Distribution of Antibiotics in Pyelonephritic Kidneys of Dogs

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TSUCHIDA, S., MIYAGAWA, I., HARADA, T. and KUMAGAI, I. *Distribution of Antibiotics in Pyelonephritic Kidneys of Dogs*. Tohoku J. exp. Med., 1978, 125 (4), 317-323 — The concentration of cefazolin sodium (hereinafter referred to as CEZ), a cephalosporin antibiotics, in the renal tissue, blood, and urine was measured in dogs with experimentally induced acute and chronic pyelonephritis in the left kidney. The results were as follows: The blood concentration of intravenously given CEZ, in terms of half life ($T_{1/2}$), was found to last longer than that in healthy animals. The tissue concentration in the acute mild pyelonephritic kidney was higher and lasted longer than that in the contralateral healthy kidney. The tissue concentration in the severe acute pyelonephritic and chronic pyelonephritic kidney was inversely lower than that in the healthy kidney. The urinary concentration and urinary recovery in the first 2-hr urine from the affected kidney were far lower than those from the healthy kidney, irrespective of severity or chronicity of inflammation. The findings in dogs suggest that the renal concentrations of antibiotics in patients with acute and mild pyelonephritis are higher and last longer than those in healthy persons, that the renal concentrations in patients with severe and chronic pyelonephritis are inversely lower than that in healthy persons, and that the urinary excretion of antibiotics in patients with pyelonephritis decreases as compared with that in healthy persons. ——— pyelonephritis; distribution of antibiotics

Chemotherapy of pyelonephritis has progressed to the point where it allows the study of therapeutic effectiveness from various standpoints, but the precise distribution of given antibiotics in the renal tissue remains unresolved. One of the reasons why the renal distribution of antibiotics has defied an approach of basic researches is the difficulty in producing suitable models that might imitate human pyelonephritis.

The present authors have recently succeeded in producing unilateral pyelonephritis in dogs (1973). This experimentally induced pyelonephritis was shown to bear a striking histological resemblance to the disease in man. The present paper is concerned with the distribution of intravenously given CEZ in the blood, urine and kidneys of dogs with experimentally produced acute and chronic unilateral pyelonephritis.

MATERIALS AND METHODS

A total of 31 mongrel dogs of both sexes weighing between 8 to 15 kg were used. Six animals served as the control, and 25 animals underwent an operation to induce pyelonephritis in the left kidney by a method reported in one of our previous papers (Tsuchida et al. 1973). Of the 25 dogs, 16 were used as a model for acute pyelonephritis 7 to 10 days after the operation when inflammation was histologically evident, and the remaining 9 animals, for the study of chronic pyelonephritis, 1 to 3 months after the operation when inflammation had grown chronic. The animals were anesthetized with Nembutal, and the lower part of both ureters was incised to insert indwelling ureteral catheters of No. 5 or 6 to reach the renal pelvis. The animals were then intravenously injected with 50 mg/kg of CEZ, and the blood and urine samples were collected at intervals. The blood was taken from the median vein of a forearm, and the urine via the two separate catheters. The kidneys were examined for histology and CEZ concentration in the cortex and medulla.

The blood, urinary, and renal tissue concentrations of CEZ were measured by thin-layer chromatography using *Bacillus subtilis* ATCC 6633 as the test organism (Nishida et al. 1970).

RESULTS

Bacteriological and histological studies showed the absence of pathogenic microorganisms or inflammatory changes in the intact kidney and the presence of microorganisms, such as *Escherichia coli*, *Pseudomonas* and *Klebsiella*, and varying severity of inflammation in the affected kidney.

The kidneys affected with acute inflammation were classified into two major groups according to their histological findings: one characterized by cellular infiltration mild enough to maintain the structure of the glomeruli and tubules, and the other by infiltration severe enough to form abscesses.

The 9 kidneys with chronic inflammation showed atrophy of the tubules, infiltration of small lymphocytes and increase in fibrous tissue.

Biological half life of CEZ concentration in blood

The mean biological half lives of CEZ were calculated from the blood concentration successfully determined 0.5, 1.0, 1.5 and 2.0 hr after an administration (Kunin et al. 1959): The value in animals with inflammation was 1.05 ± 0.45 hr for acute inflammation ($n=9$) and 0.85 ± 0.28 hr for chronic inflammation ($n=6$), and was significantly longer than that in control animals (0.59 ± 0.10 hr, $p < 0.05$ by t -test).

CEZ concentration in renal tissue

The 16 kidneys with acute inflammation were subclassified into two groups according to histological findings: 12 with mild inflammation and 4 with severe inflammation. The renal tissue (i.e. cortex and medulla) concentration on the ordinate was plotted against time after injection on the abscissa of Figs. 1 and 2. The extreme left column of these figures shows the concentrations in control animals which did not differ significantly between both kidneys and remained high for the first 3 hr. The concentrations in kidneys with acute mild inflammation were higher

and longer-lasting than those in the contralateral healthy kidney. The concentrations in kidneys with acute severe inflammation and in kidneys with chronic inflammation were inversely lower and shorter-acting from the outset.

In an attempt to clarify differences in distribution of CEZ between the inflammatory and healthy kidneys, we calculated the ratio of the tissue concentra-

Fig. 1. Cortical concentration of CEZ. A: control, 6 dogs, B: acute mild inflammation, 12 dogs. C: acute severe inflammation, 4 dogs. D: chronic inflammation, 9 dogs.

The cortical level in kidneys with acute mild inflammation is higher and longer-lasting than that in healthy kidneys. The cortical level in kidneys with acute, severe inflammation and chronic inflammation is inversely lower and shorter-lasting. ○, right kidney; ●, left kidney.

Fig. 2. Medullary concentration of CEZ. A: control, 6 dogs. B: acute mild inflammation, 12 dogs. C: acute severe inflammation, 4 dogs. D: chronic inflammation, 9 dogs.

The relative medullary concentrations and time courses of CEZ in healthy and inflammatory kidneys are the same as those illustrated in Fig. 1. ○, right kidney; ●, left kidney.

tion in the left inflammatory kidney to that in the right healthy kidney. The results are shown in Fig. 3. In control dogs the ratio was always in the vicinity of 1.0 and caused no significant difference between both kidneys. In most animals with acute mild inflammation, the ratio was greater than 1.0 and the concentration in the inflammatory kidney was significantly higher than the

Fig. 3. Left/right renal tissue concentration ratio of CEZ. A: control, 6 dogs. B: acute mild inflammation, 12 dogs. C: acute severe inflammation, 4 dogs. D: chronic inflammation 9 dogs.

In control dogs the ratio was always around 1.0. In most animals with acute mild inflammation the ratio was greater than 1.0 and increased with the passage of time. In animals with acute severe and chronic inflammation the ratio was less than 1.0. ○, cortex; ●, medulla.

concentration in the healthy kidney. In addition, the ratio increased with the passage of time. In animals with acute severe inflammation and chronic inflammation, the ratio was essentially below 1.0 except for the medullary concentration at 7 hr in animals with chronic inflammation. All the differences between inflammatory and healthy kidneys were found to be statistically significant except for the 7-hr medullary concentration in animals with chronic inflammation ($p < 0.05$ by t -test).

Urinary concentration of CEZ and urinary recovery

The urinary concentration and urinary recovery of CEZ were studied in five control animals, five with acute mild inflammation, 2 with acute severe inflammation, and 6 with chronic inflammation. Fig. 4 shows the ratio of CEZ concentration in the urine taken from the left ureter to that from the right ureter. Individual ratios calculated at intervals in an animal were averaged and represented by a dot. The ratios in control animals ranged from 0.82 to 1.60 and the difference between both kidneys was found not to reach a significant level. The ratios in

animals with inflammation were as follows: 0.31 to 0.52 in animals with acute mild inflammation, 0.31 to 0.44 in animals with acute severe inflammation, and 0.07 to 0.88 in animals with chronic inflammation. It was self-explanatory that the concentration of CEZ in the kidney of chronic inflammation was extremely low.

Fig. 4

Fig. 4. Left/right urinary concentration ratio of CEZ.

In animals with an inflammatory kidney the ratio of the left urinary concentration to the right urinary concentration was always less than 1.0.

Fig. 5. Recovery of CEZ in the first 2-hr urine. A: control, 5 dogs. B: acute mild inflammation, 5 dogs. C: acute severe inflammation, 2 dogs. D: chronic inflammation, 6 dogs.

The recovery in the inflammatory (left) kidney was always significantly lower than that in the healthy (right) kidney. The total recovery in bilateral urine samples in animals with inflammation was always significantly lower than that in control animals.

Fig. 5

Recovery of CEZ in the first 2-hr urine collected from the individual ureters is shown by a dot in Fig. 5. In control animals the recovery in the left kidney was as high as that in the right kidney, but in all the animals with inflammation the recovery in the left inflammatory kidney was significantly lowered. The recovery in the left and right urine samples added together in animals with inflammation was also significantly lower than that in control animals.

DISCUSSION

The reason why CEZ was selected and used in this study is that this compound well represents frequently prescribed antibiotics including other cephalosporins, penicillins, and even aminoglycosides for its exaggerated concentrations in the kidney.

Distribution of antibiotics in the renal tissue of animals with acute pyelonephritis has been studied by various research tools; for example, Malek et al. (1963) and Ueda (1974) used autoradiography and fluorography, and Romas and Clark (1969) used autoradiography and also measured renal tissue concentrations. Romas and Clark (1969) stated that antibiotics migrate to lesion of acute inflammation to a limited extent. Málek et al. (1963) and Ueda (1974) reported that antibiotics migrate only slightly to abscesses but more profusely than to normal tissues to lesion of acute inflammation and cause prolonged retention in such areas.

Our studies have shown that in animals with acute mild inflammation the tissue concentration in the affected kidney was higher and longer lasting than that in the healthy kidney. This finding agrees to that of Malek et al. (1963) and Ueda (1974), but seems to contradict that of Romas and Clark (1969).

This apparent discrepancy, however, must be dispelled by taking account of the fact that the inflammatory kidneys produced by Romas and Clark (1969) were of intravenously induced abscess, and essential identity of their findings with ours obtained in animals having severe abscesses needs to be ensured.

On the other hand, poor distribution of antibiotics in chronic pyelonephritis has been pointed out by a small number of reseachers such as Romas and Clark (1969) and Ueda (1974) who used rats. We, therefore, determined to confirm their performance in larger animals such as dogs by precise measurement of the tissue concentrations. As a result, the concentration in the inflammatory kidney was found to be lower than that in the healthy kidney, except for the medullary concentrations 7 hr after administration. The exceptional high concentration in the medulla must be attributable to the compound retained in numerous sporadical areas of acute inflammation. These findings strongly suggest that most antibiotics poorly reach the renal tissues of chronic inflammation.

Urinary excretion of antibiotics in patients with chronic pyelonephritis was studied by Sullivan et al. (1975) who stated that the concentrations in the urine from affected kidneys declined. Their finding agrees to ours in dogs in that the urinary concentration and urinary recovery decline when the kidney bears acute and chronic inflammation. They also stated that the decrease in urinary antibiotic concentration in patients with chronic pyelonephritis is proportional to the decrease in creatinine clearance, and suggested that the urinary excretion of antibiotics from inflammatory kidneys conforms to the "intact nephron hypothesis" (Bricker et al. 1960; Stamey and Pfau 1963).

The present studies in dogs strongly suggest that antibiotics given to patients with pyelonephritis are effective whenever inflammation is acute and mild, but may provide limited effectiveness when inflammation happens to be either chronic or severe enough to cause abscess formation.

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