Cefotaxime and Desacetylcefotaxime Pharmacokinetics in Infants and Children with Meningitis

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The pharmacokinetics and cerebrospinal fluid (CSF) penetration of cefotaxime (Ctx) and desacetylcefotaxime (dCtx) were evaluated in 13 infants and children with meningitis after dose 6 of Ctx in a multiple-dose intermittent intravenous infusion regimen (50 mg/kg every 6 h). Model-dependent and noncompartmental pharmacokinetic parameters were determined and found to be congruous. The disposition of both Ctx and dCtx was described adequately by a one-compartment, open model. Noncompartmental pharmacokinetic parameters are reported. The mean Ctx serum concentration at 0.25 h postinfusion was 121.2 μg/ml, and the mean CSF concentration at 1 h postinfusion was 6.2 μg/ml. The CSF/serum ratio was variable (0 to 20%), with a mean penetration of 10.1%. The mean Ctx elimination half-life, apparent steady-state volume of distribution, and total body clearance were 0.8 h, 0.361 liter/kg, and 0.289 liter/h per kg, respectively. For Ctx, 61% of the dose was excreted unchanged in the urine during the 6-h postinfusion period, and the estimated renal clearance was 0.174 liter/h per kg. No significant correlations were observed between Ctx pharmacokinetic parameters and demographic parameters. The mean peak concentration of dCtx in serum (21.6 μg/ml) occurred at approximately 1.5 h postinfusion, and the mean concentration in CSF at 1 h postinfusion was 5.6 μg/ml. The CSF/serum ratio was extremely variable (0 to 103%), and the mean penetration was 28.8%. The mean apparent elimination half-life for dCtx was 2.1 h.

Cefotaxime (Ctx), a cephalosporin with activity against both gram-negative and gram-positive organisms (11, 30, 34), is widely used in the treatment of bacterial meningitis in infants and children (6, 19, 20, 36). Desacetylcefotaxime (dCtx), the primary Ctx metabolite, has also been shown to possess antibacterial activity which may have an effect which is additive to that of Ctx (17, 27).

The penetration of Ctx into cerebrospinal fluid (CSF) has been evaluated previously after the determination of Ctx by microbiological methods (21, 23). Limited information is available regarding the determination of CSF diffusion of Ctx and dCtx in pediatric patients with meningitis by using high-pressure liquid chromatography (HPLC) (1; P. Bégud, D. Floret, E. J. Raynaud, J. Sarlangues, G. Teyssier, and C. Safran, Program Abstr. 24th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 236, 1984). The disposition of Ctx and dCtx in serum has also been evaluated in adults with normal and impaired renal function (16, 29, 37). Few studies, however, have characterized the serum and CSF disposition of both Ctx and dCtx in infants and children with meningitis during a therapeutic course of Ctx (15).

In the present study, we investigated the pharmacokinetics and CSF penetration of Ctx and dCtx after intravenous administration of Ctx to infants and children with bacterial meningitis by using a specific HPLC assay technique.

MATERIALS AND METHODS

Subjects. Thirteen infants and children admitted to the Arkansas Children’s Hospital with clinically suspected meningitis, CSF indicative of bacterial meningitis, or both, were included in this open study. Patients with a positive history of hepatic, renal, or cardiovascular disease were excluded. Although all subjects exhibited elevated CSF leukocyte counts and hypoglycorrhachia on admission, none had either static or progressive encephalopathy or prior evidence of central nervous system infection. Informed parental consent and, when possible, patient assent, were obtained before inclusion of subjects in the study. The study protocol was approved by the Institutional Review Board for Human Experimentation.

Laboratory evaluation. At admission, each subject received a serum electrolyte panel, a complete blood cell count with differential, and quantitation of serum creatinine and blood urea nitrogen. CSF was obtained for culture, Gram stain, cell count, and protein and glucose determinations. Blood was also obtained for culture and for immunologic and serologic testing for suspected pathogens. Determination of serum levels of hepatic enzymes and measurement of the prothrombin time and partial thromboplastin time were performed if clinically indicated. Urine was obtained on admission for urinalysis and culture. Other laboratory tests (e.g., repeat cultures, electrolytes, and urinalysis) were performed when clinically indicated.

Drug administration. Ctx (1,000 mg; Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.) was reconstituted with 3 ml of normal saline for injection, resulting in a solution containing 300 mg of Ctx per ml. An appropriate volume of the reconstituted solution was further diluted in 50...
to 100 mL of compatible intravenous fluid (e.g., 5% dextrose-0.2% sodium chloride or 5% dextrose-0.45% sodium chloride). A 50-mg/kg dose of Ctx was administered at 6-h intervals via a peripheral vein over approximately 30 min (0.53 ± 0.16 h) by using a constant infusion pump (Infrotrol 6000; Valley Laboratories, Boulder, Colo.). Infusion times varied from subject to subject depending upon age, clinical condition, and fluid requirements. Infusion rates were the same for a given patient from dose to dose and were consistent with standard antibiotic administration procedures for our institution.

**Specimen collection.** Before the second scheduled Ctx dose on day 2 of therapy, an indwelling intravenous cannula was placed in a contralateral extremity and was converted to a heparin lock for the purpose of multiple blood sampling. Blood specimens (0.7 mL) were obtained at the following approximate times: preinfusion and 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, and 6.0 h postinfusion. Blood samples were collected into glass tubes not containing anticoagulant, permitted to clot at room temperature for 30 min, and centrifuged at 2000 × g and 4°C for 20 min. The serum was harvested and frozen immediately at −70°C until analysis. Spontaneously voided urine samples were obtained via external collection bags for a 4-h interval before infusion of the Ctx study dose and at 0- to 2-, 2- to 4-, and 4- to 6-h intervals thereafter. Urine volume and pH were recorded for each collection, and 10-mL samples were promptly frozen at −70°C until analysis. Lumbar punctures were performed 1 h after Ctx infusion on the day 2 of therapy, at which time a 1-mL sample of CSF was collected for determination of Ctx and dCtx concentrations. These samples were also frozen immediately at −70°C until analysis.

**Analyses.** Concentrations of Ctx and dCtx in serum, CSF, and urine were determined by a modification of the HPLC technique of Kees et al. (22). Serum and CSF samples (0.2 mL) were combined with an internal standard (0.05 mL of a 200-mg/mL solution of cefoxitin in phosphate buffer [pH 6.0] with tetrabutylammonium hydroxide). Ctx, dCtx, and cefoxitin were separated from serum by using C-2 bonded-phase disposable extraction columns (Bond Elut; Analytichem International, Inc., Harbor City, Calif.). Urine samples were diluted with phosphate buffer, pH 6, and processed as above. Chromatography was performed on an automated HPLC system (Waters Associates, Inc., Milford, Mass.) which consisted of a sample processor (WISP 710 B), a variable wavelength UV detector (model 481), a data module (model 730) processor interconnected with a programmable system controller (model M721), a pump (model 510), and a radial compression separation system (Z module) with a reversed-phase C-18 column. The mobile phase (phosphate buffer pH 4.8, with tetrabutylammonium hydroxide and methanol; 60%/40%) was pumped at a rate of 2 mL/min, with detection of both Ctx and dCtx accomplished at a wavelength of 240 nm and at 25°C. Quantitation of both Ctx and dCtx in serum, CSF, and urine was determined by peak area ratio comparison. Calibration curves performed with spiked samples of drug-free human serum were linear over the ranges of 10 to 160 µg/mL and 5 to 80 µg/mL for Ctx and dCtx, respectively. Between-day reproducibility studies (n = 14) with Ctx at 20, 80, and 160 µg/mL resulted in coefficients of variation of <10%, and for dCtx at 20 µg/mL, the coefficient of variation was <16%. Individual calibration curves for Ctx were constructed on each day that samples were assayed. The lower limits of detection were 2 and 1 µg/mL for Ctx and dCtx, respectively.

**Pharmacokinetic evaluation.** Serum concentration versus time data were evaluated by using ESTRIP (9) to obtain initial polyexponential parameter estimates. Final parameter estimates for Ctx were determined by using KINONITE/BAS (28), an iterative, nonlinear regression analysis program. When necessary, statistical evaluation by the method of Boxenbaum et al. (8) was carried out to determine the most appropriate compartmental model for the serum concentration-versus-time data from each subject. The following compartment model-dependent pharmacokinetic parameters were calculated (35) with appropriate corrections applied to adjust for infusion time (24): elimination rate constant k1, elimination half-life (t1/2), apparent volume of distribution (V), and total body clearance (CL). The following pharmacokinetic parameters were determined by noncompartmental methods based on statistical moment theory (7, 39) and are reported unless otherwise noted: mean residence time (MRT), reciprocal of mean residence time (1/MRT), elimination half-life (t1/2), apparent steady-state volume of distribution (Vss), total body clearance (CL), and renal clearance (CLr). Serum concentration data with detectable preinfusion concentrations were corrected for the calculation of noncompartmental parameters during repetitive dosing (4).

**Statistical analysis.** All grouped data are presented as mean ± standard deviation. Covariances between demographic and pharmacokinetic parameters were calculated by using linear, least-squares regression analysis. For each regression analysis, the correlation coefficient r was calculated, and the null hypothesis that x and y are independent variables (r = 0) was tested; a Student's t test was performed, with the null hypothesis that the slope of the regression line equaled zero; and an analysis of variance was calculated, and the null hypothesis that the regression of y on x was not linear was tested. All statistical analyses followed methods outlined by Batson (3), Dixon and Massey (10), or Snedecor and Cochran (33).

**RESULTS**

Of the 13 subjects, 12 were males. Subject ages ranged from 2 months to 12 years (1.75 ± 3.17 years) with 12 of the subjects having ages of <32 months. The mean weight, height, and body surface area for the study population were

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean concn ± SD (range) (µg/mL) in serum at time postinfusion (h):</th>
<th>Mean concn ± SD (range) (µg/mL) in CSF at 1 h postinfusion</th>
<th>CSF/serum ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.25</td>
<td>1.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Ctx</td>
<td>121.2 ± 23.1 (92.7–168.1)</td>
<td>61.44 ± 26.2 (25.8–97.2)</td>
<td>1.6 ± 3.1 (0.8–2.2)</td>
</tr>
<tr>
<td>dCtx</td>
<td>13.3 ± 7.8 (0–21.5)</td>
<td>19.3 ± 11.2 (8.2–28.8)</td>
<td>7.8 ± 7.8 (0.2–20.5)</td>
</tr>
</tbody>
</table>

*Postinfusion concentrations after the administration of a 50-mg/kg dose over approximately 30 min.*
was 0.954 ± 0.79 ± 0.873 (Table 2). The dependent and parameters Pharmacokinetic curves time of iterative intercept of iterative nonlinear regressions of the data.

FIG. 1. Mean Ctx (●) and dCtx (■) concentrations in serum in 13 infants and children with meningitis. The 0.5-h Ctx concentration corresponding to the end of the infusion was estimated from the intercept of iterative nonlinear nonlinear regressions of the data.

11.7 ± 8.9 kg, 76.4 ± 28 cm, and 0.52 ± 0.26 m², respectively.

Ctx pharmacokinetics. The mean Ctx serum concentration at 15 min postinfusion was 121.2 ± 23.1 μg/ml, with concentrations falling rapidly to approximately 2 μg/ml at 6 h postinfusion (Table 1 and Fig. 1). The mean 1-h-postinfusion CSF concentration of Ctx was 6.2 μg/ml, with a mean penetration into CSF of 10.1% when expressed as a ratio of observed CSF to serum concentrations (Table 1). Ctx CSF:serum penetration ratios ranged from 0 to 20%, with nondetectable Ctx CSF concentrations in 1 of 13 subjects.

Although all individual Ctx serum concentration-versus-time curves could be fitted to a two-compartment open model, statistical evaluation indicated that a one-compartment open model adequately described the data. Pharmacokinetic parameters determined by model-dependent and noncompartmental methods were calculated (Table 2). The mean t1/2 was approximately 0.8 h, the mean

\[ V_S = 0.361 \text{ liter/kg}, \text{ and the mean CL was 0.174 liter/h per kg.} \]

These parameters were not significantly different from those determined by model-dependent methods (Table 2). Approximately 61% of the dose was excreted unchanged in the urine within 6 h postinfusion, and the mean renal clearance was 0.174 liter/h per kg (Table 3). No significant correlations were observed between Ctx pharmacokinetic parameters and demographic parameters for the study population.

dCtx pharmacokinetics. Concentrations of dCtx in serum reached a maximum value (21.6 μg/ml) between 1 and 2 h (approximately 1.5 h) postinfusion (Fig. 1). The mean dCtx serum concentrations at 0.25, 1, and 6 h postinfusion were calculated (Table 1). The mean concentration of dCtx in CSF at 1 h postinfusion was 5.6 μg/ml, representing an average CSF penetration of 28.8% (Table 1). These values ranged from 0 to 103% with nondetectable dCtx CSF concentrations in 6 of the 13 subjects (46%).

The disposition of dCtx in serum was adequately characterized by a one-compartment open model with an apparent first-order formation and elimination phase (Fig. 1). The mean apparent t1/2 for dCtx was 2.1 h when determined by model-dependent methods. Approximately 35% of the Ctx dose was excreted in the urine as dCtx during the 6-h period postinfusion. The mean CLR of dCtx was 0.363 liter/h per kg (Table 3).

**DISCUSSION**

The average peak serum Ctx concentration in our subjects (121.2 μg/ml) was in close agreement with values reported for full-term neonates (2, 26) and for infants and children (18) when normalized for differences in the dose administered. Penetration of Ctx into CSF in our patients at 1 h postinfusion (Table 1) was variable (0 to 20%) and in agreement with both theoretical considerations (32) and actual observations in experimentally induced meningitis (31).

The mean t1/2 for our subjects (0.8 h) was shorter than previously reported values for infants (1.2 h) and children (1.5 h) who had infections other than meningitis (18). It was in good agreement, however, with values reported for adults

**Table 2. Comparison of Ctx pharmacokinetic parameters calculated by using model-dependent and noncompartmental methods for 13 infants and children with meningitis**

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean ± SD</th>
</tr>
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<tr>
<td></td>
<td>( K_e ) or ( 1/MRT )</td>
</tr>
<tr>
<td>Model-dependent</td>
<td>0.873 ± 0.338</td>
</tr>
<tr>
<td>Noncompartmental</td>
<td>0.954 ± 0.381</td>
</tr>
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</table>

* Elimination rate constant; \( V \), volume of distribution. When possible (for \( K_e \) versus \( 1/MRT \), \( V \) versus \( V_S \), and \( CL \)), a test for differences between methods was performed; all differences were not significant.
0.7 to 1.3 h) with normal renal function (16, 29, 38). The Vₚk for our patients (0.361 liter/kg) was smaller than previously reported values for infants (0.71 liter/kg) and children (1.37 liters/kg) with infections other than meningitis (18), but similar to the values reported for full-term, newborn infants (0.28 to 0.44 liter/kg) (2, 26) and adults (0.21 to 0.45 liter/kg) with normal renal function (12–14, 25, 29).

In our subjects, the urinary excretion of unchanged Ctx during the 6-h postinfusion period (approximately 61%) was in close agreement with values reported for adults with normal renal function (5, 12, 14). The CLₜ of Ctx in our subjects (0.174 liter/h per kg) was similar to that in adults with normal renal function (165 ml/min per 1.73 m² or approximately 0.141 liter/h per kg) (29). The mean CL of Ctx in our subjects (0.289 liter/h per kg) was in close agreement with values reported for adults with normal renal function (approximately 0.234 to 0.307 liter/h per kg) after Ctx quantitation by HPLC (16, 29). The differences between CL of Ctx in our patients and that in full-term, newborn infants (2, 26) were consistent with expected developmental differences in renal function and body mass-water relationships between the two age groups.

The disposition of dCtx in our subjects was variable, with the apparent mean peak concentration in serum (21.6 µg/ml) occurring approximately 1.5 h after infusion of the Ctx study dose. This value was similar to those reported for full-term, newborn infants with meningitis (approximately 12 µg/ml after an intravenous Ctx dose of 50 mg/kg) and adults with normal renal function (5 µg/ml after an intravenous dose of 15 mg/kg) when adjusted for dose size (16). The penetration of dCtx into CSF relative to serum concentration at the time of sampling was highly variable (0 to 103%), with nondetectable CSF dCtx levels in 6 of 13 subjects.

The mean apparent t½ for dCtx in our subjects (2.1 h) was in close agreement with values reported for adults (1.3 to 3 h) with normal renal function (5, 16, 38). The estimated CLₜ of dCtx (0.363 liter/h per kg) was larger than the expected glomerular filtration rate for the age group of the subjects studied. Since clinical restrictions did not give us the opportunity to administer dCtx in the absence of Ctx, Vₚk and CL of dCtx could not be determined.

The CSF bacteriocidal titers against the autologous organism in our patients had a mean of 1:180 (1:8 to 1:1,024) and demonstrated microbiologically effective concentrations (36). The comparison of the MIC and MBC results in light of the CSF concentrations of Ctx and dCtx suggested that the in vitro antimicrobial effects of Ctx or Ctx plus dCtx (17, 27) were occurring in vivo when analyzing the CSF bacteriocidal levels (36). The variability in CSF/serum concentrations for both Ctx and dCtx found in our patients could be an important consideration if a given patient with meningitis did not achieve microbial CSF drug concentrations. While our single postinfusion evaluation of CSF penetration of both compounds does not permit us to address CSF disposition throughout a 6-h dosing interval, it is important to note that our evaluation was undertaken at the approximate peak time for appearance of dCtx in serum, and at a time when substantial (approximately 45 to 50 µg/ml) amounts of Ctx were also present. The variability in CSF penetration for both Ctx and dCtx should be considered in any child with meningitis caused by a microorganism with documented in vitro sensitivity who does not show a satisfactory clinical response to Ctx therapy.

In summary, the disposition of Ctx and dCtx in serum was described adequately by a one-compartment, open model. Pharmacokinetic parameters for Ctx and dCtx calculated by model-dependent and noncompartmental methods were not significantly different. No significant correlations were observed between Ctx pharmacokinetic parameters (e.g., 1/MRT, Vₚk, CL) and patient demographic parameters (e.g., weight, height, body surface area, age). In infants and children with normal renal function, a 50-mg/kg dose of Ctx given at 6-h intervals should provide adequate concentrations of Ctx in serum and CSF in the majority of patients with meningitis. The pharmacokinetic characteristics of both Ctx and dCtx must be considered when pharmacodynamic modeling and dose calculation are determined for infants and children with meningitis. Definitive statements regarding the disposition of dCtx in infants and children must await further studies in which both the parent compound Ctx and its major active metabolite dCtx can be administered separately.

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