

Pharmacokinetics of Ceftriaxone in Liver-Transplant Recipients

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The disposition of ceftriaxone was studied after a single 2 g intravenous dose in seven patients 3 to 5 days after liver transplantation. Ceftriaxone concentrations in plasma, urine, and bile were measured by HPLC, and plasma protein binding was determined by equilibrium dialysis. Plasma protein binding was nonlinear, and the unbound fraction varied between 0.05 and 0.56. Both capacity and affinity were markedly different from reported values for normal subjects. The pharmacokinetic parameters obtained were: total body clearance (TBC), 11.2 ± 7.8 mL/hr/kg total and 44.8 ± 29.1 mL/hr/kg unbound; volume of distribution (V_{area}), 224 ± 76 mL/kg total and 767 ± 432 mL/kg unbound; steady-state volume of distribution (V_{ss}), 212 ± 68 mL/kg total and 651 ± 368 mL/kg unbound; terminal disposition half-life ($t_{1/2}$), 21.6 ± 14.3 hour total and 16.3 ± 11.1 hour unbound. TBC for both total and free drug was considerably lower than literature values for normal subjects. V_{area} for total drug was greater than normal, whereas the corresponding value for free drug was smaller than normal. The plasma ceftriaxone concentrations at 12 and 24 hours were above the reported minimum inhibitory concentration (MIC). The fraction of the administered dose excreted in urine over 24 hours was $38 \pm 29\%$ and did not differ markedly from that reported for normal subjects. Less than 2% of the administered dose was excreted in 24-hour bile; however, biliary concentrations were always above MIC. Ceftriaxone can be administered once or twice daily at a dose of 2 g/day for prophylaxis in liver transplant recipients.

Ceftriaxone is a third-generation, parenteral cephalosporin with broad-spectrum activity against gram-positive and gram-negative pathogens.¹ At the University of Pittsburgh, cefotaxime, another third-generation cephalosporin, is currently used for prophylaxis before and for 5 days after orthotopic liver transplantation. Ceftriaxone offers certain advantages when compared with cefotaxime. First, ceftriaxone has a half-life of 6 to 10 hours,² and therefore, can be given less frequently than cefotaxime, which has a half-life of 1 to 2 hours.³ Second, since liver transplant recipients are prone to infection of the biliary region, an antibiotic that maintains an adequate concentration in this area is desirable. As much as 40% of parent ceftriaxone is excreted into

the biliary tract,⁴ whereas cefotaxime is eliminated solely through the kidneys as the parent compound and as the metabolites.³ Wider pathogenic spectrum is another advantage of ceftriaxone.^{1,5} Since a large fraction of the dose of ceftriaxone is excreted in the bile, the functional status of the liver is expected to influence the disposition of ceftriaxone. The objective of the present study was to elucidate ceftriaxone pharmacokinetics in orthotopic liver transplant patients, and subsequently determine an optimized dosing regimen in this patient population.

MATERIALS AND METHODS

Subjects

Seven adult orthotopic liver transplant patients, five men and two women, who were receiving intravenous cefotaxime as part of their post-operative medication were randomly chosen to participate in the present study. Written informed consent was obtained from all subjects, and the study protocol was approved by the University of Pittsburgh Institu-

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tional Review Board. Patients on any known enzyme inducers or inhibitors were excluded from the study.

Study Design

Three to 5 days after transplant, a 2 gram intravenous dose of ceftriaxone was substituted for a single dose of cefotaxime. Ceftriaxone was given as an intravenous infusion over 15 minutes. Blood samples (2.5 mL) were collected before and at 7, 15, and 30 minutes and 1, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours after the start of the infusion. Blood was centrifuged at room temperature, and the plasma was separated and frozen at -70°C until assayed. Urine (24 hr) and bile output were also collected via a catheter and a T-tube, respectively. These samples were measured, aliquoted, and frozen at -70°C until assayed.

Assay

Samples were processed by a modification of the method of Patel et al.⁶ The sample, 250 µL of plasma, 100 µL of urine, or 100 µL of bile, was added to 0.75 mL of water; 2 mL of acetonitrile containing 5 µg/mL of medazepam, the internal standard, were added. After shaking for 10 minutes and centrifugation for

10 minutes at 1500 × g, 30 µL of the supernatant were analyzed by HPLC. The chromatographic system consisted of a 150 × 4.6 mm 5µ C18 column (Supelco, Bellefonte, PA) maintained at 40°C with ultraviolet detection at 254 nm. The mobile phase consisted of acetonitrile, 1% hexadecyltrimethylammonium bromide (HTAB) in water, 1M phosphate buffer pH 7 and water (44:30:1:25). At a flow rate of 1.5 mL/min, the retention times of ceftriaxone and medazepam were 4.5 and 12 minutes, respectively (Figure 1). The standard curve was linear between 5 and 200 µg/mL and the day-to-day coefficient of variation was <15%.

Protein Binding

Five plasma samples from each patient, representing approximately every other time point, were used to determine ceftriaxone plasma protein binding by equilibrium dialysis. Plasma (400 µL) was dialyzed against an equal volume of pH 7.4 isotonic phosphate buffer at 37°C. After a 4-hour equilibration time, the buffer and plasma were removed and assayed for ceftriaxone concentrations by HPLC as described earlier. Preliminary studies indicated that equilibrium was achieved in 4 hours and that no volume shift correction was necessary. The percent of ceftriaxone bound to plasma proteins was determined by the following equation:

$$\% \text{ Bound} = (\text{Conc. in plasma} - \text{Conc. in buffer}) / \text{Conc. in plasma}$$

Data Analysis

Plasma data of total ceftriaxone were analyzed by standard noncompartmental methods.⁷ Data from the protein-binding study were fitted using MINSQ least-square parameter estimating program⁸ to the following equation⁹:

$$\beta = 1 / (1 + C_u / nP + 1 / K_a \cdot nP)$$

where β is the ratio of bound to total plasma concentration, C_u is the unbound concentration in plasma, K_a is the affinity constant of the drug-protein interaction, and nP is the capacity constant. Using parameter estimates for each subject, the unbound concentration corresponding to each time point was calculated using the following equation¹⁰:

$$C_u = 0.5 \{ -(nP + K_d - C_{tot}) + [(nP + K_d - C_{tot})^2 + 4K_d \cdot C_{tot}]^{1/2} \}$$

where K_d = 1/K_a, C_{tot} is the total concentration in plasma.

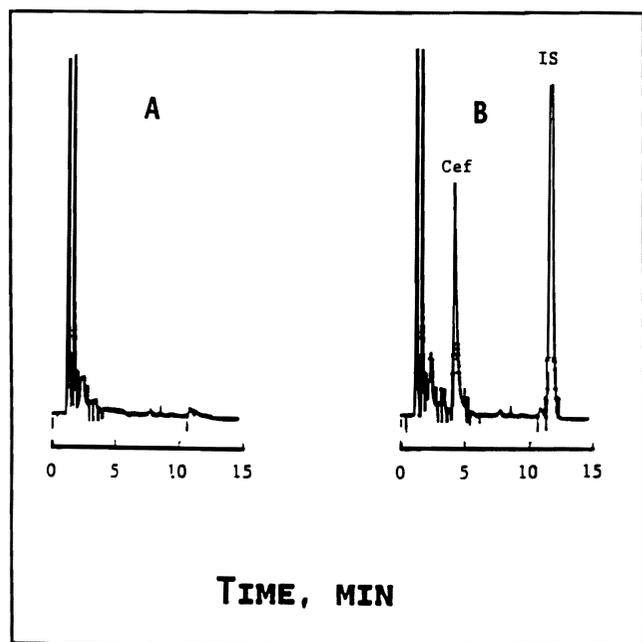


Figure 1. Representative chromatograms that were obtained from subject #6: A, blank plasma; B, plasma 10 hr after drug administration. Peaks C and IS represent drug and internal standard, respectively; estimated ceftriaxone concentration: 62 µg/mL.

TABLE I
Biochemical Profile of Liver Transplant Patients*

Pt. #	Sex	Age (yr)	BW (kg)	BUN (mg%)	SCr (mg%)	SGOT (U/L)	SGPT (U/L)	Bilirubin† (mg%)	AP (U/L)	GGT (U/L)	Albumin (g%)	TP (g%)
1	M	57	83	24	1.1	270	434	0.8/1.4	69	44	2.0	4.1
2	M	40	90	34	1.4	265	240	5.6/7.6	30	21	3.7	6.0
3	M	50	69	58	2.7*	1022	856	2.6/3.3	51	62	2.9	5.2
4	F	37	70	8	0.6	352	346	4.6/6.0	246	135	2.9	7.7
5	M	58	70	37	1.3	119	60	11.5/13.0	508	511	2.6	5.1
6	M	55	64	14	0.8	43	83	1.8/2.4	153	170	2.2	4.5
7	F	55	79	51	2.6*	114	138	1.6/2.2	56	56	2.9	5.3
Mean		50	75	32	1.5	312	308	4.1/5.1	159	143	2.7	5.4
SD		8	9	18	0.8	331	278	3.7/4.1	171	171	0.6	1.2

* Normal values: BUN, 7–22 mg%; Scr, 0.5–1.4 mg%; SGOT, 12–45 U/L; SGPT, 7–40 U/L; Bilirubin, 0.1–0.4 mg%/0.3–1.3 mg%; Alk phos, 37–107 U/L;

GGT, 8–69 U/L; Albumin, 3.5–4.8 g%; Total protein, 6.1–8.0 g%.
 † Direct/total.

Correlation among various pharmacokinetic parameters and biochemical indices of the patients was examined by linear regression.¹¹

RESULTS

The characteristics of the patients who were participating in the present study are summarized in Table I. Two patients, 3 and 7, had markedly impaired renal function as determined by a serum creatinine level (Scr) >2 mg/dl. Liver function in all the patients was below normal, as determined by various biochemical indices (Table I). Table II summarizes the pharmacokinetic parameters from plasma data; urine and bile data are shown in Table III. Table IV lists the correlations between the various pharmacokinetic parameters and biochemical indices.

Protein Binding

Nonlinearity in the plasma protein binding of ceftriaxone was evident throughout the concentration range attained in the present study; over the concentration range of the samples measured, 13 to 243 µg/mL, the unbound fraction in plasma ranged from 0.05 to 0.56. Capacity constant (nP) and affinity constant (K_a) showed considerable variability among subjects (Table II). As shown in Table II, binding parameters are markedly different from those calculated for normal subjects.⁴ No significant correlation was found between binding parameters and albumin concentration (Table IV).

Plasma

Figures 2 and 3 show the plasma concentration–time profiles of total and unbound ceftriaxone in two pa-

tients. The various pharmacokinetic parameters for total and unbound ceftriaxone are shown in Table II. Total body clearance (TBC) of total ceftriaxone was 11.2 ± 7.8 mL/hr/kg. TBC for unbound drug was 44.8 ± 29.1 mL/hr/kg. No significant correlation was found between TBC of either total or unbound drug and bilirubin levels (Table IV); only a slight trend of a negative relationship ($P < .07$) was found between the clearance of unbound drug and total bilirubin. The volume of distribution (V_{area}) for total and unbound drug was 224 ± 76 mL/kg and 767 ± 432 mL/kg, respectively. The steady-state volume of distribution (V_{ss}) was 212 ± 68 mL/kg for total ceftriaxone and 651 ± 368 mL/kg for the unbound drug in plasma. The volumes of distribution for total, but not unbound, ceftriaxone showed a significant positive correlation with bilirubin levels (Table IV). Terminal disposition rate constants (Table II) were 0.053 ± 0.039 hour⁻¹ and 0.073 ± 0.055 hour⁻¹ for total and unbound ceftriaxone, respectively, and did not correlate significantly with bilirubin levels (Table IV). The terminal disposition plasma half-life was 21.6 ± 14.3 hour for total and 16.3 ± 11.1 hour for unbound ceftriaxone. The mean residence time (MRT) for total and unbound drug was 29.9 ± 20.6 hour and 21.3 ± 16.7 hour, respectively.

Urine and Bile

The percentage of dose that was excreted in urine over 24 hours (Table III) was $47.2 \pm 29.6\%$ and did not correlate significantly with Scr or BUN (Table IV). Estimated percent that was excreted in urine at time infinity was $68.3 \pm 22.4\%$ and correlated inversely with Scr and BUN (Table IV). Renal clearance, calcu-

CEFTRIAXONE IN LIVER-TRANSPLANT PATIENTS

TABLE II

Pharmacokinetics of Ceftriaxone in Liver Transplant Recipients

	Patient Number							Mean ± SD	
	1	2	3	4	5	6	7	Mean ± SD	Normal Subjects*
I. Protein Binding									
nP, mM × 10 ⁴	1.64	3.45	2.47	2.95	1.26	1.04	4.22	2.43 ± 1.19	4.33 ± 0.87
Ka, mM ⁻¹ × 10 ⁻⁴	5.92	1.74	5.90	1.76	1.48	9.83	0.56	3.89 ± 3.40	6.49 ± 1.15
II. Total Drug									
C _{max} , µg/mL	290	218	306	315	245	560	293	318 ± 112	257 ± 17
C ₁₂ , µg/mL	61	84	90	33	48	54	117	70 ± 29	46 ± 7
C ₂₄ , µg/mL	21	68	81	13	28	19	104	48 ± 36	15 ± 4
TBC, mL/hr	994	368	311	1706	945	1059	260	806 ± 526	1190 ± 150
mL/hr/kg	12.0	4.1	4.5	24.4	13.5	16.5	3.3	11.2 ± 7.8	
MRT, hr	12.5	58.8	44.6	8.5	25.8	10.7	48.5	29.9 ± 20.6	
V _{ss} , L	12.4	21.7	13.9	14.5	24.4	11.4	12.6	15.8 ± 5.1	
mL/kg	150	241	201	207	349	178	159	212 ± 68	
V _{area} , L	13.1	20.9	16.3	14.7	26.7	12.7	12.1	16.6 ± 5.3	10.1 ± 1.0
mL/kg	158	232	236	210	381	199	153	224 ± 76	
β, hr ⁻¹	0.076	0.018	0.019	0.116	0.035	0.083	0.021	0.053 ± 0.039	
t _{1/2} , hr	9.2	39.4	36.3	6.0	19.6	8.3	32.4	13.1 [†]	5.8 (4.7-6.8)‡
III. Unbound Drug									
C _{max} , µg/mL	187	70	154	157	178	492	140	197 ± 136	
C ₁₂ , µg/mL	10	16	11	6	21	11	42	17 ± 12	
C ₂₄ , µg/mL	2	12	9	2	11	2	37	11 ± 12	
TBC, mL/hr	4322	2318	3085	7163	2245	2980	794	3272 ± 2019	14940 ± 2160
mL/hr/kg	52.1	25.8	44.7	102.3	32.1	46.6	10.0	44.8 ± 29.1	
MRT, hr	6.6	44.9	25.0	6.2	21.0	4.7	40.7	21.3 ± 16.7	
V _{ss} , L	28.6	104.1	77.2	44.3	47.2	14.0	32.3	49.7 ± 31.0	
mL/kg	345	1156	1119	634	674	218	409	651 ± 368	
V _{area} , L	38.8	102.7	104.0	54.3	54.0	20.2	31.1	57.9 ± 33.3	162 ± 18
mL/kg	467	1141	1507	776	771	315	394	767 ± 432	
β, hr ⁻¹	0.111	0.023	0.030	0.132	0.042	0.148	0.026	0.073 ± 0.055	
t _{1/2} , hr	6.2	30.7	23.4	5.3	16.7	4.7	27.2	9.5 [†]	7.6

* Data for total ceftriaxone obtained from ref 6 (Patel); data for unbound ceftriaxone from ref 4.

† Harmonic mean.

‡ Range in parentheses.

TABLE III

Pharmacokinetics of Ceftriaxone in Liver Transplant Recipients

	Patient Number							Mean ± SD	
	1	2	3	4	5	6	7	Mean ± SD	Normal Subjects*
I. Urine									
% Exc, 24 hr	83.2	10.9	36.1	81.9	31.7	66.1	20.6	47.2 ± 29.6	42 ± 10
Cl _R mL/hr†	975	133	217	1572	474	796	146	616 ± 534	533 ± 128
Cl _R mL/hr/kg†	11.7	1.5	3.2	22.5	6.8	12.4	1.8	8.6 ± 7.6	
% Exc, inf‡	98.1	36.1	69.8	92.2	50.1	75.2	56.2	68.3 ± 22.4	
II. Bile									
Av Conc, µg/mL	108	— [§]	57	14	24	18	134	59 ± 51	
% Exc, 24 hr	1.21	—	0.55	0.13	0.25	0.26	1.74	0.69 ± 0.65	
Cl _B , mL/hr†	14.18	—	3.31	2.49	3.74	3.13	12.33	6.53 ± 1.35	
% Exc, inf	1.43	—	1.06	0.15	0.40	0.30	4.75	1.35 ± 1.74	40

* Data from ref 6.

† Calculated from 24 hr urine and plasma data.

‡ Estimated from renal clearance and total body clearance.

§ Bile not collected.

^{||} Estimated from biliary clearance and total body clearance.

* Data from ref 2.

TABLE IV

Correlations Between Pharmacokinetic Parameters and the Biochemical Indices of Liver Transplant Recipients

	Bilirubin		Albumin	SCR	BUN
	Unbound	Total			
I. Binding Parameters					
nP, mM × 10 ⁴			NS		
Ka, mM ⁻¹ × 10 ⁻⁴			NS		
II. Total Drug					
TBC, mL/hr	NS	NS			
mL/hr/kg	NS	NS			
β, hr ⁻¹	NS	NS			
V _{ss} , L	↑ 0.003	↑ 0.001	NS		
mL/kg	↑ 0.0001	↑ 0.0001	NS		
V _{area} , L	↑ 0.001	↑ 0.001	NS		
mL/kg	↑ 0.001	↑ 0.002	NS		
III. Unbound Drug					
TBC, mL/hr	NS	NS			
mL/hr/kg	NS	NS			
β, hr ⁻¹	NS	NS			
% Exc ₂₄				NS	NS
Cl _R , mL/hr				NS	NS
mL/hr/kg				↓ 0.05	↓ 0.02
% Exc _{inf}				↓ 0.02	↓ 0.025

lated from 24-hour urine and plasma data, was 8.6 ± 7.6 mL/hr/kg and correlated inversely with both Scr and BUN.

The percentage of the dose excreted in bile over 24 hour was 0.69% ± 0.65 (Table III) and did not correlate significantly with bilirubin levels (Table IV).

Various pharmacokinetic parameters that were

calculated in the present study were compared with corresponding literature values in healthy volunteers for total and unbound ceftriaxone (Tables II and III). For both total and unbound drug, TBC was lower in the liver transplant patients; the difference is more pronounced with respect to unbound as compared with total drug. V_{area} for total ceftriaxone was

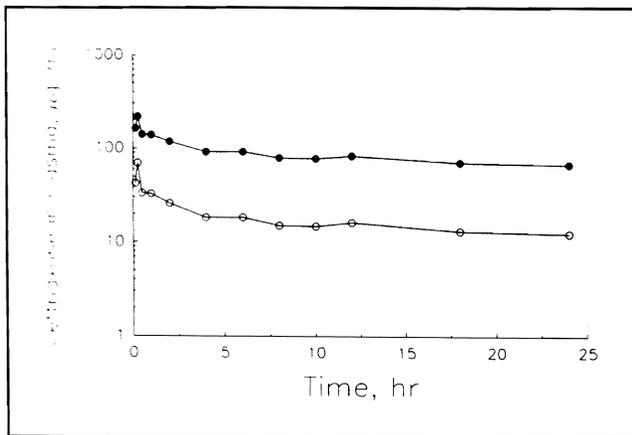


Figure 2. Plasma concentration-time profile of total (●) and estimated unbound (○) ceftriaxone in a liver transplant recipient (#2) after a 2 g dose given as a 15-min intravenous infusion.

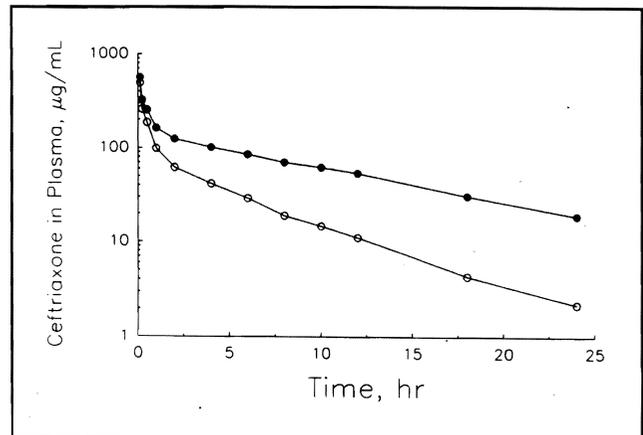


Figure 3. Plasma concentration-time profile of total (●) and estimated unbound (○) ceftriaxone in a liver transplant recipient (#6) after a 2 g dose given as a 15-min intravenous infusion.

considerably greater, whereas that of unbound drug was smaller in the liver transplant recipients compared with normal subjects. Plasma ceftriaxone concentrations after 12 hours (C_{12}) and 24 hours (C_{24}) were considerably higher in this patient group as compared with normal subjects who were receiving the same dose of the drug.

DISCUSSION

Ceftriaxone offers certain practical advantages such as a longer half-life and higher biliary excretion as compared with cefotaxime. The present study determined whether ceftriaxone disposition in liver transplant recipients during the early post-operative period is different from its disposition in healthy subjects, and determined whether a 2 g/day dose will provide plasma ceftriaxone concentrations above the reported MIC.

Ceftriaxone exhibits nonlinear kinetics and comparison of the parameters that were calculated in the present study for total drug with literature values in normal subjects was therefore confined to data from subjects who were receiving the same dose, i.e., 2 g. Since binding is the only nonlinear process in ceftriaxone disposition,^{4,8,12,13} the unbound drug is expected to behave linearly, and comparison was made among various reports regardless of the dose.

Most of the pharmacokinetic parameters that were calculated in the present study were notably different from literature values for normal subjects and exhibited much greater variability (Tables II and III). Such variability in kinetics may be related to the patient population that was studied. Even though C_{max} observed in this study was comparable to that observed in normal subjects, much higher concentration was maintained at 12 and 24 hours after drug administration (Table II). In all subjects, C_{24} was higher than the MIC_{50} of most susceptible organisms.¹⁴ The mean TBC of unbound ceftriaxone that was obtained in this study is approximately one fifth of the value reported for normal subjects (Table II). Such reduction could be explained on the basis of compromised liver function in the early post-operative period. Injury to the organ that was incurred by cold ischemia and warm reperfusion, resulting in an impairment of drug uptake by hepatocytes and of biliary excretion, may account for the reduction in the unbound clearance of ceftriaxone. In addition, four of the seven patients who were studied had a bilirubin concentration of greater than 2 mg/dL. Minor changes in the pharmacokinetic parameters of total ceftriaxone have been observed in patients

with liver disease¹⁵ and in patients with cholecystectomy.¹⁶

The volume of distribution of total drug is greater in patients than in normal subjects, whereas the opposite is observed with unbound volume of distribution (Table II). The larger volume of distribution is the result of decreased plasma protein binding due to decreased albumin concentration and decreased affinity of ceftriaxone for plasma proteins. In addition, the positive correlation that was obtained between the volume of distribution of total ceftriaxone and bilirubin, may indicate competition between with ceftriaxone and bilirubin for albumin binding sites. The reduction in unbound volume of distribution may be a reflection of the decrease in the uptake of ceftriaxone by body tissues.

The half-life of ceftriaxone was significantly increased in liver transplant patients. It was not possible to account for the dose that was administered by urinary and biliary excretion in 24 hours. The percentage of dose that was excreted in urine over 24 hours did not differ from literature value for normal subjects who were receiving the same dose, whereas the percent that was excreted in bile was greatly reduced; however, such a comparison may be misleading because in normal subjects 24-hour urinary or biliary excretion approximates the total amount eliminated by the respective route, whereas in patients, in whom the terminal disposition half-life of ceftriaxone is markedly longer, the 24-hour urinary or biliary excretion is only a fraction of the total amount that is eliminated via each route. A better comparison may be made between the estimated percent that was excreted in urine or bile at time infinity in patients to the 24-hour urinary or biliary excretion in normal subjects (Table III).

It could be inferred from the large fraction that was eliminated by urinary excretion and the small fraction that was eliminated in bile that the kidneys contribute more to the elimination of ceftriaxone in liver transplant recipients than in normal subjects. Although total 24-hour biliary recovery of ceftriaxone (Table III) was markedly lower than that reported in normal subjects,² the pooled biliary concentration in all subjects (Table V) was higher than the MIC_{50} of most of the susceptible organisms.¹⁴

In conclusion, the disposition of ceftriaxone in liver transplant recipients in the early post-operative period is considerably different from normal subjects. Clearance, binding, volume of distribution, and half-life are different from normal subjects, and lower doses of ceftriaxone may be sufficient to prevent infection. Due to high variability in the clearance, a minimum dose of 2 g/day is expected to

maintain adequate antibiotic concentrations in all patients.

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