CASE REPORTS

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Gentamicin Nephrotoxicity —Morphologic and Pharmacologic Features

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GENTAMICIN, an aminoglycoside antibiotic, is commonly prescribed for treatment of serious infections with Gram-negative bacteria. The drug is thought to be primarily excreted unchanged by glomerular filtration. Adjustment of dosage based on this measure is widely thought to avoid excessively high serum concentrations and thereby minimize extrarenal and renal toxicity.[1,2] Although human gentamicin nephrotoxicity has been reported, pathophysiologic data are limited because of the complex clinical circumstances in which the drug is administered.[3,4] In the Fisher 344 rat strain, given doses similar to those used clinically, proximal tubular cells undergo changes suggestive of cellular autophagy—such as numerous cytosegresomes with whorled inclusions probably of cell membrane origin.[5] Harrison and coworkers noted similar changes in Sprague-Dawley rats only with higher doses and attributed them to lysosomal injury.[6] Luft and associates have correlated these morphologic features in rats with accumulation of gentamicin in the renal cortex. They found a renal tissue half-life of 109 hours compared with a serum half-life of 35 minutes.[7] We report similar pathologic findings in a patient six weeks after a course of gentamicin therapy. Despite the long duration since therapy was discontinued low levels of gentamicin were detected in the renal cortex and urine implying significant tissue accumulation. This phenomenon would appear to be incompatible with renal gentamicin handling by glomerular filtration alone.

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Report of a Case

After 4,320 rads of preoperative irradiation in a 52-year-old woman with adenocarcinoma of the endometrium, radical hysterectomy was done with enflurane anesthesia on April 26, 1975. During operation the right ureter was transected and primarily repaired. The left ureter was injured also and reimplantation into the bladder was required. On the 12th postoperative day a temperature to 105°F developed and a left-sided pelvic abscess was drained with prompt defervescence. On May 21 fever returned. Both blood and urine cultures grew Pseudomonas aeruginosa sensitive *in vitro* to gentamicin. An intravenous pyelogram showed a normal right collecting system. The left ureter was duplicated with obstruction of the lower system at the ureterovesical junction. The patient was transferred to the University of Oregon Health Sciences Center, where a left nephrostomy was carried out under nitrous oxide anesthesia. Administration of gentamicin, 1 mg per kg of body weight given intramuscularly every eight hours, was begun. Before antibiotic therapy, laboratory studies gave the following values: hematocrit reading, 32 percent; blood urea nitrogen (BUN), 7 mg per 100 ml; creatinine, 1 mg per 100 ml, and creatinine clearance 96 ml per minute. The patient was 165 cm (5 ft 5 in) tall and weighed 79 kg (174 lb). No diuretics or other antibiotics were administered during her stay in hospital. The clinical course is detailed in Figure 1. The urine culture rapidly became sterile. However, in view of the documented bacteremia, a 14-day course of therapy was recommended. Because of deteriorating renal function, dosage was decreased despite appropriate peak and trough

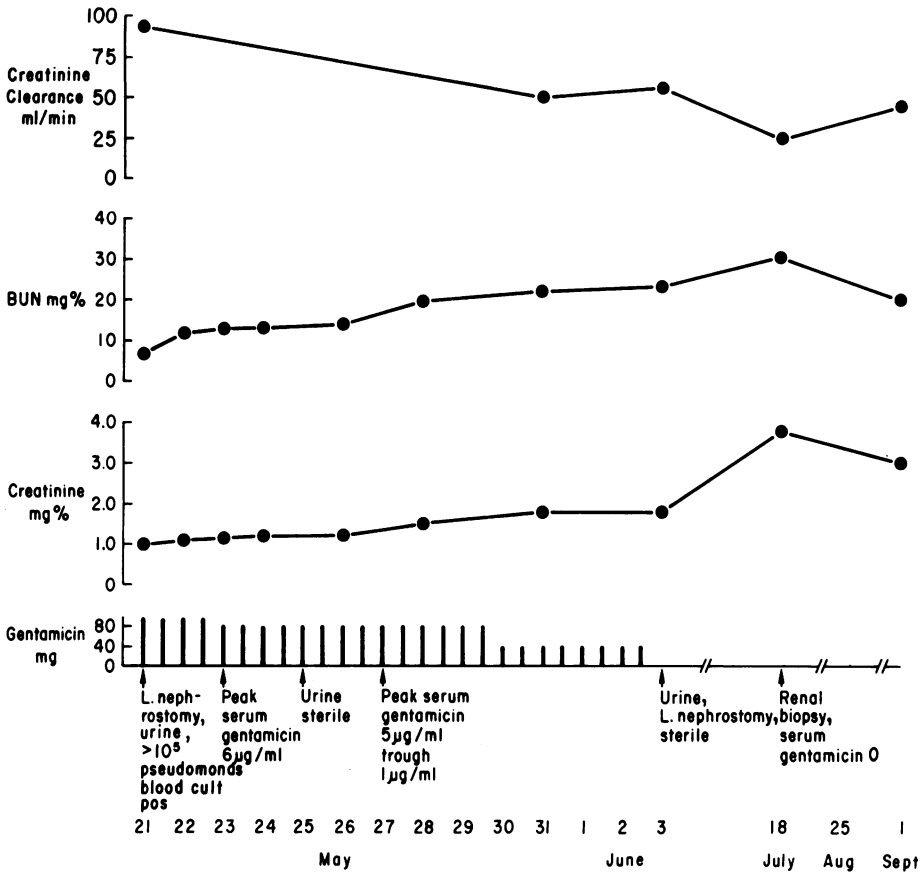

Figure 1.—Clinical course of the patient is shown. Progressive deterioration of renal function reached peak six weeks after last dose of gentamicin was given.

gentamicin serum levels on May 27. Total gentamicin dosage for the 14-day course was 1,840 mg with a maximum individual dose of 1.3 mg per kg of body weight. She was discharged on the 14th day and no medications were ordered.

When the patient presented for follow-up one month after discharge, she had complaint of fatigue, weight loss and weakness. Weight was 72 kg (158.7 lb). Findings on physical examination and vital signs were normal. Analysis of urine showed tubular epithelial cells, a pH of 6.0 and 10 to 15 leukocytes per high power field. Cultures from the left nephrostomy and urine were sterile. The protein level on a 24-hour urine study was 920 mg. The following values for electrolytes were noted: sodium, 142 mEq per liter; potassium 4.2 mEq per liter; chloride 113 mEq per liter; bicarbonate 18 mEq per liter. BUN was 36 mg per 100 ml, creatinine 3.7 mg per 100 ml and creatinine clearance 41 ml per minute. An intravenous pyelogram showed mild right-sided calyceal dilatation and a left nephrostogram showed no ureteral obstruction. On July 18, 1975, a right-sided open renal biopsy was done. Specimens of bladder urine, left nephrostomy urine and renal cortical tissue were analyzed for gentamicin by a modification of the radio-enzymatic assay of Smith and Smith.[8] Findings for renal cortical tissue showed a concentration of 30 μg per gram of wet tissue, while both urine samples showed 1.1 μg per ml. A serum gentamicin level obtained on the same day was 0.

Light microscopy showed normal glomeruli but significant swelling, vacuolization and necrosis of proximal and distal tubular cells. In addition interstitial fibrosis and tubular dilatation were prominent. On ultrastructural examination of tubular cells, myeloid bodies, numerous cytosegresomes and mitochondrial swelling were noted (Figures 2 and 3). There was no glomerular or tubular deposition of immunoglobulins or complement.

There was gradual improvement in renal function in the patient as assessed by BUN and creatinine values following volume repletion and bicarbonate therapy. At last observation creatinine clearance was 66 ml per minute.

Discussion

Gentamicin, a widely used aminoglycoside antibiotic with a serum half-life of two hours, has been reported to cause reversible renal failure in

man due to proximal tubular necrosis.[3,4] It has been difficult to ascertain the determinants of nephrotoxicity in man due to the serious underlying diseases for which the drug is prescribed. Gyselink and co-workers in studying the renal handling of gentamicin in man proposed almost complete quantitative excretion of administered drug by glomerular filtration.[1] If this is true significant drug accumulation and presumably nephrotoxicity should be minimized by adjusting the drug dosage to the glomerular filtration rate in a patient.[2] Recent morphologic observations by Kosek and associates in rats showed proximal tubular cell ultrastructural lesions in animals without renal failure given as little as 1 mg per kg of body weight of gentamicin per day.[5] Renal cortical tissue uptake has been confirmed by Luft and co-workers in rats given single doses of gentamicin.[7] These authors reported a renal cortical half-life of 109 hours with a serum half-life of 35 minutes. Kalmeter and Kamme detected gentamicin in the urine of a patient a month after treatment.[9] Alfthan and co-workers have shown renal concentrations 20 times that of serum in renal tissue of patients with normal renal function treated with single doses of gentamicin before urologic operations were carried out.[10] The present case provides direct evidence in a patient of ultrastructural lesions similar to those described in rats and documents evidence of tissue accumulation six weeks after therapy was discontinued. Wellwood found similar proximal tubular changes on electron microscopy in three renal allograft recipients receiving administration of gentamicin. Details of dosage and serum gentamicin levels, however, were not specified.[11]

It is of note that the drug was not given in excessive dosage nor did the peak serum levels one hour after a dose or trough levels directly before a dose exceed the recommended values.[12] It is possible that previous radiation therapy, urosepsis or urinary tract obstruction predisposed to nephrotoxicity. The lack of pathologic evidence for such processes plus the normal creatinine clearance measured before therapy make these possibilities unlikely. It has been reported that furosemide,[13] cephalosporins,[14,15] and methoxyflurane potentiate aminoglycoside nephrotoxicity;[16] however, none of these agents were given to our patient. Enflurane, the anesthetic administered during original surgical procedure in the patient, has been reported rarely to cause nonoliguric acute renal failure;[17,18] however, renal function was clearly normal up to one month following anesthesia.

The exact determinants of the tissue gentamicin

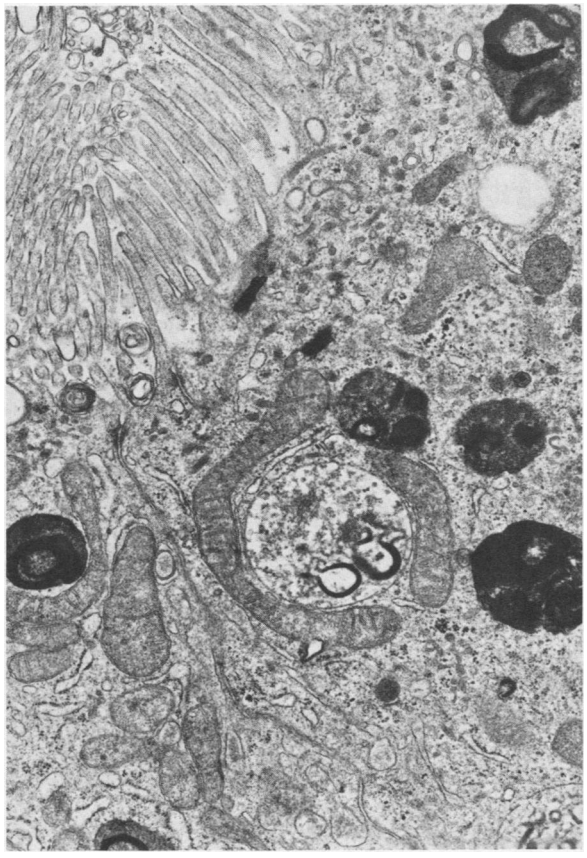

Figure 2.—A proximal tubule cell with numerous lysosomes containing dark granular debris and myeloid bodies. There is focal swelling of the endoplasmic reticulum. There are several myeloid bodies in the intervillous spaces. (upper left) 24,000x

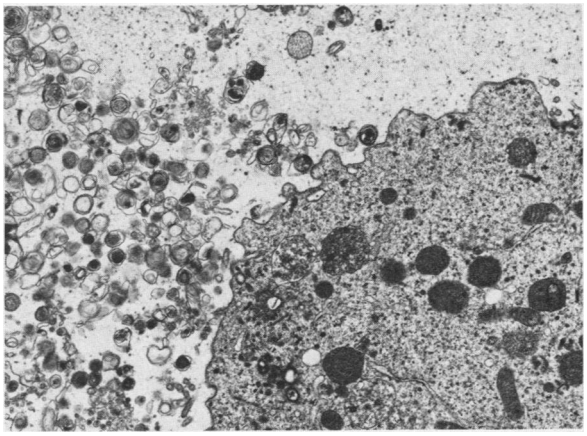

Figure 3.—A distal convoluted tubule cell and lumen filled with cytoplasmic debris and numerous unicentric myeloid bodies. The cell contains numerous lysosomes and a few small mitochondria. 24,000x

accumulation in our patient and its relation to deterioration of function remains speculative. Nonetheless, detection of nephrotoxicity by monitoring BUN and creatinine levels as customarily carried out may be too insensitive to detect early signs of tubular damage. Luft and co-workers have found in rats that lysosomal enzymuria and proteinuria are early indicators of nephron dysfunction.[19] Similar observations have been reported by Wellwood and associates in renal transplant patients.[11] It is clear from the present report that current dosage recommendations will not always insure freedom from nephrotoxicity.

Summary

Partially reversible nonoliguric renal failure developed in a patient while gentamicin therapy was being carried out. Dosage was monitored by peak and trough serum gentamicin levels and serum values never exceeded 6 μg per ml and 1 μg per ml, respectively. Six weeks after therapy was discontinued a renal biopsy study showed proximal tubular necrosis with numerous cytosegresomes, myeloid bodies and mitochondrial swelling on electron microscopy. Similar lesions have been recently reported in experimental aminoglycoside nephrotoxicity in rats. At the time of renal biopsy the renal cortical gentamicin concentration was 30 μg per gram of wet tissue, the serum gentamicin value was 0 and the urine gentamicin value was 1.1 μg per ml. It is concluded that gentamicin can cause proximal tubular lesions in man similar to those described in rats. The significant renal tissue uptake of the drug that occurs may have pathophysiologic significance in nephrotoxicity.

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