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Univariate and Multivariate Analyses of Risk Factors Predisposing to Auditory Toxicity in Patients Receiving Aminoglycosides

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Risk factors predisposing to auditory toxicity of aminoglycosides were analyzed from records of 187 patients enrolled in three prospective randomized trials comparing the toxicity of netilmicin, tobramycin, and amikacin. Patients were eligible if they received three or more days of therapy and at least two serial audiograms were available. The overall auditory toxicity rate was 9.6% (18 of 187). Auditory toxicity was detected in 4.4, 10.8, and 23.5% of patients given netilmicin, tobramycin, and amikacin, respectively ($P = 0.05$). In the univariate analysis, patients who developed auditory toxicity were significantly older ($P = 0.01$) and had a significantly higher ($P = 0.04$) percentage of trough levels of netilmicin or tobramycin above 2 mg/liter or amikacin above 5 mg/liter. In the final logistic regression model, only age was retained as independently influencing the development of auditory toxicity ($P < 0.00001$). Conversely, factors that did not add significantly to the prediction of auditory toxicity were aminoglycoside serum levels, total aminoglycoside dose, duration of therapy, sex, peak temperature, presence of bacteremia, shock, liver cirrhosis, dehydration, previous otic pathology or renal failure, and development of renal toxicity. At least in certain populations, age is the most important predisposing factor for the development of auditory toxicity in patients receiving aminoglycosides.

Despite the introduction of many new beta-lactams, aminoglycosides retain an important role in the therapeutic armamentarium (1, 23, 33, 42). At least 5 to 15% of patients receiving netilmicin, tobramycin, or amikacin will develop an impairment in the glomerular function (11, 12, 18, 19, 34, 36), most often reversible, and the percentage may be even higher among those receiving gentamicin (36). Ototoxicity, frequently irreversible, is the other major adverse effect of aminoglycosides (11, 12, 18, 19, 34, 36). In the only published clinical study using a multivariate statistical approach (24), the overall rate of auditory toxicity in patients treated with gentamicin, tobramycin, or amikacin was 22.3%. In this study, patients with auditory toxicity underwent therapy for a longer period, were more likely to be bacteremic, dehydrated, or have an underlying liver dysfunction, and on the average, had a higher temperature than those without auditory toxicity (24). Other predisposing factors such as male sex or advanced age have also been identified in clinical and experimental studies (4, 6, 9, 13, 16, 22, 28, 29, 35, 37, 41). A trend toward a lower ototoxic potential for netilmicin has been confirmed in several randomized and open clinical studies (10, 15, 18, 38, 40). However, the risk factors for ototoxicity developing in patients given netilmicin have not been analyzed.

We determined the risk factors for auditory toxicity by using univariate and multivariate statistical techniques for a combined population from three prospective, randomized, double-blind trials comparing the toxicity of amikacin, tobramycin, and netilmicin.

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MATERIALS AND METHODS

Patients. The aminoglycoside trials were designed to compare the toxicity of tobramycin and amikacin (trial 1) and tobramycin and netilmicin (trials 2 and 3). The details of trials 1 and 2 have been published (10, 11). The design of trials 2 and 3 was exactly the same. Patients hospitalized in the general medical wards or the infectious disease ward of a 1,000-bed teaching hospital were eligible if they received at least three days of therapy with tobramycin, amikacin, or netilmicin and were able to cooperate in obtaining serial audiograms.

Methods. Aminoglycoside levels in serum obtained before (trough concentration) and 1 h after (peak concentration) an aminoglycoside dose were measured on day 1 and every third day during therapy, after each dosage change, and after every change in serum creatinine concentration of >0.5 mg/liter. Determinations were performed by high-pressure liquid chromatography by a modification of the methods reported by Barends et al. (3) in trials 2 and 3. In trial 1, determinations were performed by radioimmunoassay (tobramycin radioimmunoassay kit from Nuclear Medical Systems, Inc., Newport Beach, Calif.; amikacin radioimmunoassay kit from Diagnostic Products Corp., Los Angeles, Calif.) with stored frozen (−20°C) serum samples and were not available until the end of the trial. The loading dose was 1.7 mg/kg of total body weight for tobramycin or netilmicin and 7.5 mg/kg for amikacin. Dosage adjustments were performed with the nomogram of Sarubbi and Hull (30) in trial 1. In trials 2 and 3, the aminoglycoside doses were administered every 8 h for tobramycin or netilmicin and every 12 h for amikacin and adjusted to obtain trough serum levels below 2 mg of netilmicin or tobramycin per liter or below 5 mg of amikacin per liter and peak levels between 5 and 12 mg of netilmicin or tobramycin per liter and between 20 and 30 mg of amikacin per liter.

Apart from the aminoglycoside type, levels in serum, total aminoglycoside dose, and duration of therapy, a series of other variables cited in the literature as possibly influencing the development of auditory toxicity were determined to be either present or absent, for categorical variables, or were recorded, for quantitative variables. These variables included the age and sex of the patient, duration of therapy, total aminoglycoside dose, aminoglycoside serum levels, initial serum creatinine concentration, serum urea nitrogen/serum creatinine ratio, development of concurrent nephrotoxicity, initial auditory acuity, concurrent administration of furosemide or beta-lactams, presence of bacteremia, shock, or diabetes mellitus, peak temperature, and presence of liver cirrhosis.

The presence of an underlying renal failure was defined as a basal creatinine concentration greater than 1.5 mg/100 ml. Aminoglycoside-related nephrotoxicity was defined as a rise in the serum creatinine concentration of 0.5 mg/100 ml or more if the initial (last determination before the initiation of aminoglycoside therapy) creatinine level was <3 mg/100 ml or a rise of 1 mg/100 ml or more if the initial creatinine level was >3 mg/100 ml. The rise was estimated by subtracting the creatinine level before therapy from the highest creatinine level. An episode of bacteremia or fungemia was determined by one or more clinically valuable blood cultures. Shock was defined as either a systolic blood pressure of <80 mm Hg, with a urine output of <500 ml/24 h, or a fall in the systolic blood pressure of >50 mm Hg. Liver cirrhosis was determined by a positive liver biopsy or by consistency of clinical presentation and follow-up (hepatic insufficiency or ascites). A diagnosis of diabetes mellitus was made if the fasting serum glucose level was above 140 mg/100 ml or the patient required the administration of oral hypoglycemic drugs or insulin. The initial serum urea nitrogen/serum creatinine ratio was used to indirectly estimate (24) the state of hydration. Audiograms were obtained in a soundproof auditory test chamber with an audiometer (Amplaid 300; Amplaid Spa., Milan, Italy) at 250, 500, 1,000, 2,000, 4,000, and 8,000 Hz on day 1 or 2, on day 7 of therapy, and every 7 days if therapy continued. Patients who were given at least 3 days of therapy with tobramycin, netilmicin, or amikacin and who were able to be moved to a soundproof room and cooperate in the obtention of serial audiograms were evaluated for auditory toxicity. Slight auditory toxicity was defined as a decrease in the auditory threshold of 15 dB in at least two frequencies in the range of 250 to 8,000 Hz either unilaterally or bilaterally. Auditory toxicity was considered mild if the decrease in the auditory threshold was 20 dB or more, also in at least two frequencies. The initial auditory acuity was considered abnormal when, in the first audiogram, the auditory threshold was below the accepted standards for a population of similar age living in the same area (M. Bonet, Ph.D. thesis, University of Barcelona, Barcelona, Spain, 1984).

Statistical analysis. The chi-square test, with the correction of Yates or the Fisher exact test when necessary, and Student's *t* test were used in the univariate analysis (2). Arbitrarily chosen scores of 1, 2, and 3 were applied to netilmicin, tobramycin, and amikacin, respectively, to calculate the possible presence of a linear trend in auditory toxicity (2). The aim of the univariate analysis was to define the relationship of each factor individually to the development of auditory toxicity.

All factors were then tested in a step-forward logistic regression analysis (7, 17, 32) with 0.05 as a limit for entering or removing terms. The age of the patient, duration of treatment, and serum urea nitrogen/serum creatinine ratio were entered in the analysis as continuous measures. Since the duration of treatment and the total aminoglycoside dose were highly correlated ($r = 0.73$ and $P = 0.01$ for netilmicin and tobramycin; $r = 0.67$ and $P = 0.03$ for amikacin), only the duration of treatment was included in the logistic regression analysis. Since the aminoglycoside type was considered a categorical variable with three categories (netilmicin, tobramycin, and amikacin), it was entered in the model as two dummy variables automatically generated by the statistical program. The remaining variables were considered categorical factors and were valued as 0 if absent or normal and as 1 if present or abnormal. The obtained logistic equation or model allows the estimated probability of developing auditory toxicity to be calculated for any given values of the categorical or continuous variables selected for the final model.

All calculations were performed by using the 4F, 3D, 6D, and LR routines of the BMDP (version, April 1985) software package (BMDP Statistical Software, Inc., University of California) in the computer facilities of the Central University of Barcelona, Barcelona, Spain.

TABLE 1. Relationship between development of auditory toxicity and type of aminoglycoside administered

Aminoglycoside	No. in study population	No. (%) with auditory toxicity:	
		≥15 dB[a]	≥20 dB[b]
Netilmicin	68	3 (4.4)	0 (0)
Tobramycin	102	11 (10.8)	8 (7.8)
Amikacin	17	4 (23.5)	2 (11.8)
Total	187	18 (9.6)	10 (5.3)

[a] Chi-square = 6.5; $P = 0.04$. Chi-square for linear trend = 6.2; $P = 0.01$.
[b] Chi-square = 6.1; $P = 0.05$. Chi-square for linear trend = 5.6; $P = 0.02$.

RESULTS

During the three clinical trials, 187 patients were treated for three or more days with netilmicin, tobramycin, or amikacin and were able to be moved to a soundproof room and cooperate in the obtention of serial audiograms.

A slight or mild hearing loss (≥15 dB) occurred in 18 patients (9.6%), and a mild hearing loss (≥20 dB) occurred in 10 patients (5.3%). The lowest percentage of auditory toxicity was associated with the administration of netilmicin, and the highest percentage was associated with the administration of amikacin. The toxicity trend of netilmicin < tobramycin < amikacin was statistically significant (Table 1). Two patients had a hearing loss of 40 or more dB, and in one, who received tobramycin, the hearing loss was clinically significant. For the remaining univariate analysis and for the multivariate analysis, only the overall auditory toxicity (hearing loss, ≥15 dB) was considered.

In the univariate analysis (Table 2), the patients who developed auditory toxicity were significantly older ($P = 0.01$), the percentage with an abnormally high trough level of aminoglycosides was significantly higher ($P = 0.04$), and the proportion of the latter group with an initial serum creatinine concentration above 1.5 mg/100 ml was almost significantly higher ($P = 0.13$). The results of the stepwise logistic regression analysis are shown in Table 3. After adjustments for confounding variables, only age was retained as significantly and independently influencing the development of auditory toxicity. The probability of developing auditory

TABLE 2. Univariate association of risk factors with development of auditory toxicity

Risk factor	Auditory toxicity		P value
	No (n = 169)	Yes (n = 18)	
Age (yr)	46.8 ± 20.2[a]	59.9 ± 21.2	0.01
Sex			
Female	83 (49.1)[b]	11 (61.1)	
Male	86 (50.9)	7 (38.9)	0.32
Duration of therapy (days)	9.8 ± 4.7	7.9 ± 3.3	0.08
Total dose of aminoglycosides (g)			
Tobramycin and netilmicin	2.2 ± 1.12	2.4 ± 2.1	0.5
Amikacin	6.6 ± 2.7	6.4 ± 2.9	0.9
High[c] mean trough level of aminoglycoside	18 (10.7)	5 (27.8)	0.04
High[d] mean peak level of aminoglycoside	10 (5.9)	1 (5.5)	0.95
Initial serum creatinine above 1.5 mg/100 ml	11 (6.5)	3 (16.7)	0.13
Serum urea nitrogen/creatinine ratio	9.8 ± 20.2	16.1 ± 25.3	0.22
Concurrent nephrotoxicity	8 (4.7)	1 (5.6)	0.9
Abnormal initial auditory acuity	24 (14.2)	3 (6.7)	0.78
Concurrent administration of:			
Furosemide	7 (4.1)	0	0.97
Beta-lactams	136 (80.5)	13 (72.2)	0.6
Bacteremia	42 (24.9)	1 (5.5)	0.12
Shock	9 (5.3)	2 (11.1)	0.34
Diabetes	4 (2.4)	1 (5.6)	0.44
Peak temp above 38.5°C	36 (21.3)	7 (38.9)	0.63
Liver cirrhosis	11 (6.5)	0	0.25

[a] Mean ± standard deviation.
[b] Number (%).
[c] Above 2 mg of tobramycin or netilmicin per liter or above 5 mg of amikacin per liter.
[d] Above 10 mg of tobramycin or netilmicin per liter or above 30 mg of amikacin per liter.

toxicity, estimated by using the equation of the final logistic model, as a function of the age of the patient is shown in Fig. 1. The estimated probability of developing auditory toxicity ranged from 3% when the age was 14 years to 26% when the age was 90 years. The logistic regression yielded similar results when only the variables known at the time of starting the treatment were included, the duration of therapy was replaced by the total aminoglycoside dose, only the trough or peak aminoglycoside levels in serum were entered in the model instead of both, and the presence or absence of mild auditory toxicity (hearing loss, ≥20 dB) was used as a dependent variable instead of the overall auditory toxicity (auditory decrease, ≥15 dB). The same model was obtained when a step-backward analysis was used instead of the step-forward analysis. Finally, no interactions could be found between age (used as a categorical variable with a cutoff point of 60 years), duration of treatment, and trough aminoglycoside levels in serum.

TABLE 3. Step-forward logistic regression analysis of risk factors for auditory toxicity[a]

Risk factor	Coefficient	Chi-square	P value
Age	0.032	5.27	0.02
Constant	−3.92	21.24	<0.00001

[a] Model chi-square = 5.9; $P = 0.015$. $P_x = 1/[1 + e^{-(-3.92 + 0.032 \times \text{age})}]$, where P_x is the probability of developing auditory toxicity and $e = 2.7183$.

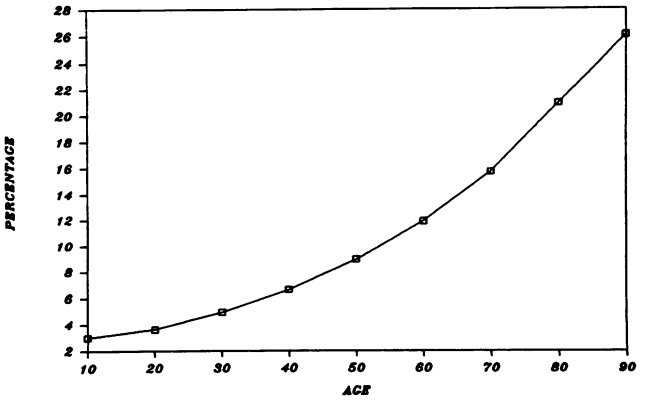

FIG. 1. Percentage of auditory toxicity, estimated by using the final logistic model, represented as a function of age.

DISCUSSION

Low grades of a reversible glomerular nephrotoxicity and auditory toxicity are the major adverse effects associated with the administration of aminoglycosides (11, 12, 18, 19, 34, 36). The frequency of auditory toxicity ranges from 2 to 44% (22, 26, 33, 39), and although the auditory decrease most often is not very intense, in at least 50% of the cases, it is irreversible (24). This represents a serious threat for auditory function, primarily in old or immunosuppressed individuals likely to need successive courses of antibiotic treatment for pyelonephritis and other severe infections.

The risk of developing auditory toxicity has been associated with the type of aminoglycoside administered (18). We found a significant trend toward a lower ototoxic potential for netilmicin; this has also been found in some experimental models (5, 8, 14, 20, 27) and in several, but not all, open and randomized clinical studies (4, 10, 15, 18, 21, 38, 40). Several factors have been identified by univariate statistical techniques as predisposing individuals to auditory toxicity (4, 9, 13, 16, 18, 22, 28, 35, 37, 41). A multivariate approach, however, seems more appropriate since the variables cited in the literature are often very interrelated. Conversely, a drawback of the multivariate models is that they are often applicable only to patients with clinical characteristics similar to those of the sample from which the model was derived. For example, the duration of treatment was selected for the final multivariate model of aminoglycoside nephrotoxicity only after including in the analysis a sample of patients with unusually long courses of aminoglycoside therapy (25, 31). Apart from the aminoglycoside type, we identified age and the presence of an abnormally high trough level as predisposing factors for development of auditory toxicity, and only age was retained in the final logistic model. All of these factors have been cited previously (4, 6, 9, 16, 18, 22, 24, 35, 37). Conversely, Moore et al. (24), also using a multivariate approach, identified a significant association between auditory toxicity and the duration of therapy, presence of shock, dehydration, liver dysfunction, and peak temperature, but age did not reach statistical significance in either the univariate or multivariate analysis. This striking difference can be explained, at least in part, by the different characteristics of the populations; a substantial number of our patients were treated with netilmicin instead of gentamicin, and we accepted the development of auditory toxicity only when the auditory decrease was detected in at least two frequencies instead of one. In fact, when an

auditory decrease in only one frequency was accepted as a criterion of ototoxicity, the 22.3% overall auditory toxicity rate obtained by Moore et al. (24) was very similar to the 28.3% obtained in our study.

In summary, we found that patients who developed auditory toxicity were most likely being treated with amikacin or tobramycin instead of netilmicin, had a greater percentage of abnormally high trough levels, and were older. Only age was retained in the final logistic model, and the estimated probability of developing auditory toxicity ranged from 3 to 26% as age increased from 14 to 90 years. We conclude that, at least in certain populations, age is an important predisposing factor for the development of auditory toxicity in patients treated with aminoglycosides.

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