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Excretion of Cefprozil into Human Breast Milk

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The excretion of cefprozil into breast milk in nine healthy, lactating female subjects was investigated. Each subject received a single 1,000-mg oral dose of cefprozil consisting of *cis* and *trans* isomers in an approximately 90:10 ratio. Serial blood, urine, and breast milk samples were collected and analyzed for the concentrations of the *cis* and *trans* isomers by a specific high-pressure liquid chromatography-UV assay. The mean pharmacokinetic parameters for both isomers were essentially the same. The mean peak concentrations in plasma for the *cis* isomer were 14.8 μg/ml, and the area under the concentration curve was 54.8 μg · h/ml. The mean values of elimination half-life, renal clearance, and urinary excretion for the *cis* isomer were 1.69 h, 164 ml/min, and 60%, respectively. The mean concentrations in milk of the *cis* isomer over a 24-h period ranged from 0.25 to 3.36 μg/ml, with the maximum concentration appearing at 6 h after dosing. The average maximum concentration in milk of the *trans* isomer was less than 0.26 μg/ml. The concentrations of the *trans* isomer in plasma and in breast milk were about 1/10 of those for the *cis* isomer. Less than 0.3% of the dose was excreted in breast milk for both isomers of cefprozil. Even if one assumes that the concentration of cefprozil in milk remains constant at 3.36 μg/ml (the highest concentration of cefprozil observed in breast milk), an infant ingesting an average of 800 ml of milk per day will be exposed to a maximum amount of about 3 mg of cefprozil per day. This value represents about 0.3% of the maternal dose. Low excretion of cefprozil in breast milk and the excellent safety profile of cefprozil suggest that this cephalosporin may be administered to nursing mothers when indicated.

Cefprozil is an oral cephalosporin consisting of *cis* and *trans* isomers in an approximately 90:10 ratio. The structure is similar to that of other oral cephalosporins with a propenyl side chain. Cefprozil has a broad antimicrobial spectrum. It is reported to be more active than cefaclor and cephalexin against streptococci, *Listeria monocytogenes*, and *Haemophilus influenzae* (12). Comparison of cefprozil and cefaclor against *Staphylococcus aureus* isolates, the MICs of cefprozil and cefaclor against 50% of the strains tested are 0.5 and 1 μg/ml, respectively, for the strains lacking penicillinase and 2 and 8 μg/ml, respectively, for the strains producing penicillinase. Cefprozil has activity comparable to that of cefaclor and is more active than cephalexin against members of the family *Enterobacteriaceae* (5, 8, 12, 17).

Cefprozil demonstrates dose-proportional pharmacokinetics in the oral dose range of 250 to 1,000 mg (1, 3). The elimination half-life ($t_{1/2}$) of cefprozil is about 1.3 h. At the 1,000-mg dose level, the maximum concentration in plasma C_{max} is around 18 μg/ml and appears at about 1.5 h after dosing (1, 3). The values for human serum protein binding of the *cis* and *trans* isomers are approximately 36 and 44%, respectively (20). Cefprozil is cleared primarily by urinary excretion, and approximately 55 to 70% of intact cefprozil is recovered in urine (1, 3). The pharmacokinetics of the two isomers have been shown to be similar after oral administration (18, 20, 21).

Antibiotics have been widely used in nursing women to treat bacterial infections. Thus, nursing women are potential recipients of therapy with cefprozil. Because of increasing emphasis on the breast-feeding of infants, evaluation of the excretion of drugs into breast milk is important. This study was designed to investigate the extent of excretion of cefprozil into human breast milk after the administration of a single 1,000-mg oral dose of cefprozil to lactating women.

MATERIALS AND METHODS

Antibiotics. Cefprozil was supplied as a capsule containing approximately 250 mg of cefprozil (lot 20823). Each 1,000-mg dose was individually packaged in a bottle containing four 250-mg cefprozil capsules.

Subjects. Nine healthy, lactating female volunteers were selected. All subjects had decided to discontinue breast feeding their infants prior to recruitment into the study. Time of lactation was between 6 and 12 months. The subjects were selected with no history or evidence of chronic infectious disease, heart disease, renal disease, hepatic disease, pulmonary obstructive disease, bronchial asthma, hypertension, or glaucoma. Subjects did not have a history of drug hypersensitivity or intolerance. Physical examination, EKG, and clinical laboratory results indicated these women were healthy. The subjects had a mean ± standard deviation age of 29 ± 3 years (range, 24 to 35), a mean body weight of 59 ± 7 kg (range, 48 to 68), and an average height of 164 ± 8 cm (range, 147 to 174).

Study design. This was an open, single-dose study designed to determine the extent of excretion of cefprozil into human breast milk. Nine women entered the clinical site on the evening prior to the dosing study day and stayed until 24 h after dosing. After signing an informed consent, each subject received a single oral 1,000-mg dose of cefprozil. All

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subjects fasted overnight prior to dosing and until 4 h postdose.

Drug administration. Four capsules of 250 mg of cefprozil were administered one at a time directly to the subjects. The capsules were swallowed with 200 ml of tap water without chewing or crushing the dosage form. The subjects remained ambulatory for at least 10 min every half-hour during the first 2 h after drug intake.

Sample collection. Approximately 5 ml of blood was collected at each sampling time into tubes containing 143 U of sodium heparin. The blood samples were taken at predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, and 12 h after dosing. Blood samples were centrifuged, and the resulting plasma was prepared within 1 h after collection and stored at −20°C.

Urine samples were collected from each subject over the following intervals: predose and 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h after dosing. Urine specimens were kept refrigerated during the collection period. The volume and the pH of each collection were measured to the closest 1 ml and 0.1 pH units, respectively. Exactly 5 ml of urine was transferred to a screw-cap polypropylene tube containing 5 ml of 0.02 M acetate buffer, pH 3.8. The buffer-diluted urine was mixed thoroughly and stored frozen at −20°C.

Breast milk samples were collected from each subject according to the following schedule: predose and 2, 4, 6, 8, 12, and 24 h after dosing. The subjects were instructed to aspirate each breast of all available milk at the scheduled times. A mechanical pump was used to achieve as complete a collection as possible. Milk samples were stored in separate collection vessels for each time point. The volume of each collection was measured to the closest 1 ml. Exactly 5 ml of milk was transferred to a screw-cap polypropylene tube and stored frozen at −20°C.

Sample analyses. Plasma, urine, and breast milk samples were analyzed for intact *cis* and *trans* isomers of cefprozil by validated high-pressure liquid chromatography-UV methods (20). Plasma, urine, and breast milk quality control (QC) samples were prepared prior to the initiation of the study and sent to the clinical site. They were returned with the study samples and assayed with the study samples to verify the accuracy, precision, and reproducibility of the assay and the stability of the *cis* and *trans* isomers during storage and shipment.

Standard curves in plasma and urine were linear for both isomers. The standard curves of the two isomers ranged from 0.1 to 20.0 μg/ml for the plasma assay and from 5 to 500 μg/ml for the urine assay. The lowest quantification limits for both isomers were 0.1 and 5 μg/ml in the plasma and urine assays, respectively. The between-day and within-day errors for plasma and urine QC samples were less than 15 and 4%, respectively, for both isomers. The mean observed QC concentrations deviated less than 12 and 3% from the corresponding nominal concentrations for both isomers in plasma and urine, respectively.

Standard curves for the *cis* and *trans* isomers in breast milk were also linear. The standard curves of the two isomers ranged from 0.05 to 7.5 μg/ml. The lowest quantification limits for both isomers were 0.05 μg/ml. The between-day and within-day errors for breast milk QC samples were less than 3% for both isomers. The mean observed QC concentrations deviated less than 9% from the corresponding nominal concentrations for both isomers.

The performance of standard curves and QCs indicated these analyses were accurate, precise, and reproducible.

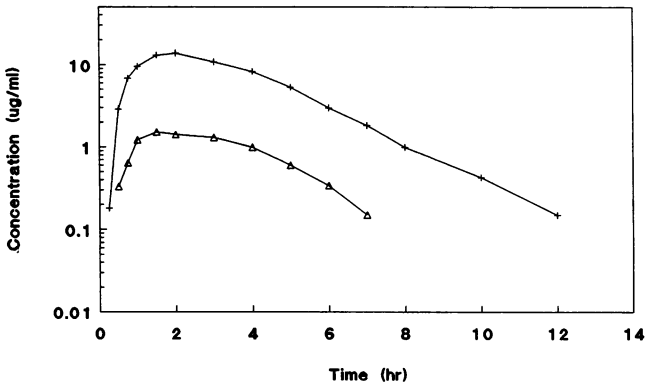

FIG. 1. Mean C versus t curve for the *cis* and *trans* isomers of cefprozil. +, *cis* isomer; △, *trans* isomer.

The QC results also demonstrated that both isomers were stable during sample storage and shipment.

Pharmacokinetic analyses. Noncompartmental pharmacokinetic parameters were calculated by standard methods (9, 16): the C_{max}, the corresponding sampling time (T_{max}), area under the concentration in plasma (C) versus time (t) curve from 0 h to infinity ($AUC_{0-\infty}$), the area under the first moment of the C versus t curve (AUMC), mean residence time in the body (MRT), elimination $t_{1/2}$, total urinary recovery as percentage of dose administered (%UR), and renal clearance (CL_R). Terminal elimination rate constants (β) were estimated for C versus t profiles by performing linear least-squares regression analysis of the linear segment of the log C versus t data. The data were fitted to the following function: $\ln C = \ln B - \beta t$, starting with the last three C versus t datum points. The procedure continued, adding preceding datum points one at a time, until C_{max} was reached. The terminal log-linear portion was defined by the data set for which the mean square error term from the regression was minimized. Elimination $t_{1/2}$ was estimated by dividing −0.693 by β. AUC and AUMC from 0 h to t_m, the time at which the drug concentration appeared to decline in a log-linear manner, were calculated by using the trapezoidal rule. From t_m to t_n, the last nonzero datum point, the log-trapezoidal rule was used, and then the data were extrapolated to infinity (16).

RESULTS

Safety assessment. A total of seven subjects experienced mild to moderate nausea, and two of the seven subjects also experienced vomiting at 8 min and 1 h after dosing. Two subjects had no adverse experiences at all. Treatment was not needed for any of the adverse experiences, and none lasted beyond 4 h after dosing.

No significant laboratory abnormalities occurred during the study. No abnormal findings were noted on poststudy physical examinations.

Pharmacokinetics. The mean C versus t profiles for the *cis* and *trans* isomers are presented in Fig. 1. Although two subjects vomited after the administration of cefprozil, there was no apparent decrease in the values of AUC, C_{max}, or %UR. The mean pharmacokinetic parameters C_{max}, T_{max}, MRT, $t_{1/2}$, $AUC_{0-\infty}$, %UR, and CL_R for the intact *cis* and *trans* isomers of cefprozil are provided in Table 1.

Cefprozil consists of the *cis* and *trans* isomers in an approximately 90:10 ratio. The C_{max} and $AUC_{0-\infty}$ values for

TABLE 1. Mean (standard deviation) pharmacokinetic parameters for the *cis* and *trans* isomers of cefprozil after oral administration of 1,000 mg of cefprozil

Isomer	C_{max} (μg/ml)	T_{max}[a] (h)	MRT (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg · h/ml)	CL_R (ml/min)	%UR
cis	14.8 (3.2)	2.0 (1.5–3.0)	3.38 (0.39)	1.69 (0.37)	54.8 (10.9)	164 (33)	60 (7)
trans	1.9 (0.8)	2.0 (1.0–3.0)	3.41 (0.59)	1.35 (0.56)	6.2 (1.2)	161 (65)	46 (9)

[a] Median (minimum–maximum) reported.

the *trans* isomer were approximately 1/10 of the values observed for the *cis* isomer. The respective mean values of C_{max} and $AUC_{0-\infty}$ were 14.8 μg/ml and 54.8 h · μg/ml for the *cis* isomer and 1.9 μg/ml and 6.2 h · μg/ml for the *trans* isomer. The values of CL_R and %UR were similar for the two isomers. The respective mean values for CL_R and %UR were 164 ml/min and 60% for the *cis* isomer and 161 ml/min and 46% for the *trans* isomer. The other pharmacokinetic parameters, such as T_{max}, $t_{1/2}$, and MRT, were essentially the same for the two isomers. The respective values of $t_{1/2}$ and MRT were 1.69 and 3.38 h for the *cis* isomer and 1.35 and 3.41 h for the *trans* isomer. The median values of T_{max} for both isomers were 2 h.

Cefprozil concentrations in breast milk increased and decreased slowly over the 24-h period after dosing in comparison with the *C* versus *t* profile. The mean concentrations in milk of the *cis* isomer were in the range of 0.3 to 3.4 μg/ml and generally peaked at 6 h after dosing. Because of the relatively slower elimination from milk than plasma (Fig. 2), the concentrations in breast milk of the *cis* isomer were higher than those in plasma from 6 h after dosing. The mean concentration in milk of the *cis* isomer at 24 h after dosing was 0.3 μg/ml, while most of the concentrations in plasma at 12 h were less than the assay quantification limit (0.1 μg/ml). Therefore, the ratios of concentration in breast milk to concentration in plasma (M/P) of the *cis* isomer increased with time. The mean M/P ratio increased from 0.05 at 2 h postdose to 5.67 at 12 h postdose (Table 2). The ratio of M/P $AUC_{0-\infty}$ was 0.6 ± 0.2.

Only 22 of 63 breast milk samples had quantifiable concentrations (≥0.05 μg/ml) of the *trans* isomer, which is consistent with the *trans* isomer representing about 10% of the *cis* isomer. Since only trace amounts of *trans* isomer were found in the breast milk samples, no M/P ratio was calculated.

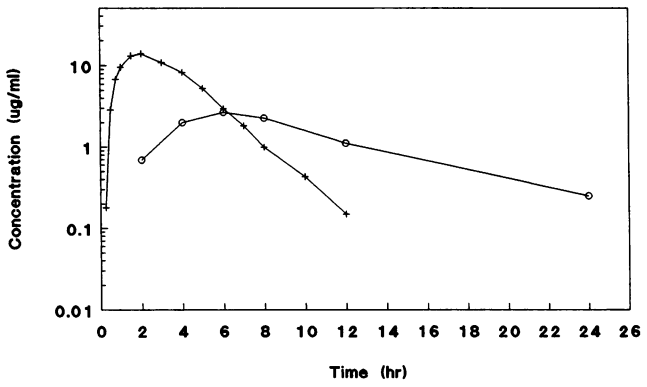

FIG. 2. Mean concentrations in plasma and milk for the *cis* isomer of cefprozil. +, plasma; ○, milk.

DISCUSSION

The overall pharmacokinetic characteristics of cefprozil are consistent with those previously reported for young female subjects (4a). The low concentration of cefprozil in breast milk is comparable with values previously reported for other β-lactam antibiotics. The peak concentrations in breast milk of ampicillin (4, 13), amoxicillin (11), cephalexin (11, 14), cefroxadine (14), and cefadroxil (11, 13) after approximately a 1-g oral dose was given were 0.9, 0.8, 0.5, 0.4, and 1.6 μg/ml, respectively. When parenteral β-lactam antibiotics were administered at a 1-g dose, the breast milk levels were also low. The peak concentrations in milk were 2.4, 1.5, 1.7, 1.6, and <0.5 μg/ml for cefsulodin (6), cefazolin (24), ceftriaxone (10), cefotaxime (15), and cefoxitin (7), respectively.

Excretion of a drug across the capillary endothelium into the alveolar cells and, subsequently, into the lumen with the milk is determined by a number of factors. In general, drugs with high bioavailability, low protein binding, small volumes of distribution, and long plasma $t_{1/2}$ have a great potential to be excreted in milk. However, certain other physicochemical properties such as the degree of drug ionization in maternal plasma and lipophilicity are also important determinants. Most drugs enter the breast milk by diffusion of the nonionized form of the drug. Cefprozil is a weak acid (low pKa) and therefore is more ionized in the maternal plasma, relative to many drugs with higher pKa's. Further, many weak acids exhibit low lipophilicity, and these two characteristics may explain cefprozil's low excretion into breast milk. This phenomenon is also observed in other cephalosporins and penicillins, all of which are weak acids.

The M/P ratio does not necessarily remain constant under all conditions and at all times after dosing, as was the case with cefprozil (Table 2). It is common to find that the M/P ratio increases with time after drug administration. The ratio may be affected by milk volume, pH level, protein and fat content of the milk, and physicochemical properties of the drug. Pharmacokinetic characteristics of a drug have been demonstrated to affect the M/P ratio over different times

TABLE 2. Mean (standard deviation) concentrations in breast milk and M/P ratios for the *cis* isomer of cefprozil

Time (h)	Concn (μg/ml)	M/P ratio
0	<LLQ[a]	<LLQ
2	0.7 (0.3)	0.05 (0.02)
4	2.5 (1.5)	0.31 (0.13)
6	3.4 (2.3)	1.26 (0.65)
8	2.9 (2.1)	2.87 (1.26)
12	1.3 (0.7)	5.67 (1.86)
24	0.3 (0.1)	ND[b]

[a] LLQ, lowest limit quantifiable.
[b] ND, not determined because concentrations in plasma were below the lowest limit quantifiable.

postdose (23). Therefore, use of the M/P ratio to estimate drug dose in milk for the general population is difficult. A much better estimation is given by the use of the maximum concentration in breast milk value and an estimate of the daily milk consumption in infants. The mean peak concentration in breast milk of cefprozil is 3.4 μg/ml when a 1-g dose is administered to a mother. Even if one assumes that the concentration of cefprozil in milk remains constant at 3.36 μg/ml (the highest concentration of cefprozil observed in breast milk), an infant ingesting an average of 800 ml of milk (22) per day will be exposed to a maximum amount of about 3 mg of cefprozil per day. This value represents about 0.3% of the maternal dose. The recommended dosing regimen for cefprozil in the treatment of most infections is a 500-mg dose twice a day. Cefprozil exhibits linear pharmacokinetics in the dose range of 250 to 1,000 mg. Therefore, it is reasonable to assume that the peak concentration in breast milk would average around 1.7 μg/ml when 500 mg of cefprozil is administered to a mother. Therefore, the extent of exposure to cefprozil for an infant could be less than the above estimation. The limited amount of cefprozil exposure to an infant probably would not cause significant clinical concern on the basis of the excellent safety profile of cefprozil in adults (1, 3). It is most likely that cefprozil is completely absorbed in infants, as in adults (19). Therefore, cefprozil should not cause the infant diarrhea associated with most parenteral antibiotics, when incomplete absorption disturbs the oropharyngeal flora.

In summary, low excretion of cefprozil in breast milk and the excellent safety profile of cefprozil suggest that this cephalosporin may be administered to nursing mothers when indicated.

REFERENCES

1. **Barbhaiya, R. H., C. R. Gleason, W. C. Shyu, R. B. Wilber, R. R. Martin, and K. A. Pittman.** 1990. Phase I study of single-dose BMY-28100, a new oral cephalosporin. Antimicrob. Agents Chemother. **34**:202–205.
2. **Barbhaiya, R. H., U. A. Shukla, C. R. Gleason, W. C. Shyu, and K. A. Pittman.** 1990. Comparison of the effects of food on the pharmacokinetics of cefprozil and cefaclor. Antimicrob. Agents Chemother. **34**:1210–1213.
3. **Barbhaiya, R. H., U. A. Shukla, C. R. Gleason, W. C. Shyu, R. B. Wilber, R. R. Martin, and K. A. Pittman.** 1990. Phase I study of multiple-dose cefprozil and comparison with cefaclor. Antimicrob. Agents Chemother. **34**:1198–1203.
4. **Branebjerg, P. E., and L. Heistergberg.** 1987. Blood and milk concentrations of ampicillin in mothers treated with pivampicillin and in their infants. J. Perinat. Med. **15**:555–558.

4a. **Bristol-Myers Squibb Company.** Unpublished data.

5. **Chin, N. X., and H. C. Neu.** 1987. Comparative antibacterial activity of a new oral cephalosporin, BMY 28100. Antimicrob. Agents Chemother. **31**:480–483.
6. **Cho, N., K. Fukunaga, and K. Kunii.** 1989. Pharmacokinetic studies on cefsulodin in perinatal period. Jpn. J. of Antibiot. **42**:2735–2743.
7. **Dubois, M., D. Delapierre, L. Chanteux, R. Lambotte, R. Kramp, and A. Dresse.** 1981. A study of the transplacental transfer and the mammary excretion of cefoxitin in humans. J. Clin. Pharmacol. **21**:477–483.
8. **Eliopoulos, G. M., E. Reiszner, C. Wennersten, and R. C. Moellering, Jr.** 1987. In vitro activity of BMY-28100, a new oral cephalosporin. Antimicrob. Agents Chemother. **31**:653–656.
9. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics, 2nd ed., p. 409–417. Marcel Dekker, Inc., New York.
10. **Kafetzis, D., D. C. Brater, J. E. Fanourgakis, J. Voyatzis, and P. Georgakopoulos.** 1983. Ceftriaxone distribution between maternal blood and fetal blood and tissues at parturition and between blood and milk postpartum. Antimicrob. Agents Chemother. **23**:870–873.
11. **Kafetzis, D. A., C. A. Siafas, P. A. Georgakopoulos, and C. J. Papadatos.** 1981. Passage of cephalosporins and amoxicillin into the breast milk. Acta Pediatr. Scand. **70**:285–288.
12. **Leitner, F., T. A. Pursiano, R. E. Buck, Y. H. Tsai, D. R. Chisholm, M. Misiek, J. V. Desiderio, and R. E. Kessler.** 1987. BMY-28100, a new oral cephalosporin. Antimicrob. Agents Chemother. **31**:238–243.
13. **Matheson, I., M. Samseth, and H. A. Sande.** 1988. Ampicillin in breast milk during puerperal infections. Eur. J. Clin. Pharmacol. **34**:657–659.
14. **Matsuda, S.** 1984. Transfer of antibiotics into maternal milk. Biol. Res. Pregnancy. **5**:57–60.
15. **Novick, W. J.** 1982. Levels of cefotaxime in body fluids and tissues. Rev. Infect. Dis. **4**(Suppl.):346–353.
16. **Riegelman, S., and P. Collier.** 1980. The application of statistical moment theory to the evaluation of *in vivo* dissolution time and absorption time. J. Pharmacokinet. Biopharm. **8**:509–534.
17. **Scribner, R. K., M. I. Marks, and B. D. Finkhouse.** 1987. In vitro activity of BMY-28100 against common isolates from pediatric infections. Antimicrob. Agents Chemother. **31**:630–631.
18. **Shyu, W. C., K. A. Pittman, R. B. Wilber, G. R. Matzke, and R. H. Barbhaiya.** 1991. Pharmacokinetics of cefprozil in healthy subjects and patients with renal impairment. J. Clin. Pharmacol. **31**:362–371.
19. **Shyu, W. C., V. R. Shah, D. A. Campbell, R. B. Wilber, K. A. Pittman, and R. H. Barbhaiya.** The absolute bioavailability and dose proportionality of cefprozil. J. Clinical Pharmacol., in press.
20. **Shyu, W. C., U. A. Shukla, V. R. Shah, E. A. Papp, and R. H. Barbhaiya.** 1991. Simultaneous high pressure liquid chromatography analysis of cefprozil diastereoisomers in a pharmacokinetic study. Pharm. Res. **8**:992–996.
21. **Shyu, W. C., R. B. Wilber, K. A. Pittman, D. C. Garg, and R. H. Barbhaiya.** 1991. Pharmacokinetics of cefprozil in healthy subjects and patients with hepatic impairment. J. Clin. Pharmacol. **31**:372–376.
22. **Wilson, J. T.** 1981. Drug in breast milk, p. 7–9. ADIS Press Australia Pty. Ltd., Balgowlash, Australia.
23. **Wilson, J. T., R. D. Brown, J. L. Hinson, and J. W. Dailey.** 1985. Pharmacokinetic pitfalls in the estimation of the breast milk/plasma ratio for drugs. Annu. Rev. Pharmacol. Toxicol. **25**:667–689.
24. **Yoshioka, H., K. Cho, M. Takimoto, S. Maruyama, and T. Shimizu.** 1979. Transfer of cefazolin into human milk. J. Pediatr. **94**:151–152.