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Impaired Clearance of Ceftizoxime and Cefotaxime after Orthotopic Liver Transplantation

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The pharmacokinetics of ceftizoxime (CZX) and of cefotaxime (CTX) were studied in five children and five adults after orthotopic liver transplantation (OLT). Delayed clearance of CZX (clearance of 0.21 to 1.26 ml/min per kg [body weight]) and CTX (clearance of 0.40 to 1.49 ml/min per kg) occurred in 7 of the 10 OLT patients. We conclude that abnormal CZX and CTX clearance is common after OLT and may be associated with minimal change in serum creatinine.

Cefotaxime (CTX) in combination with ampicillin is used in our institution for surgical prophylaxis before and after orthotopic liver transplantation (OLT). The objective of this study was to evaluate the disposition of CTX and ceftizoxime (CZX), the accumulation of the desacetyl metabolite of CTX (DACTX), and the relationship of the pharmacokinetics of these compounds to renal and hepatic function after OLT.

Five children, 14 to 62 months old, and five adults were enrolled in the study within 72 h after OLT. The research protocol was approved by the Human Rights Committee, University of Pittsburgh, Pittsburgh, Pa., and parental or patient consent was obtained before subject enrollment. Medications at the time of study included CTX, cyclosporine, methylprednisolone, ampicillin, nystatin, morphine, hydralazine, furosemide, captopril, and oral antacids.

CTX at approximately 25 mg/kg (body weight) per dose for children and 1.0 g per dose for adults was administered intravenously before surgery and continued every 6 h during the postoperative period. A single dose of CZX in the same amount was substituted for a scheduled CTX dose and infused intravenously. Blood samples were obtained before and at 0.5, 1, 2, 4, 6, 6.5, 7, 8, 10, and 12 h after the initiation of the CZX or CTX infusion. The samples were centrifuged, and the plasma was separated and frozen at −70°C. All the samples were assayed within 8 weeks of study.

Plasma samples for measurement of CZX, CTX, and DACTX content were assayed in duplicate by using a modification of a previously described high-pressure liquid chromatographic method (4). The resultant peaks of DACTX, CZX, and CTX were detected at 4.0, 7.2, and 13.5 min, respectively. Of the other drugs which the patients were receiving, only ampicillin was detected under the above-stated conditions, and it was separated from the compounds of interest.

The method of reverse superposition was used to generate single-dose curves for CTX from the plasma concentration-time data (1). The elimination rate constants for CZX and CTX were calculated by linear regression of the natural logarithm of the plasma concentration versus time for postadministration datum points. The area under the plasma concentration-time curve from 0 h to infinity was calculated by using the trapezoidal method. Systemic drug clearance was determined by dividing the dose administered by the area under the curve. The apparent volume of distribution at steady state was calculated by the statistical moment theory (2).

The characteristics of the patients are shown in Table 1. Higher serum bilirubin values with slow improvement in hepatic function were noted postoperatively in pediatric patient 1. In the adult group, the liver of patient 9 may have had some ischemic damage during harvesting. In the pediatric patients, peak concentrations of 33.9 to 67.2 μg/ml were measured after the administration of a single dose of CZX, with a 6-h average concentration of 11.6 μg/ml (range, <1.0 to 26.0 μg/ml). After the 1.0-g CZX dose in adults, peak concentrations ranged from 74.0 to 98.8 μg/ml, with 6-h concentrations of 8.2 to 42.0 μg/ml. Peak concentrations of 45 to 112.5 μg/ml were measured in the pediatric patients after the administration of multiple doses of CTX, with a 6-h average concentration of 11.2 μg/ml (range, 1.0 to 34.5 μg/ml). In the adults, peak concentrations of CTX ranged from 66.0 to 169.5 μg/ml, with 6-h concentrations of 5.1 to 72.0 μg/ml after the 1.0-g CTX dose. Calculated pharmacokinetic parameters for CTX and CZX are shown in Table 2.

Highly variable concentrations of the metabolite DACTX were detected in the 10 subjects. No evidence of DACTX was found in serum from patient 1, who demonstrated delayed recovery of liver function. Accumulation of DACTX (>20 μg/ml) during the dosage interval was documented in

TABLE 1. Patient demographics[a]

Patient	Age	Wt (kg)	Total bilirubin (mg/dl)	SGOT (U/ml)	SGPT (U/ml)	Creatinine (mg/dl)
1	33 mo	15.0	22.6	1,038	634	0.2
2	30 mo	10.9	1.6	362	439	0.2
3	17 mo	12.0	5.5	704	663	0.2
4	62 mo	17.9	8.1	840	813	0.6
5	14 mo	8.7	8.7	1,502	769	0.7
6	53 yr	60.1	10.8	203	242	2.1
7	49 yr	62.0	14.8	448	552	1.4
8	45 yr	59.9	7.4	127	135	4.2
9	51 yr	79.6	3.7	2,528	1,668	1.6
10	23 yr	73.5	8.5	772	864	1.0

[a] SGOT, Serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

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TABLE 2. Pharmacokinetic parameters for CZX and CTX[a]

Patient	CZX			CTX		
	$t_{1/2}$ (h)	CL (ml/min per kg)	V_{ss} (liters/kg)	$t_{1/2}$ (h)	CL (ml/min per kg)	V_{ss} (liters/kg)
1	1.7	5.88	0.60	1.4	6.64	0.53
2	2.7	2.63	0.54	1.2	4.65	0.43
3	1.5	5.59	0.63	1.8	2.75	0.30
4	5.8	0.62	0.31	2.3	0.95	0.19
5	11.7	0.56	0.55	5.3	0.83	0.37
6	12.1	0.40	0.42	4.9	0.75	0.32
7	5.7	0.68	0.33	3.1	0.91	0.23
8	14.9	0.21	0.27	7.1	0.40	0.24
9	4.1	1.26	0.37	2.2	1.49	0.22
10	5.2	0.88	0.35	3.2	1.31	0.34

[a] $t_{1/2}$, half-life; CL, clearance; V_{ss}, volume of distribution at steady state.

patient 5 (Fig. 1) and in patients 4, 6, and 8 in association with impaired renal function.

A 45% incidence of bacteremia has been reported after OLT during a 24-month period at our institution (5). The most frequent infecting pathogens were *Enterococcus* sp., *Staphylococcus* sp., *Escherichia coli*, *Citrobacter* sp., and *Bacteroides* sp. The combination of ampicillin plus an extended-spectrum cephalosporin provides acceptable antibacterial coverage for these organisms.

The clearance rate of CTX was impaired in our OLT patients beyond normal predictions based on renal function. Matzke and co-workers (3) defined a clear relationship between renal function and CTX clearance. Although none of our OLT patients should have had severe renal impairment based on serum creatinine, two children and all of the adults had CTX clearance rates paralleling the severe renal insufficiency group described by Matzke et al. The explanation for the discrepancy between serum creatinine and CTX clearance is unknown.

CTX regimens with doses of 25 mg/kg at 6-h intervals resulted in acceptable peak and trough concentrations in plasma in our pediatric subjects. Standard 1.0-g doses of CTX should be administered to adult OLT patients at 8-h intervals. Our study supports a dosage interval of 12 h for CZX in OLT patients, but clinical experience with CZX in OLT patients must be acquired before definite recommendations can be made.

At least 16 centers in North America now perform OLT operations. The drug regimens of OLT patients are complex and frequently contain cephalosporin antibiotics for prophylactic or therapeutic treatment. We demonstrated that the

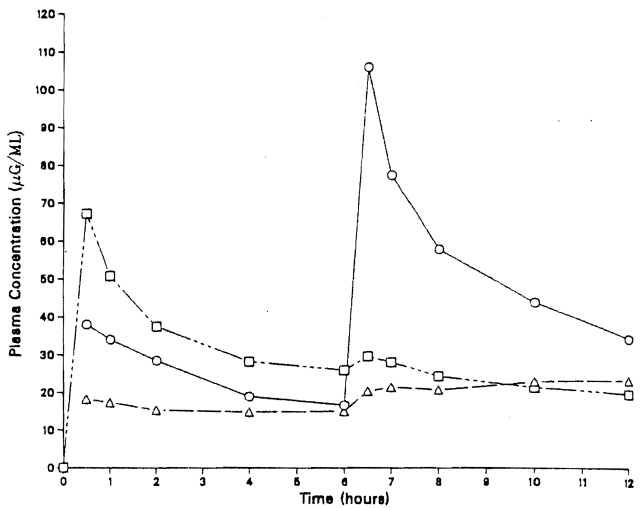

FIG. 1. Plasma concentration versus time in patient 5. A dose of 25 mg of CZX per kg (□) was given at time 0, and 25 mg of CTX per kg (○) was given at 6 h. DACTX (△) is also shown.

clearance of CTX was decreased in OLT patients and was not in proportion to changes in serum creatinine. CZX half-lives are longer than those of CTX, so a longer dosage interval is necessary.

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