Comparative Nephrotoxicity among Aminoglycosides and Beta-Lactam Antibiotics

Summary: Five hundred thirty-seven elderly male patients with complicated urinary tract infections who received treatment with aminoglycosides (gentamicin, tobramycin, sisomicin, or netilmicin) or beta-lactam antibiotics (ticarcillin, amoxicillin, or cefamandole) were reviewed with respect to nephrotoxic reactions. Nephrotoxicity was defined as a 31% increase in serum creatinine during treatment for patients with pretreatment creatinine clearances $\geq 30$ ml/min, or an 18% increase in those patients with a pretreatment creatinine clearance $< 30$ ml/min. Renal toxicity correlated with advanced age and reduced renal function in the aminoglycoside groups. For patients with pretreatment creatinine clearances $> 30$ ml/min, treatment groups were comparable for all relevant clinical and therapeutic features. Among these treatment groups, tobramycin was the least nephrotoxic of the aminoglycosides. Nephrotoxicity, as defined above, was lower for the beta-lactam antibiotics than for the aminoglycoside groups combined; however, the decrease was not significant. The mean serum creatinine, however, increased significantly in all patients following aminoglycoside treatment and this increase was significantly higher than in the beta-lactam group.

Introduction

Nephrotoxicity is a major side effect of treatment with the newer aminoglycosides (1-3) such as gentamicin, with clinical symptoms ranging from relatively insignificant changes in laboratory parameters for renal function to acute renal failure (4). The aminoglycosides appear to concentrate in the renal cortex where the most prominent toxic effect is seen in the proximal tubular system (5). Increasing evidence indicates that the alkaline drugs are taken up by the epithelial cells from the tubular lumen in competition with compounds such as the aminoacids (6, 7). The cells subsequently undergo changes, beginning with vacuolization and the appearance of myeloid bodies and end with necrosis and gross sloughing of the tubular lining (8). The aminoglycosides vary in their nephrotoxic potential: neomycin has the highest potential, streptomycin the lowest (1, 5). The frequency of nephrotoxicity to gentamicin is apparently decreasing, due mainly to greater awareness of the attending physician and better monitoring of serum creatinine levels and serum concentrations of gentamicin during treatment (9). Toxicity studies on laboratory animals have indicated that tobramycin and the newer aminoglycosides, sisomicin and netilmicin, have less nephrotoxic potential than gentamicin (10, 11, 16). However, the latter two drugs have not yet been approved by the Federal Drug Administration for general use.

Assessment of nephrotoxicity in man is usually based upon changes in the routine parameters for determination of renal function, i.e. serum creatinine, creatinine clear-


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Definitions of nephrotoxicity itself. Interpretation of is complicated by widely varying definitions or lack of definitions of nephrotoxicity itself. According to Brøchner-Mortensen changes in creatinine clearance and BUN are unreliable measurements of changes in renal function because of inaccurate urine collection in the former and dependence on unrelated factors such as nitrogen metabolism and urine flow rate in the latter (12, 13). Serum creatinine determination appeared to be the most reliable of the routine methods (12, 13) except during conditions of acute renal change. Such changes can occur in various clinical conditions, e. g. hypotension, shock, or immediately after major surgery (14). Comparison of three different clearance methods in normal clinical routine showed that two determinations of serum creatinine which differ by more than 31% when the glomerular filtration rate (GFR) is \( \geq 30 \) ml/min and more than 18% when GFR is \(< 30 \) ml/min have a 95% probability of reflecting a true change in a patient's renal function (12, 13).

In the present study, we wished to evaluate the methods of estimating nephrotoxicity rates in the clinical setting and compare the rates in the newer aminoglycosides with those of gentamicin and antibiotics of the \( \beta \)-lactam group. This laboratory has conducted a number of studies concerning treatment of complicated urinary tract infections with gentamicin, tobramycin, sisomicin and netilmicin and various \( \beta \)-lactam antibiotics over the past six or seven years (15-25). The similarity in type of infections and the remarkably uniform patient population at this facility over the years justified our retrospective approach.

Materials and Methods

This study was based upon data from patients admitted to the urology ward of the William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin, during the period of 1972-1978 who were treated for urinary tract infections with one of the aminoglycosides (gentamicin, tobramycin, sisomicin or netilmicin), or one of the \( \beta \)-lactam antibiotics (ticarcillin, amoxicillin, or cefamandole). The patients were included in 12 different protocols (15-25), eleven of which have been published. Seven of these studies were prospective, randomized protocols in which the patients were treated with either one of two different drugs or two to four different dosage regimens of one drug. Three of the four remaining protocols dealt with the efficacy of tobramycin, sisomicin or netilmicin in patients with various degrees of renal impairment (15, 16, 25), and one protocol investigated the efficacy and pharmacokinetics of cefamandole in patients with normal and impaired renal function (20). Protocols concerning treatment with \( \beta \)-lactam antibiotics were included in order to compare nephrotoxic reactions to aminoglycosides with those of a group of antibiotics not normally considered nephrotoxic.

The following information, if available, was recorded about each patient: sex (all males), age, weight, type of infection, infecting microorganism, underlying diseases, major operations during hospital stay, duration of treatment and drug dosage, previous treatment with aminoglycosides (within one year prior to study), or other antibiotics (within one month prior to study), concomitant treatment with other potentially nephrotoxic drugs, and serum creatinine and BUN before and after treatment. To secure a uniform evaluation of the study population, estimation of pretreatment renal function was based upon nomogram creatinine clearance (26), since 24 h creatinine clearance was not measured before treatment in all patients. The serum creatinine was used as the variable for assessment of nephrotoxicity, which was defined as a significant increase in serum creatinine during treatment according to the 95% significance limits: 31% for patients with a pretreatment creatinine clearance \( \geq 30 \) ml/min, and 18% for patients with a pretreatment creatinine clearance \(< 30 \) ml/min (12). Nephrotoxic reaction was excluded when the following conditions were involved: 1) a nephro-urological explanation for the change in renal function, and 2) a major operation performed within three days prior to the change in serum creatinine. Serum creatinine determinations were routinely done by the laboratory service on an auto-analyzer (Technicon SMA 12-60). The accuracy of these determinations, as based upon a control serum (1.6 mg/100 ml), was 1.6 \pm 0.2 mg/100 ml (2 SD) over the whole study period. The variation coefficient for these determinations was 0.03-0.04 over a range of 0.6-11.0 mg/100 ml. All drugs were given in recommended dosages for an average of seven days. Ticarcillin and cefamandole were injected intramuscularly in doses of 1 g every 8 h and 1.5-3 g every 8 h, respectively. Amoxicillin was administered intramuscularly for three days in doses of 1 g every 6 h, followed by the same dosage orally for four days. All aminoglycosides were administered by intramuscular injection, with gentamicin being given as 1 mg/kg every 8 h or 80 mg every 8 h, and tobramycin as 1 mg/kg every 8 h. Netilmicin was usually administered in doses of 2 mg/kg every 12 h, but in one study (23), four different dosage schedules (1-2.5 mg/kg every 8 h) were tested. The dosages in the sisomicin group were 1 mg/kg every 12 h, 50-80 mg every 8 0r 12 h, or 50-100 mg/day as a single dose or divided into two doses. The monitoring of aminoglycoside therapy was usually based on determinations of serum aminoglycoside concentrations and renal function parameters. Methods of adjustment varied with the different studies: reduction of dose with fixed interval (15), increase in interval with fixed doses (16), or according to a formula incorporating dose and serum creatinine (25). Drug accumulation during therapy was not found for any of the aminoglycosides except for netilmicin administered in 8 hourly dosage intervals (23). No correlation, however, could be demonstrated between nephrotoxicity and trough or peak concentrations of netilmicin (25). Statistical methods employed included the \( t \) test for independent and paired observations, one-way analysis of variance with log transformation in skewed distributions (27), \( X^2 \) test for contingency table, and \( X^2 \) test in the method of individual df based on the principle of orthogonality (28). \( P \) values \(< 0.05 \) were considered significant.

Results

Some patients participated in more than one study on separate admissions and therefore, were included in more than one treatment group. All 537 patients included in our study had complicated urinary tract infections due to obstruction of the lower urinary tract, benign hypertro-