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Nephrotoxicity of Cephalosporin-Gentamicin Combinations in Rats

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To study the possibility that cephalosporins augment the nephrotoxicity of gentamicin, groups of rats were given four hourly subcutaneous doses of: gentamicin (5 mg/kg), gentamicin plus cephalothin (100 mg/kg), gentamicin plus cefazolin (20 mg/kg), gentamicin plus cefazolin (50 mg/kg), gentamicin plus cephaloridine (50 mg/kg), or saline diluent for 15 days. Periodic measurements were made of urine volume, urine osmolality, urine protein excretion and lysosomal enzymuria, as well as blood urea nitrogen, creatinine clearance, and drug concentrations in renal cortex and medulla. Tissue was examined by light and electron microscopy. Enzymuria and proteinuria increased early in the course of all treatment groups, whereas urine osmolality declined. No distinct patterns of these variables were discernable among the groups. Gentamicin alone, gentamicin plus cephalothin, and gentamicin plus cefazolin (20 mg/kg) caused the same significant fall in glomerular filtrate rate from control values by day 15 ($P < 0.05$). Gentamicin plus cefazolin (50 mg/kg) and gentamicin plus cephaloridine failed to cause a decline in glomerular filtration rate compared with controls ($P > 0.05$). Gentamicin concentrations in renal cortex were 5 to 10 times higher than those in medulla in all groups. Cephaloridine and cefazolin (50 mg/kg) also displayed a gradient pattern in renal cortex, whereas cephalothin and cefazolin (20 mg/kg) did not. Cytosegrosomes with myeloid figures were characteristic ultra-structural changes seen in all groups; however, they tended to be smaller with less numerous myeloid bodies in the groups receiving gentamicin plus cephalothin, cefazolin (50 mg/kg), or cephaloridine. Cephalosporins did not augment gentamicin toxicity. High doses of cefazolin and cephaloridine protected kidneys from gentamicin nephrotoxicity. The protection may involve intracellular drug interaction within the renal cortex.

The nephrotoxic potential of gentamicin is well documented in both man and experimental animals (10, 12, 20, 28). The nephrotoxicity of cephalothin has been the subject of a number of recent articles; however, careful pathological documentation in man and experimental animals remains incomplete (5, 19, 21, 24). Reports alleging increased nephrotoxicity of cephalothin and gentamicin in combination have appeared periodically as well (2, 4, 11, 16). These reports are controversial since other variables associated with acute renal failure, such as sepsis, gastrointestinal hemorrhage, shock and disseminated intravascular coagulation, frequently occur in these patients (25). Any augmentation of the potential nephrotoxicity of gentamicin by the presence of cephalothin or other cephalosporins would have important clinical consequences. To investigate such a possibility, we studied the nephrotoxicity of cephalosporin-gentamicin combinations in a rat model.

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MATERIALS AND METHODS

Adult, male Sprague-Dawley rats weighing 200 to 250 g were selected, housed singly in metabolic cages, allowed free access to water, and fed a standard Purina rat diet ad libitum. The metabolic cages were equipped with screens below the animals' living space to avoid contamination of the specimens with feces or other debris. The design of the cages was such that the animals were unable to contaminate the specimens with food or drinking water. The 24-h urine samples were collected under mineral oil to preclude evaporation. Five experimental groups of 18 rats each were studied and an additional group of 30 rats served as sham-injected controls.

Group 1 received gentamicin (5 mg/kg) at 4-h

intervals subcutaneously for 15 days. The gentamicin was diluted in 0.5 ml of normal saline. Urine specimens were collected on days 3, 5, 8, 10, 12, and 15, at which time urine protein excretion, urine osmolality, and the excretion of urinary enzymes were measured. Six animals each were sacrificed 4 h after a previous injection of antibiotic on days 5, 10, and 15. Serum was collected for the measurement of blood urea nitrogen and creatinine clearance. The kidneys were removed and were examined by light and by electron microscopy. In addition, homogenates were prepared for the measurement of antibiotic concentrations in renal tissue. On days 4 and 11, small aliquots of serum were collected from a tail vein 1 h before and 1 h after an antibiotic injection; the serum concentrations of the antibiotics were measured.

Groups 2, 3, 4, and 5 received gentamicin (5 mg/kg) and in addition either cephalothin (100 mg/kg), cefazolin (20 mg/kg), cefazolin (50 mg/kg), or cephaloridine (50 mg/kg) at 4-h intervals. The drugs were not mixed, but rather were injected separately in 0.25 ml of normal saline diluent. The collection of urine, serum, and kidney specimens was identical to that of group 1.

Six control animals accompanied each of the five groups. These animals were handled in an identical fashion, but were injected with 0.5 ml of normal saline every 4 h for 15 days.

Urine protein was determined by a biuret method; blood urea nitrogen and creatinine were measured by standard autoanalyzer techniques (15). Osmolality was determined by freezing point depression.

Enzymes measured in urine were the lysosomal hydrolases beta-*N*-acetyl-hexosaminidase and alpha-fucosidase. Enzyme activities were measured in urine utilizing the synthetic substrates para-nitrophenyl-*N*-acetyl-glucosaminide and para-nitrophenyl-alpha-1-fucoside in final concentrations of 4 mM in 60 mM citrate-phosphate buffer (pH 4.2) and 60 mM acetate buffer (pH 5.2), respectively. The reactions were initiated by adding 50 μl of dialyzed urine and then incubating at 37 C for 15 min in the case of beta-*N*-acetyl-hexosaminidase, or adding 100 μl of dialyzed urine and incubating at 37 C for 60 min in the case of alpha-fucosidase. The procedures have been described in detail by Patel et al. (17, 18).

Portions of the kidneys taken at the time of sacrifice were fixed in cold 4% glutaraldehyde solution in 0.1 M phosphate buffer (pH 7.4), postfixed in cold 1% phosphate-buffered osmium tetroxide solution, and embedded in Epon 812 epoxy resin. Ultra-thin sections were stained with uranyl acetate and lead citrate, and viewed under a Philips 300 electron microscope. Additional samples were fixed in 10% buffered formalin, embedded in paraffin, stained with hematoxylin and eosin or by the periodic-acid-Schiff reaction, and examined by light microscopy.

Antibiotic concentrations in serum and renal tissue were measured by an agar well-diffusion method (29). *Bacillus subtilis* served as the marker organism. A cephalosporinase was added to the plates used for gentamicin assay, whereas cephalosporins were assayed in the presence of gentamicin by the addition of 6% sodium chloride (12 g/200 ml of media) to plates used for cephalosporin assay (3, 26). Kidney tissue was weighed, homogenized, and diluted as necessary with phosphate buffer (pH 8). Those kidneys acquired on day 15 were further divided into cortex and medulla. The fractions were homogenized and similarly analyzed. Serum concentrations were measured directly unless the values were so high as to require dilution in pH 8 buffer. Serum concentrations are expressed as micrograms per milliliter, whereas tissue concentrations are expressed as micrograms per gram of tissue.

RESULTS

Urine volume, which is not graphically displayed, increased from a mean control value of 9 ml/24 h following all treatments so that by day 10, all groups displayed a urine output greater than 11 ml/24 h ($P < 0.05$). No single treatment regimen caused a consistently greater degree of polyuria than did the others.

Urine osmolality (Fig. 1) decreased for all treatment groups so that by day 8, all groups had a urine osmolality significantly lower than that of controls ($P < 0.05$). Animals treated with gentamicin plus cephalothin and gentamicin plus cephaloridine maintained a higher urine osmolality than did the other groups. The difference was significant by day 15 ($P < 0.05$).

All treatment regimens caused proteinuria (Fig. 1) which was significantly greater than that of controls by day 8 ($P < 0.05$). The regimens produced no easily discernible pattern.

All treatment groups displayed enzymuria. The urinary excretion of beta-hexosaminidase for all treatment groups was significantly increased over that in controls by day 5 (Fig. 2). Gentamicin plus cefazolin (20 mg/kg) resulted in a greater and earlier excretion of beta-hexosaminidase than did the other treatments. The difference was significant on days 5, 8, 10 and 12 ($P < 0.05$). The excretion of alpha-fucosidase (Fig. 2) was significantly increased over that of controls in all treatment groups by day 5 ($P < 0.05$). No patterns among the regimens were evident. By day 15, the excretion of this enzyme by all treatment groups had declined considerably.

The blood urea nitrogen determinations are displayed in Fig. 3. The groups receiving gentamicin alone, gentamicin plus cephalothin, and gentamicin plus cefazolin (20 mg/kg) showed increases in blood urea nitrogen which were significant over that of controls by day 15 ($P < 0.05$). The combinations of gentamicin plus cefazolin (50 mg/kg) and gentamicin plus cephaloridine failed to engender a significant rise in concentration of blood urea nitrogen.

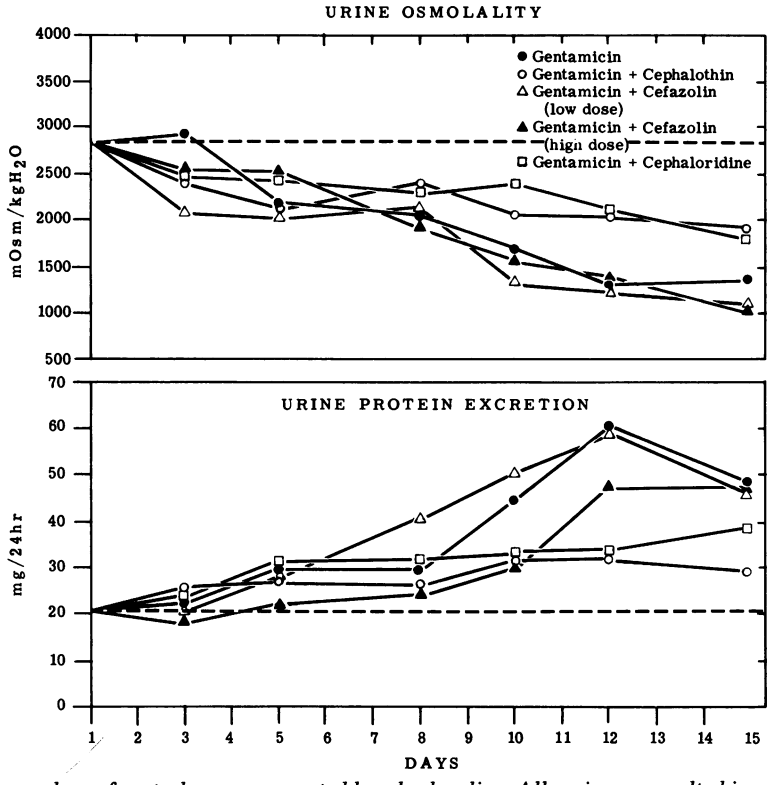

FIG. 1. *Mean values of controls are represented by a broken line. All regimens resulted in a decline in urine osmolality and progressive proteinuria.*

The results of the creatinine clearance determinations were similar (Fig. 3). The decrease in creatinine clearance caused by gentamicin alone and by the combinations of gentamicin plus cephalothin and of gentamicin plus cefazolin (20 mg/kg) were significantly altered from controls by day 15 ($P < 0.05$). The combinations of gentamicin plus cefazolin (50 mg/kg) and of gentamicin plus cephaloridine failed to cause a decline in the endogenous creatinine clearance.

The mean of the serum concentrations of gentamicin 1 h after injection in all treatment groups was 5 μg/ml. The mean concentration 1 h after injection was 38 μg/ml for cephalothin, 41 μg/ml for cefazolin (20 mg/kg), 87 μg/ml for cefazolin (50 mg/kg), and 16 μg/ml for cephaloridine. The drugs did not tend to accumulate in serum during the course of treatment. The 1-h preinjection concentrations were zero or negligible.

The concentrations of gentamicin in renal cortical tissue at sacrifice appear in Fig. 4. All five regimens caused high gentamicin concentrations that were apparent on day 5 and remained constant thereafter. The addition of the cephalosporins had no effect on the concentrations of gentamicin in the renal cortex, which were similar in the five treatment groups ($P > 0.05$). The lower portion of Fig. 4 displays the concentrations of cephalosporin in the renal cortical tissue at sacrifice. Tissue concentrations of cephalothin were uniformly low. Cefazolin (20 mg/kg) achieved a renal tissue concentration of 24 μg/g by day 10. Cefazolin (50 mg/kg) achieved concentrations exceeding 40 μg/g on all days tested. Cephaloridine concentrations exceeded 60 μg/g on days 5 and 15, and were 114 μg/g on day 10. When assessed in cortex and medulla, and gentamicin concentrations were four to five times higher in the cortex than in juxtamedullary tissue or medulla. No difference in distribution was found in the case of cephalothin or of low-dose cefazolin. The cortical concentrations of cefazolin (50 mg/kg) and cephaloridine were three times those found in medulla.

Renal tubular changes discernible by light microscopy on day 5 were minimal in all treatment groups and consisted of cytoplasmic swelling with mold vacuolar degeneration involving primarily the pars convoluta of the proximal tubules. By day 10, two of the six rats receiving gentamicin alone displayed focal necrosis of

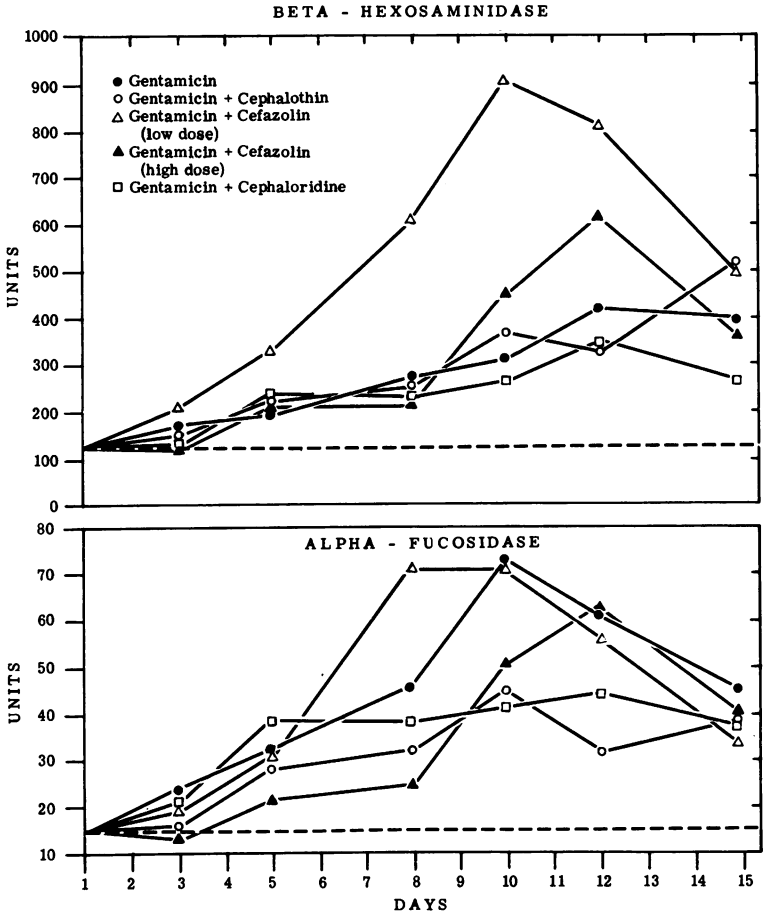

FIG. 2. *Mean values of controls are represented by a broken line. All regimens resulted in lysosomal enzymuria. No pattern among the regimens was evident. Units represent micrograms of para-nitrophenol produced per 24-h urine volume per hour.*

proximal tubules involving 20 to 30% of the nephrons. The proximal tubules of the remaining nephrons revealed slight flattening of the cells, prominent nucleoli, and luminal distension. The rats receiving gentamicin-cephalosporin combinations had more pronounced and extensive cytoplasmic vacuolization with loss of the brush border. The combinations of gentamicin-cephalothin, gentamicin-cefazolin (50 mg/kg), and gentamicin-cephaloridine did not exhibit complete necrosis of the tubular cells. Gentamicin-cefazolin (20 mg/kg), on the other hand, did result in focal or patchy tubular necrosis, as did gentamicin alone. By day 15, all rats receiving gentamicin alone or gentamicin-cefazolin (20 mg/kg) exhibited extensive necrosis with wide-spread regeneration. The regenerating cells were flat, with basophilic cytoplasm, prominent nucleoli, and frequent mitotic figures. Two of the six rats receiving gentamicin-cefazolin (50 mg/kg) displayed similar changes, whereas the remaining four animals in this group had much less extensive changes. The rats receiving gentamicin-cephalothin or gentamicin-cephaloridine exhibited changes similar to those seen on day 10. Necrosis of the proximal tubules in these animals did not occur.

Electron microscopic changes were most prominent in the proximal convoluted tubules. Cytosegrosomes containing numerous myeloid figures were present in the proximal tubular epithelial cells of all animals on day 5. The cytosegrosomes tended to be larger and the myeloid figures more abundant in the gentamicin and gentamicin-cefazolin (20 mg/kg) groups (Fig. 5). The cytosegrosomes found in the other groups were smaller in size and their myeloid

figures were less abundant, especially in the group receiving gentamicin-cephaloridine (Fig. 6). In addition, the groups receiving a gentamicin-cephalosporin combination showed swelling and loss of microvilli, numerous uncoated cytoplasmic vacuoles, and mitochondrial swelling.

DISCUSSION

In man, antibiotics are given so as to achieve peak and trough serum concentrations which are effective against pathogenic microorganisms. The dosage schedules take into consideration the antibiotic half-lives and repeat doses are given accordingly. In animal studies of nephrotoxicity, the drugs generally are given as a single daily dose. Frame et al. reported that rabbits receiving gentamicin had a greater degree of kidney damage if the drug was given in divided doses rather than as a single daily injection (8). In the present study, we attempted to mimic the human situation. The 5-mg/kg dose of gentamicin achieved a peak 0.5-h concentration of 10 μg/ml and 1-h concentration of 5 μg/ml. This finding was not unexpected. Although a 200-g rat weighs only 1/350th of its 70-kg counterpart, it has 1/60th the surface area (7). When calculated on a basis of surface area rather than weight, a 1 to 2-mg/kg dose in man corresponds to a 5- to 10-mg/kg dose in the rat. The 30- to 35-min gentamicin half-life in the rat necessitated administration of the drug every 4 h (13). The doses of cephalosporins were also chosen to achieve serum concentrations encountered in humans.

The nephrotoxicity of gentamicin and other aminoglycosides has been described in detail (12, 14). The involvement is confined to the pars convoluta of the proximal tubule. The electron microscopic finding is the appearance of cytosegrosomes with myeloid bodies within the proximal tubular epithelium. Cytosegrosomes are thought to represent modified lysosomes engaging in autophagy. The myeloid bodies represent ingested membranous material, possibly endoplasmic reticulum (12). Gentamicin and other aminoglycosides have a proclivity for accumulating in renal cortex in man and in experimental animals (1, 13, 14). Recently, we reported that whereas the half-life of gentamicin in the serum of the rat was 30 min, its half-life in renal cortical tissue was 109 h (13). It is possible that the nephrotoxicity of gentamicin and of other aminoglycosides is related to accumulation of the drugs in the renal cortex (13).

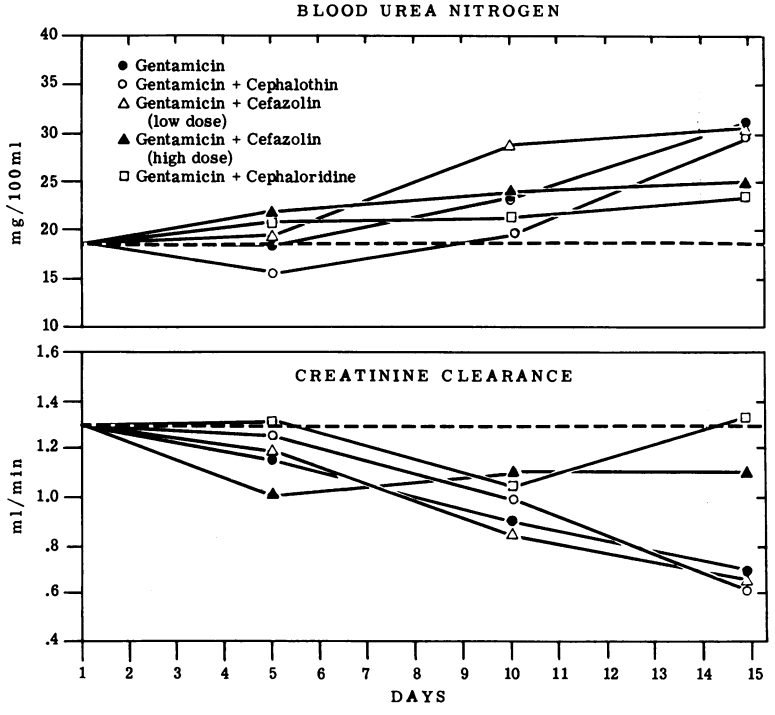

FIG. 3. *Mean values of controls are represented by a broken line. Significant increases in blood urea nitrogen and declines in creatinine clearance occurred with gentamicin alone, gentamicin plus cephalothin, and gentamicin plus cefazolin (20 mg/kg).*

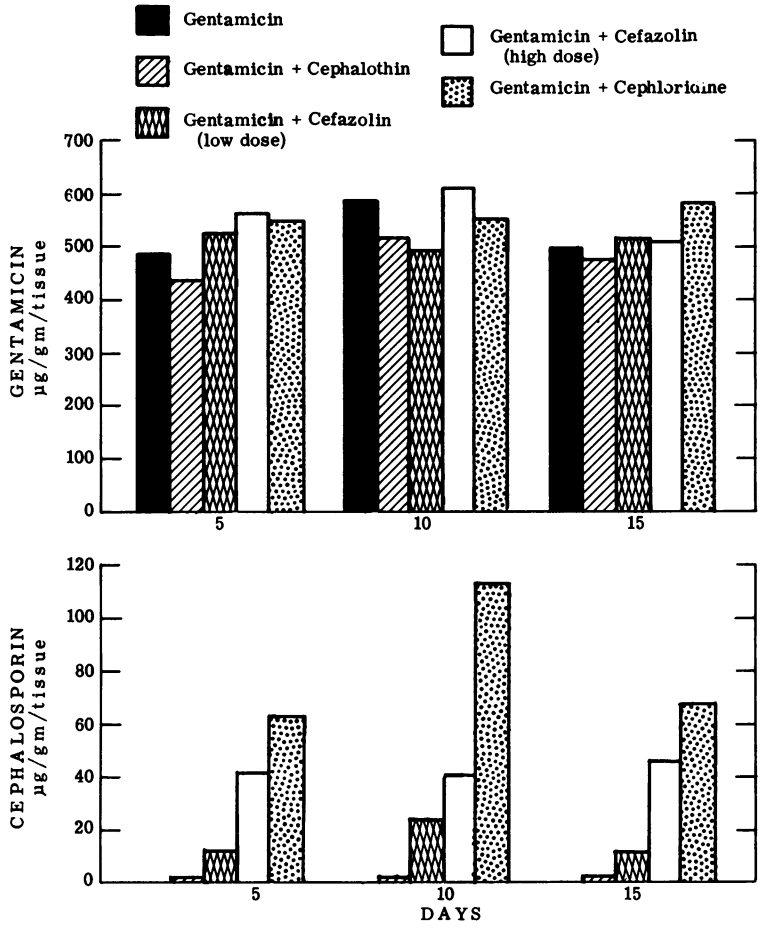

FIG. 4. *The concentrations of antibiotics in the renal cortex. Cortical concentrations of gentamicin were similar in the five treatment groups and were not altered by the addition of the cephalosporins. Cephaloridine and cefazolin achieved appreciable cortical concentrations.*

Of the cephalosporins, the nephrotoxicity of cephaloridine has been studied in the greatest detail. Welles et al. found that rats tolerated daily subcutaneous doses of 500 mg/kg for 5 months (27). Although the kidneys of these animals increased in weight, no histological changes were observed by light microscopy. Silverblatt et al. extended the knowledge of the nephrotoxic action of cephaloridine in the rabbit by fixation in vivo of renal tissues for light and electron microscopy (23). Changes in the uniformity and height of the brush border of the proximal tubules were detected within 1 h of a 200-mg/kg dose of cephaloridine. The mitochondria of these cells were less elongated and appeared more randomly aligned than normal.

Our data indicate that at the doses given, gentamicin and gentamicin in combination with the cephalosporins resulted in polyuria, decline in urine osmolality, proteinuria, and an increase in the excretion of lysosomal enzymes. The lysosomal enzymes were the earliest indicators of toxicity, but the concentrations found did not successfully discriminate between the regimens. Lysosomal enzymes have been used successfully in discriminating among different aminoglycosides of varying nephrotoxicity (14). The addition of a cephalosporin to the gentamicin regimen failed to increase nephrotoxicity of any of the treatment groups. In fact, those renal function tests reflecting the glomerular filtration rate indicated that high-dose cefazolin and cephaloridine provided protection against the nephrotoxicity engendered by gentamicin. The blood urea nitrogen and creatinine clearance of these groups showed no change over the course of the treatment period, whereas gentamicin alone, gentamicin plus cephalothin, and gentamicin plus low-dose ce-

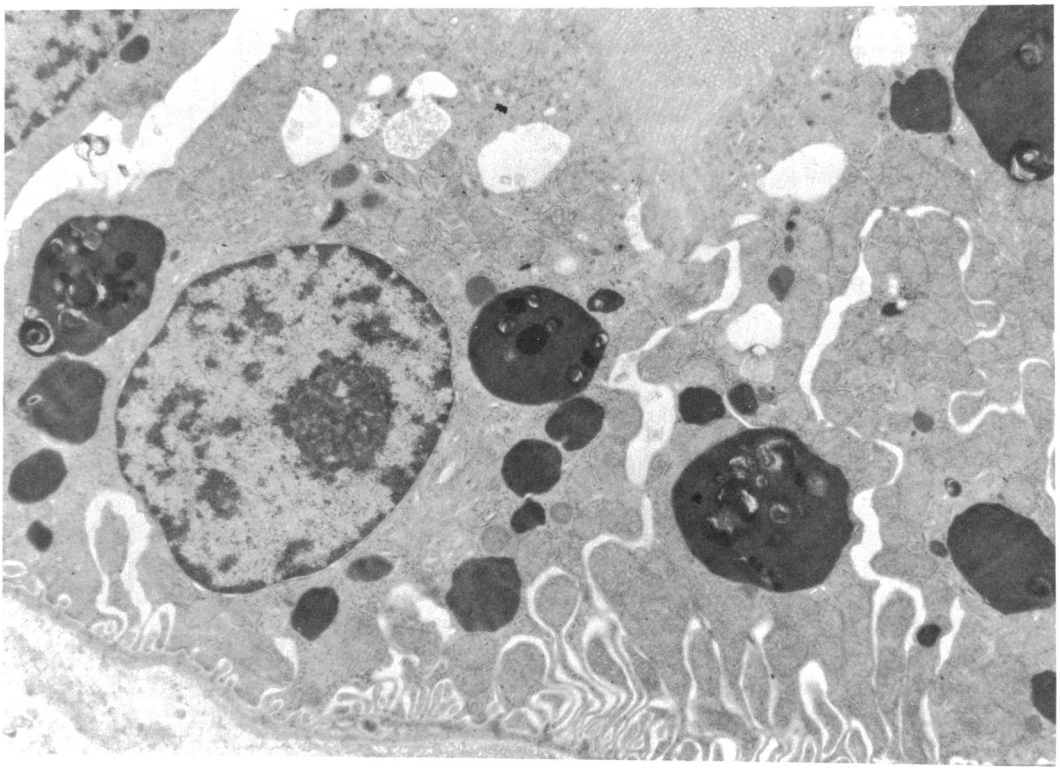

FIG. 5. *Electron micrograph of a proximal tubular epithelial cell from the gentamicin-cefazolin (20 mg/kg) group. Numerous large cytosegrosomes containing myeloid figures are noted in a proximal tubular cell (× 8,250). Similar changes were present in the group receiving gentamicin alone.*

fazolin were accompanied by a significant decline in glomerular filtration rate. The ultrastructural changes suggest that cephalothin, cephaloridine, and cefazolin (50 mg/kg) inhibited the formation of giant cytosegrosomes. The smaller number of myeloid figures seen in the cytosegrosomes of the animals receiving gentamicin-cephaloridine or gentamicin-cefazolin (50 mg/kg) suggests a decrease in the formation of this material or perhaps its enhanced excretion. The loss of microvilli and mitochondrial swelling seen in the groups receiving a gentamicin-cephalosporin combination are changes previously reported in animals receiving cephalosporin antibiotics (22).

Harrison et al. reported that, in the rat, the simultaneous administration of cephalosporins did not enhance the morphological appearance of gentamicin (9). Dellinger et al. recently reported protection against gentamicin-induced nephrotoxicity in Fischer 344 rats (6). Their animals received gentamicin as a single daily injection in doses of 6, 12, 25, and 50 mg/kg for 10 days. They reported a striking decrease in tubular necrosis at each dose level of gentamicin with the addition of cephalothin, which was given in doses of 200, 400, or 800 mg/kg per day. Those rats receiving gentamicin at 50 mg/kg per day uniformly demonstrated a rise in plasma creatinine and blood urea nitrogen, whereas only 2 of 15 rats receiving this same dose of gentamicin in combination with any dose of cephalothin did so. The protection from gentamicin nephrotoxicity by cephalothin was afforded only when both agents were given simultaneously. Our data, as well as those of Dellinger and his colleagues, indicate that, in the rat, cephalosporins do not augment the nephrotoxicity of gentamicin. Moreover, some cephalosporins appear to be capable of exerting a protective effect.

In our animals, gentamicin achieved high concentrations in renal cortex, which were not altered by the presence of cephalosporins. In those instances in which cephalosporins exerted a protective effect, they too achieved high concentrations in renal cortex. Evidence suggests that the aminoglycosides in renal cortex are intracellular or are bound to plasma membrane (13). The mechanism of aminoglycoside

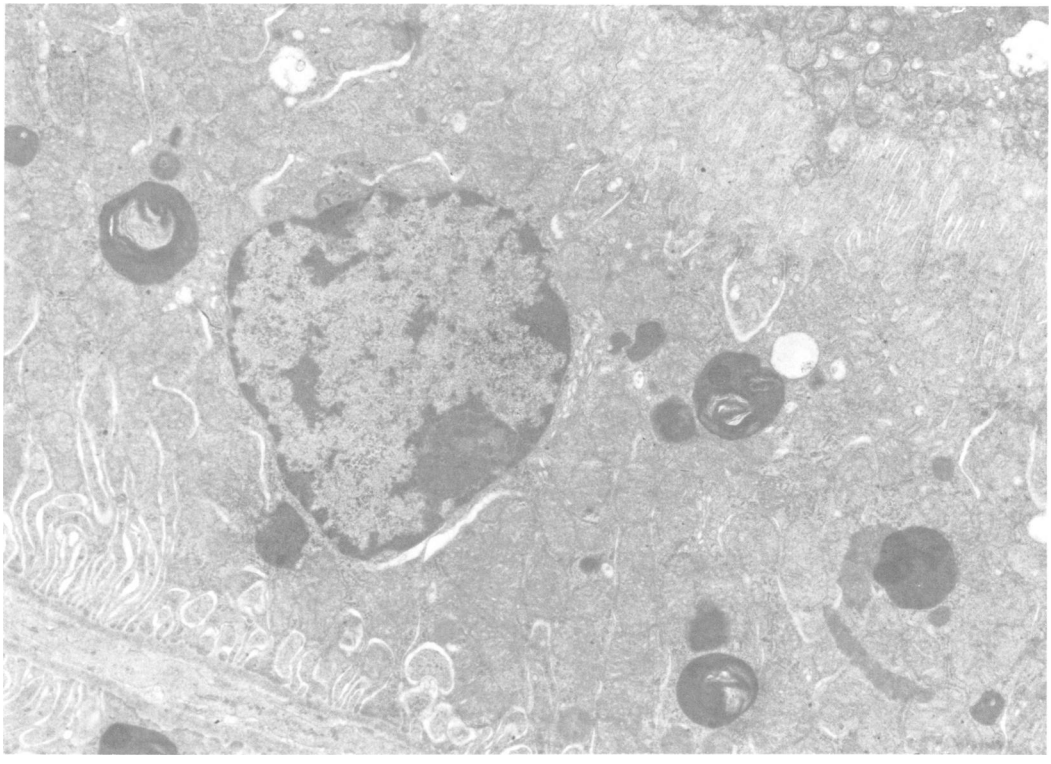

FIG. 6. *Electron micrograph of a proximal epithelial cell from the gentamicin-cephaloridine group. Cytosegrosomes in the proximal tubular cell are smaller in number and size than those of the gentamicin-cefazolin (20 mg/kg) group (× 8,250).*

nephrotoxicity is unknown, but it is possible that high concentrations of cephalosporins in renal cortex interfered with or altered the toxic properties of gentamicin. The precise explanation for the apparent protective effect afforded by cephalosporins in the nephrotoxicity of gentamicin must await elucidation of the exact mechanism and location of renal cortical aminoglycoside binding.

ACKNOWLEDGMENTS

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