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Concentration of Antibiotics in Renal Interstitial Fluid: An Experimental Model

H.-U. Eickenberg, N. G. Waterman, and L. Scharfenberger

Section of Urology, Department of Surgery, University of Louisville School of Medicine, and Price Institute for Surgical Research, Health Sciences Center, Louisville, Kentucky, U. S. A.

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Summary. In a new canine experimental model the time concentration relationship of cephalothin in serum, urine, soft tissue interstitial fluid (STIF) and renal interstitial fluid (RIF) were compared simultaneously. Antibiotic concentration in RIF was less than urinary levels but exceeded the serum concentration. Urinary antibiotic concentration does not necessarily reflect concentration in the renal interstitium. This model helps to understand the basic pharmacokinetics of antibiotics in the renal interstitium where pyelonephritis occurs.

Key words: Renal interstitial fluid, Soft tissue interstitial fluid, Antibiotic concentration, Pyelonephritis, Experimental canine model.

Pyelonephritis is primarily an infection of the renal medulla and interstitium, but most studies in the literature today deal with the importance of antibiotic levels in blood versus antibiotic levels in urine in the treatment of pyelonephritis, because it is commonly believed that urine levels reflect renal tissue concentrations (5, 7, 10, 11, 12). To measure the concentration of antibiotics in the renal interstitial fluid (RIF) and to compare it with the levels found in the urine, plasma, and soft tissue interstitial fluid (STIF) a new experimental canine model will be described using multiperforated polypropylene capsules implanted into the renal parenchyma.

Materials and Methods

In a time-concentration comparison the antibiotic level in the interstitial fluid of the kidney (RIF), interstitial fluid of the soft tissue of the abdominal wall (STIF), serum and urine were measured after the intravenous injection of the antibiotic cephalothin.

Multiperforated polypropylene balls measuring 20 mm in diameter were implanted in the tissues of the flank and abdomen in four adult mongrel dogs. Two 10 mm balls connected with each other by tubing at each end (Fig. 1) were implanted in the renal parenchyma and a T-tube was inserted in the ipsilateral ureter. These capsules were identical to those employed by Waterman and Kastan (13) for determining antibiotic changes in interstitial fluid. After a period of 4-6 weeks, healing had occurred sufficiently to permit physiological fluid exchange with the capillaries. Cephalothin,

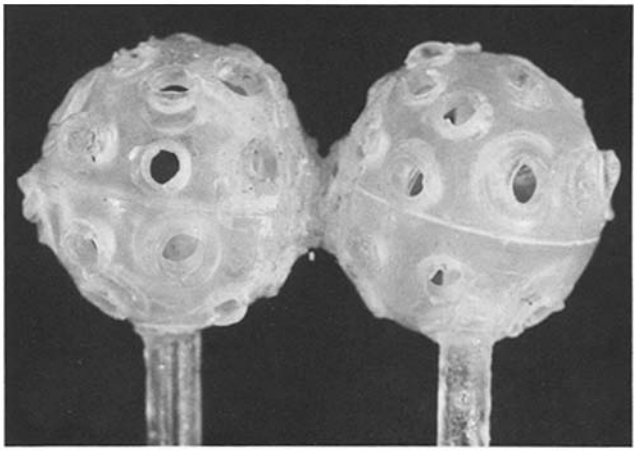

Fig. 1. Polypropylene balls

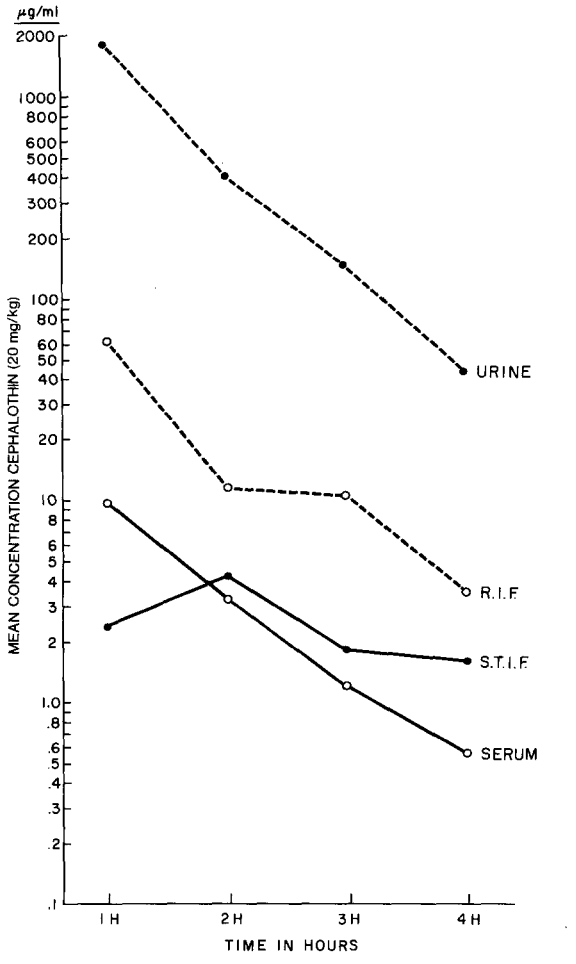

Fig. 2. Time-concentration correlation of RIF, STIF, serum, and urine levels after injection of 20 mg/kg cephalothin

20 mg/kg, was given intravenously. Serial samples of blood, RIF, and STIF were obtained by withdrawal of the blood from a peripheral vein and from interstitial fluid in the capsules with a 25-gauge hypodermic needle. The urine was allowed to drip from the T-tube and samples were taken at 1-hour intervals for 4 hrs. Microbiological assays of antibiotic concentrations in the specimens collected were done by the disc method using Bacillus subtilis as described by Sabath and associates (9). The time and concentration of cephalothin in micrograms per milliliter of serum, RIF, STIF, and urine were then compared graphically.

Results

One hour following injection, there was a much greater concentration of cephalothin in the urine (1800 µg/ml) than the peak quantity occurring in the serum (9.9 µg/ml) (Fig. 2). The antibiotic concentration in the RIF (60,3 µg/ml) at 1 hr was in between the simultaneously measured urine (1800 µg/ml) and serum (9.9 µg/ml) levels but exceeded the STIF (2.4 µg/ml) concentration.

At 2 hrs the serum level (3.2 µg/ml) had decreased rapidly and was less than both the RIF (11.5 µg/ml) and STIF (4.1 µg/ml) concentrations. At that time the interstitial fluid antibiotic (RIF and STIF) began slowly diffusing back into the plasma. This was probably attributable to the fact that the later concentration gradient from the interstitial to the vascular compartment was less than the earlier gradient from the capillaries into the interstitial fluid which occurred shortly after the intravenous injection. After 4 hrs only a very low concentration was found in the serum (0.55 µg/ml), whereas RIF (3.5 µg/ml) remained at a higher level.

Discussion

The concentration of an antibiotic in the fluids of the body is generally inferred from measurement of the drug in the blood, tissue homogenates, or lymph (3, 11). Some methods using radioisotope-tagged drugs show the distribution but not the concentration (4), while others have assumed the concentration in fluids such as inflammatory exudates (8). Renal lymph concentration of antibiotics have shown high concentrations because of pyelolymphatic backflow (3). Fluid obtained from a Silastic device implanted subcutaneously is tissue fluid, the equivalent of natural interstitial fluid and in direct communication with it (1, 2, 6). Our own laboratory, as well as others, has measured the concentration of antibacterial agents in the interstitial fluid of the abdominal wall (2, 13), liver (13), and now in the renal interstitial fluid (RIF). Multi-perforated capsules implanted in the renal parenchyma are in direct communication with the tissue fluids and fluid obtained from those capsules is the increment of natural interstitial fluid. This new method for measuring interstitial fluid and pressure is based on the principle of allowing a considerable period of time for tissue fluid to come into equilibrium with fluid in the measuring device.

Comparative blood urea nitrogen and creatinine determinations and p-amino hippurate clearance in RIF and urine demonstrated the difference between capsule fluid and urine. Radiographically there was no demonstrable connection between the capsule and the renal collecting system after the intracapsular injection of Hypaque material. These findings together with the histological changes around and inside the capsule are discussed in a separate paper. However, radiological, histological, and bio-

chemical studies confirmed the claim of physiologists that the implanted capsules provide interstitial fluid without contamination by urine or blood. Contrary to previously held concepts, the urine concentration of an antibiotic does not necessarily reflect the coexisting drug level in the renal interstitium. Our model may ultimately provide a better understanding of the factors of importance in selecting the appropriate drug for the treatment of renal infection. This model may also help to study the basic pharmocokinetics of antibiotics and may suggest guidelines in the therapy of pyelonephritis.

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H.-U. Eickenberg, M.D.
N.G. Waterman, M.D.
L. Scharfenberger, M.S.
Section of Urology
University of Louisville
School of Medicine
Louisville, KY 40201
U.S.A.