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Penetration of Cefprozil into Middle Ear Fluid of Patients with Otitis Media

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Penetration of cefprozil into the middle ear fluid was investigated in patients with chronic otitis media. A total of 89 patients ranging from 7 months to 11 years old participated in the study. The middle ear fluid was removed by ventilation tubes inserted through the tympanic membrane at times ranging from 0.38 to 5.97 h after oral administration of a single dose of 15 or 20 mg/kg of body weight. A blood sample was also collected as soon as the middle ear fluid was removed. Plasma samples were analyzed for the concentration of cefprozil by a high-performance liquid chromatographic assay. Middle ear fluid samples were analyzed for the concentration of cefprozil by a microbiological assay. The concentrations of cefprozil in plasma ranged from 0.38 to 15.97 μg/ml at the 15-mg/kg dose level and from 1.28 to 21.47 μg/ml at the 20-mg/kg dose level. The corresponding middle ear fluid concentrations of cefprozil ranged from 0.06 to 4.44 μg/ml and from 0.17 to 8.67 μg/ml, respectively. Cefprozil penetrates well into middle ear fluid in patients with chronic otitis media.

Cefprozil is a new oral cephalosporin. It has a spectrum of activity similar to that of cefaclor but greater activity against staphylococci and *Haemophilus influenzae* (2, 3, 5, 7, 10). It is also active against group A streptococci (3, 5) and *Moraxella catarrhalis* (2, 5). Cefprozil is more stable than cefaclor against penicillinase-producing *Staphylococcus aureus* isolates (7). In light of the broad antibacterial spectrum of cefprozil, it is expected to be an important addition to the armamentarium of antibiotics for the treatment of otitis media. The objective of the present study was to investigate the penetration of cefprozil in the middle ear fluid after administration of a single cefprozil dose of 15 or 20 mg/kg of body weight to patients undergoing ventilation tube installation for chronic otitis media infection with effusion. Chronic infection was confirmed by laboratory tests, clinical evaluation, and the patient's history.

A total of 89 male and female patients, ranging from 7 months to 11 years old, were enrolled from Children's National Medical Center in Washington, D.C. (20 patients), Children's Hospital of Alabama (29 patients), and Columbia-Presbyterian Medical Center in New York, N.Y. (40 patients). The patients' guardians gave written informed consents prior to participating in the study. Patients with indications of the need of placement of a tympanotomy tube were selected. None of the patients had a history or presence of clinically significant gastrointestinal, hepatic, renal, or hematological diseases. Patients did not have histories of a serious reaction to cephalosporins or penicillins. The patients had a mean age of 4.6 ± 3.1 years and a mean body weight of 20.1 ± 11.4 kg. Patients were randomly assigned to receive either a 15- or 20-mg/kg dose of cefprozil in a suspension formulation (250 mg of cefprozil per 5 ml of suspension). On the morning of the scheduled surgery (after an 8-h fast), patients received a 15- or 20-mg/kg dose of cefprozil and middle ear fluid was collected between 0.38 and 5.97 h postdose. Middle ear fluid was collected from one or both ears with a capillary tube at the time of insertion of the ventilation tube. One blood sample per patient, approximately 3 ml, was collected as soon as the middle ear fluid was obtained. The middle ear fluid samples were examined carefully to ensure no contamination of the sample by blood (contaminated samples were discarded). Within 30 min of collection, the blood sample was centrifuged at 1,000 × *g* at 0 to 5°C to separate the plasma. The middle ear fluid and plasma samples were stored frozen at or below −20°C pending analysis.

Plasma samples were analyzed for cefprozil by a validated high-performance liquid chromatography (HPLC)–UV method (11). Middle ear fluid samples from the left and right ears were combined, if collected from both the ears, and were analyzed for the concentration of cefprozil by a microbiological assay using *Micrococcus luteus* A24959 as the test organism and BBL Seed Agar Antibiotic Agar 1 as the test medium (7). The volume of middle ear fluid was estimated on the basis of the diameter of the tube, i.e. 10 μl of middle ear fluid per cm of tube. A total volume of 200 μl of normal saline was used to flush the middle ear fluid out of the tube. To ensure all the middle ear fluid was removed from the tube, the tube was cut into 3- to 4-mm pieces and then sonicated with the flushed solution for 5 min. Quality control samples containing cefprozil in plasma and middle ear fluid were prepared prior to the sample analysis and analyzed together with the study samples to verify the accuracy, precision, and reproducibility of the assay.

The standard concentrations ranged from 0.1 to 20 μg/ml for plasma samples and from 0.02 to 5 μg/ml for middle ear fluid samples. The lower limits of quantification were 0.1 and 0.02 μg/ml for plasma and middle ear fluid, respectively. The intra- and interday precision and accuracy levels of the quality

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TABLE 1. Concentrations of cefprozil in plasma and middle ear fluid of patients receiving a single 15-mg/kg oral dose

Time[a] postdose (h)	Cefprozil concn (μg/ml) in:	
	Plasma	Middle ear fluid
0.38	6.28	1.17
0.43	9.55	3.00
0.52	8.4	0.17
0.70	14.86	0.28
0.75	2.23	0.12
0.75	1.59	0.13
0.87	1.64	0.17
0.90	7.91	0.25
0.95	15.97	0.74
0.97	4.86	0.83
1.03	7.77	0.54
1.13	7.59	0.06
1.15	2.84	0.17
1.25	14.06	1.05
1.47	11.86	1.83
1.50	10.66	5.00
1.52	8.43	2.00
1.55	11.12	0.23
1.67	2.23	2.44
1.75	5.79	0.10
1.77	10.82	1.67
1.78	9.00	0.17
1.85	10.80	3.11
1.85	8.62	1.00
1.88	8.72	4.44
1.98	7.70	0.22
2.02	6.61	0.25
2.08	10.28	0.42
2.12	8.14	1.00
2.17	10.11	0.69
2.22	9.97	2.00
2.60	11.29	0.40
2.75	5.21	0.17
2.83	12.33	0.24
3.00	6.27	0.10
3.22	11.99	1.29
3.23	8.39	1.83
4.17	13.04	0.26
4.97	0.38	0.18
5.78	1.03	0.30

[a] Each time point represents one patient.

TABLE 2. Concentrations of cefprozil in plasma and middle ear fluid of patients receiving a single 20-mg/kg oral dose

Time[a] postdose (h)	Cefprozil concn (μg/ml) in:	
	Plasma	Middle ear fluid
0.48	1.28	0.17
0.48	5.25	0.17
0.50	4.57	2.50
0.53	3.98	0.35
0.60	10.47	0.75
0.73	5.57	0.83
0.73	2.70	0.25
0.83	14.61	5.12
0.90	15.96	0.50
1.08	21.47	8.67
1.08	3.81	0.42
1.12	17.13	1.25
1.20	13.01	5.00
1.33	17.07	3.22
1.42	13.94	0.38
1.62	12.56	0.83
1.67	14.34	2.00
1.73	8.67	0.17
1.75	10.18	1.67
1.83	7.89	0.83
1.92	15.87	2.75
1.93	15.09	1.50
1.95	9.94	2.50
2.00	11.58	0.42
2.03	10.92	2.94
2.10	14.88	1.00
2.25	8.30	0.50
2.38	10.22	1.70
2.57	13.89	0.25
2.70	6.50	0.30
2.72	12.03	2.50
2.75	5.26	1.44
2.80	7.73	1.72
2.97	8.36	3.52
3.55	7.31	0.86
4.08	5.92	6.20
4.58	6.50	0.94
4.83	2.55	0.42
5.28	2.79	0.30
5.97	2.20	0.59

[a] Each time point represents one patient.

control samples for plasma (2 and 5 μg/ml) and middle ear fluid (0.5 and 3 μg/ml) were less than 10% relative standard deviation. The predicted concentrations of the quality control samples in plasma and middle ear fluid deviated less than 8% from the corresponding nominal concentrations for both matrices. The microbiological assay correlated well with the HPLC assay. The predicted concentrations of the quality control samples from both assays were within ±15% of each other.

The concentrations of cefprozil in plasma and middle ear fluid following administration of 15- and 20-mg/kg oral doses are shown in Tables 1 and 2, respectively, and presented in Fig. 1. A total of nine middle ear fluid samples had volumes too small for analysis. The concentrations of cefprozil in plasma ranged from 0.38 to 15.97 μg/ml after administration of the 15-mg/kg oral dose and 1.28 to 21.47 μg/ml after administration of the 20-mg/kg oral dose. The concentrations of cefprozil in middle ear fluid after administration of 15- and 20-mg/kg oral doses ranged from 0.06 to 4.44 and 0.17 to 8.67 μg/ml, respectively. The penetration of cefprozil into the middle ear fluid was rapid, as indicated by the substantial concentrations (0.17 to 3.00 μg/ml) occurring within 30 min after administration (Tables 1 and 2). The MIC of 90% of strains tested (MIC_{90}) of cefprozil against the most common pathogens associated with middle ear fluid are 0.25, 2, and 2 μg/ml for *Streptococcus pneumoniae*, *H. influenzae*, and *M. catarrhalis*, respectively. The levels of cefprozil in the middle ear fluid remained greater than the MIC_{90} for *S. pneumoniae* for at least 6 h after administration of a 15- or 20-mg/kg dose. The levels of cefprozil in some of the middle ear fluid samples also exceeded the MIC_{90} of *H. influenzae* and *M. catarrhalis*.

The penetration of cefprozil into middle ear fluid is comparable to that of many other oral cephalosporins and penicillins. At 2 h after administration of a 750-mg dose of cefuroxime, the middle ear fluid levels were 0.73 to 1.70 μg/ml (8). At 2 to 5 h after a single 250-mg dose of cefuroxime axetil, the middle ear fluid concentrations of cefuroxime were 0.20 to 4.85 μg/ml (4). The middle ear fluid concentrations of amoxicillin were 0.17 to 5.6 μg/ml at 0.5 to 4 h after an amoxicillin dose of 15 mg/kg of body weight (6). Following a 15-mg/kg cefaclor dose, the

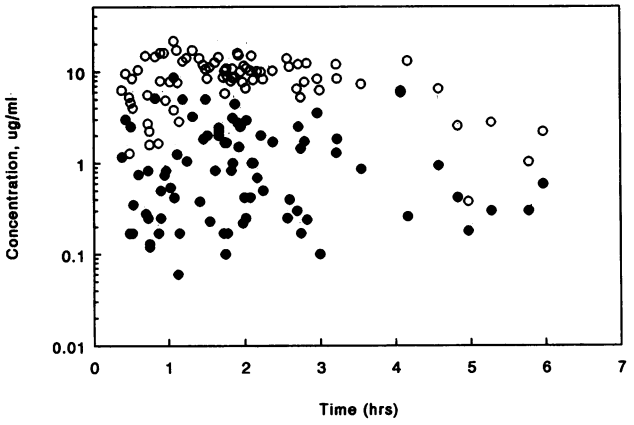

FIG. 1. Individual profiles of cefprozil concentrations in plasma and middle ear fluid versus time for patients receiving a single 15- or 20-mg/kg oral dose. ○, plasma; ●, middle ear fluid.

middle ear fluid concentrations were 1.3 to 3.8 μg/ml at 0.5 to 2 h after administration (6). Similar results were reported for penicillin V, erythromycin estolate, ampicillin, and trimethoprim (9). The corresponding middle ear fluid concentrations at about 1 h postdosing were 0.17 μg of penicillin V per ml after a 10-mg/kg dose, 1.95 μg of erythromycin per ml after a 10-mg/kg dose, 0.25 μg of ampicillin per ml after a 25-mg/kg dose, and 0.37 μg of trimethoprim per ml after a 4-mg/kg dose (9). All these agents have been used in treating patients experiencing otitis media.

In the phase III trials of treatment of recurrent otitis media, clinically significant improvement was observed after oral administration of a dosage of 15 mg/kg every 12 h (1, 12). Comparable clinical outcomes were found under the dosing regimens of 15 and 20 mg/kg every 12 h (data on file). Cefprozil eradicated 91% of *S. pneumoniae* strains, 95% of *H. influenzae* strains, and 86% of *M. catarrhalis* strains causing acute otitis media (1). The time the middle ear fluid (from chronic otitis media) concentration remained above the MIC_{90} was shorter for *H. influenzae* and *M. catarrhalis* than for *S. pneumoniae*. Comparable clinical outcomes in the treatment of recurrent otitis media caused by the three organisms were observed (1, 12). The results suggest that concentrations that exceed MIC_{90} may not be necessary for effective treatments when host defense mechanisms are adjunctly involved. It is also possible that penetration levels of cefprozil into middle ear exudate may be higher during the infection period than the noninfection period.

In summary, cefprozil penetrates well into middle ear fluid in patients with chronic otitis media.

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