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NOTES

Effects of Moxalactam and Cefotaxime on Rabbit Renal Tissue

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To determine and compare the effects of moxalactam and cefotaxime on kidneys, we gave these drugs in doses of 750 and 1,500 mg/kg to rabbits for 7 days. Cephaloridine was included as a positive control. Neither moxalactam nor cefotaxime at either dose caused lysosomal enzymuria, changes visible by light microscopy or increased plasma creatinine. Both drugs caused minor alterations in glomerular ultrastructure at the higher dose. Cephaloridine, on the other hand, caused widespread renal functional and morphological damage. We conclude that in rabbits, both moxalactam and cefotaxime are remarkably nonnephrotoxic.

Cefotaxime and moxalactam are new β-lactam antibiotics that have remarkable in vitro activity against many clinically relevant gram-positive and gram-negative bacteria (3). Both compounds also appear to be relatively free of noxious side effects. The renal toxicology of cefotaxime in comparison with other cephalosporins has recently been described (2). To our knowledge, details on the effect of moxalactam on kidneys have not been published. We therefore compared the effects of cefotaxime and moxalactam on rabbit kidneys, which provide a sensitive model for cephalosporin nephrotoxicity (5). Cephaloridine was included to provide a positive control.

Seven groups of six New Zealand male white rabbits weighing from 2.0 to 3.5 kg were housed singly in cages and given free access to food and water. On the day before the first injection (day 0) and on day 7, the animals were placed in suitable metabolism cages for 24-h urine collection. The regimen and dose for each group are shown in Table 1. Drugs were given as a single daily subcutaneous injection in 2 ml of saline diluent. To reflect renal function, the excretion of the lysosomal enzyme *N*-acetylglucosaminidase and the concentration of creatinine in plasma were determined. Tissue was examined by light microscopy and scanning electron microscopy. The techniques used to measure enzymuria and creatinine have been outlined elsewhere (4). Renal tissue was fixed in situ by in vivo perfusion with 1% procaine in normal saline followed by 2.5% glutaraldehyde in 0.075 M sodium cacodylate–HCl buffer (pH 7.4). The tissue from each rabbit was examined without prior knowledge of the regimen. Details of the microscopic procedures have been described previously (1). The data were analyzed by two-way analysis of variance.

TABLE 1. Urinary *N*-acetylglucosaminidase and plasma creatinine levels before treatment and at sacrifice[a]

Drug	Dose (mg/kg)[b]	*N*-acetylglucosaminidase		Plasma creatinine	
		Day 0	Day 7	Day 0	Day 7
Moxalactam	750	4.8 ± 0.1	5.9 ± 0.5	1.0 ± 0.1	1.1 ± 0.1
Cefotaxime	750	5.0 ± 0.2	6.8 ± 0.8	0.9 ± 0.1	1.1 ± 0.1
Cephaloridine	100	5.2 ± 0.1	15.6 ± 2.8[c]	1.1 ± 0.1	4.2 ± 1.0[c]
Moxalactam	1,500	5.4 ± 0.1	11.3 ± 2.6	1.0 ± 0.1	1.1 ± 0.1
Cefotaxime	1,500	5.3 ± 0.4	10.8 ± 2.9	0.9 ± 0.1	1.0 ± 0.1
Cephaloridine	200	5.2 ± 0.1	27.9 ± 8.0[c]	1.1 ± 0.1	13.9 ± 1.5[c]
Diluent control (saline)		5.1 ± 0.2	5.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.1

[a] Values are given as the mean for six rabbits ± the standard error.
[b] Drugs were given as a single daily subcutaneous injection in 2 ml of saline diluent.
[c] $P < 0.05$.

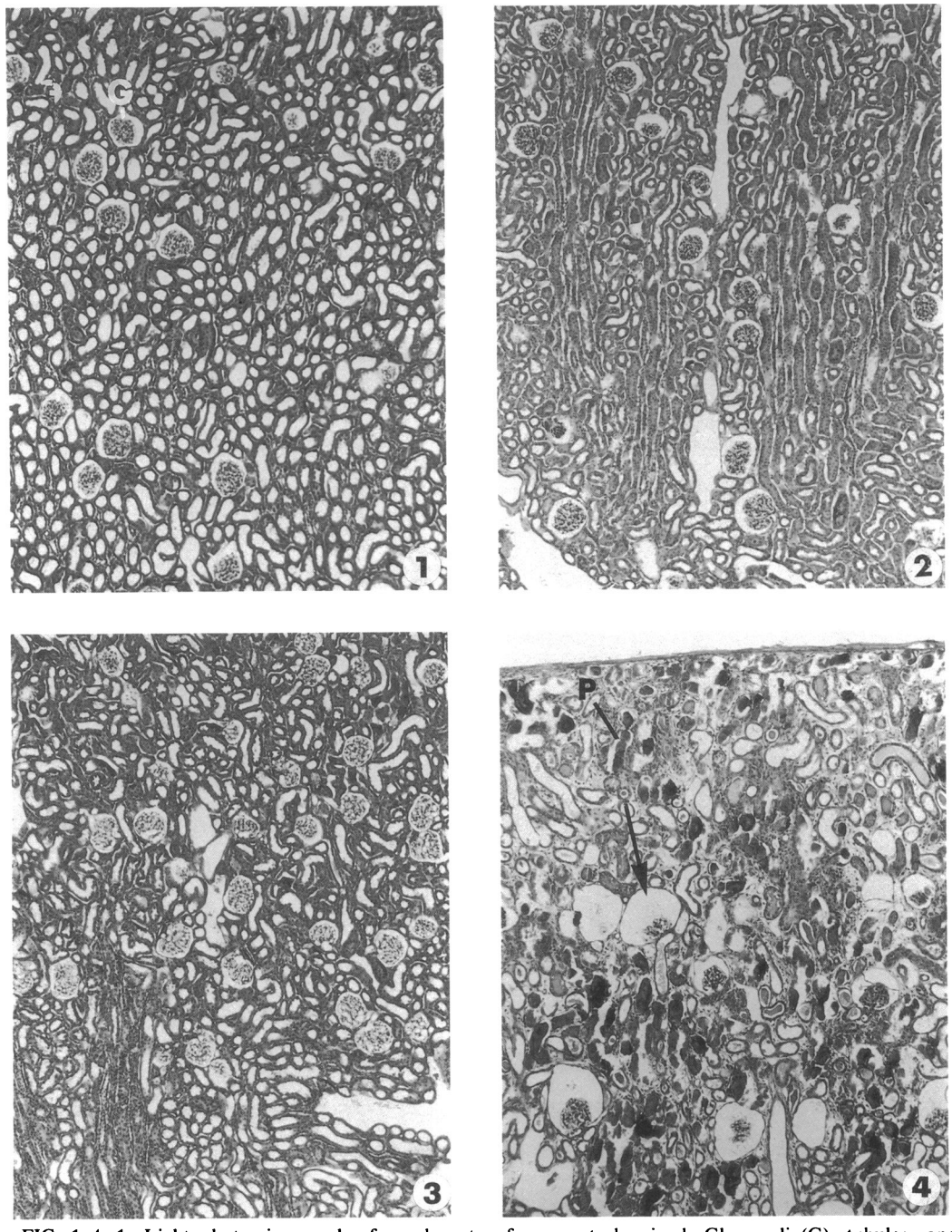

FIG. 1–4. 1. Light photomicrograph of renal cortex from control animal. Glomeruli (G), tubules, and interstitium appear normal. 2. Renal cortex from an animal receiving moxalactam at 1,500 mg/kg. This section is indistinguishable from the control. 3. Renal cortex from an animal receiving cefotaxime at 1,500 mg/kg. This section is indistinguishable from the control. 4. Renal cortex from an animal receiving cephaloridine at 200 mg/kg. Bowman's capsules are greatly enlarged (arrow). The proximal tubules (P) are necrotic. Casts are present and there is interstitial infiltrate. (All figures, ×50.)

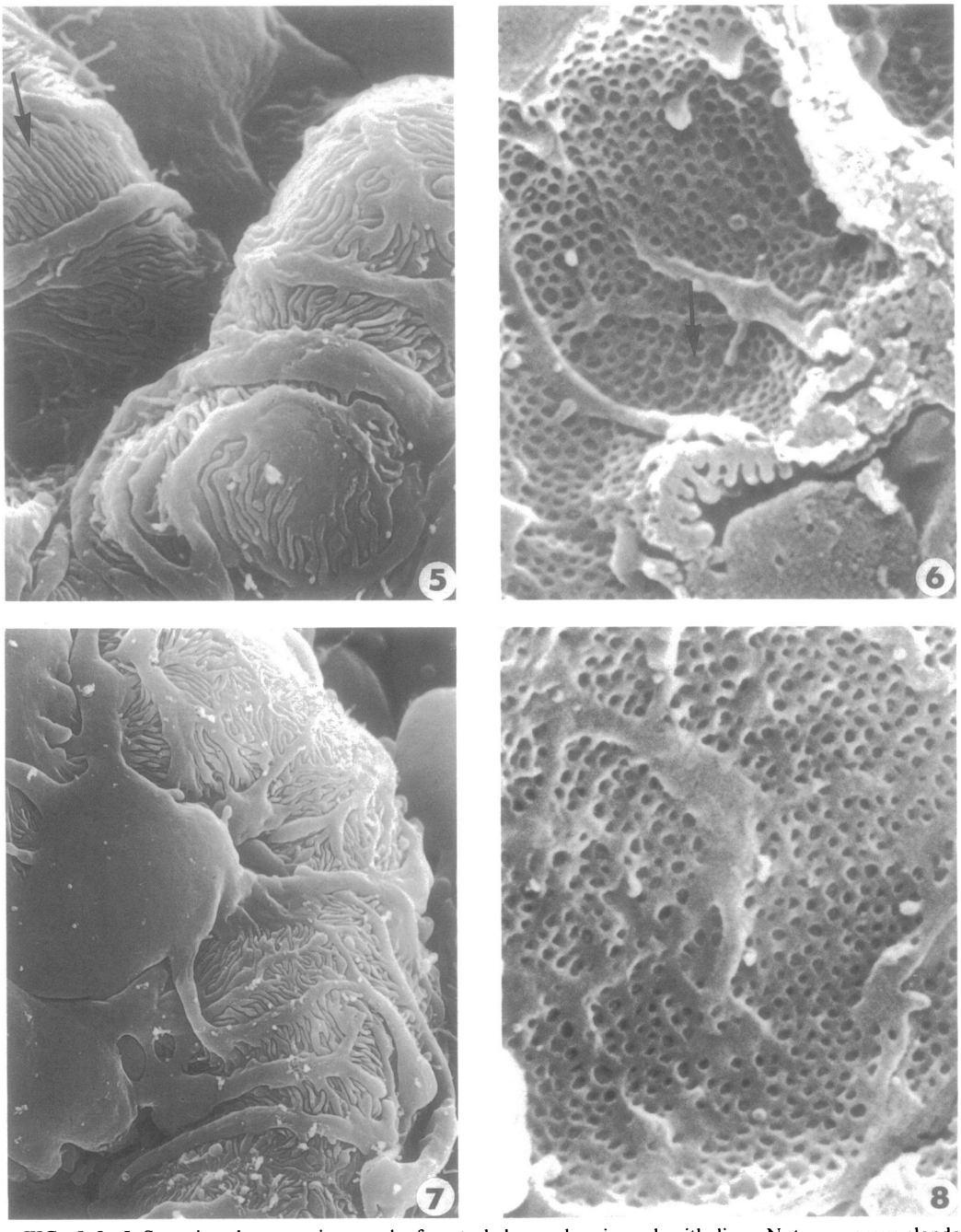

FIG. 5–8. 5. Scanning electron micrograph of control glomerular visceral epithelium. Note numerous slender interdigitating foot processes (arrow) (×4,200). 6. Scanning electron micrograph of glomerular capillary endothelium. Note endothelial fenestrae (arrow), 80 to 100 nm in diameter, and slender cytoplasmic ridges (×17,000). 7. Glomerular visceral epithelium from animal receiving moxalactam at 1,500 mg/kg. The surface is normal (×4,200). 8. Glomerular capillary endothelium from same animal. The endothelial fenestrae now are somewhat irregular in size (30 to 100 nm) (×17,000).

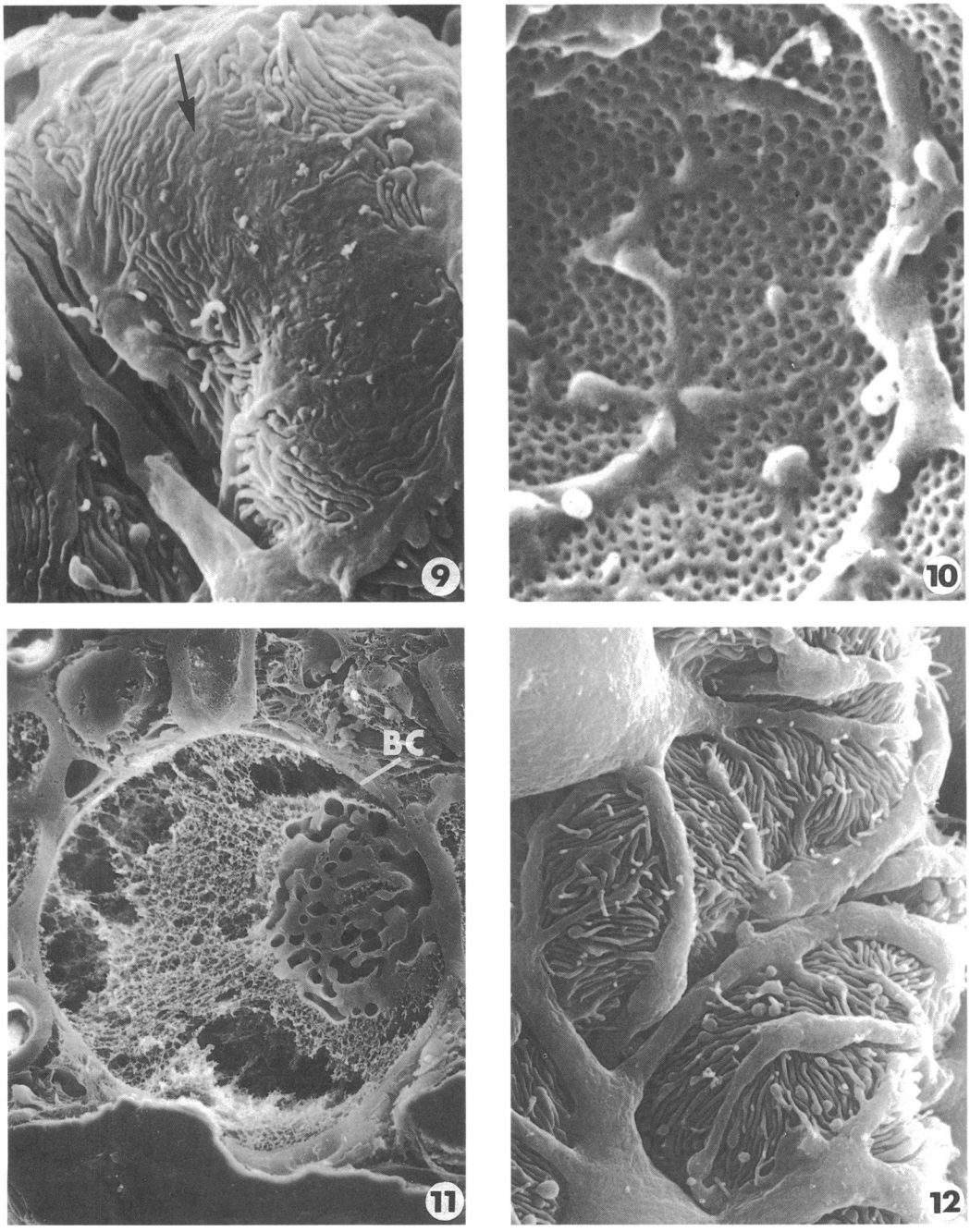

FIG. 9–12. 9. Glomerular visceral epithelium from an animal receiving cefotaxime at 1,500 mg/kg. The foot processes (G) of many cells show smudging and blunting (×8,500). 10. Glomerular capillary endothelium from the same animal. The endothelial fenestrae are mildly irregular (30 to 100 nm) (×17,000). 11. Bowman's capsule (BC) and glomerular tuft from an animal receiving cephaloridine at 200 mg/kg. The debris-filled capsule is three times the normal size, whereas the glomerular tuft is normal (×420). 12. Glomerular visceral epithelium from the same animal. The structures are normal in appearance (×5,800).

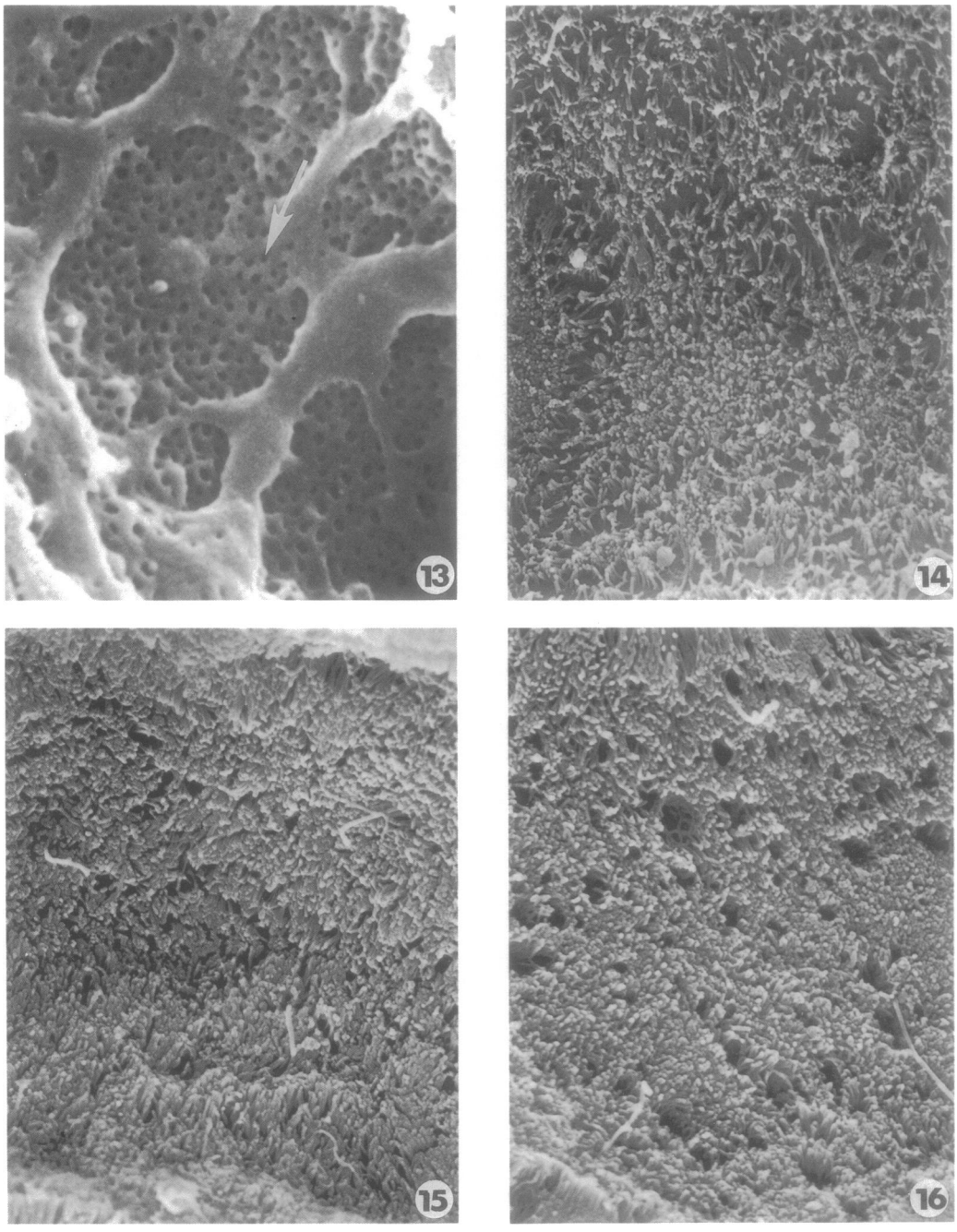

FIG. 13–16. 13. Glomerular capillary endothelium from an animal receiving cephaloridine at 200 mg/kg. The fenestrae (arrow) are uniformly small (30 to 50 nm), and the cytoplasmic processes are more numerous and larger than normal (×17,000). 14. Proximal tubule from same animal. The normally luxuriant brush border is largely denuded of microvilli (×4,200). 15. Proximal brush border from an animal which received moxalactam at 1,500 mg/kg for 7 days. The apical surface shows a normal luxuriant arrangement of microvilli (×4,200). 16. Proximal brush border from an animal receiving cefotaxime at 1,500 mg/kg for 7 days. The microvilli appear normal (×4,200).

To determine the volume of the glomerular tuft and Bowman's capsule, light micrographs were taken with a Zeiss photomicroscope onto Kodak Panatomic X film and enlarged to a final magnification of ×270. The micrographs were analyzed by a computer digitizing system and Quantigraph program.

Enzymuria and plasma creatinine values are shown in Table 1. Neither cefotaxime nor moxalactam affected either variable; however, the enzymuria caused by these drugs approached significance at the higher dose ($0.05 < P < 0.1$). Cephaloridine affected both variables at both doses ($P < 0.05$).

Neither moxalactam nor cefotaxime caused changes detectable by light microscopy (Fig. 1–3). The absence of such changes precluded the use of the histological grading scale which we usually employ. Cephaloridine, on the other hand, resulted in severe proximal tubular necrosis at either dose (Fig. 4). Scanning electron microscopy revealed modest changes in the visceral epithelium and capillary endothelium caused by moxalactam and cefotaxime (Fig. 5–10). Mild irregularity in endothelial pore size was observed at the higher dose with both moxalactam (Fig. 8) and cefotaxime (Fig. 10), and cefotaxime also caused some visceral epithelial podocyte blunting (Fig. 9). Cephaloridine (Fig. 11–14) resulted in a marked increase in the diameter of Bowman's capsule (2.2×10^6 μm^3 for cephaloridine compared with 6.6×10^5 μm^3 for the control; Fig. 4 and 11), which was consistent with intraluminal tubular obstruction. No change was noted in the volume of the glomerular tuft (3.4×10^5 μm^3 for cephaloridine compared with 3.0×10^5 μm^3 for the control). Endothelial fenestral pore size was diminished with cephaloridine (Fig. 13), a feature especially associated with aminoglycoside nephrotoxicity (1). The proximal tubular brush border (Fig. 14–16) was denuded as well in the animal which received cephaloridine.

Our data suggest that moxalactam and cefotaxime are minimally nephrotoxic as these drugs caused minor changes detectable only by sophisticated scanning electron microscopic techniques at 10 to 25 times the weight-calculated human dose. Cephaloridine, on the other hand, caused profound renal injury at these doses. Extrapolation of our results to humans will require further experience with these two new drugs.

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