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Protective Effect of Piperacillin against Nephrotoxicity of Cephaloridine and Gentamicin in Animals

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The protective effect of piperacillin against the nephrotoxicity of cephaloridine and gentamicin was examined in experimental animals. In rabbits, piperacillin was infused at a dose of 1 mg/kg (body weight) per min over 225 min and cephaloridine (300 mg/kg) was intravenously administered as a bolus 45 min after the start of a drip infusion. Blood urea nitrogen, serum creatinine, and *N*-acetyl-β-D-glucosaminidase (NAG) in urine were measured as the renal toxicological parameters before and 24 h after cephaloridine dosing. Although the single administration of cephaloridine significantly elevated these parameters, the elevation was prevented by the concomitant administration of piperacillin. The protective effect of piperacillin was superior to those of cephalothin and fosfomycin. In rats, piperacillin (1,000 mg/kg) was intravenously administered and immediately followed by the intramuscular administration of gentamicin (100 mg/kg) every 24 h for 5 days. When piperacillin was concomitantly administered with gentamicin, the elevations of blood urea nitrogen, serum creatinine, and urinary NAG were significantly lower than when gentamicin was given alone. The concomitant administration of piperacillin resulted in a significant protective effect against the nephrotoxicity of cephaloridine in rabbits and of gentamicin in rats. Histopathological observation also supported the protective effect of piperacillin. The protective mechanism of piperacillin might be the inhibition of transport from the peritubular side to tubular cells for cephaloridine and from both the peritubular and luminal sides for gentamicin.

Large doses of cephaloridine cause acute renal cell lesions of the proximal tubules in experimental animals (1, 4, 6, 24, 29). Gentamicin shows both nephrotoxicity and ototoxicity in a variety of experimental animals (10, 11, 15, 17, 18, 20–23) and humans (16, 31). Therefore, many attempts have been made to prevent nephrotoxicity by administering protective agents (2, 3, 5, 7, 9, 14, 25, 26, 28). For example, probenecid (7, 25, 28), *p*-aminohippurate (26), and other organic anions (7) have been found to reduce the nephrotoxicity of cephaloridine in experimental animals.

Previously, we reported the pharmacokinetic changes of cefazolin and cefoperazone in combination with piperacillin in rabbits (13). Urinary excretion of cefazolin and cefoperazone was reduced, and subsequently, drug half-lives in serum were prolonged by the concomitant administration of piperacillin. However, the urinary excretion of piperacillin was not affected by the concomitant administration of cefazolin or cefoperazone. From the fact that these three β-lactams were mainly excreted by tubular secretion, piperacillin seemed to have a higher affinity for the tubular secretion system in rabbits. It is therefore expected that the higher affinity of piperacillin to the tubular secretion system would protect against the nephrotoxicity due to cephaloridine and gentamicin.

In this paper, we report the protective effect of piperacillin against the nephrotoxicity of cephaloridine in rabbits and of gentamicin in rats.

MATERIALS AND METHODS

Antibiotics. Cephaloridine (Shionogi & Co., Ltd., Osaka, Japan), gentamicin (Essex Nippon Co., Ltd., Osaka, Japan), piperacillin (Toyama Chemical Co., Ltd., Tokyo, Japan), cephalothin (Shionogi & Co., Ltd., Osaka, Japan), and fosfomycin (Meiji Seika Kaisha Ltd., Tokyo, Japan) were commercial preparations. These antibiotics were dissolved in physiological saline.

Animals. The investigations were carried out in Japanese white adult male rabbits weighing 2.8 to 3.1 kg and Wistar male rats weighing 295 to 365 g.

Protective effect of piperacillin against the nephrotoxicity of cephaloridine in rabbits. Rabbits were randomly assigned to four groups and were housed individually in metabolic cages to collect urine. They were fed with a commercial rabbit chow RM-4 (Sankyo Labo Service Co., Ltd., Tokyo, Japan) and received tap water ad libitum. Urine samples for 24 h before dosing were collected with metabolic cage and bladder cannulation, and blood was also withdrawn from the auricular vein before dosing. The rabbits then received piperacillin administration via a drip infusion at a dose of 1.0 mg/kg (body weight) per min through the auricular vein over 225 min. The control group animals received an equivalent volume of physiological saline (0.2 ml/kg per min) instead of piperacillin. At 45 min after starting a constant infusion, cephaloridine (300 mg/kg) was intravenously administered as a bolus into the auricular vein. Similarly, the drip infusion of cephalothin (1.1 mg/kg per min) or fosfomycin (1.1 mg/kg per min) was carried out over 225 min, and cephaloridine was administered under the same procedure. The rabbits were put in the box during the drug administration and thereafter were kept in metabolic cages. At 24 h after cephaloridine dosing, blood samples were obtained after the collection of urine samples was completed. The rabbits were then anesthetized by an intravenous administration of pentobarbital

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(30 mg/kg) and were sacrificed by sectioning the aorta abdominalis.

Blood samples were allowed to clot at room temperature. Thereafter, serum was separated by centrifugation at 1,200 × *g* for 15 min at 4°C. Blood urea nitrogen (BUN) and serum creatinine (SCr) were analyzed by using the Hitachi model 705 autoanalyzer. Urine samples were centrifuged at 1,200 × *g* for 10 min at 4°C after measuring urine volume. The supernatant was subjected to the determination of *N*-acetyl-β-D-glucosaminidase (NAG) activity. NAG activity was determined by spectrophotometry, with sodio-*m*-cresolsulphonphthaleinyl-*N*-acetyl-β-D-glucosaminide as the substrate, and was expressed as international units per urine collected for 24 h. Kidney samples were prepared by the standard operation of hematoxylin and eosin staining for light microscopic observation.

Measurement of levels of cephaloridine in serum. Rabbits received the drug via a drip infusion at a dose of 1.0 mg/kg per min of piperacillin through the auricular vein over 225 min. At 45 min after starting the infusion of piperacillin, cephaloridine (50 and 300 mg/kg) was intravenously administered as a bolus into the auricular vein. The control group rabbits received physiological saline via a drip infusion, with a flow rate of 0.2 ml/kg per min. Blood samples were withdrawn from the auricular vein opposite the ear used for the drug administration and were allowed to clot at room temperature. Serum was separated by centrifugation (1,200 × *g*, 10 min), and cephaloridine levels were measured by high-performance liquid chromatography.

Serum (0.5 ml) was mixed with 0.5 ml of methanol for deproteinization. The mixture was vigorously shaken for 30 s and centrifuged at 1,200 × *g* for 10 min at 4°C. The supernatant was injected into a high-performance liquid chromatographic system. Samples were run on a column (inner diameter, 4 mm; length, 300 mm) of Nucleosil 10C18 (Macherey-Nagel GMBH & Co., Düren, Federal Republic of Germany) at ambient temperature with a flow rate of 2.0 ml/min. The mobile phase for cephaloridine consisted of 15% CH_3CN, 0.2% 1 M CH_3COOH, and 2% 1 M CH_3COONa in water. The eluate was monitored at 254 nm.

Protective effect of piperacillin against the nephrotoxicity of gentamicin. Rats were randomly assigned to five groups with 10 rats each and were housed individually in metabolic cages. They were fed with a commercial rat chow MF (Oriental Yeast Co., Ltd., Tokyo, Japan) and received tap water ad libitum. Rats of group 1 to group 5 received the following regimens with each drug or control vehicle given once daily for 5 days: group 1, 0.9% saline (4 ml/kg) intravenously and 0.9% saline (2.5 ml/kg) intramuscularly; group 2, piperacillin (1,000 mg/4 ml per kg) intravenously and 0.9% saline (2.5 ml/kg) intramuscularly; group 3, 0.9% saline (4 ml/kg) intravenously and gentamicin (100 mg/2.5 ml per kg) intramuscularly; group 4, 3.6% saline (4 ml/kg) (equivalent mole of sodium chloride to 1,000 mg of piperacillin per kg dissolved in 0.9% saline) intravenously and gentamicin (100 mg/2.5 ml per kg) intramuscularly; and group 5, piperacillin (1,000 mg/4 ml per kg) intravenously and gentamicin (100 mg/2.5 ml per kg) intramuscularly. The rats were placed in metabolic cages to collect urine samples 24 h prior to the first administration, and the urine samples were collected at 24-h intervals. After the urine volume was measured, urine samples were centrifuged at 1,200 × *g* for 10 min. The supernatant was subjected to the measurement of NAG activity. The rats were sacrificed 24 h after the final administration. Blood samples were obtained from the inferior vena cava under ether anesthesia, and BUN and SCr were analyzed. Kidney samples were then prepared for histopathological study.

Measurement of gentamicin in serum and the renal cortex and medulla. For the determination of gentamicin concentrations in serum and the renal cortex and medulla, rats received gentamicin with and without piperacillin. After 2, 6, and 24 h, rats were anesthetized with ether, and blood was obtained from the aorta abdominalis. The kidney was then removed from the rat, and the renal cortex and medulla were dissected free. Each sample was weighed, minced, and then homogenized in M/15 phosphate buffer (pH 7.0) at a volume-to-weight ratio of 4:1 using ice-cold silanized glass homogenizer fitted with a Teflon pestle. The supernatant was obtained by centrifugation at 1,200 × *g* for 10 min at 4°C. Gentamicin levels in serum and supernatant were determined by high-performance liquid chromatography, as described by Maitra et al. (19) with a slight modification. Tobramycin was used as the internal standard.

Histopathological score. Histopathological sections of kidney were evaluated independently by a pathologist who was unaware of the regimens used. The extent and distribution of lesions were graded from 0 to 5 (0 was normal). In grade 1, less than 10% of the nephrons were recognized; in grade 2, 10 to 25% of the nephrons were recognized; in grade 3, 26 to 50% of the nephrons were recognized; in grade 4, 51 to 75% of the nephrons were recognized; and grade 5, greater than 75% of the nephrons were recognized.

RESULTS

Protective effect of piperacillin against the nephrotoxicity of cephaloridine. The protective effect of piperacillin against the nephrotoxicity of cephaloridine in rabbits is shown in Fig. 1. When cephaloridine (300 mg/kg) was intravenously administered together with a drip infusion of saline, the values of BUN, SCr, and urinary NAG activity were significantly increased by 4.5, 5.1, and 6.9 times, respectively. When cephaloridine was administered together with a drip infusion of piperacillin at 1.0 mg/kg per min, these parameters remained unchanged. The protective effect of piperacillin against the nephrotoxicity of cephaloridine was superior to those of cephalothin and fosfomycin in rabbits.

Histopathological analysis of the rabbits. Renal tissue specimens obtained 24 h after cephaloridine administration were pathologically examined with a microscope. For a single administration of cephaloridine (300 mg/kg), histopathological changes were found, such as necrosis, desquamation and degeneration of proximal tubular cells, cell infiltration in the interstitium, and hyaline cast formation in lumens of tubules. These cell lesions were found in proximal tubular cells but not in distal tubular cells (Fig. 2A). However, no pathological lesions were observed when cephaloridine was given in combination with piperacillin (Fig. 2B).

Effect of piperacillin on the pharmacokinetics of cephaloridine in rabbits. Figure 3 shows the drug levels in serum after the intravenous administration of 50 and 300 mg of cephaloridine per kg, with and without piperacillin in rabbits. When cephaloridine was intravenously administered at a dose of 50 mg/kg, which does not cause nephrotoxicity, both the drug levels in serum and the half-life of cephaloridine during drip infusion of piperacillin (1.0 mg/kg per min) were elevated and slightly prolonged, respectively, as compared with the values for cephaloridine given without piperacillin. On the other hand, when cephaloridine (300 mg/kg) was administered alone, the drug half-life in serum was gradually prolonged with the passage of time, as compared with that of

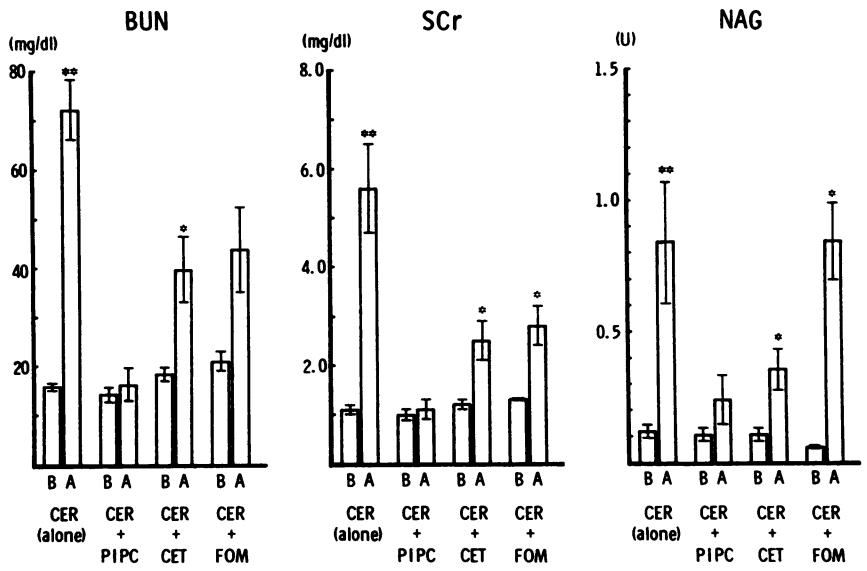

FIG. 1. Protective effect of piperacillin, cephalothin, and fosfomycin (FOM) against the nephrotoxicity of cephaloridine in rabbits. Cephaloridine (300 mg/kg) was intravenously administered with a drip infusion of saline [CER(alone)], piperacillin (CER+PIPC), cephalothin (CER+CET), and fosfomycin (CER+FOM). BUN, SCr, and urinary NAG activity were measured before (B) and 24 h after (A) cephaloridine dosing. Values are expressed as the mean ± standard error of 4 to 8 rabbits. Statistical significance by paired the Student's t test is as follows: *, $P < 0.05$; **, $P < 0.01$.

cephaloridine (50 mg/kg) alone; this change correlated well with the elevation of BUN and SCr. However, when cephaloridine (300 mg/kg) was concomitantly administered with piperacillin (1.0 mg/kg per min), the drug levels in serum and the half-life of cephaloridine were lowered and reduced, respectively, and BUN and SCr showed nearly the same levels as those observed before cephaloridine administration. The half-life of cephaloridine in serum was similar to that of cephaloridine (50 mg/kg) in combination with piperacillin. The renal cortex and medulla levels of cephaloridine in combination with piperacillin were significantly ($P < 0.05$) reduced (6 h after cephaloridine dosing), as compared with cephaloridine alone. In particular, renal cortex levels of cephaloridine were about 1/25 that of cephaloridine alone.

Protective effect of piperacillin against the nephrotoxicity of gentamicin. The protective effect of piperacillin against the nephrotoxicity of gentamicin in rats is shown in Fig. 4 and 5. As compared with a 0.9% saline control, a significant elevation ($P < 0.01$) of BUN and SCr was observed in the rats receiving gentamicin with and without piperacillin. However, these parameters were significantly suppressed ($P < 0.05$) in the combination with piperacillin, as compared with gentamicin alone (Fig. 4). Urinary NAG activity of gentamicin alone showed a gradual increase with the passage of time. Particularly, the values of NAG activity soared 24 h after the last administration. However, the elevation of NAG activity was significantly suppressed ($P < 0.05$) in combination with piperacillin, as compared with gentamicin alone (Fig. 5). Combination with the equivalent mole of sodium chloride to 1,000 mg of piperacillin per kg did not show as great a protective effect as did the combination with piperacillin.

Histopathological analysis of the rats. Rats given gentamicin alone developed tubular necrosis, degeneration, dilation, together with regeneration of proximal tubular cells, cell infiltration in interstitium, and hyaline cast formation in lumens of tubules. However, no cell lesion was found in distal tubular cells. By the combination with piperacillin, these abnormalities were reduced; especially, necrosed cells were significantly ($P < 0.05$ by U-test) reduced (Table 1).

Effect of piperacillin on the pharmacokinetics of gentamicin in rats. While no significant difference was observed in the levels of gentamicin alone and in combination with piperacillin in the renal medulla, the levels of gentamicin in the renal cortex were significantly reduced by the concomitant administration of piperacillin, as compared with those of gentamicin alone (Fig. 6).

DISCUSSION

Many researchers have reported the nephrotoxicity of cephaloridine in experimental animals. The mechanism of nephrotoxicity due to cephaloridine is considered to be the selective, high, and long-lasting accumulation in tubular cells. That is, while there is little or no net secretion of cephaloridine into urine (6, 7, 29), cephaloridine is actively transported into the rabbit tubular cells (25, 27) and the subsequent movement of cephaloridine across the luminal cell membrane is restricted, resulting in unusually high intracellular concentrations because of the diffusion block between cell water and tubular fluid (26). Therefore, it is postulated that the tubular toxicity of cephaloridine in rabbits is directly related to the local intracellular concentrations.

Since the sensitivity to the nephrotoxic action of cephaloridine is in the order of rabbit > monkey > mouse > hen > rat (6), we therefore used rabbits in the present experiment. The nephrotoxicity was induced with a good reproducibility with a single intravenous dose of 300 mg of cephaloridine per kg in rabbits. The values of BUN, SCr, and NAG activity were significantly increased by the administration of cephaloridine alone, whereas the increase of these parameters was significantly reduced by the concomitant administration of piperacillin. Moreover, the histopathological improvement in combination with piperacillin also revealed the significant protective effect against the nephro-

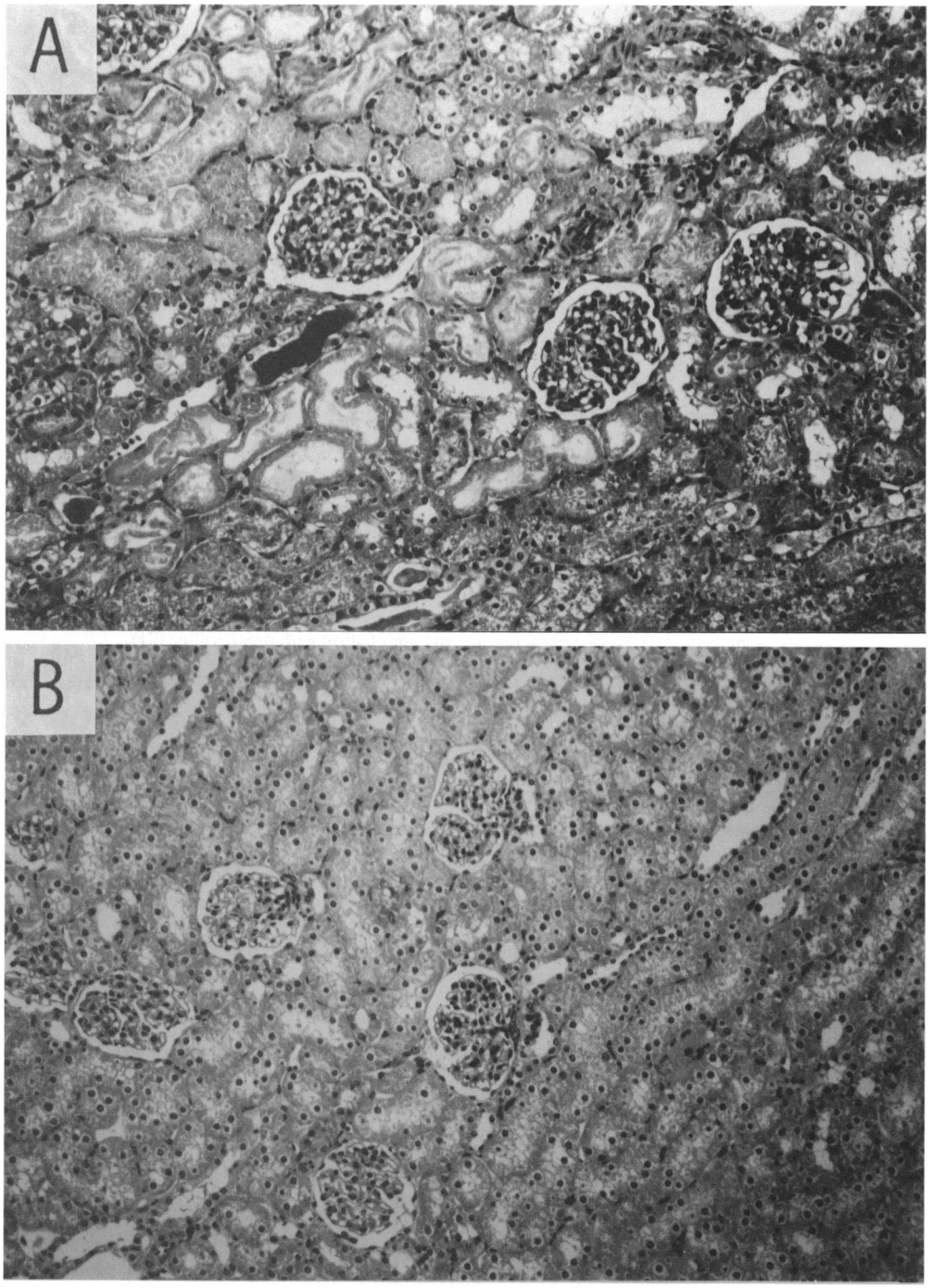

FIG. 2. Light micrograph of rabbit kidney. Cephaloridine at a dose of 300 mg/kg was administered with a drip infusion of saline (0.2 ml/kg per min [A]) or with piperacillin (1.0 mg/kg per min [B]). Renal tissue specimens were obtained 24 h after administration of cephaloridine. Magnification, ×100.

toxicity of cephaloridine in rabbits. This protective activity was superior to those of cephalothin and fosfomycin in rabbits.

To study this protective mechanism of piperacillin, the pharmacokinetic changes of the cephaloridine were examined in rabbits. When cephaloridine (300 mg/kg) was administered alone, the drug half-life in serum was prolonged, in accordance with the elevation of the values of BUN and SCr. On the other hand, the half-life of cephaloridine, in combination with piperacillin, in serum was reduced with these toxicological parameters unchanged, as compared with cephaloridine alone. It was similar to that of the intravenous administration of 50 mg/kg, a dose which does not cause nephrotoxicity, in combination with piperacillin. These results indicated that higher and prolonged levels of cephaloridine in serum at a dose of 300 mg/kg alone were due to the reduction of the renal function by cephaloridine itself, while the improved elimination of cephaloridine, in combination

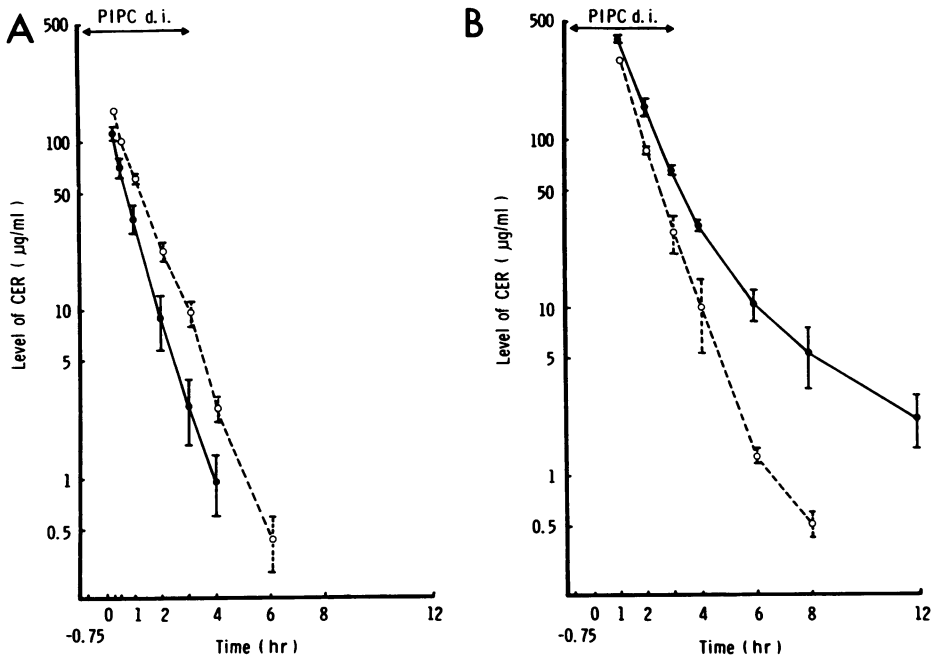

FIG. 3. Effect of piperacillin on the levels of cephaloridine in serum in rabbits. (A) Levels of cephaloridine (CER) in serum at an intravenous dose (i.v.) of 50 mg/kg alone (saline, 0.2 ml/kg per min), and in combination with piperacillin (PIPC; 1.0 mg/kg per min). (B) Levels of cephaloridine in serum when cephaloridine (300 mg/kg) was intravenously administered with a drip infusion (d.i.) of saline (0.2 ml/kg per min) or with piperacillin (1.0 mg/kg per min). Symbols: ●, levels of cephaloridine in serum alone; ○, levels of cephaloridine in combination with piperacillin.

with piperacillin, from blood was not due to the acceleration of cephaloridine elimination by piperacillin but to the preservation of normal kidney function by piperacillin. The levels of cephaloridine in renal cortex, when concomitantly administered with piperacillin, were significantly reduced, as compared with cephaloridine alone. Moreover, the levels and half-life of cephaloridine in serum were, respectively, elevated and slightly prolonged by the concomitant administration with piperacillin (Fig. 3A). Therefore, the probable mechanism of protection by piperacillin might be the competitive inhibition of transport in proximal tubular cells from the peritubular side (blood) for cephaloridine, as seen in the case of probenecid (7, 25, 28) and *p*-aminohippurate (26).

The nephrotoxicity of gentamicin has been widely investigated with various experimental models. Just et al. (15) and Silverblatt and Kuehn (23) reported that aminoglycosides

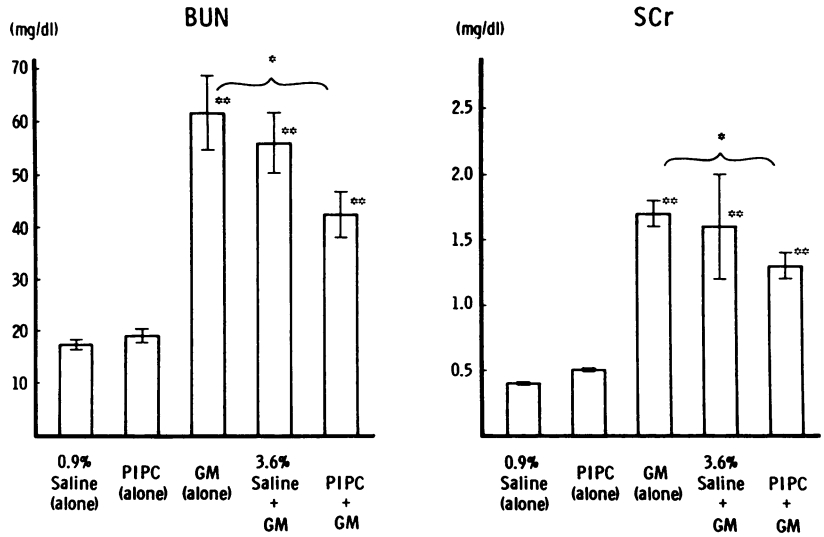

FIG. 4. Effect of piperacillin against the nephrotoxicity of gentamicin in rats. Rats received 0.9% saline alone, piperacillin alone [PIPC (alone)], gentamicin alone [GM (alone)], gentamicin in combination with 3.6% saline (3.6% saline+GM), and gentamicin in combination with piperacillin (PIPC+GM) for 5 days. Piperacillin (1,000 mg/kg) was intravenously administered, and then gentamicin (100 mg/kg) was immediately intramuscularly administered. BUN and SCr were measured 24 h after the last administration. Values are expressed as the mean ± standard error of 8 to 10 rats. Statistical significance by Student's *t* test is as follows: *, $P < 0.05$; **, $P < 0.01$.

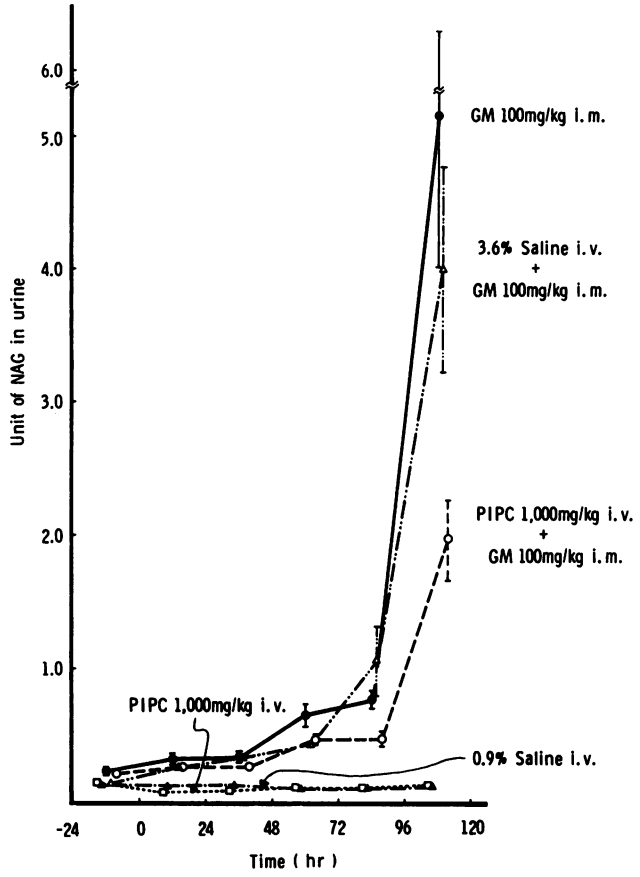

FIG. 5. Effect of piperacillin (PIPC) against the nephrotoxicity of gentamicin (GM) in rats. Values are expressed as the mean ± standard error of 8 to 10 rats. Drug abbreviations and statistical significance are as in the legend to Fig. 4. i.v., Intravenously; i.m., intramuscularly.

were transported from the luminal side to the renal tubular cells as a result of pinocytosis. Pastoriza-Munoz et al. (21) also reported the renal accumulation of gentamicin across both apical and peritubular membranes of proximal tubular epithelium in rats. Barza et al. (3) reported that there was a close relationship between the accumulation of aminoglycosides in the kidney and the extent of nephrotoxicity, and moreover, they showed a remarkable relationship between the reduction of aminoglycoside-induced nephrotoxicity and

TABLE 1. Histologic toxicity score in rats given gentamicin alone and gentamicin in combination with piperacillin

Renal morphology	Toxicity score of rats given:	
	GM alone[a]	GM + PIPC[b]
Tubular necrosis	28	14[c]
Tubular degeneration	28	21
Tubular dilation	8	4
Tubular regeneration	10	9
Hyaline cast formation	7	3
Cell infiltration in interstitium	20	14

[a] Rats receiving 100 mg of gentamicin (GM) per kg alone for 5 days.
[b] Rats receiving 1,000 mg of piperacillin (PIPC) per kg and 100 mg of gentamicin (GM) per kg for 5 days.
[c] Statistical difference ($P < 0.05$) by U test.

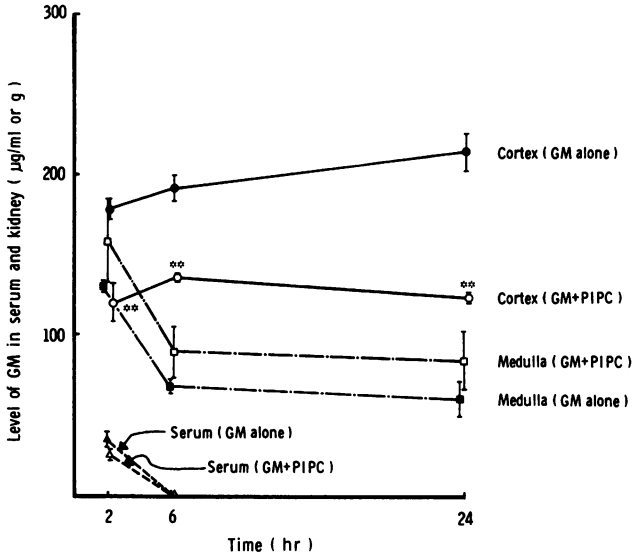

FIG. 6. Effect of piperacillin on serum and renal cortex and medulla levels of gentamicin in rats. Rats received an intravenous dose of 1,000 mg of piperacillin (PIPC) per kg and then received an intramuscular dose of 100 mg of gentamicin per kg (GM+PIPC). Values are expressed as the mean ± standard error of 4 to 5 rats. Statistical significance by Student's t test is as follows: **, $P < 0.01$.

the reduction of aminoglycoside concentration in the renal cortex when aminoglycoside and cephalosporin antibiotics were coadministered. Therefore, we determined the gentamicin levels in the renal cortex, with and without piperacillin. The gentamicin levels were significantly reduced in combination with piperacillin. It was considered that this reduction resulted in the suppression of the gentamicin nephrotoxicity, as shown in Fig. 4 and 5.

From these findings, the mechanism of protection by piperacillin might be the competitive inhibition of transport in proximal tubular cells from both the peritubular and luminal sides for gentamicin. However, the effect of piperacillin seemed insufficient against the nephrotoxicity of gentamicin in this experiment. To explain these results, two probable reasons can be offered. The first possibility is that with the dosage and route used for piperacillin, the effective time or effective amount or both for protection might be not sufficiently obtained. The second possibility is that gentamicin might be transported through two possible routes, i.e., via the cation transport system or the phospholipid layer or both in proximal tubular cells.

Concerning the protection against the nephrotoxicity of aminoglycosides, many researchers reported the protective agents and mechanism. In their reports, they proposed the accelerated elimination from the body by sodium D-glucarate (12), inhibition of transport into proximal tubular cells by cephalothin (8), and stabilization of lysosomal membrane by fosfomycin (14). With respect to the protection of penicillins against aminoglycoside nephrotoxicity, Bloch et al. (5) and English et al. (9) have reported the reduction of gentamicin nephrotoxicity by cephalothin or carbenicillin and tobramycin nephrotoxicity by ticarcillin, respectively. However, the mechanism of reduction of the nephrotoxicity due to these penicillins is not clear. Therefore, it would be necessary to firmly establish the protective mechanism and potential role of these drugs.

In this report, we have indicated that piperacillin has not only a broad spectrum of antibacterial activity but also a

potential role as a protective agent against the nephrotoxicity due to some antibiotics in animals. Therefore, it would be necessary to confirm the protective effects of piperacillin to confirm its use in clinical practice.

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