Aminoglycosides

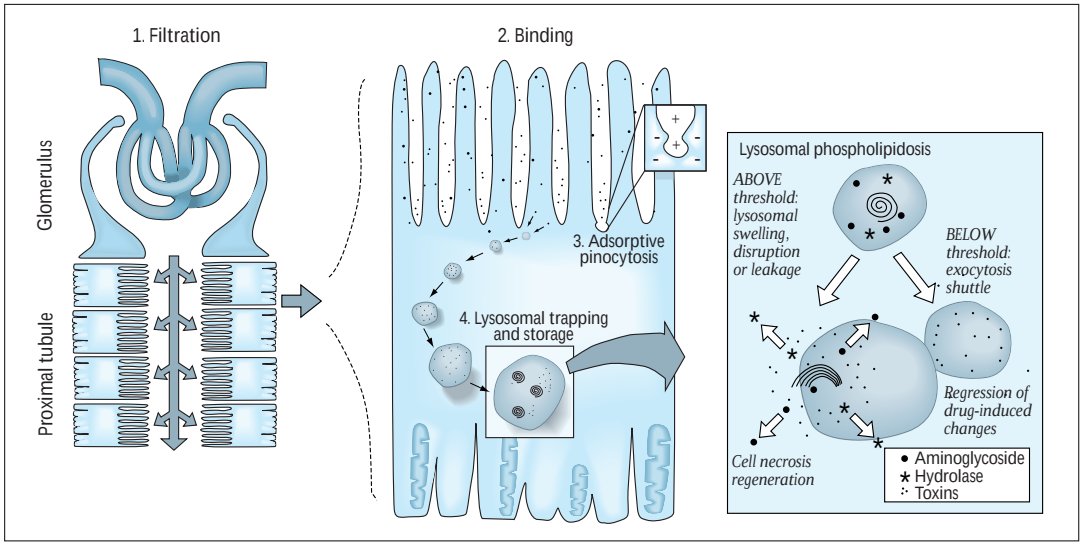

FIGURE 11-3

Renal handling of aminoglycosides: 1) glomerular filtration; 2) binding to the brush border membranes of the proximal tubule; 3) pinocytosis; and 4) storage in the lysosomes [3].

Nephrotoxicity and otovestibular toxicity remain frequent side effects that seriously limit the use of aminoglycosides, a still important class of antibiotics. Aminoglycosides are highly charged, polycationic, hydrophilic drugs that cross biologic membranes little, if at all [4,5]. They are not metabolized but are eliminated unchanged almost entirely by the kidneys. Aminoglycosides are filtered by the glomerulus at a rate almost equal to that of water. After entering the luminal fluid of proximal renal tubule, a small but toxicologically important portion of the filtered drug is reabsorbed and stored in the proximal tubule cells. The major transport of aminoglycosides into proximal tubule cells involves interaction with acidic, negatively charged phospholipid-binding sites at the level of the brush border membrane.

After charge-mediated binding, the drug is taken up into the cell in small invaginations of the cell membrane, a process in which megalin seems to play a role [6]. Within 1 hour of injection, the drug is located at the apical cytoplasmic vacuoles, called endocytotic vesicles. These vesicles fuse with lysosomes, sequestering the unchanged aminoglycosides inside those organelles.

Once trapped in the lysosomes of proximal tubule cells, aminoglycosides electrostatically attached to anionic membrane phospholipids interfere with the normal action of some enzymes (*ie*, phospholipases and sphingomyelinase). In parallel with enzyme inhibition, undigested phospholipids originating from the turnover of cell membranes accumulate in lysosomes, where they are normally digested. The overall result is lysosomal phospholipidosis due to nonspecific accumulation of polar phospholipids as "myeloid bodies," so called for their typical electron microscopic appearance. (*Adapted from* De Broe [3].)

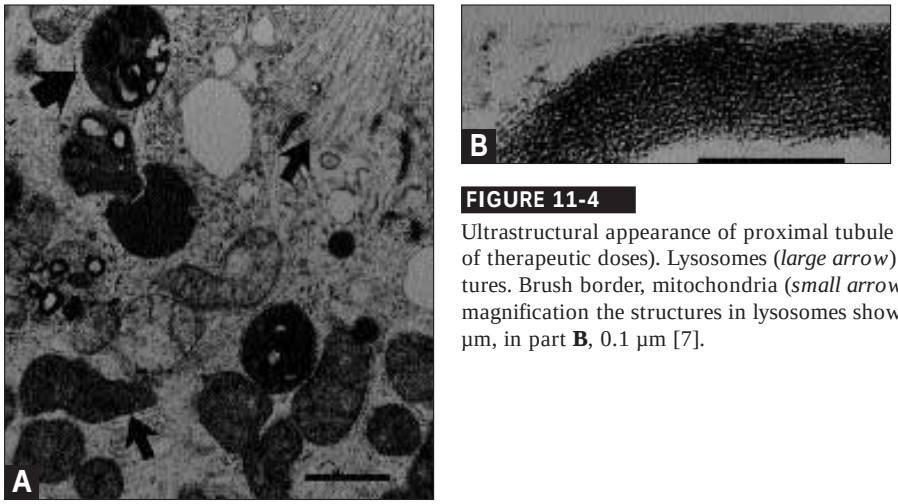

FIGURE 11-4

Ultrastructural appearance of proximal tubule cells in aminoglycoside-treated patients (4 days of therapeutic doses). Lysosomes (*large arrow*) contain dense lamellar and concentric structures. Brush border, mitochondria (*small arrows*) and peroxisomes are unaltered. At higher magnification the structures in lysosomes show a periodic pattern. The bar in **A** represents 1 µm, in part **B**, 0.1 µm [7].

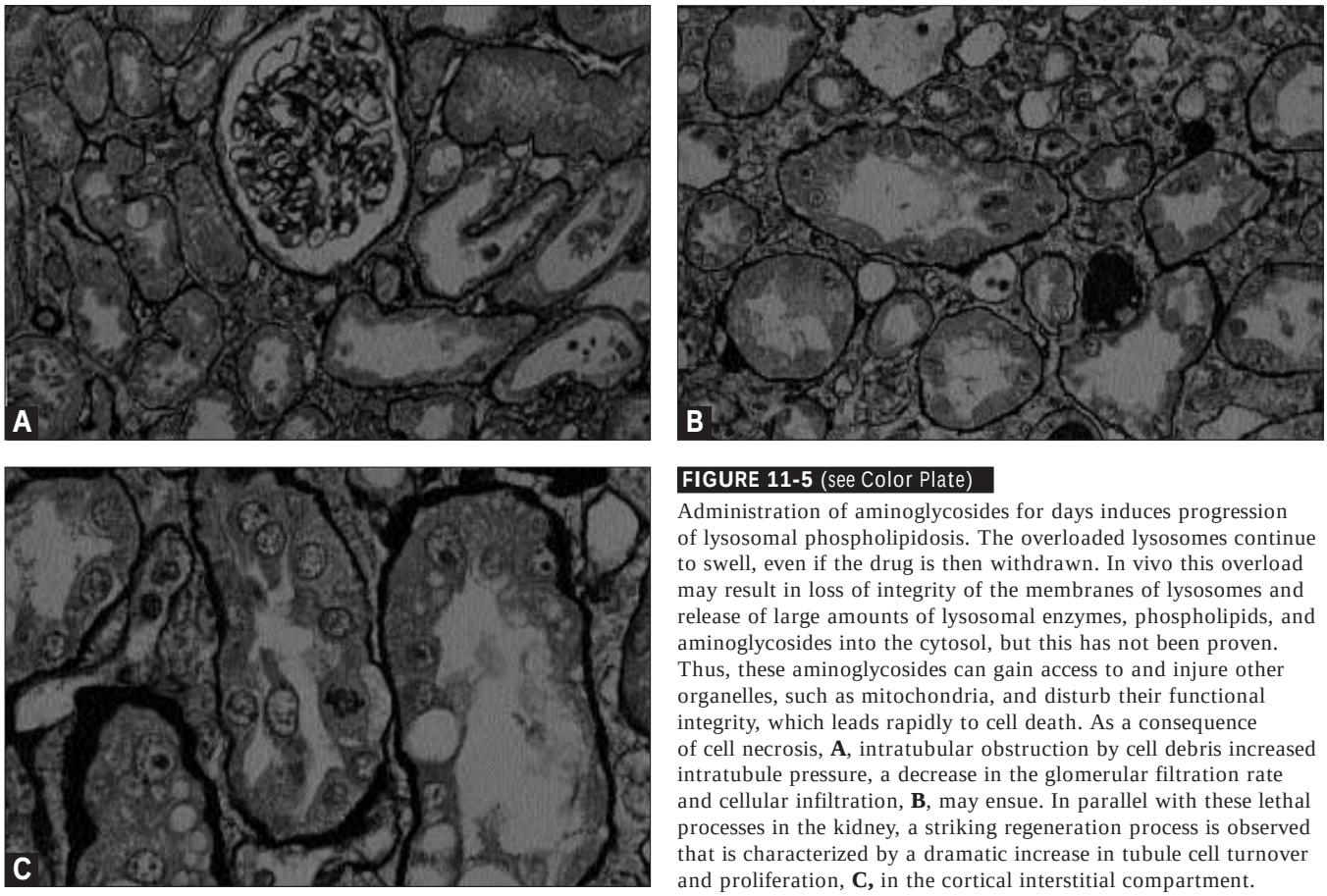

FIGURE 11-5 (see Color Plate)

Administration of aminoglycosides for days induces progression of lysosomal phospholipidosis. The overloaded lysosomes continue to swell, even if the drug is then withdrawn. In vivo this overload may result in loss of integrity of the membranes of lysosomes and release of large amounts of lysosomal enzymes, phospholipids, and aminoglycosides into the cytosol, but this has not been proven. Thus, these aminoglycosides can gain access to and injure other organelles, such as mitochondria, and disturb their functional integrity, which leads rapidly to cell death. As a consequence of cell necrosis, **A**, intratubular obstruction by cell debris increased intratubule pressure, a decrease in the glomerular filtration rate and cellular infiltration, **B**, may ensue. In parallel with these lethal processes in the kidney, a striking regeneration process is observed that is characterized by a dramatic increase in tubule cell turnover and proliferation, **C,** in the cortical interstitial compartment.

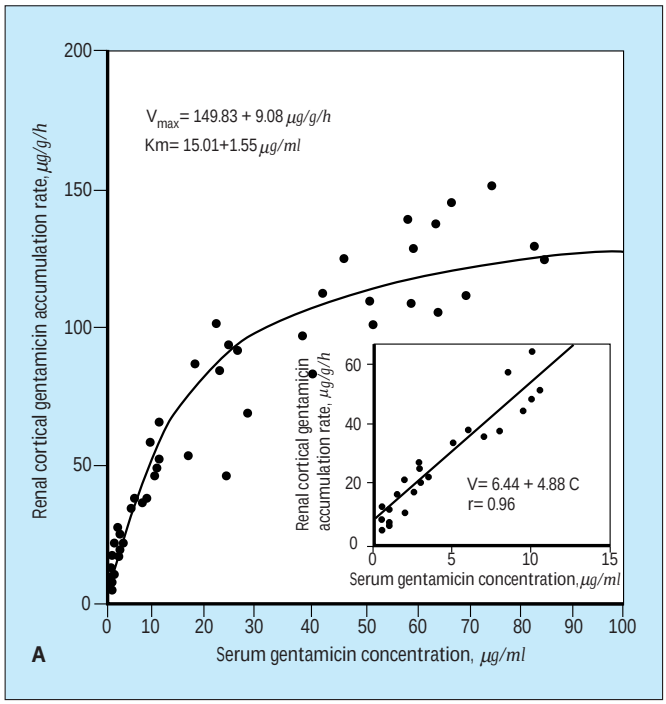

FIGURE 11-6

A, Relationship between constant serum levels and concomitant renal cortical accumulation of gentamicin after a 6 hour intravenous infusion in rats. The rate of accumulation is expressed in micrograms of aminoglycoside per gram of wet kidney cortex per hour, due to the linear accumulation in function of time. Each point represents one rat whose aminoglycosides were measured in both kidneys at the end of the infusion and the serum levels assayed twice during the infusion [8].

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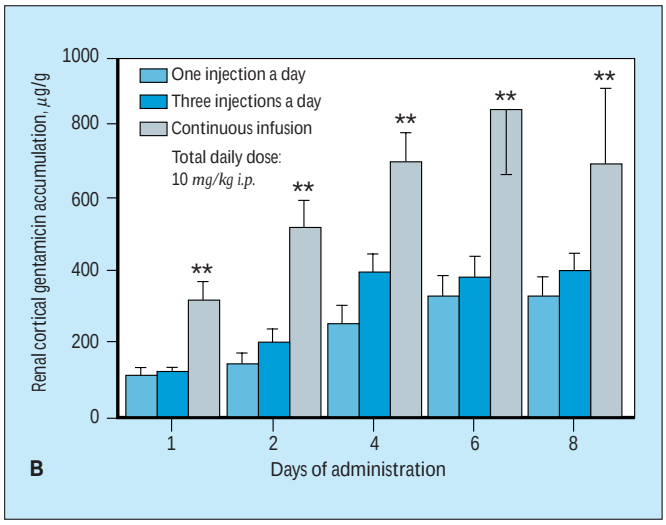
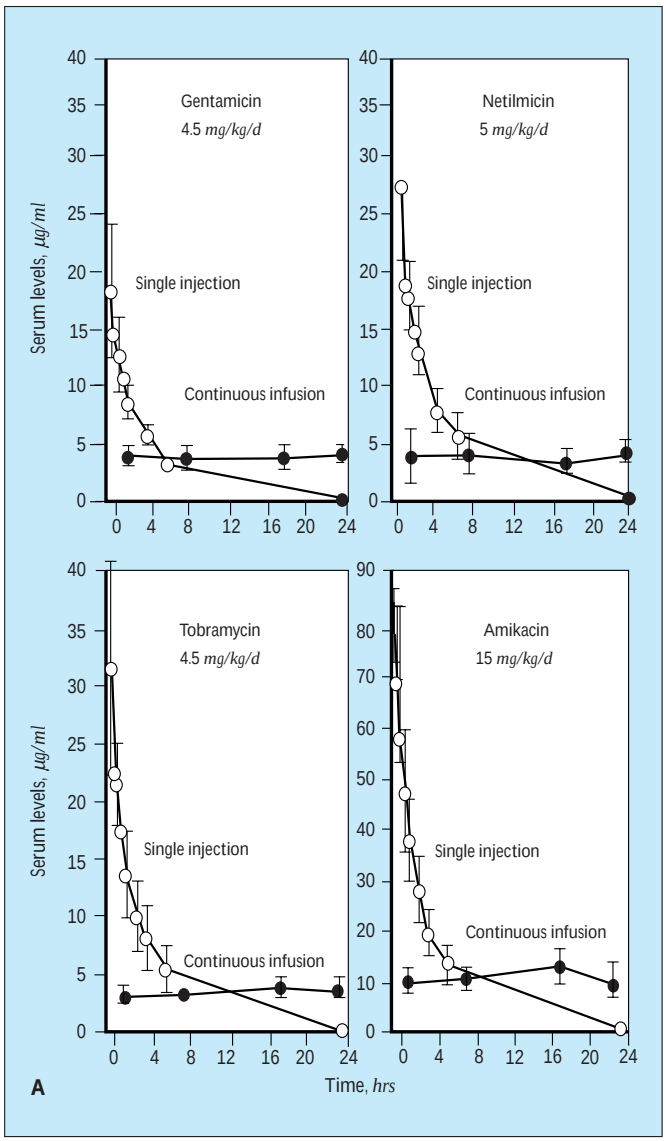


FIGURE 11-6 *(Continued)*

B, Kidney cortical concentrations of gentamicin in rats given equal daily amounts of aminoglycoside in single injections, three injections, or by continuous infusion over 8 days. Each block represents the mean of seven rats ±SD. Significance is shown only between cortical levels achieved after continuous infusion and single injections (asterisk—$P < 0.05$; double asterisk—$P < 0.01$) [9].

In rats, nephrotoxicity of gentamicin is more pronounced when the total daily dose is administered by continuous infusion rather than as a single injection. Thus, a given daily drug does not produce the same degree of toxicity when it is given by different routes. Indeed, renal cortical uptake is "less efficient" at high serum concentration than at low ones. A single injection results in high peak serum levels that overcome the saturation limits of the renal uptake mechanism. The high plasma concentrations are followed by fast elimination and, finally, absence of the drug for a while. This contrasts with the continuous low serum levels obtained with more frequent dosing when the uptake at the level of the renal cortex is not only more efficient but remains available throughout the treatment period. V_{max}—maximum velocity.



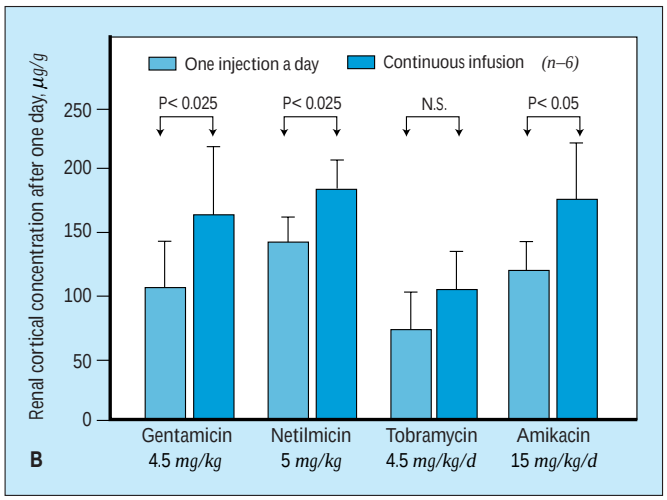


FIGURE 11-7

Course of serum concentrations, **A**, and of renal cortical concentrations, **B**, of gentamicin, netilmicin, tobramycin, and amikacin after dosing by a 30-minute intravenous injection or continuous infusion over 24 hours [10,11].

Two trials in humans found that the dosage schedule had a critical effect on renal uptake of gentamicin, netilmicin [10], amikacin, and tobramycin [11]. Subjects were patients with normal renal function (serum creatinine concentration between 0.9 and 1.2 mg/dL, proteinuria lower than 300 mg/24 h) who had renal cancer and submitted to nephrectomy. Before surgery, patients received gentamicin (4.5 mg/kg/d), netilmicin (5 mg/kg/d), amikacin (15 mg/kg/d), or tobramycin (4.5 mg/kg/d) as a single injection or as a continuous intravenous infusion over 24 hours. The single-injection schedule resulted in 30% to 50% lower cortical drug concentrations of netilmicin, gentamicin, and amikacin as compared with continuous infusion. For tobramycin, no difference in renal accumulation could be found, indicating the linear cortical uptake of this particular aminoglycoside [8]. These data, which supported decreased nephrotoxic potential of single-dose regimens, coincided with new insights in the antibacterial action of aminoglycosides (concentration-dependent killing of gram-negative bacteria and prolonged postantibiotic effect) [12]. N.S.—not significant.