ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1983, p. 479–480
0066-4804/83/030479-02$02.00/0

Vol. 23, No. 3

Ceftazidime Levels in Human Breast Milk

JORGE D. BLANCO,[1]* JAMES H. JORGENSEN,[2] YOLANDA S. CASTANEDA,[1] AND SHARON A. CRAWFORD[2]

Departments of Obstetrics and Gynecology[1] and Pathology,[2] The University of Texas Health Science Center at San Antonio, San Antonio, Texas 78284

Received 15 December 1982/Accepted 27 December 1982

Ceftazidime in the breast milk of 11 puerperal women were determined by bioassay. Each patient received 2 g of ceftazidime intravenously every 8 h for 5 days. The mean (± standard deviation) ceftazidime concentrations in the milk were: 3.8 ± 2.0 (before the next dose), 5.2 ± 3.0 (1 h after), and 4.5 ± 1.7 μg/ml (3 h after). Ceftazidime was excreted in breast milk at relatively constant levels between days 2 and 4 of therapy.

Newer cephalosporins have been used widely in postpartum women (2, 3, 6), but little is known about their transfer into human breast milk. The available information is limited to only a few cephalosporins and is derived from experiments with a single antibiotic dose (1, 7, 8). In clinical practice, patients receive therapeutic antibiotics for several days. With multiple doses, accumulation of cephalosporins in breast milk could occur. This study describes the levels of ceftazidime (CAZ) in the breast milk of patients being treated for postpartum endometritis.

From May to August 1982, we collected serum and breast milk samples from women receiving 2 g of CAZ intravenously every 8 h. All patients had endometritis after cesarean section. During days 2 to 4 of therapy, 5 ml of serum and 5 to 10 ml of breast milk were collected. Since breast milk collection would stimulate further breast engorgement, no attempt was made to empty the breast completely. The samples were collected 30 min before, 1 h after, and 3 h after an antibiotic infusion. Each blood sample was centrifuged, and the serum was stored at −72°C. Immediately after collection, the breast milk was vigorously mixed and stored at −72°C.

Within a month of collection, each sample was assayed for CAZ by an agar diffusion bioassay with *Escherichia coli* ATCC 25922. Molten heart infusion agar (Difco Laboratories, Detroit, Mich.) (pH 7.4) was seeded with the *E. coli* and allowed to solidify in 150- by 15-mm plastic petri dishes. Duplicate 25-μl portions of each sample and of the standards were then placed in 6-mm wells cut into the seeded agar. The CAZ standards were prepared in pooled normal human sera at concentrations of 40, 20, 10, and 1 μg/ml and in antibiotic-free breast milk with concentrations of 20, 10, 5, and 1 μg/ml. After incubation of the assay plates for 18 to 20 h, the zone of inhibition around each well was measured, and standard curves were constructed. The concentration of the samples was determined from the standard curve with the appropriate diluent (9). All samples with zone diameters larger than the standards were reassayed after dilution in serum or antibiotic-free milk.

Continuous data were analyzed by an unpaired, two-tailed Student's *t* test.

A total of 11 patients participated in the study and received an average of 12.6 ± 1.7 doses of CAZ. We collected 14 breast milk samples before the next CAZ dose, 12 samples 1 h after a dose, and 10 samples 3 h after a dose. The mean concentrations (± standard deviation [SD]) of milk collected at each time were 3.8 ± 2.0, 5.2 ± 3.0, and 4.5 ± 1.7 μg/ml, respectively. These values were not statistically different.

Serum samples were obtained from eight patients before and 1 h after a dose. The mean (± SD) levels for these pairs were 7.6 ± 3.8 and 71.8 ± 47.7 μg/ml, respectively.

Fifteen of the milk samples were collected before the patient had received seven doses of CAZ (approximately the midway point of therapy), and 21 samples were collected after seven doses. A comparison of these two groups shows that the mean CAZ level in breast milk before seven doses was 3.9 ± 1.6, as compared with 4.9 ± 2.7 μg/ml for the breast milk collected after seven doses. Individual analysis of the predose, 1-h, and 3-h mean levels among the milk collected before and after seven doses also reveals no significant difference at any time interval.

The mean weight (± SD) for the 11 patients was 72.7 ± 16.1 kg. There was no correlation between the weight of the patient and the CAZ concentrations in breast milk.

At present there is little information about the levels of cephalosporins in breast milk, but these agents are increasingly being used to treat puerperal women (2, 3, 6). Also, many of the reports

describe single-dose experiments which are not similar to the multiple doses usually administered in clinical practice.

Dubois and co-workers did not detect cefoxitin in human breast milk after a 1-g intramuscular injection; however, the lower limit of the antibiotic assay was 0.5 μg/ml (1). With a single 1-g dose of cefotaxime intravenously, Kafetzis et al. found mean antibiotic levels in breast milk of 0.26 ± 0.08 μg/ml 1 h after a dose and 0.30 ± 0.1 μg/ml 3 h after a dose (7). A different report by Kafetzis and co-workers showed low mean levels of antibiotics in breast milk after a single 1-g intravenous dose of cephalothin, cephapirin, or cefotaxime (8). Yoshioka and colleagues described the levels of cefazolin in the breast milk of patients receiving multiple 2-g doses intravenously (10). In this study, the mean (± SD) levels at 2, 3, and 4 h after infusion were 1.25 ± 0.88, 1.51 ± 0.16, and 1.16 ± 0.97 μg/ml, respectively. These antibiotic levels are higher than those in the other reports, but it is unclear whether the higher mean concentrations were due to the pharmacokinetic properties of the cefazolin or to the multiple-dose design.

In the present study, the mean CAZ levels in breast milk are markedly higher than those in the above-mentioned reports. The higher levels are probably the result of the multiple-dose design and the pharmacokinetic properties of CAZ itself. CAZ, in humans, is metabolically stable and is excreted unchanged by glomerular filtration. It has a low degree of protein binding (10%) yet a relatively long serum half-life for a cephalosporin (1.8 h) (4, 5). These properties favor transfer of the drug into breast milk. There is, however, no progressive accumulation of CAZ in breast milk, as evidenced by the similar levels before and after seven doses. The fact that 80% of CAZ is excreted 8 h after a dose may explain the lack of accumulation (4).

CAZ is excreted in breast milk at concentrations higher than those of other previously reported cephalosporins; however, the levels may be due to the multiple-dose regimen of the study. The concentration of CAZ excreted in breast milk remained constant between days 2 and 4 of therapy.

This study was supported by a grant from Glaxo, Inc., Research Triangle Park, N.C., and was approved by the Institutional Review Board of The University of Texas Health Science Center at San Antonio.

LITERATURE CITED

1. **Dubois, M., D. Delapierre, L. Chanteux, J. Demonty, R. Lambotte, R. Kramp, and A. Dresse.** 1981. Study of the transplacental transfer and the mammary excretion of cefoxitin in humans. Clin. Pharmacol. Ther. **21**:477–483.
2. **Gibbs, R. S., J. D. Blanco, Y. S. Castaneda, and P. J. St. Clair.** 1980. Therapy of obstetrical infections with moxalactam. Antimicrob. Agents Chemother. **17**:1004–1007.
3. **Gibbs, R. S., J. D. Blanco, Y. S. Castaneda, and P. J. St. Clair.** 1982. A double-blind, randomized comparison of clindamycin-gentamicin versus cefamandole for treatment of post-cesarean endomyometritis. Am. J. Obstet. Gynecol. **144**:261–267.
4. **Harding, S. M., J. Ayrton, J. E. Thornton, A. J. Munro, and M. I. J. Hogg.** 1981. Pharmacokinetics of ceftazidime in normal subjects. J. Antimicrob. Chemother. **8**(Suppl. B):261.
5. **Harding, S. M., A. J. Munro, J. E. Thornton, J. Ayrton, and M. I. J. Hogg.** 1981. The comparative pharmacokinetics of ceftazidime and cefotaxime in healthy volunteers. J. Antimicrob. Chemother. **8**(Suppl. B):263–272.
6. **Hemsell, D. L., F. G. Cunningham, C. M. Nolan, and T. T. Miller.** 1982. Clinical experience with cefotaxime in obstetric and gynecologic infections. Rev. Infect. Dis. **4**(Suppl.):S432–S438.
7. **Kafetzis, D. A., C. V. Lazarides, C. A. Siafas, P. A. Georgakopoulos, and C. J. Papadatos.** 1980. Transfer of cefotaxime in human milk and from mother to fetus. J. Antimicrob. Chemother. **6**(Suppl. A):135–141.
8. **Kafetzis, D. A., C. A. Siafas, P. A. Georgakopoulos, and C. J. Papadatos.** 1981. Passage of cephalosporins and amoxicillin into the breast milk. Acta Paediatr. Scand. **70**:285–288.
9. **Sabath, L. D., and J. P. Anhalt.** 1980. Assay of antimicrobics, p. 485–490. *In* E. H. Lennette, A. Balows, W. J. Hausler, Jr., and J. P. Truant, (ed.), Manual of clinical microbiology, 3rd ed. American Society for Microbiology, Washington, D.C.
10. **Yoshioka, H., K. Cho, M. Takimoto, S. Marayama, and T. Shimizu.** 1979. Transfer of cefazolin into human milk. J. Pediatr. **94**:151–152.