ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 1976, p. 733-735
Copyright © 1976 American Society for Microbiology
Vol. 10, No. 4
Printed in U.S.A.

Concentration of Cefamandole in Serum Interstitial Fluid, Bile, and Urine

N. G. WATERMAN,* H. U. EICKENBERG, AND L. SCHARFENBERGER

Price Institute of Surgical Research, and the Department of Surgery, University of Louisville School of Medicine, Health Sciences Center, Louisville, Kentucky 40201*

Received for publication 2 June 1976

Cefamandole readily diffuses from the serum into soft tissue interstitial fluid. The rate of diffusion differs little from that of cephalothin. The concentrations of antibiotic were greater in bile and urine during the entire period of study than is necessary to kill susceptible pathogenic bacteria present in these fluids.

Cefamandole is a relatively new derivative of the cephalosporins. It has been found to be very active against gram-positive cocci and gram-negative bacilli. The in vitro activity against penicillin susceptible and resistant *Staphylococcus aureus* is excellent (1, 6, 7). Cefamandole has also been found to be effective against a significant number of clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* resistant to other cephalosporins (1). Because of the susceptibility of many of the bacteria causing nosocomial infections, we believe it necessary to determine the character of the excretion and diffusion of the drug from the serum into other body fluids. A comparison of time-serum changes in cefamandole concentration in soft tissue interstitial fluid, bile, and urine was undertaken.

MATERIALS AND METHODS

Multiperforated polypropylene balls measuring 15 mm in diameter were implanted in the tissues of the flank and abdominal wall in six adult mongrel dogs. T-tubes were inserted in the common ducts. After a period of 4 to 6 weeks, sufficient healing had occurred to permit physiological exchange of capsule fluid with the capilliaries. These capsules are identical to those described by Waterman and Kastan (9) for the measurement of antibiotic concentrations in interstitial fluid.

A 20-mg amount of cefamandole nafate per kg of body weight was given intravenously to each animal. Serial blood specimens were obtained by venipuncture. Interstitial fluid from the abdominal wall was withdrawn from the implanted capsule with a 23-gauge needle, and bile was obtained from the T-tube. All specimens were obtained hourly for 4 h. Microbiological assays of antibiotic concentrations in serum, interstitial fluids, and bile were performed by the agar diffusion method described by Sabath and co-workers, using *Bacillus subtilis* as the assay organism (8). Antibiotic standards for the serum level determinations were prepared in pooled canine serum, those for bile concentrations were prepared in pooled canine bile, and those for interstitial fluid levels were prepared in M/15 phosphate buffer (pH 6.0). The concentrations of antibiotics in serum, bile, and interstitial fluids of the liver and abdominal wall soft tissue at varying times were then compared among animals by an analysis of variance.

Multiperforated polypropylene balls measuring 20 mm in diameter were implanted in the flank and abdomen of six adult mongrel dogs. Two 10-mm multiperforated balls connected by polyethelene tubing inserted in the central portion of the capsule were implanted in the renal parenchyma, and a T-tube was inserted in the ipsilateral ureter. The occluded ends of the polyethelene tubes and long limb of the T-tube were sutured beneath the flank skin. After 4 weeks, healing was sufficient to permit physiological fluid exchange between renal interstitium and capsules. The dogs were anesthetized with thiopental sodium and given 20 mg of cefamandole per kg intravenously. Serial samples of blood were drawn from peripheral veins, renal interstitial fluid was extracted from the polyethelene tubing, and soft tissue interstitial fluid was obtained from the capsules with 23-gauge hypodermic needles. The urine was allowed to drip from the T-tube with samples taken at hourly intervals for 4 h. This method of study has been described by Eickenberg and colleagues (4, 5) for determining the concentration of cephalothin in renal interstitial fluid. Completed studies to be published show that in the creatinine, blood urea nitrogen, and *para*-amino hippuric acid clearance test measurements and radio-opaque dye injection X-ray studies there is no communication between the renal capsules and the excretory system. The time concentrations of the cephalosporins in serum, renal interstitial fluid, soft tissue interstitial fluid, and urine were compared by an analysis of variance.

RESULTS

Figure 1 shows the average and the variation in the time concentration changes of serum to interstitial fluid. The serum level remained greater than the interstitial fluid for more than

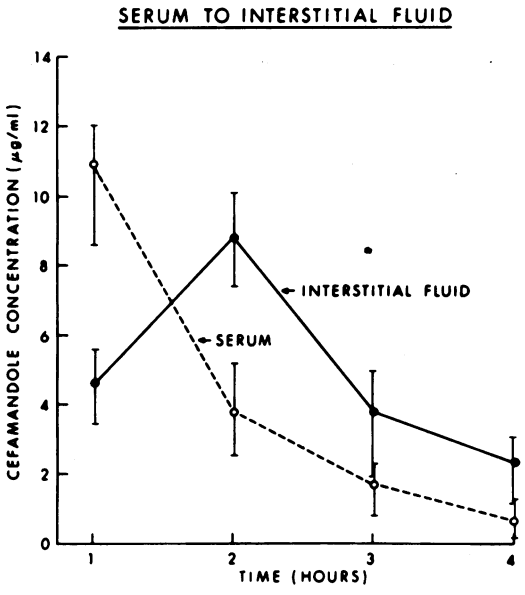

FIG. 1. *Comparison of the concentrations of cefamandole in serum and interstitial fluid at 1 to 4 h after a 20-mg/kg intravenous dose.*

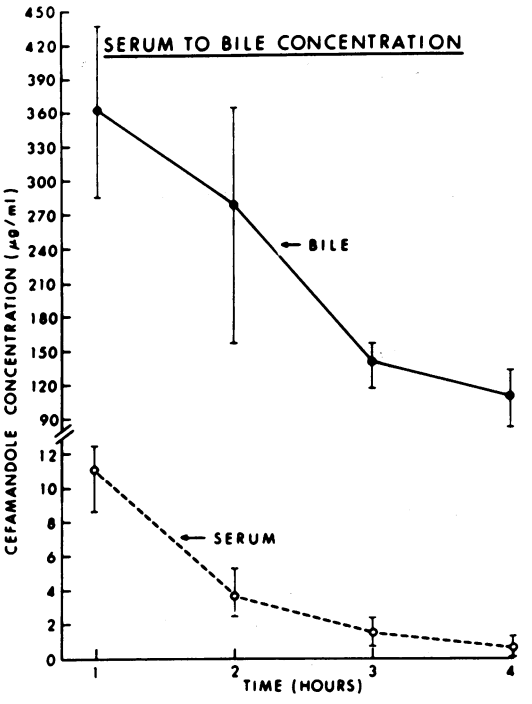

FIG. 2. *Comparison of the serum and bile concentrations at 1 to 4 h after intravenous injection of 20 mg/kg.*

1 h. By 2 h, the antibiotic concentration was greater in the interstitial fluid. As a result of excretion, secretion, and metabolism, the serum concentration became less and the antibiotic began to diffuse back into the vascular compartment. Figure 2 graphically illustrates the average and variation in serum-to-bile concentrations. The bile concentration was 360 μg at 1 h and decreased to 120 μg at 4 h and to 40 μg at 6 h. The analysis of variance showed the relationship during the times of measurement to be significant ($P < 0.01$).

Figure 3 shows that the average and variation in the urine and renal interstitial fluid concentrations, measured as described by Eickenberg and associates (4, 5), are quite high and greatly exceed the concentrations in the serum and in the extrarenal soft tissue interstitial fluid. Cefamandole had an initial peak concentration in the urine of 8,200 μg/ml within 60 min of the single intravenous injection. The greatest quantity appearing in the serum within an hour was 11 μg/ml. After 1 h, the antibiotic concentration in the renal interstitial fluid was 42.6 μg/ml and was greater than both the simultaneously measured serum level (11 μg/ml), and the control soft tissue interstitial fluid concentration (4.6 μg/ml). After 2 h, the serum level (3.9 μg/ml) was less than that in the renal interstitial fluid (38 μg/ml) and soft tissue interstitial fluid (8.8 μg/ml). After 4 h, only a very low concentration was found in

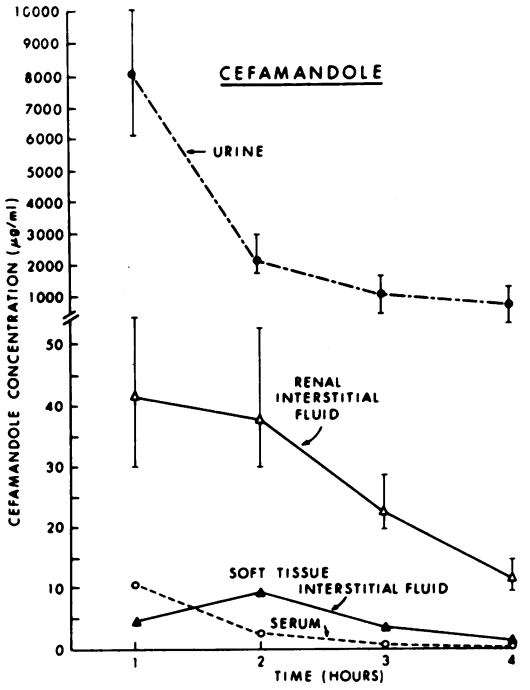

FIG. 3. *Concentrations of cefamandole in serum, soft tissue interstitial fluid, renal interstitial fluid, and urine after intravenous injection of 20 mg/kg.*

serum. The concentration in renal interstitial fluid was 12.6 μg/ml and remained higher than in the soft tissue interstitial fluid (2.4 μg/ml). The analysis of variance showed the relationships to be significant ($P < 0.01$).

DISCUSSION

Cefamandole readily diffuses into body soft tissue interstitial fluid. The rate of diffusion differs little from that of cephalothin (9). Both antibiotic agents increase to satisfactory tissue fluid concentrations in less than 1 h, and the serum and tissue fluids are nearly the same between 90 min and 2 h. The protein binding of cefamandole in pooled dog sera measured by the ultrafiltration method is 40% and is similar to cephalothin (10), and it is consistent with other cephalosporin dog sera protein-binding studies (12). The quantity excreted or secreted into bile is excellent. A comparison with concentrations of other antibiotics in bile previously measured in this laboratory (11) shows the concentration of cefamandole to be greater than that of cephalothin, tetracycline, and ampicillin when each was injected intravenously in the same dosage. Cefazolin was the only antimicrobial agent measured that showed a greater concentration than cefamandole.

The concentrations of cefamandole in urine and renal interstitial fluid were greater than those with cephalothin. Both drugs were measured in the same laboratory animals used by Eickenberg and colleagues (5) to determine renal interstitial fluid antibiotic concentrations.

The concentrations of cefamandole diffusing into interstitial fluid and excreted in bile and urine are greater than those obtained with cephalothin. The graphic patterns of the time concentration changes are very similar. The quantities measured during the period of study were sufficient to be active against most susceptible pathogenic bacteria present in the studied fluids.

ACKNOWLEDGMENT

This work was sponsored by a grant from Eli Lilly & Co.

LITERATURE CITED

1. **Bodey, G. P., and S. Weaver.** 1976. In vitro studies of cefamandole. Antimicrob. Agents Chemother. 9:452–457.
2. **Calnan, J. S., J. J. Pflug, G. D. Chisholm, and L. M. Taylor.** 1972. Pathophysiology of tissue fluid. Proc. R. Soc. Med. 65:715–719.
3. **Chisholm, G. D., P. M. Waterworth, J. S. Calnan, and L. Garrod.** 1973. Concentration of antibacterial agents in interstitial tissue fluid. Br. Med. J. 1:569–573.
4. **Eickenberg, H. U., N. G. Waterman, and L. Scharfenberger.** 1975. Renal interstitial fluid, urine, and serum antibiotic concentration. Surg. Forum 26:589–591.
5. **Eickenberg, H. U., N. G. Waterman, and L. Scharfenberger.** 1975. Concentration of antibiotics in renal interstitial fluid. An experimental model. Urol. Res. 3:165–167.
6. **Eykyn, S., C. Jenkins, A. King, and I. Phillips.** 1973. Antibacterial activity of cefamandole, a new cephalosporin antibiotic, compared with that of cephaloridine, cephalothin, and cephalexin. Antimicrob. Agents Chemother. 3:657–661.
7. **Neu, H. C.** 1974. Cefamandole, a cephalosporin antibiotic with an unusually wide spectrum of activity. Antimicrob. Agents Chemother. 6:177–182.
8. **Sabath, L. D., J. I. Casey, P. A. Ruch, L. L. Stumpf, and M. Finland.** 1976. Rapid microassay for circulating nephrotoxic antibiotics. Antimicrob. Agents Chemother. 10:83–90.
9. **Waterman, N. G., and L. B. Kastan.** 1972. Interstitial fluid and serum antibiotic concentrations. Arch. Surg. 105:192–196.
10. **Waterman, N. G., L. Scharfenberger, and M. Raff.** 1974. Rate of binding of antibiotics to canine serum protein. Antimicrob. Agents Chemother. 5:294–295.
11. **Waterman, N. G., M. J. Raff, L. Scharfenberger, and P. A. Barnwell.** 1976. Antibiotic concentrations in hepatic interstitial and wound fluid. Surg. Gynecol. Obstet. 142:235–238.
12. **Waterman, N. G., M. J. Raff, L. Scharfenberger, and P. A. Barnwell.** 1976. Protein binding and concentrations of cephaloridine and cefazolin in serum and interstitial fluid of dogs. J. Infect. Dis. 133:642–647.