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Comparison of the Nephrotoxicity and Auditory Toxicity of Tobramycin and Amikacin

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A total of 157 patients were treated with tobramycin or amikacin in a controlled prospective randomized trial. Dosages were adjusted to renal function according to a nomogram. Trough and peak aminoglycoside levels were available at the end of the trial. Of the above total, 113 recipients of nine or more doses of tobramycin or six or more doses of amikacin, without other apparent cause of renal failure, were evaluated for nephrotoxicity. Thirty-six patients were evaluated for auditory toxicity. The patients in groups evaluated for either nephrotoxicity or auditory toxicity were similar with respect to intensity and etiology of bacterial disease, concurrent exposure to other antimicrobial drugs, age and sex distribution, initial serum creatinine level, and total dose and duration of antimicrobial therapy. Nephrotoxicity of similar severity developed in 4 of 59 (6.8%) recipients of tobramycin and in 7 of 54 (13.1%) recipients of amikacin ($P > 0.05$). Mild auditory toxicity developed in 3 of 19 (15.7%) recipients of tobramycin and in 2 of 17 (11.7%) recipients of amikacin ($P > 0.05$). When patients with abnormally high mean trough or peak aminoglycoside levels were excluded from comparison, nephrotoxicity was 6.12 and 5.12% ($P > 0.05$) and auditory toxicity was 17.6 and 7.69% ($P > 0.05$) in the groups given tobramycin and amikacin, respectively. We conclude that the nephrotoxicity and auditory toxicity of amikacin and tobramycin are not significantly different and that such toxicities are indeed infrequent events when the dosages of these drugs are adjusted to hold blood levels within the safe boundaries suggested by the studies of others.

Despite the introduction of new cephalosporins and penicillins, aminoglycosides still have their place in the therapeutic armamentarium (W. L. Hewitt and S. C. Schimpf, Abstr. 12th Int. Congr. Chemother. 1981), nephrotoxicity and ototoxicity being the major factors limiting their clinical utility (19, 33). Although gentamicin has been the first-choice aminoglycoside for years (2), tobramycin is at least as effective and seems to be significantly less toxic in laboratory animals (1, 3, 8, 16, 20, 37) and in clinical studies (14, 17, 26, 29, 30, 33, 35, 37). Amikacin, effective in the treatment of infections with gentamicin- and tobramycin-resistant gram-negative bacilli (21-23, 31, 34), has a proven role as a reserve drug (1, 21, 23). It may become the aminoglycoside of first choice for nosocomial and life-threatening community-acquired diseases in those hospitals and geographical areas where there is a high incidence of infections with gentamicin-resistant gram-negative bacilli. However, to date there has been no prospective randomized study of the comparative toxicities of tobramycin and amikacin in an unselected group of patients (5, 21). The results of the first prospective randomized controlled trial comparing the nephrotoxicity and auditory toxicity of tobramycin and amikacin have been set forth in this report.

MATERIALS AND METHODS

Patients. Patients admitted to a general internal medicine ward with suspected sepsis, urinary or biliary tract infection, or pneumonia for whom aminoglycoside therapy was considered indicated by a doctor other from the investigators were candidates for entry into the trial. Informed consent was obtained in each case. Patients infected with an organism known to be resistant to tobramycin or amikacin or who had received an aminoglycoside in the previous 30 days were not entered into the study. Patients who received nine or more doses of tobramycin or six or more doses of amikacin were evaluated for nephrotoxicity if they had no other cause of acute renal failure, and for auditory toxicity if they were able to cooperate with serial audiograms. Decisions were made without

knowledge of which aminoglycoside had been administered.

Methods. The trial was prospective and controlled. Drug assignments were random. Serum aminoglycoside level measurements and appropriate dosage changes according to a nomogram (28) were supervised by a member of the group who was not blind to the regimen. The evaluation of nephrotoxicity and auditory toxicity was performed by an investigator who was blind with respect to therapeutic regimen. Consequently, the patient and the clinical investigator responsible for each case evaluation did not know which drug had been given. Antibiotic therapy other than aminoglycosides and nonantibiotic therapy were not controlled in the trial protocol.

The loading doses of tobramycin and amikacin (1.7 and 7.5 mg/kg of body weight, respectively) were administered intravenously over 20 to 30 min. Maintenance doses were given intravenously every 8, 12, or 24 h for tobramycin and every 12 or 24 h for amikacin and adjusted for renal function according to the Sarubbi and Hull nomogram (28). Thus, for a case with a creatinine clearance of 70 ml/min, the maintenance doses of tobramycin and amikacin were 1.29 and 6.6 mg/kg of total body weight every 8 and 12 h, respectively. Plasma aminoglycoside levels just before and 1 h after starting drug administration were measured on the first and every third day during therapy. Determinations were performed by radioimmunoassay (Tobramycin RIA Kit; Nuclear Medical Systems, Inc., Newport Beach, Calif., and Amikacin RIA Kit, Diagnostic Products Corp., Los Angeles, Calif.). The lower limit of detection was 0.4 μg/ml for tobramycin and 1.5 μg/ml for amikacin. The within- and between-assay coefficients of variation were 3.5 and 7.2% for tobramycin at 6 μg/ml and 4.2 and 7.6% for amikacin at 15 μg/ml. Determinations were performed in stored frozen serum samples that had been kept at −20°C for not more than 3 months. Results were not available until the end of the trial. Trough and peak aminoglycoside levels above 2 and 10 μg/ml, respectively, for tobramycin and above 10 and 40 μg/ml, respectively, for amikacin are potentially toxic (21, 33) and, for the purpose of this study, were considered as abnormally high. To correct the differences in maintenance dosage and in patterns of administration, total dose and levels of amikacin, when compared with those of tobramycin were divided by factors of 3.5 and 5, respectively.

Serum creatinine was measured before therapy and on every third day until 2 days after cessation of therapy or until patient death. Additional follow-ups were not performed regularly. Nephrotoxicity was defined as a rise in serum creatinine of 0.5 mg/dl or more if the initial level was less than 3 mg/dl or a rise of 1 mg/dl or more if the initial creatinine level was 3 mg/dl or above (15, 33). The rise was estimated by subtracting the creatinine level before therapy from the highest creatinine level during therapy. Creatinine was measured by a modified Jaffe method in an automated multichannel analyzer (Prisma; Clinicon, Bromma, Sweden); the daily variation at our institution was less than 0.2 mg/dl.

Audiograms were performed in a soundproof auditory test chamber with an audiometer (Amplaid 300; Amplaid SpA, Milan, Italy) at 250 to 8,000 Hz on day 1 or 2 and day 7 of therapy and every 7 days if therapy continued. Slight auditory toxicity was defined as a decrease in auditory threshold of 15 dB at any frequency in the range of 250 to 8,000 Hz either unilaterally or bilaterally. Auditory toxicity was considered mild if a decrease in auditory threshold was 20 dB or more at any frequency in the same range.

Previously reported criteria were followed for diagnosing the infections and for measuring the clinical response (32, 36). Each treated patient was assigned to only one category or type of infection. Patients with positive blood cultures from an unknown origin or from an endovascular source were reported as having bacteremia.

Statistical methods. Chi-square tests, with the Yates correction when necessary, and Fisher's exact tests were used to compare proportions, and Student's *t* test was used to compare means. A two-tailed analysis was decided upon before the study began. We selected our sample size to detect differences of nephrotoxicity of about 12% from an estimated control incidence of 15%, with a probability of an alpha error of less than 0.05 and a beta-type error of less than 0.25.

RESULTS

Of the 157 patients initially entered in the trial, 30 (12 given tobramycin and 18 given amikacin) were excluded because they received fewer than six doses of amikacin or nine doses of tobramycin, and 14 (7 given tobramycin and 7 given amikacin) were excluded because they had another potential cause of acute renal failure. The other causes of renal failure were hypotension or shock in eight patients, dehydration in three, and hepatorenal syndrome in three.

The nephrotoxicities of tobramycin and amikacin were then compared in the remaining 113 patients, 59 given tobramycin and 54 given amikacin. The two groups did not differ (Table 1) in mean age, sex ratio, initial creatinine levels, duration of therapy, total dose and mean trough and peak levels of aminoglycosides, presence of previous renal disease, concurrent drug administration, and causative agents. The mean increase in serum creatinine level was similar in both treatment groups, 0.042 ± 0.24 mg/dl in the group given tobramycin versus 0.23 ± 1.13 mg/dl in the group given amikacin ($P > 0.05$, not significant). Nephrotoxicity developed in 6.8% of the patients given tobramycin and 13% of the patients given amikacin, (Table 1, $P > 0.05$, not significant). The severity of nephrotoxicity was also similar in both treatment groups. Among the patients who developed nephrotoxicity, the mean increases in serum creatinine levels in the group given tobramycin (0.6 ± 0.2 mg/dl) were similar to the mean increases in the group given amikacin (0.8 ± 0.47 mg/dl) ($P > 0.05$). Among the patients with nephrotoxicity, two in the tobramycin group died and four in the amikacin group died. In no case did acute renal failure develop, and nephrotoxicity was not considered to be the cause of any of those deaths. When patients exhibiting nephrotoxicity were com-

TABLE 1. Characteristics and rates of nephrotoxicity of 59 patients given tobramycin and 54 given amikacin

Characteristics of patients and rates of nephrotoxicity	Tobramycin[a]	Amikacin[a]
Age (yr)	59 ± 20.4	58 ± 23.2
Initial creatinine level (mg/dl)	1 ± 0.3	1.1 ± 0.5
Duration of therapy (days)	8.3 ± 3.2	8.5 ± 4.4
Total dose (g)	2.1 ± 3	6.3 ± 3[b]
Mean trough level (μg/ml)	1 ± 0.7	4.5 ± 4.5[b]
Mean peak level (μg/ml)	4.1 ± 1.4	23.5 ± 9[b]
Previous renal disease (no. of patients)	4	1
Concurrent drug (no. of patients)		
Penicillins	40	35
Cephalosporins	2	3
Metronidazol	2	5
Furosemide	5	8
Suspected type of infection (no. of patients)		
Bacteremia	15	14
Urinary tract	26	26
Pneumonia	13	13
Biliary tract	5	1
Nephrotoxicity[c]		
Whole group	4/59 (6.8%)	7/54 (13%)
Normal aminoglycoside serum levels	3/49 (6.1%)	3/39 (5.1%)
Abnormally high aminoglycoside serum levels	1/10 (10%)	4/15 (27%)

[a] Values are mean ± standard deviation. No *P* values were significant.

[b] Amikacin total dose and levels were corrected for difference in dosage and pattern of administration before comparison.

[c] Number of patients with toxicity/number of patients evaluated (percentage of patients with toxicity).

pared with those without nephrotoxicity, there were no differences with respect to age, sex ratio, duration of therapy, total dose, initial creatinine levels, peak and trough aminoglycoside levels, source of infection, and concurrent drug therapy. When patients with abnormally high levels of aminoglycoside were excluded from the comparison, nephrotoxicity appeared in 6.1% of the patients on tobramycin and in 5.12% of those on amikacin ($P > 0.05$, not significant) (Table 1).

A total of 36 patients, 19 given tobramycin and 17 given amikacin, were evaluated for auditory toxicity. Apart from those excluded because they received fewer than nine doses of tobramycin or six doses of amikacin (30 patients), the rest were excluded because of a lack of cooperation in serial audiograms or because they could not be transferred to a soundproof room. The two groups were homogeneous (Table 2). Slight or mild auditory toxicity (a decrease of 15 or more dB) developed in 42.1% of the patients given tobramycin and in 35.2% of those given amikacin ($P > 0.05$, not significant). Mild auditory toxicity (decrease of 20 or more dB) developed in 15.7 and 11.7% of patients given tobramycin and amikacin, respectively ($P > 0.05$, not significant). Since serial audiograms were performed with a relatively small group of patients, only differences in auditory toxicity of 25% or greater would have been detected (Table 2). Severity of auditory toxicity was similar in both groups and ranged from 15 to 30 dB at frequencies of 500 to 8,000 Hz. The percentage of patients who developed auditory toxicity did not differ significantly when those with abnormally high levels of aminoglycosides were excluded (Table 2). There were no significant differences in mean age, sex ratio, duration of therapy, total dose and levels of aminoglycosides, initial creatinine levels, concurrent therapy, source of infection, and causative agents among patients with slight or mild auditory toxicity and those without.

DISCUSSION

Although toxicities of tobramycin and amikacin have been extensively studied previously (9, 10, 18, 21, 24), they have never been compared in a prospective randomized trial involving an unselected group of patients (21). Similar rates of nephrotoxicity (ca. 20%) were found for tobramycin and amikacin in a prospective randomized trial designed primarily to compare clinical efficacy in patients with cancer (12). In this trial, the criteria for nephrotoxicity were not strictly defined, and no attempt was made to evaluate auditory toxicity. In another prospective nonrandomized trial in an intensive care unit, the incidences of nephrotoxocity were 25 , 22.8, and 36.3% among recipients of amikacin, tobramycin, and gentamicin, respectively (26). There were only 16 patients in the amikacin group; how they were selected to receive this antibiotic is unclear (21, 26).

The dosage of the aminoglycoside was strictly defined in our trial, and adjusted dosages followed the guidelines of Sarubbi and Hull (28). We believe that this is a realistic approach to

TABLE 2. Characteristics of 19 patients given tobramycin and 17 given amikacin compared for auditory toxicity

Characteristics of patients and rates of auditory toxicity	Tobramycin[a]	Amikacin[a]
Age (yr)	48.1 ± 22.8	53.5 ± 23
Initial creatinine level (mg/dl)	1 ± 0.21	1.15 ± 0.4
Duration of therapy (days)	9.4 ± 3.8	9.5 ± 3.9
Total dose (g)	2.2 ± 1	4.5 ± 4.5[b]
Mean trough level (μg/ml)	0.9 ± 0.6	4 ± 4[b]
Mean peak level (μg/ml)	4 ± 1.7	21.5 ± 15[b]
Previous otic disease (no. of patients)	7	2
Concurrent drugs (no. of patients)		
Penicillins	12	13
Cephalosporins	1	0
Metronidazol	0	1
Furosemide	1	3
Suspected type of infection (no. of patients)		
Bacteremia	6	3
Urinary tract	9	8
Pneumonia	4	5
Biliary tract	0	1
Mild auditory toxicity (decrease ≥20 dB)[c]		
Whole group	3/19 (15.7)	2/17 (11.7)
Normal aminoglycoside serum levels	3/17 (17.6)	1/13 (7.7)
Abnormally high aminoglycoside serum levels	0/2 (0)	1/4 (25)
Slight auditory toxicity (decrease ≥15 dB)[c]		
Whole group	8/19 (42.1)	6/17 (35.2)
Normal aminoglycoside serum levels	6/17 (35.3)	4/13 (30.7)
Abnormally high aminoglycoside serum levels	2/2 (100)	2/4 (50)

[a] Values are mean ± standard deviation. No *P* values were significant.

[b] Amikacin total dose and levels were corrected for difference in dosage and pattern of administration before the comparison.

[c] Number of patients with toxicity/number of patients evaluated (percentage of patients with toxicity).

identification of the actual rates of tobramycin and amikacin toxicity. Ideally, doses of aminoglycosides should be adjusted according to serum levels of the drug (27). The true rate of aminoglycoside toxicity can be obtained when studies are performed under this condition, provided that the rest of the variables which may exert some influence on the toxicity can be controlled. For this reason, we also reported and compared the rates of nephrotoxicity when patients with abnormally high levels of aminoglycosides were excluded. In our study, the rates of nephrotoxicity did not reach a statistically significant difference and, indeed, the nephrotoxicities of tobramycin and amikacin were almost identical when patients with abnormally high levels of aminoglycoside were excluded.

No differences in slight or mild auditory toxicity were found. However, with the small group of patients under study, only differences of 25% or greater would have been detected. In our study, we found rates of auditory toxicity similar or higher (25, 32) than those reported previously. Criteria defining auditory toxicity are often not clearly reported (5, 6, 13) or are different from one investigator to another (4, 7, 11, 32). In addition, testing of hearing at the bedside is not well standardized (19), patients in worse condition are likely to be included, and readings, mainly those of the first audiogram, may be falsely low, thus decreasing sensitivity to the detection of auditory toxicity. Furthermore, we have considered either unilateral or bilateral decreases in auditory threshold, but often this point is not stated (11, 18, 32, 33) or auditory toxicity is only admitted when a bilateral decrease occurs (4, 32) or when it occurs at more than one frequency (19). Serial evaluation of vestibular function has been difficult (19) and was not attempted in our study.

In conclusion, no statistically significant differences have been found in nephrotoxicity and auditory toxicity of tobramycin and amikacin. Such toxicities were infrequent events when the dosages of these drugs were adjusted to hold blood levels within the safe boundaries suggested by the studies of others (21, 26). Finally, we believe that tobramycin and amikacin should be selected for reasons other than nephrotoxicity or auditory toxicity unless smaller differences can be demonstrated in a similar but larger trial.

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