

Pharmacokinetics and Protein Binding of Ceftriaxone during Pregnancy

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The purpose of the present work was to study the pharmacokinetics and the protein binding (free fraction of the drug) of ceftriaxone (CTX) during pregnancy. Nine pregnant women (ages, 20 to 34 years) whose gestational ages ranged from 28 4/7 to 40 5/7 weeks were included. The diagnosis of infection was established in all cases; i.e., four women had chorioamnionitis and five women had pyelonephritis. The following triple antibiotic therapy was infused with the aim of achieving cure: CTX, 2 g once every 24 h (constant rate over 60 min); tobramycin, 3 mg/kg of body weight once every 24 h; and ornidazole, 1 g/day. Two series of blood samples were collected, i.e., during the first day of treatment (on day 1), to establish the primary pharmacokinetic profile of CTX, and at the plateau (on day 7), to evaluate a possible accumulation of the drug. This was an open, noncompartmental study, with each patient serving as her own control. Concentrations of total and unbound CTX in serum were measured by a high-performance liquid chromatographic method. Pharmacokinetic analysis was done by a noncompartmental method. Data were compared by a Wilcoxon *t* test (a *P* value of ≤ 0.05 was considered significant). Data were also compared with those obtained for healthy subjects who received similar treatments. (i) The tolerance to treatment was excellent, and in all cases patients had a complete remission without premature delivery. (ii) No accumulation of CTX was noted during the treatment, and the profiles of the drug determined at days 1 and 7 were not significantly different. (iii) The pharmacokinetic parameters measured in pregnant patients during the third trimester of pregnancy were similar to those measured in healthy subjects. (iv) Residual concentrations of total and unbound CTX measured at 24 h were greater than the MICs for allegedly susceptible organisms, both on day 1 and at steady state. (v) During the final 3 months of pregnancy, the dosage schedule of CTX (2-g infusion per day) required no particular adjustment (i.e., neither a loading dose nor any increase in the maintenance dose).

Ceftriaxone (CTX) is the first broad-spectrum cephalosporin prescribed on a single-daily-administration basis (24). This dosage schedule, which is unusual for a beta-lactam antibiotic, has been validated by a number of clinical studies since CTX came onto the market (11, 31). A pharmacodynamic and bacteriological approach taken together with the specific pharmacokinetics of the compound have formed the theoretical basis of a simplified administration schedule compared with those for other beta-lactams with shorter half-lives (9). The dosage recommended by the manufacturer (a single injection of 1 to 2 g every 24 h) is the consequence of an essential peculiarity of CTX: its prolonged terminal half-life (between 6.5 and 8.5 h) (21). The antibacterial spectrum of CTX is similar to that of other broad-spectrum cephalosporins. However, in comparison with other members of the group, it is less active against anaerobic organisms such as *Bacteroides fragilis* and *Clostridium perfringens*, and in common with all cephalosporins, it is inactive against *Listeria monocytogenes* (9).

In obstetric practice, CTX has a role to play in the treatment of genital tract infections (8, 14). The question of the use of CTX during pregnancy may seem more open to discussion in view of the extent of its antibacterial spectrum. In fact, its ease of use and the quality of its tolerability, which have been shown in other patient categories, encourage us to use it on a regular basis when an infection caused by susceptible organisms occurs during the final 3 months of

pregnancy (25, 27, 29). It has been shown that the systemic and local tolerabilities of CTX are excellent, with the absence of any nephrotoxicity (15, 16). In addition, experiments in the rat, mouse, and monkey have shown the absence of embryotoxicity, teratogenicity, and mutagenicity (14). As with many important drugs that are used to treat serious infections during pregnancy, the available information for CTX is generally absent or too fragmentary to enable use of a therapeutic approach that is entirely free of risk. It is also important to attempt to optimize the conditions under which recent beta-lactams are used in order to provide alternative solutions to infectious situations which are becoming increasingly problematic.

In view of these points and considering the relatively meager anti-infectious arsenal available for use in pregnant patients (fluoroquinolones have made no contribution in this area), it is important to refine our knowledge of the disposition of CTX in order to better master its use in pregnant patients during the final 3 months of pregnancy. A clinical kinetic study was undertaken in patients hospitalized during the final 3 months of pregnancy with severe infections that justified treatment with a major antibiotic, including CTX. Since the study was carried out on the ground, an attempt was made to identify the kinetic behavior of CTX and to compare those data with data obtained for healthy subjects.

MATERIALS AND METHODS

Subjects. Nine women (ages, between 20 and 34 years; gestational ages, between 28 4/7 and 40 5/7 weeks of amen-

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TABLE 1. Epidemiologic, morphometric, and biologic data for the patients

Characteristic ^a	Patient no.									Mean \pm SD
	1	2	3	4	5	6	7	8	9	
Age (yr)	34	30	26	31	30	26	31	30	20	29 \pm 4.09
Height (cm)	172	163	169	165	176	163	173	162	160	167 \pm 5.66
Wt (kg)	69	61	78	57	75	49	82	72	74	69 \pm 10.76
Parity ^b	G3, P2	G3, P2	G1, P0	G3, P2	G3, P2	G1, P0	G1, P0	G1, P0	G1, P0	
Gestational age (wk) ^c	31 6/7	28 4/7	40 5/7	38 1/7	29 6/7	34 4/7	39 5/7	29 4/7	38 6/7	
Urea (2.5 to 7.5 mmol/liter)	2.7	3	2.9	2.5	3.7	2.9	5.5	4.5	3.8	3 \pm 0.98
Creatinine (45–105 μ mol/liter)	53	60	65	50	70	63	82	62	67	64 \pm 9.40
Total serum bilirubin (<17 μ mol/liter)	6	4	8	5	6	6	8	6	10	7 \pm 1.81
ALAT ^d (<40 IU/liter)	20	28	26	25	30	15	27	19	26	24 \pm 4.90
ASAT ^e (<40 IU/liter)	16	18	19	13	28	14	25	18	24	19 \pm 5.15
Total serum proteins (65–80 g/liter)	65	70	69	66	65	64	63	64	68	66 \pm 2.45
Albumin (37–42 g/liter)	36.5	28.9	33.2	39.8	25.1	33.8	28.4	24.1	31.7	31.3 \pm 5.17

^a Values in parentheses are the reference values of the laboratory.

^b G, gravida number; P, parity number.

^c Gestational age at the beginning of the treatment.

^d ALAT, alanine aminotransferase.

^e ASAT, asparagine aminotransferase.

orrhoea; monofetal pregnancies in all cases) were included in the study. They were hospitalized with signs of infection, characterized in particular by a temperature of $\geq 38.5^{\circ}\text{C}$ and leukocytosis (between 15,000 and 20,000 leukocytes per mm^3). Individual and mean \pm standard deviation (SD) biometric parameters are given in Table 1. Bacteriological specimens (blood cultures and vaginal specimens consisting of cervix, endocervix, posterior fornix, and midstream urine specimens) as well as a complete blood count were obtained for all patients before starting treatment for infection. The following triple antibiotic therapy was prescribed while awaiting bacteriology results: CTX, 2 g once every 24 h; ornidazole, 1 g once every 24 h; and tobramycin, 3 mg/kg of body weight once every 24 h. In all cases the drugs were infused over 1.0 h with an electric syringe. The addition of ornidazole was justified by the limits of the antimicrobial spectrum of CTX (i.e., anaerobic organisms). This empirical treatment was continued after 48 h only in those cases in which the infectious agent(s) responsible was definitely identified and shown to be susceptible to CTX. The following organisms were identified: *Escherichia coli* (five patients; three patients with pyelonephritis and two patients with chorioamnionitis), *Proteus mirabilis* (two patients with chorioamnionitis), *Pseudomonas aeruginosa* (one patient with pyelonephritis), and *Klebsiella pneumoniae* (one patient with pyelonephritis). This was an open, nonrandomized study, with each patient serving as her own control.

Patients were clearly informed and gave their consent for two series of peripheral blood samples to be drawn during the treatment. The trial was approved by the Ethics Committee of the Paul Brousse Hospital (Villejuif, France) in March 1990.

Design. CTX was given on a curative basis. Tobramycin and ornidazole were infused independently of CTX as single daily doses (4).

Dosing. The nine subjects were given a 2,000-mg daily infusion of CTX. The drug was dissolved and diluted in 50 ml of saline (0.9% NaCl).

Blood samples. During the first (on day 1) and second (on day 7) periods of analysis, venous blood samples were drawn into heparinized tubes via a Cathlon catheter inserted into a vein on the side contralateral to the CTX infusion. Sample times were as follows: 0, 0.50, 1, 2, 4, 8, 12, 16, 20, and 24

hours on day 1 and then 0 (residual concentration from previous administration), 0.50, 1, 4, 8, 12, and 24 h on day 7. The first analysis period enabled definition of the individual and initial pharmacokinetic behaviors of CTX, while the aim of the second analysis period was to evaluate the fate of the antibiotic under steady-state conditions and, in particular, to assess any possible systemic accumulation. All blood samples were labeled and numbered and were then quickly taken to the laboratory and centrifuged (at $2,000 \times g$ and 5°C for 10 min). Sera were decanted and immediately frozen at -30°C (two tubes per sample) until the time of assay, i.e., at day 7 plus 24 h.

Analysis. Samples were assayed by high-performance liquid chromatography (HPLC) combined with UV spectrophotometric detection at 274 nm. The HPLC technique (ion-pair reversed-phase chromatography) complied with the analytical recommendations of Trautmann and Haefelfinger (28). CTX (Rocéphine; Roche Laboratories, Neuilly-sur-Seine, France) and latamoxef (Eli Lilly Laboratories, Saint-Cloud, France), which was used as an internal standard, were kindly provided by the suppliers. The method used a test specimen of 100 μl of serum, and its lower limit of sensitivity was 0.5 $\mu\text{g/ml}$. The accuracy of the assay method, which was studied at target values of 1.0, 75, and 250 mg/liter (serum loaded with CTX in vitro), gave coefficients of variation of 0.2, 4.5, and 7.2, respectively. The linear range of the assay was between 0 and 300 mg/liter. Under the analysis conditions, the retention times of CTX and the internal standard were 2.1 and 2.8 min, respectively. All samples were assayed in duplicate. Control runs were performed regularly.

Protein binding. The extent of CTX binding to plasma proteins was determined on day 1 with an ultrafiltration system. The Ultrafree CL device (UFC4LG25; Millipore, Saint-Quentin-en Yvelines, France) was used (18). In brief, 1 ml of the plasma sample was placed in the filter cup (upper part of the device), which is separated from the filtrate cup by an ultrafiltration membrane. Ultrafiltration was obtained under nitrogen pressure (4 kg/cm^2). The device was kept under these conditions for 2 h (at 37°C). In the ultrafiltrate (filtrate cup), the concentrations of unbound CTX were determined by the same method described above.

Pharmacokinetic and statistical analysis. The program used

for the pharmacokinetic analysis was run on a Macintosh LC 4Mo/FDHD40 computer. Data were analyzed by a noncompartmental method (23). The terminal-phase rate constant (β ; in hours⁻¹) was determined as the slope of the terminal monoexponential decline in the concentration in serum with time by the least-squares method. The terminal half-life ($t_{1/2\beta}$; in hours) was calculated by the equation $t_{1/2\beta} = 0.693/\beta$. The area under the concentration-time curve from time zero to time t of the last sample (AUC_{0-t}) was calculated by the trapezoidal rule and was extrapolated to infinity by the following equation: $AUC_{t-\infty} = C_t/\beta$, where C_t is the concentration of the drug in plasma for the last sample withdrawn at time t . The mean residence time (MRT; in hours) after intravenous infusion was calculated by the formula of Yamaoka et al. (30):

$$MRT = \frac{\int_0^{\infty} tCdt}{\int_0^{\infty} Cdt} - \frac{T}{2} \quad (1)$$

where T represents the time over which the drug was infused. Total clearance (CL; ml/min) from serum was calculated by the following equation: $CL = \text{dose}/AUC_{0-\infty}$ after a single dose and $CL = \text{dose}/AUC_{0-24}$ after the seventh dose, where AUC_{0-24} is the AUC between two administrations at steady state. In all cases the apparent volume of distribution (V ; in liters) was determined as follows: $V = CL/\beta$.

The apparent volume of distribution at steady-state (V_{ss} ; in liters) was calculated by the following equation proposed by Benet and Galeazzi (1): $V_{ss} = MRT (\text{dose}/AUC_{0-\infty})$ (equation 2). The maximum concentration in serum, the minimum concentration in serum, and the time to maximum concentration in serum were experimental values. Ceftriaxone was infused over 60 min. Consequently, the time to the maximum concentration in serum always coincided with the end of the intravenous infusion.

Accumulation ratios were estimated with the following equations proposed by Colburn (6) in 1983; $R_1 = AUC_{0-\infty}^1/AUC_{0-24}^1$ and $R_2 = AUC_{0-24}^7/AUC_{0-24}^1$, where AUC_{0-24}^1 and AUC_{0-24}^7 are the AUCs during a 24-h dosing interval and from time zero to infinity following the single dose, respectively, and AUC_{0-24}^7 is the AUC during a 24-h dosing interval measured at steady state after the seventh infusion. R_1 is the predicted or theoretical accumulation ratio, and R_2 is the experimental value.

The method of superimposition was used to predict the concentration in serum after repeated administrations; concentrations in serum from the first dose of CTX were summed, and the concentrations from subsequent doses over time were predicted. The predicted levels were compared with the concentrations measured in serum after the repeated doses.

The pharmacokinetic parameters based on unbound CTX and noted as $t_{1/2\beta_u}$, AUC_u , V_u , V_{ss_u} , CL_u were calculated by using the same equations given above. The unbound fraction (f_u) was estimated as follows: $f_u = (AUC_{\text{unbound}}/AUC_{\text{total}}) \times 100$ (equation 3).

CTX binding kinetics in the sera of the women were studied. A Scatchard-type analysis was performed to estimate the number of binding sites per mole of albumin (n) and the association constant. Results were compared with those of different investigators (17, 22, 26).

All results are expressed as means \pm SDs. Each patient was used as her own control, and kinetic data obtained from each period of analysis were compared by the Wilcoxon t test. Furthermore, mean pharmacokinetic results obtained after the first dose of CTX were compared with the data obtained for healthy subjects (19, 26). Finally, a P value of ≤ 0.05 was considered statistically significant. Correlation coefficients between pharmacokinetic parameters and biological and morphometric data were systematically determined by regression analysis.

Laboratory monitoring of patients. A complete blood count (specific quantification of hematologic values) was obtained daily from the first to the last day of treatment. The body temperatures of the patients were measured four times a day until they became normal.

Local and systemic tolerability and treatment efficacy. Although CTX was never prescribed alone, overall tolerability and efficacy were evaluated. The bacteriological efficacy of treatment was assessed by studying cultures of samples until they became negative, the regression of pyrexia, and normalization of the blood count. The local and systemic tolerabilities of treatment (renal function and venous tolerance) were monitored regularly (repeated clinical and laboratory assessments).

RESULTS

The mean treatment duration was 10 ± 2 days. Local and systemic tolerabilities were excellent, and no notable adverse reactions to CTX were seen. Pain at the injection site was reported by two patients, and superficial phlebitis was seen in one patient. Pyrexia regressed in less than 30 h in all patients, while leukocytosis disappeared in less than 72 h. Recovery was not accompanied by premature labor. In Fig. 1, we used cartesian and semilogarithmic coordinates to compare the mean \pm SD profiles of changes in the concentrations of CTX in serum after the first infusion (on day 1) and at steady state (on day 7). The two profiles are virtually superimposable. Furthermore, this concept was confirmed by the determination of theoretical and experimental accumulation ratios of 1.080 and 0.941, respectively, for R_1 and R_2 . The first infusion of CTX was followed by a biexponential decrease in concentrations, represented by the following mean equation: $F(x) = 208.77 e^{-0.123x} + 170.78 e^{-0.109x}$. This finding was in agreement with data in the literature (19, 20). At steady state, the mean decrease appeared to be monoexponential. This phenomenon is probably due to a sampling interval between the time to the maximum concentration in serum and the following sampling point that was too large. Individual and mean pharmacokinetic parameters obtained after each analysis period are given in Table 2. There was little dispersal of results, in particular at steady state. During the final 3 months of pregnancy, there were no statistically significant differences between parameters determined after the first administration and at steady state. On days 1 and 7, mean data associated with changes in the total CTX concentration were compared with those determined by Pollack et al. (21) in 1982, the only slight difference being that in their study the second period of analysis was on day 4. Kinetic parameters associated with the free fraction of CTX were compared with those obtained in the study of Stoeckel et al. (26) in 1981, which involved six healthy subjects dosed with 1,500 mg of CTX. Although individual data for the studies cited above were not available, mean values of the main parameters (total or free fraction of CTX) in all cases were very similar to ours (Table 2). Our patients

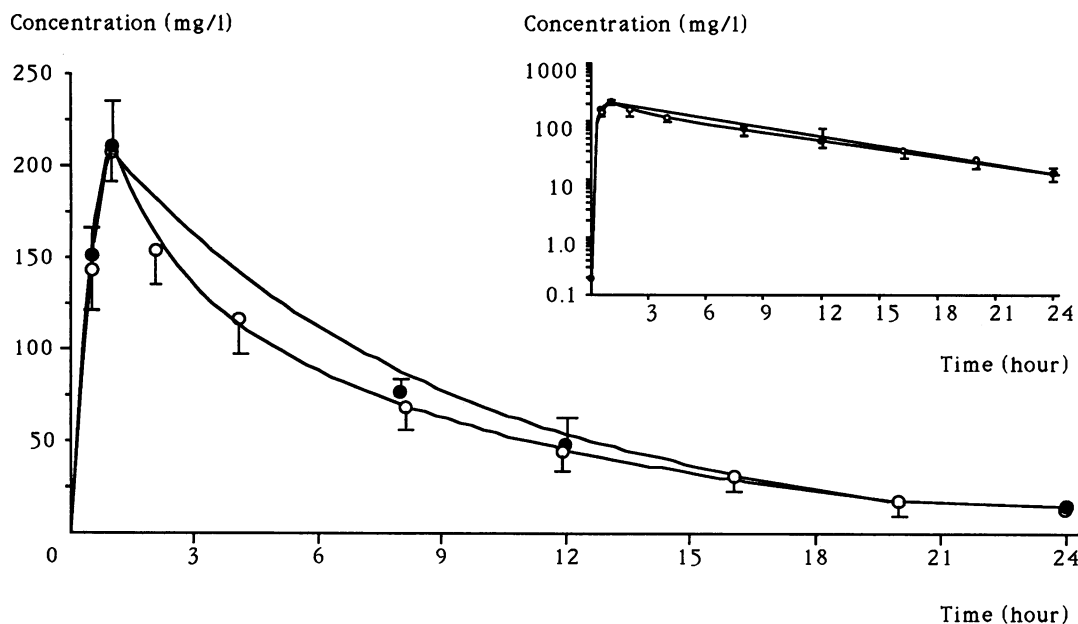


FIG. 1. Mean \pm SD concentrations of CTX in serum after single (first infusion; open circles) and multiple (seventh infusion; closed circles) 2,000-mg infusions ($n = 9$). (Inset) Log-linear plot of the same data.

had relative hypoalbuminemia, i.e., 31.3 ± 5.17 g/liter (which is often found in the third trimester of pregnancy), which nevertheless caused no significant change in the distribution of CTX (26).

Mean \pm SD concentrations of free CTX measured at each sampling time on day 1 were as follows: 15.65 ± 4.67 , 16.75 ± 10.58 , 12.40 ± 5.47 , 6.41 ± 4.37 , 6.08 ± 4.16 , 2.57 ± 0.85 , 0.52 ± 0.50 , and 0.21 ± 0.05 mg/liter. The mean proportion of the free fraction (equation 3) in relation to the total fraction of CTX was $7.42 \pm 4.2\%$; this was close to the values determined by other investigators (17, 22, 26), who used a dosage schedule that was the same or similar to that prescribed here. Study of the protein binding of CTX by the Scatchard technique revealed evidence in our patients of the existence of two types of sites characterized by association

constants of 6.40×10^5 and 7.57×10^7 M $^{-1}$ and numbers of binding sites per mole of albumin of 0.77 and 0.42 M, respectively. Figure 2 shows the relationship between mean concentrations of f_u determined on day 1 and the corresponding values of total CTX. The binding of CTX to albumin was saturable (overall linear changes in f_u in relation to total antibiotic concentrations).

DISCUSSION

The pharmacokinetics of CTX have been evaluated under various pathophysiological circumstances and in healthy subjects (19, 20). The existence of nonlinear kinetics, which has no apparent effect on therapeutic efficacy, has been shown by Stoeckel et al. (26) and Patel and colleagues (19,

TABLE 2. Comparison of pharmacokinetic parameters obtained in pregnant women after the first 2,000-mg infusion and at the plateau^a

Pharmacokinetic parameter ^a	Total CTX				Unbound drug ^b	
	Patients ($n = 9$) ^b		Healthy volunteers ($n = 8$)		Patients ($n = 9$), day 1	Healthy men ($n = 6$), day 1
	Day 1	Day 7	Day 1	Day 4		
C_{max} (mg/liter)	224.3 ± 31.3	214.8 ± 35.6	239	260	33.2 ± 10.3	
C_{min} (mg/liter)	12.88 ± 3.53	12.53 ± 2.34	13	15	0.17 ± 0.31	
T_{max} (h)	1.0	1.0	0.5	0.5	1.0	
AUC_{0-t} (mg · h/liter)	$1,459 \pm 229$	$1,593 \pm 181^c$			104.7 ± 51.5	
$AUC_{0-\infty}$ (mg · h/liter)	$1,588 \pm 225$	$1,713 \pm 201$			107.6 ± 55.5	102.6 ± 16.2
CL (ml/min)	21.40 ± 2.95	19.5 ± 2.4	21.7	22.7	250.6 ± 104.9	249 ± 36
V (liters)	12.54 ± 2.72	10.5 ± 1.6	11.7	12.3	152.0 ± 58.0	162 ± 18
V_{ss} (liters)	11.25 ± 1.84	9.66 ± 1.04			145.2 ± 54.8	
MRT (h)	9.29 ± 0.99	8.70 ± 0.57			9.51 ± 1.31	
$t_{1/2\beta}$ (h)	6.77 ± 1.07	6.49 ± 0.66	6.2	6.2	7.04 ± 1.21	7.6 ± 1

^a C_{max} , maximum concentration in serum; C_{min} , minimum concentration in serum; T_{max} , time to maximum concentration in serum; AUC_{0-t} and $AUC_{0-\infty}$, areas under the concentration-time curves from time zero to time t and from time zero to infinity, respectively; CL, clearance; V , volume of distribution; V_{ss} , volume of distribution at steady state; MRT, mean residence time; $t_{1/2\beta}$, terminal half-life. Data were compared with the mean parameters obtained with eight healthy volunteers (21) treated by the same schedule and with six healthy men (26) each receiving a 1,500-mg infusion.

^b Values are means \pm SDs.

^c $P \leq 0.05$ versus infusion on day 1.

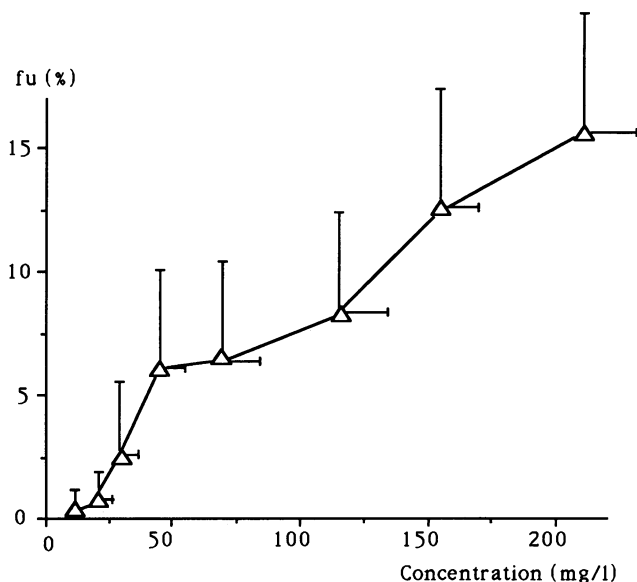


FIG. 2. Relationship between mean f_u and mean concentration of total ceftriaxone in serum. f_u is defined as the concentration in the ultrafiltrate divided by the initial concentration in the filtration device.

20). The increase in dosage was not accompanied by a proportional increase in AUC (19, 20). This resulted in an increase in total CL explained by a dose-related increase in the f_u and the corresponding AUC ($AUC_{0-\infty}^{f_u}$) (20, 21). A dose-related increase in V has also been reported. In total, a proportional increase of CL and V in the same direction did not result in any significant modification in $t_{1/2\beta}$ in the study subjects (26). This was attributed to saturation of the binding of CTX to transport proteins in serum (albumin in particular), leading to an increase in the amount of the f_u that was capable of reaching sites of infection (9). Other studies involving repeated administration have been undertaken. In a review devoted to repeated administration, Patel and Kaplan (20) showed (Table 2) that with a dosage schedule (route, timing, dose) identical to that which we used, the results obtained by Pollack et al. (21) for total CTX were very close to our own, although the second kinetic study was done on day 4 rather than day 7 (21). There have been few studies of CTX in patients (15). With respect to the free fraction of CTX, Table 2 enables comparison of our results with those obtained by Stoeckel et al. (26) after administration of a dose of 1,500 mg to six healthy volunteers; values of the various parameters were very similar. The kinetics of total CTX are nonlinear, while those of the free fraction are linear because of concentration-dependent protein binding (17, 22, 26).

In common with Popick et al. (22), we found evidence of two types of albumin binding sites. According to Stoeckel et al (26), one of these sites (a site of high affinity and low capacity) is saturable, which would explain the existence of concentration-dependent binding. The nonlinearity mentioned above has been found at the tissue level (15). It appears that the obstacle put up by a tissue to the penetration of xenobiotic compounds is overcome starting from a certain concentration gradient, and this occurs all the more easily when the gradient is higher (31). Thus, because

cephalosporins are antibiotics with a time-dependent immediate effect, the use (in the most serious types of disease) of high doses of CTX (on the order of 2 g) could theoretically favor high peak concentrations in tissue that could increase the diffusible free fraction (3, 8, 12, 13, 16, 21). The concentrations of free CTX determined 20 to 24 h after the start of the first administration (on day 1) were still notably above the MICs for the target organisms (2, 5, 10).

The final question is whether CTX accumulates in fetal tissues and, if so, whether it is dangerous. A possible toxic impact linked to a high level of transplacental penetration remains to be evaluated, but it is important to bear in mind the life-threatening risk associated with the infection itself and the need to achieve effective antibacterial concentrations at the site of infection (often, the fetoplacental unit in the present study). Few data on the behaviors of other cephalosporin antibiotics are available. However, the tolerability of a similar drug, i.e., cefotaxime (the reference for CTX), has been shown previously (7). Finally, children born to the trial patients showed normal initial development, and their growth was normal at the time of submission of the manuscript.

In summary, we found that (i) the pharmacokinetic behavior of CTX in pregnant women during the final 3 months of pregnancy is comparable (at the same dosage schedule of 2 g once every 24 h) to that in healthy adult volunteers. (ii) When indications are carefully weighed, CTX can be prescribed during pregnancy to patients with severe obstetric or genitourinary tract infections. Residual concentrations of total and free CTX measured at 24 h were greater than the MIC for allegedly susceptible organisms, both on day 1 and at steady state. (iii) During the final 3 months of pregnancy, the dosage schedule of CTX (2-g infusion per day) requires no particular adjustment, i.e., neither a loading dose nor any increase in the maintenance dose. The pharmacokinetic assets of CTX thus enable a reduction in the required nursing care and the cost of treatment. (iv) In patients with the most severe infections, it is preferable to combine CTX with a synergistic antibiotic (an aminoglycoside such as tobramycin or amikacin) and, if necessary, with an antianaerobic agent (e.g., ornidazole), which covers the antibacterial spectrum not covered by CTX while retaining a simplified dosage schedule.

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