Concentration Relationships of Cefaclor in Serum, Interstitial Fluid, Bile, and Urine of Dogs

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Received for publication 7 August 1978

The concentrations of cefaclor in the serum, urine, bile, and tissue fluids of the abdominal wall, kidney, and liver of dogs were compared over a 4-h period after oral administration of a single dose of this drug. The concentration of cefaclor in the soft-tissue interstitial fluid peaked 2 h after administration, thereby demonstrating a diffusion rate similar to those of other cephalosporins. Both urine and bile concentrations greatly exceeded the serum levels, whereas none of the tissue fluid concentrations were greater than the serum concentrations at the times of measurement.

Cefaclor is a relatively new semisynthetic cephalosporin derived from cepalexin. The oral form of the drug is currently being evaluated because of its proclivity for absorption by the intestine. Although its in vitro activity against Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis is similar in range to those of other oral cephalosporins, cefaclor has been shown to be significantly more active at lower and more easily attainable concentrations against the cephalosporin-susceptible Enterobacteriaceae as well as staphylococci, streptococci, and gonococci (2, 9–11). The antibiotic is excreted in high concentrations in the urine of humans and experimental animals (7, 12).

To evaluate the efficacy of cefaclor, the rates of diffusion from the serum into the urine, bile, and the tissue fluids of the abdominal wall, kidney, and liver were determined.

MATERIALS AND METHODS

Multiperforated polypropylene balls measuring 20 mm in diameter were implanted in the soft tissues of both the flank and the abdominal wall in 10 large adult mongrel dogs, each of which weighed approximately 40 kg. A similar ball measuring 10 mm in diameter was implanted into a bluntly dissected incision in the right lobe of the liver of each dog. A T-tube was then inserted into the common duct, and a polyethylene tube was inserted into the capsule within the liver. The opposite end of the polyethylene tube and the long limb of the T-tube in the common duct was sutured beneath the abdominal skin just below the right costal margin. The materials and methods used in this study were identical to those previously described by Waterman and associates for the measurement of antibiotic concentrations in soft tissues, bile, and liver (13–15).

During the same operation, polyethylene tubing was inserted into the central portion of a multiperforated polypropylene ball measuring 10 mm in diameter. The capsule and tube were then implanted in the left renal parenchyma. The opposite occluded limb of the polyethylene tubing was sutured beneath the skin on the left flank. The method used in our study was described by Eickenberg et al. (5, 6) for determining the concentration of cephalothin in renal interstitial fluid. Other investigators (1, 3, 4) have used similar containers to collect and measure drug concentrations within tissues.

A period of 4 to 6 weeks was required for sufficient healing and arterIALIZATION of the tissues lining the inner walls of the multiperforated capsules and for physiological exchange of capsular fluid and capillaries. This experimental model permitted the almost simultaneous collection of serum, fluid from the soft tissue of the abdominal wall, fluid from the tissues of the liver and kidney, bile collected from the T-tube, and urine from a urinary bladder catheter.

One gram of cefaclor was administered orally to fasting dogs. Forty-five minutes later, the dogs were anesthetized with thiopental sodium. To determine the antibiotic concentrations in the serum, interstitial tissue fluid, renal tissue fluid, liver tissue fluid, bile, and urine, specimens were taken at hourly intervals for 4 h. Serial blood specimens were obtained by venipuncture. Interstitial fluid from the abdominal wall was withdrawn from the implanted capsules with a 23-gauge hypodermic needle. Bile was obtained from the long limbs of the T-tubes, and urine was collected from a Foley catheter inserted in the urinary bladder. Liver and renal tissue fluids were extracted from the subcutaneous polyethylene tubings.

Microbiological assays of antibiotic concentrations were performed by the agar diffusion method described by Sabath and co-workers (8), which uses Bacillus subtilis (ATCC 6633) as the assay organism. Standards to determine the antibiotic concentrations in the serum, bile, and urine were prepared in pooled canine serum, pooled canine bile, and pooled canine urine (pH 4.5), respectively, whereas standards to de-
termine the concentrations in the abdominal wall, liver, and renal capsule fluids were prepared in phosphate buffer (pH 4.5). All specimens were prepared and kept at 4°C. Assays were performed within 1 h after fluid collection to prevent loss of cefaclor activity due to tissue enzyme hydrolysis (12).

RESULTS

Table 1 delineates the hourly measurement of the antibiotic concentrations. The level remained higher in the serum than in the interstitial fluid throughout the 4 h. The interstitial fluid concentration measured 4.45 µg/ml at 1 h increased to 8 µg/ml at 2 and 3 h, and then decreased to 6.5 µg/ml at 4 h. Concentrations in the urine were very great despite decreasing concentration in the serum. The concentration in the bile had decreased by 50% at 4 h. During the first 2 h, the fluid level within the kidney was higher than the level in the soft tissue, but it decreased to a comparatively lesser concentration at 3 and 4 h. The concentration in the hepatic fluid remained less than that of the soft tissue and renal capsule fluid during the entire 4 h.

DISCUSSION

Cefaclor readily diffuses into soft-tissue interstitial fluid. The antibiotic concentration in the capsule implanted in the liver peaked at 2 h, as is seen with cephalothin (13). The quantity excreted in the urine is very large. The quantity measured in bile shows that the drug is actively excreted in bile at a concentration more than sufficient to be effective against susceptible pathogens. The quantities of cefaclor diffusing into the soft-tissue and renal extravascular fluids were generally similar and showed similar patterns of diffusion. The concentration in the liver extravascular fluid was less than that in the soft-tissue interstitial fluid, even though the drug was actively excreted by the liver into the bile. This was possibly due to the presence of liver enzymes and to the drug being more labile to metabolism in dogs. If this is so, the same concentrations may not result from studies with other experimental animals (12).

The high concentration in the serum recorded at 1 h after intravenous administration of a cephalosporin does not occur when the drug is administered orally. When cefaclor was administered intravenously in our laboratory and in a reported experimental study (12), changes in the concentration in the serum were similar to those of other cephalosporins. In our study, the level of cefaclor in the interstitial fluid was less than the concentrations in the serum during the entire 4 h. The pattern of change in concentration recorded with cefaclor is also seen with the tetracyclines (1, 4, 14), where the serum concentrations remain greater than the soft-tissue fluid concentrations. Our studies involving other cephalosporins (5, 14, 15) revealed that concentrations in the serum and interstitial fluid equilibrate 2 h after oral administration. The serum concentrations of most antibiotics, except tetracyclines, become less after equilibration than those of tissue fluid as the drugs are excreted and metabolized.

Cefaclor is well absorbed when administered orally and is excreted in the urine in a relatively high concentration. The drug is also excreted by the liver, as are other cephalosporins, though in relatively lesser concentrations. Comparison of the pharmacokinetics of intravenous and oral cephalosporins is difficult because of many variables. Sullivan and associates (12) have shown that 75% of [14C]cefaclor is absorbed from the gastrointestinal tract and that the remaining bioavailability of the intact antibiotic is 60% in dogs. These studies indicate that cefaclor, as well as other cephalosporins, entering the vascular compartment readily diffuses into soft-tissue interstitial and organ fluids.

ACKNOWLEDGMENTS

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

LITERATURE CITED
