

Relationship Between Aminoglycoside-Induced Nephrotoxicity and Auditory Toxicity

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Received for publication 12 March 1979

We have reviewed our data from 391 patients entered into three prospective, double-blind studies of aminoglycosides and evaluated 127 cases to determine whether aminoglycoside-induced auditory toxicity and nephrotoxicity are independent events. The cases selected for evaluation included all patients treated for greater than 3 days (mean, 7.7 days) who had serial creatinine determinations and were able to cooperate with serial bedside audiograms (250 to 8,000 Hz). Patients received either gentamicin, tobramycin, or amikacin. Drug dosage was altered to keep serum levels 1 h after administration between 5 and 10 $\mu\text{g}/\text{ml}$ (gentamicin or tobramycin) or 20 and 40 $\mu\text{g}/\text{ml}$ (amikacin). The investigators evaluating auditory toxicity and nephrotoxicity were blind to the aminoglycoside being administered. The incidence of auditory toxicity in the nephrotoxic group (18.2%) was not significantly different from that in the nonnephrotoxic group (15.2%) ($P = 0.75$; Fisher exact test). There was no statistical difference between the nephrotoxic and auditory toxic groups in patient age, total dose of aminoglycoside, initial creatinine level, duration of therapy, or concurrent use of furosemide or cephalothin. We conclude that aminoglycoside-induced auditory toxicity and nephrotoxicity are independent events when the drug is administered for approximately 7 days and when aminoglycoside levels are maintained within a predefined range.

Ototoxicity and nephrotoxicity are major factors limiting the clinical utility of aminoglycosides. Ototoxicity may develop as cochlear (auditory) or vestibular dysfunction. Since ototoxicity may be related to renal dysfunction (2, 3), it might be expected that the development of nephrotoxicity and the development of ototoxicity would be interrelated events. However, a dependent relationship might also be explained by an accumulation of high serum aminoglycoside levels in patients with nephrotoxicity. The two events might be independent if the drug dosage were altered in patients with renal dysfunction to maintain serum levels within a predefined range. We have analyzed our data from two completed and one ongoing prospective, double-blind comparison of aminoglycosides (4, 6) to determine whether the auditory toxicity and the nephrotoxicity induced by gentamicin, tobramycin, and amikacin are independent events. In all three studies, drug dosage was altered to keep aminoglycoside levels within a predefined range.

MATERIALS AND METHODS

The design of the comparative aminoglycoside trials used in this report has been previously published (4,

6). Initial intravenous aminoglycoside doses were 2 mg of gentamicin or tobramycin per kg, or 8 mg of amikacin per kg. Subsequent doses were given every 8 h. During the first 24 h, this dosage was calculated from a nomogram to correct for the effect of renal dysfunction. Within 24 h, plasma aminoglycoside levels were measured, and the aminoglycoside dose was altered to maintain the level 1 h after a 20- to 30-min infusion between 5 and 10 $\mu\text{g}/\text{ml}$ for gentamicin or tobramycin and between 20 and 40 $\mu\text{g}/\text{ml}$ for amikacin. Serum creatinine levels were measured in a Beckman creatinine analyzer, using the alkaline picrate technique (standard deviation, 0.13 mg/100 ml). Measurements were made before therapy, on days 2, 3, and 4, and on every third day of therapy, and then 2 days after therapy. Bedside pure-tone audiometry was performed by using a Maico-MA 20 Audiometer (Maico Hearing Instruments, Minneapolis, Minn.), equipped with ear muffs to exclude ambient noise. Measurements of acuity were taken at 250, 500, 1,000, 2,000, 4,000 and 8,000 Hz on days 1 and 7 of therapy and 2 days after therapy. Plasma aminoglycoside levels were measured on days 1, 2, 4, and 7, and every third day thereafter during therapy. If the dosage was altered or renal function changed, levels were measured daily until they were within the desired range. Levels were measured by using a radioenzymological assay (5). The other antibiotics administered included penicillin, methicillin, nafcillin, and cephalothin. Penicillin was administered with gentamicin or amikacin; methicillin, nafcillin, or

cephalothin was administered with gentamicin or tobramycin.

Patients were evaluated for nephrotoxicity and auditory toxicity if they received nine doses or more of the aminoglycosides and if the patients could cooperate with serial audiograms. The change in creatinine during therapy was determined as the highest creatinine level during therapy or within 48 h after therapy minus the initial creatinine level. If the initial serum creatinine level was less than 3.0 mg/ml, a rise during therapy of greater than 0.4 mg/100 ml was categorized as nephrotoxicity. Changes of less than 0.4 mg/100 ml were categorized as no nephrotoxicity. If the initial value was greater than or equal to 3.0 mg/100 ml, a rise of greater than 0.9 mg/100 ml was considered significant. If no other cause of acute renal failure was identified within 72 h before the change in serum creatinine, the change was attributed to drug administration and termed definite nephrotoxicity. If another cause was identified and the rise in creatinine could not be definitely attributed to drug administration, these cases were termed possible nephrotoxicity. A decrease of greater than 10 dB in auditory acuity at any frequency in the range of 250 to 8,000 Hz was categorized as auditory toxicity. Changes of 10 dB or less were categorized as no auditory toxicity.

RESULTS

Of the 391 patients entered into the studies, both auditory and renal function could be evaluated in 127. All patients evaluated for both types of toxicity have been included in this analysis. The relationship between auditory toxicity and definite nephrotoxicity was as follows. Both auditory toxicity and nephrotoxicity developed in 4 patients; nephrotoxicity alone developed in 18; auditory toxicity alone developed in 16; and 89 patients had normal auditory and renal function. The development of auditory toxicity and nephrotoxicity was not statistically related ($P = 0.750$, Fisher exact test). Auditory toxicity developed in 20 (15.7%), and definite nephrotoxicity developed in 22 (17.3%). Auditory toxicity or nephrotoxicity or both developed in 38 (30.0%). The measured probability of both events occurring together was 4/127 (3.1%) and is approximately equal to the product of the measured probabilities of each individual event; the calculated probability of both events occurring together = the measured probability of nephrotoxicity (17%) \times the measured probability of ototoxicity (15%) = 2.7%. The similarity between the measured and calculated probability of both events occurring together also supports an independent relationship between nephrotoxicity and auditory toxicity.

The demographic characteristics of the groups evaluated for nephrotoxicity and auditory toxicity are shown in Table 1. The groups with and without nephrotoxicity and the groups with and without auditory toxicity were similar in mean

TABLE 1. Demographic characteristics

| Group | Mean age (yr) | Mean total dose (g) | | Mean initial creatinine level (mg/100 ml) | Patients with creatinine level >1.5 mg/100 ml | Duration of therapy (days) ^a | Patients given: | | | | |
|-------------------|---------------|--------------------------|----------|---|---|---|-----------------|------------|------------------------|-----------------------|----|
| | | Gentamicin or tobramycin | Amikacin | | | | Gentamicin | Tobramycin | Concurrent cephalothin | Concurrent furosemide | |
| Nephrotoxicity | 53.1 | 2.6 | 13.5 | 1.4 | 14 | 7.5 | 55 | 27 | 23 | 15 | 19 |
| | 58.2 | 2.5 | 13.5 | 1.7 | 6 | 8.4 | 15 | 5 | 2 | 6 | 3 |
| Auditory toxicity | 54.5 | 2.5 | 13.4 | 1.5 | 16 | 7.3 | 57 | 27 | 23 | 15 | 20 |
| | 50.5 | 3.0 | 13.8 | 1.2 | 4 | 9.6 | 13 | 5 | 2 | 6 | 2 |

^a $P < 0.05$; no other differences were significant, as determined by t test (parametric data) or Fisher exact test (nonparametric data).

age, mean total dose of aminoglycoside, mean initial creatinine, number with an initial creatinine of greater than 1.5 mg/100 ml, number given furosemide, type of aminoglycoside given, and number receiving cephalothin. Duration of therapy correlated with the development of nephrotoxicity and ototoxicity in each group. Mean 1 h post-dose aminoglycoside levels were within the predefined range in 123 (96.9%) patients. Four patients had mean 1 h post-dose aminoglycoside levels exceeding the range; three developed toxicity and one did not. The highest mean peak aminoglycoside level was 10.9 μg of gentamicin per ml in a patient who developed auditory toxicity but not nephrotoxicity.

Since the concomitant administration of cephalothin and either gentamicin or tobramycin has been associated with a higher incidence of nephrotoxicity (6), we also evaluated our data excluding patients who received cephalothin. Of the 87 cases that were then evaluated, 24 (27.6%) developed either nephrotoxicity, auditory toxicity or both. Auditory toxicity developed in 12 (13.8%) and nephrotoxicity in 15 (17.2%). The measured probability of both events occurring together was 3/87 (3.4%) and is approximately equal to the product of the measured probabilities of each individual event (2.4%). The development of auditory toxicity and the development of nephrotoxicity also were not statistically related ($P = 0.683$, Fisher exact test). The demographic characteristics of those patients not receiving cephalothin were similar to those of the total study population analyzed in this report.

DISCUSSION

Our data indicate that the nephrotoxicity and the auditory toxicity induced by gentamicin, tobramycin, and amikacin may be independent events when 1 h post-dose aminoglycoside levels are maintained within the range of 5 and 10 μg of gentamicin or tobramycin per ml and within the range of 20 and 40 μg of amikacin per ml and when therapy is administered for an average of 7.7 days. It is important to emphasize that this conclusion can only be drawn when 1 h post-dose levels are maintained within these ranges and when therapy is administered for this duration. Since aminoglycoside-induced toxicity is

related to aminoglycoside dosage and duration of therapy, it is possible that giving larger doses for more prolonged periods of time would result in the occurrence of nephrotoxicity and the occurrence of auditory toxicity being concordant events. However, the dose and duration of therapy used in our studies closely approximates that utilized in many clinical circumstances.

Most clinical trials assessing the relative toxicity of different aminoglycosides have compared the incidence of nephrotoxicity and the incidence of ototoxicity separately. However, we have shown that one type of toxicity may develop without the other. Since these events may be independent, comparing the incidence of each separately does not accurately reflect the total risk of developing either type of toxicity. The total risk for either type of toxicity might better be measured by summing the number of patients developing either or both types of toxicity, or could also be calculated from the incidence of each independent event, using a standard statistical method (multiplicative law for independent events) (1). It is important to emphasize, however, that the nephrotoxicity of these agents is usually reversible, whereas the auditory toxicity may be permanent. Therefore, weighting the individual toxicities might also be considered. We propose that this type of analysis should be used in future clinical trials assessing the relative toxicity of aminoglycosides.

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