223.9 ± 276 (875.8–1487.3)
Young children (n = 5)	6.6 ± 0.6 (6.0–7.4)	401 ± 79 (312–509)	0.71 ± 0.15 (0.48–0.86)	0.45 ± 0.1 (0.35–0.58)	1,225.1 ± 309 (965.1–1720.9)

[a] Mean ± standard deviation (range in parentheses).

ml). As seen from Table 3, the mean total protein content of plasma was 45 mg/ml in infants and 50 mg/ml in young children. The albumin concentrations were 29 and 33 mg/ml, respectively.

Urine concentrations and renal excretion. Urine samples over a time period of 12 h were collected from 8 (4 infants, 4 young children) out of 10 patients. Table 4 shows the mean urinary concentrations of ceftriaxone in both infants and young children after a single intravenous dose of 50 mg/kg. The mean total urinary excretion, expressed as a percentage of dose recovered intact in the urine during the 0- to 12-h period, was 43.4 ± 6.7% in infants and 51.5 ± 4.7% in young children. The value in infants might be somewhat low because of inherent difficulties in total urine collection in this age group.

Renal clearance. Table 4 shows a pronounced influence of concentration on Cl_R^T in both infants and young children after the 50-mg/kg dose. The weight-corrected Cl_R^T values declined in infants from 0.67 ml/min per kg at the 0- to 3-h interval to 0.22 ml/min per kg at the 9- to 12-h interval. The corresponding values in young children were 0.75 and 0.25 ml/min per kg. A mean renal clearance for total drug (Cl_R^T) was also calculated for the 0- to 12-h period and averaged 0.38 ml/min per kg in infants and 0.45 ml/min per kg in young children.

Safety. Ceftriaxone administered intravenously as a 5-min infusion was well tolerated; neither local nor systemic reactions were observed.

DISCUSSION

In this study, we report the pharmacokinetics of total (bound plus unbound) ceftriaxone in infants and young children. For ethical reasons it was not possible to draw large enough blood samples from these patient populations to establish their entire plasma protein binding characteristics. Therefore, we were unable to establish the relevant pharmacokinetics of ceftriaxone with respect to free (unbound) drug concentrations in pediatric patients. However, major changes in the disposition of ceftriaxone as compared to adults should be detectable from total plasma concentration-time data, in particular, changes in $t_{1/2(\beta)}$ and f_u which were found to be dose independent. To compare dose-dependent pharmacokinetic parameters such as Cl_S^T and $V_{D(\beta)}$ between children and adults, plasma concentration-time profiles of healthy subjects

TABLE 3. Protein binding of ceftriaxone in plasma of infants and children

Patients		Total ceftriaxone concn (μg/ml)	Unbound ceftriaxone (% ± SD)	No. of determinations	Albumin concn (mg/ml)	Total protein (mg/ml)
Category	No.					
Infants	1	161	15.9 ± 0.1	2	29.2	44.1
	2	146.7	13.4 ± 1.2	3	ND[a]	ND
	4	154	20.1	1	26.0	42.7
	5	147	13.6	1	32.9	48.0
Young children	6	165	14.5 ± 0.9	2	ND	ND
	7	118.3	14.9 ± 0.7	3	31.9	46.2
	8	177.2	21.6 ± 0.6	5	ND	ND
	9	202	17.2 ± 1.3	2	34.6	52.7
	10	146	13.8 ± 1.0	3	33.8	51.0

[a] ND, Not determined.

TABLE 4. Urinary concentrations, percent recovery, and weight-corrected renal clearance with reference to total ceftriaxone (Cl_R^T) during selected intervals in four infants and four children

Patient category	Time (h)	Ceftriaxone concn (μg/ml)	Recovery (%)	Cl_R^T (ml/min per kg)
Infants	0–3	3,117 ± 970	27.1 ± 7.1[a]	0.67 ± 0.12[a]
	3–6	1,336 ± 665	9.7 ± 7.2[a]	0.29 ± 0.16[a]
	6–9	592 ± 410	4.3 ± 1.6	0.23 ± 0.04
	9–12	547 ± 398	2.3[b]	0.22[b]
			43.4 ± 6.7	
Young children	0–3	2,150 ± 1,826	35.6 ± 3.7	0.75 ± 0.09
	3–6	740 ± 369	8.6 ± 2.0	0.34 ± 0.11
	6–9	476 ± 327	4.6 ± 1.8	0.30 ± 0.13
	9–12	230 ± 115	2.7 ± 1.0	0.25 ± 0.09
			51.5 ± 4.7	

[a] One patient showed an apparent mixup in the first two collecting intervals.

[b] Represents the mean of two values only since there was apparently no complete urine collection during this interval in the two other patients.

were chosen which were similar to those in pediatric patients. Plasma profiles observed in healthy volunteers after a 1,500-mg dose (23) were best suited for comparison purposes.

The plasma concentration-time data for total drug in infants and children could be described by a biexponential equation. However, as in the previous studies (21, 23) the pharmacokinetic analysis by a simple two-compartment model was not feasible since clearance changes (particularly changes in Cl_R^T; see Table 4) occurred in these infants and children after the 50-mg/kg intravenous dose. The apparently time-dependent renal clearance was previously attributed to saturable protein binding of the drug to serum albumin. The threefold difference in Cl_R^T between the 0- to 3- and the 9- to 12-h periods indicates that the same saturable binding characteristics can be found in the pediatric patients after the 50-mg/kg dose. A direct verification of this saturable binding characteristic was not possible in the pediatric patients, since the amount of plasma available was limited. However, by pooling plasma samples, a measurement was possible for each patient at a therapeutically relevant plasma concentration (120 to 200 μg/ml; Table 3). At these concentrations the plasma protein binding of ceftriaxone was generally lower in infants and young children (Table 3) than in healthy adults. This decrease in binding corresponded well with a decrease in plasma concentrations of albumin (Table 3), the major binding protein of ceftriaxone (23). Consequently, at comparable total plasma concentrations the therapeutically important free concentrations should be higher in infants and children than in adults.

Compared to cefotaxime and moxalactam (7, 8), ceftriaxone showed in the pediatric patients a comparable volume of distribution (0.4 liter/kg) but a much lower average clearance (0.7 ml/min per kg), which resulted in its considerably longer biological half-life (6.5 h). In comparison, the reported half-life for moxalactam is 1.6 to 1.8 h (8, 20), that for ceftriaxone is 0.7 to 1.0 h (7, 15), and that for cefoperazone is 1.4 h (25). The long half-life of ceftriaxone is of particular clinical relevance since it thus requires less frequent administration in pediatric patients as compared to other cephalosporins. In comparison to healthy adults, both the weight-corrected total systemic clearance (Cl_S^T) and volume of distribution [$V_{D(\beta)}$] increased several-fold (Table 2). The increase was slightly greater for Cl_S^T than for $V_{D(\beta)}$, resulting in the small reduction of $t_{1/2(\beta)}$. The comparative increase in the volume of distribution in the pediatric patients might be the result of the lower plasma protein binding (17) and the relatively larger extracellular space in this age group (6).

The greater total systemic clearance we observed in these patients cannot be fully accounted for by the lower protein binding; a more effective total systemic clearance in relation to the body weight must, in addition, be invoked. Moreover, it is of interest that both components of Cl_S^T, renal (Cl_R^T) and nonrenal (Cl_T^{NR}) clearance, must be larger in the pediatric patients, since the fraction of ceftriaxone excreted unchanged in the urine for the 0- to 12-h period (infants, 43%; young children, 52%) is comparable to what was found before for the same time period in healthy adults (46% for a 500-mg dose; 52% for a 1,500-mg dose) (23).

On the basis of our pharmacokinetic data in infants and young children, a dosage schedule of 50 mg of ceftriaxone per kg given intravenously every 12 h would lead to little accumulation of

drug in plasma during the steady state (16) and would give plasma peak concentrations of 200 to 300 μg/ml and plasma trough concentrations of 30 to 40 μg/ml. Ceftriaxone penetration into CSF through inflamed meninges of children was reported to result in CSF levels which are from 5 to 15% of the concurrent plasma levels (3). It is concluded that after 50-mg/kg doses of ceftriaxone twice daily, the drug concentrations in both plasma and CSF will be constantly orders of magnitude higher than the susceptibilities of the three principal pathogens (*H. influenzae*, *S. pneumoniae*, and *N. meningitidis*) that cause bacterial meningitis in childhood, since minimal inhibitory concentrations for 90% of these bacteria are ≤0.1 μg/ml (4, 14, 22, 28). It must, however, be emphasized that this dosage recommendation is only preliminary for this investigative antibiotic. Once sufficient clinical experience in treating childhood meningitis has been accumulated, the long half-life of ceftriaxone may enable once-daily administration for the disease.

ACKNOWLEDGMENTS

We thank K. H. Trautmann and V. Trüb for their excellent technical assistance and analytical work.

LITERATURE CITED

1. **Ahronheim, G. A., B. Reich, and M. I. Marcks.** 1979. Penicillin-intensive pneumococci. Case report and review. Am. J. Dis. Child. **133**:187–191.
2. **Anderson, K. C., M. J. Maurer, and A. S. Dajani.** 1980. Pneumococci relatively resistant to penicillin: a prevalence survey in children. J. Pediatr. **97**:939–941.
3. **Cadoz, M., F. Denis, H. Félix, and I. Diop Mar.** 1981. Treatment of purulent meningitis with a new cephalosporin—rocephin (13-9904). Clinical, bacteriological and pharmacological observations in 24 cases. Chemotherapy **27**(Suppl. 1):57–61.
4. **Eickhoff, T. C., and J. Ehret.** 1981. Comparative in vitro studies of Ro 13-9904, a new cephalosporin derivative. Antimicrob. Agents Chemother. **19**:435–442.
5. **Feldman, W. E., and T. Zweighaft.** 1979. Effect of ampicillin and chloramphenicol against *Streptococcus pneumoniae* and *Neisseria meningitidis*. Antimicrob. Agents Chemother. **15**:240–242.
6. **Friis-Hansen, B.** 1954. The extracellular fluid volume in infants and children. Acta Paediatr. **43**:444–458.
7. **Heimann, G., M. Eickschen, and K. Seeger.** 1980. Pharmacokinetics of cefotaxime in children. Infection **8**(Suppl. 4): S454–S459.
8. **Kaplan, S. L., E. O. Mason, H. Garcia, S. J. Kverland, E. M. Loiselle, D. C. Anderson, A. A. Mintz, and R. D. Feigin.** 1981. Pharmacokinetics and cerebrospinal fluid penetration of moxalactam in children with bacterial meningitis. J. Pediatr. **98**:152–157.
9. **Kenny, J. F., C. D. Isburg, and R. H. Michaels.** 1980. Meningitis due to *Haemophilus influenzae* type b resistant to both ampicillin and chloramphenicol. Pediatrics **66**:14–16.
10. **Marchou, B., T. Van Tho, and M. Armengaud.** 1981. Diffusion of ceftriaxone (Ro 13-9904/001) in the cerebrospinal fluid. Comparison with other beta-lactam antibiotics in dogs with healthy meninges and in dogs with experimental meningitis. Chemotherapy **27**(Suppl. 1):37–41.
11. **Meissner, H. C., and A. L. Smith.** 1979. The current status of chloramphenicol. Pediatrics **64**:348–356.
12. **Metzler, C. M., G. L. Elfring, and A. J. McEwen.** 1974. A package of computer programs for pharmacokinetic modeling. Biometrics **30**:562–563.
13. **Nelson, J. D.** 1980. The increasing frequency of beta-lactamase producing *Haemophilus influenzae* B. (Letter.) J. Am. Med. Assoc. **244**:239.
14. **Neu, H. C., N. J. Meropol, and K. P. Fu.** 1981. Antibacterial activity of ceftriaxone (Ro 13-9904), a beta-lactamase-stable cephalosporin. Antimicrob. Agents Chemother. **19**:414–423.
15. **Papadatos, C. J., D. A. Kafetzis, and J. Kanarios.** 1980. Cefotaxime in the treatment of severe paediatric infections. J. Antimicrob. Chemother. **6**(Suppl. A):243–248.
16. **Patel, I. H., K. Miller, R. Weinfeld, and J. Spicehandler.** 1981. Multiple intravenous dose pharmacokinetics of ceftriaxone in man. Chemotherapy **27**(Suppl. 1):47–56.
17. **Rowland, M., and T. N. Tozer.** 1980. Clinical pharmacokinetics, concepts and applications. Lea & Febiger, Philadelphia.
18. **Sack, C. M., J. R. Koup, and A. L. Smith.** 1980. Chloramphenicol pharmacokinetics in infants and young children. Pediatrics **66**:579–584.
19. **Schaad, U. B., G. H. McCracken, Jr., C. A. Loock, and M. L. Thomas.** 1981. Pharmacokinetics and bacteriologic efficacy of moxalactam, cefotaxime, cefoperazone, and Rocephin in experimental bacterial meningitis. J. Infect. Dis. **143**:156–163.
20. **Schaad, U. B., G. H. McCracken, Jr., N. Threlkeld, and M. L. Thomas.** 1981. Clinical evaluation of a new broad-spectrum oxa-beta-lactam antibiotic, moxalactam, in neonates and infants. J. Pediatr. **98**:129–136.
21. **Seddon, M., R. Wise, A. P. Gillett, and R. Livingston.** 1980. Pharmacokinetics of Ro 13-9904, a broad-spectrum cephalosporin. Antimicrob. Agents Chemother. **18**:240–242.
22. **Shelton, S., J. D. Nelson, and G. H. McCracken, Jr.** 1980. In vitro susceptibility of gram-negative bacilli from pediatric patients to moxalactam, cefotaxime, Ro 13-9904, and other cephalosporins. Antimicrob. Agents Chemother. **18**:476–479.
23. **Stoeckel, K., P. J. McNamara, R. Brandt, H. Plozza-Nottebrock, and W. H. Ziegler.** 1981. The effects of concentration-dependent plasma protein binding on the pharmacokinetics of ceftriaxone (Ro 13-9904), a new parenteral cephalosporin. Clin. Pharmacol. Ther. **29**:650–657.
24. **Syriopoulou, V., D. Scheifele, A. L. Smith, P. M. Perry, and V. Howie.** 1978. Increasing incidence of ampicillin resistance in *Haemophilus influenzae*. J. Pediatr. **92**:889–892.
25. **Toyonaga, Y., Y. Kurosu, H. Yoshikawa, K. Kumagai, T. Takahashi, and M. Hori.** 1980. Experimental and clinical studies on cefoperazone. Jpn. J. Antibiot. **33**:820–840.
26. **Trautmann, K. H., and P. Haefelfinger.** 1981. Determination of Ro 13-9904 in plasma, urine and bile by means of ion-pair reversed phase chromatography. J. High Resolut. Chromatogr. Chromatogr. Commun. **4**:54–59.
27. **Uchiyama, N., G. R. Greene, D. B. Kitts, and L. D. Thrupp.** 1980. Meningitis due to *Haemophilus influenzae* type b resistant to ampicillin and chloramphenicol. J. Pediatr. **97**:421–424.
28. **Verbist, L., and J. Verhaegen.** 1981. In vitro activity of Ro 13-9904, a new beta-lactamase-stable cephalosporin. Antimicrob. Agents Chemother. **19**:222–225.