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Cumulative and Acute Toxicity of Repeated High-Dose Tobramycin Treatment in Cystic Fibrosis

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Forty-six patients with cystic fibrosis and chronic bronchopulmonary *Pseudomonas aeruginosa* infection entered a study of tobramycin-related chronic and acute nephro- and acousticovestibular toxicity. The patients (mean age, 15.7 years) had previously received 2-week courses of tobramycin therapy, for a mean cumulative total of 279 days each. The cumulative tobramycin dose ranged from 632 to 7,644 mg/kg. The patients were studied before and at the end of a 2-week course of treatment with tobramycin (10 to 20 mg/kg per day) to discriminate between acute and chronic toxicity. In patients studied at the beginning of the present course of treatment, the glomerular filtration rate, measured as 24-h creatinine clearance, did not correlate with the cumulative dose of tobramycin received during previous courses. Eighteen patients (39%) had a reduced glomerular filtration rate compared with normal values (mean, 12.5% reduction) but normal serum creatinine values. Two patients (5%) had a high-frequency hearing deficit (above 8 kHz), but only one deficit was possibly related to tobramycin. No chronic vestibular toxicity was observed. During the course of treatment, no patients developed acute nephrotoxicity. After 2 weeks of treatment 32% had a slightly reduced hearing threshold (15 to 30 dB) in two or more high frequencies, and 28% had a fall in vestibular response greater than 25% of the initial value but remained within normal limits. Thus, the acute and chronic toxicity of repeated high-dose tobramycin treatment in cystic fibrosis patients seems to be very mild.

Chronic bronchopulmonary infection with *Pseudomonas aeruginosa* is a major, and ultimately fatal, complication of cystic fibrosis (CF) (30). Although *P. aeruginosa* is rarely eradicated by antimicrobial chemotherapy (34), intensive antipseudomonas chemotherapy has improved the prognosis significantly (37). Under a policy of giving regular and elective intravenous courses of antipseudomonal drugs every 3 months, 91% of patients with chronic *P. aeruginosa* infection at the Danish CF center are now expected to survive the infection for at least 9 years (28). The treatment of this infection usually consists of a combination of a beta-lactam antibiotic and an aminoglycoside (15, 16). Owing to its higher antipseudomonal activity (16, 29), tobramycin has been the aminoglycoside of choice, and since 1972 it has been used extensively at the Danish CF center.

Because of increased longevity the majority of CF patients become exposed to very high cumulative doses of tobramycin. Whereas the acute nephro- and acousticovestibular toxicity of tobramycin is well known (17, 25), knowledge of possible cumulative toxicity of repeated courses of tobramycin is less and largely limited to experience with CF patients (7, 31, 38).

In this study we report our findings of renal and acousticovestibular function in a group of CF patients who, to our knowledge, have received the largest cumulative dose of tobramycin yet published and who were treated with 10 to 20 mg of tobramycin per kg per day.

MATERIALS AND METHODS

Forty-six patients with CF and chronic bronchopulmonary *P. aeruginosa* infection were examined. All were hospitalized for routine intravenous antipseudomonal treatment. There were 25 males, age 10 to 35 years (mean, 17.5 years), and 21 females, age 8 to 29 years (mean, 13.5 years). Children less than 8 years old were excluded as they could not cooperate in the otological tests. At the time of entry into the study the patients had been chronically infected with *P. aeruginosa* for an average of 6.7 years (range, 10 months to 15.8 years) and had been given 2 to 52 courses (mean, 20) of tobramycin treatment, equivalent to a mean cumulative total exposure to tobramycin of 279 days each (range, 28 to 689 days). None of the patients had a history of acute nephro- or ototoxicity during previous courses of tobramycin.

At the present admission they were given 9.8 to 19.4 mg of tobramycin per kg per day (average, 15.1 mg/kg per day) for 14 days as intravenous bolus injections divided in three daily doses. According to the susceptibility pattern of *P. aeruginosa*, tobramycin was given in combination with one of the following beta-lactam antibiotics: piperacillin (300 mg/kg per day; $n = 24$), ceftazidime (150 mg/kg per day; $n = 14$), carbenicillin (500 mg/kg per day; maximal daily dose of 22.5 g; $n = 3$), and cefsulodin (150 mg/kg per day; $n = 2$). Three patients were initially given piperacillin and later changed to ceftazidime. Six patients received tobramycin as monotherapy owing to either resistance of *P. aeruginosa* or hypersensitivity to beta-lactams. All drugs were given intravenously in three divided daily doses. No patients had received tobramycin within 2 months before the study. No patients received loop diuretics or known nephro- or ototoxic drugs other than tobramycin throughout the admission. Thirty-two patients had previously inhaled neomycin (500 mg/day) for a total mean of 38 days. None of them had received this treatment for the last 3 years. Individual patient records were reviewed, and the cumulative tobramycin dosage was calculated.

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TABLE 1. Number of patients participating in the various examinations (n = 46)[a]

Examination	No. of patients	
	Day 1	Day 13
Conventional audiometry	42	38
HFA	42	38
ENG (30°C)	35	32
ENG (30°C + 44°C)	25	19
Creatinine clearance	45	37
Serum creatinine	46	45
Serum creatinine + creatinine clearance	45	37

[a] All patients studied on day 13 were also studied on day 1.

Otological examinations were performed on day 1 of admission just after the first dose of tobramycin and were repeated 13 days later between doses 40 and 41. On both occasions, a variety of studies was performed in the afternoon, including otoscopy, tympanometry with measurements of stapedial reflex thresholds (Madsen ZO72 impedance bridge); conventional pure-tone audiometry, and speech reception threshold. Pure-tone audiometry was performed in the frequency range of 125 to 8,000 Hz (Madsen OB70 audiometer). High-frequency audiometry (HFA) from 4 to 20 kHz was performed by a quasi-freefield technique in a soundproof booth as previously described (27). All patients were evaluated concerning factors which might influence the hearing ability, such as previous ear infections, heriditary hearing loss, perinatal circumstances (hyperbilirubinemia, anoxia), exposure to noise, and head injuries.

Finally, a differential caloric test was performed, irrigation with 30 and 44°C water. Eye movements were recorded with horizontal electronystagmography (ENG). The maximal speed of the slow phase was analyzed by computer, and the sum of responses was calculated and compared with normal values (39).

Auditory and vestibular toxicity were evaluated with respect to possible chronic (cumulative) damage and acute damage. When considering chronic damage caused by the cumulative intake of tobramycin, the results from the examination on day 1 and information from the questionnaire were compared with age- and sex-matched normal values (26, 39).

Acute ototoxicity was defined as a decrease of at least 15 dB in perceptive hearing thresholds in one or both ears at two or more adjacent frequencies on day 13 compared with day 1. Acute vestibular toxicity was defined as a decrease in the sum of vestibular responses exceeding 25% of the initial value.

Renal function studies included 24-h endogenous creatinine clearance (J. Brøchner-Mortensen, Ph.D. thesis, Laegeforeningens Forlag, University of Copenhagen, Copenhagen, Denmark) done on the first and last day of admission. Urine and serum creatinine were analyzed on an automatic analyzer. Creatinine clearance was corrected to a body surface area of 1.73 m^2. Freshly voided urine samples were examined for casts and albumin (Clinistix) on days 1 and 14.

Chronic nephrotoxicity was defined as a creatinine clearance lower than 1.6 ml/s per 1.73 m^2; if serum creatinine was within the normal range (0.8 to 1.2 mg/dl) renal impairment was graded as slight.

Acute nephrotoxicity was defined as a decrease in creatinine clearance greater than 30% and a simultaneous increase in serum creatinine greater than 0.5 mg/dl.

Patients whose conditions met the criteria for chronic and acute nephro- and ototoxicity but who had another cause of functional impairment were not considered to have tobramycin-related toxicity, because the exact cause of toxicity could not be determined.

Table 1 shows the number of patients participating in the various examinations. All patients studied on day 13 were also studied on day 1. Eleven patients did not participate in the day 1 ENG: one had acute otitis media, one had a perforation of an eardrum, one developed severe nausea and further examination was stopped, and eight refused because they thought it unpleasant. Because irrigation elicited nausea, especially in the youngest patients, irrigation was performed at only 30°C in 10 patients. The discomfort of irrigation caused some patients to refuse examination on day 13.

Tobramycin concentrations in serum were measured on days 3, 7, and 10 in venous blood samples drawn 8 h after previous bolus injection (trough level) by an enzyme-immunological method (EMIT Lab 5000; Syva Corp., Palo Alto, Calif.). Trough values were routinely adjusted to concentrations between 1 and 2 mg/liter of serum.

Statistics. The Student t test, Pratt's test for nonparametric paired differences (32), and the Spearman rank-correlation test were used. $P < 0.05$ was considered significant.

RESULTS

The 46 patients had received antipseudomonal treatment for a total of 14,249 days, of which tobramycin was given for 12,813 days, the difference being due to monotherapy with beta-lactams. The patients had received a cumulative dose of tobramycin ranging from 632 to 7,644 mg/kg (mean, 2,947 mg/kg).

Tobramycin concentration in serum. Trough concentration was measured on days 3, 7, and 10, and in three different patients trough levels were found above 2 mg/liter and the following doses were reduced accordingly. Peak levels (30 min postinjection) were measured in 10 patients and ranged from 15 to 18 mg/liter.

Chronic nephrotoxicity. Creatinine clearance did not decrease as a function of increasing cumulative dose of tobramycin. The correlation coefficient (r = 0.11) indicates that only 1% ($=r^2$) of the observed distribution can be explained as covariation between the cumulative dose of tobramycin

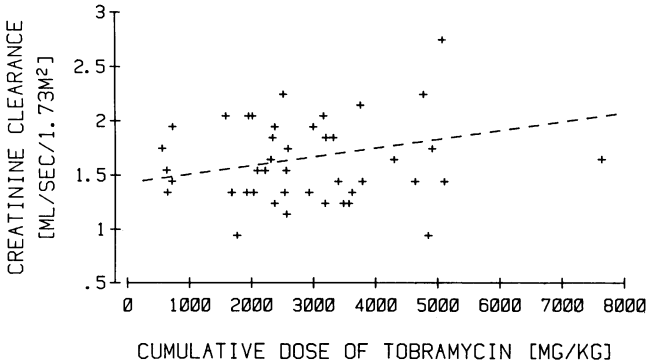

FIG. 1. Correlation between total cumulative dose of tobramycin and glomerular filtration rate, measured as 24-h creatinine clearance in CF patients with chronic *P. aeruginosa* lung infection.

and clearance (Fig. 1). The mean creatinine clearance was 1.7 ± 0.4 ml/s per 1.73 m^2. Of 46 patients, 18 (39%; 95% confidence limits, 25 to 55%) had a creatinine clearance below 1.6 ml/s per 1.73 m^2. The creatinine clearance was between 1 and 2 standard deviations below the normal mean in 12 patients and below 2 standard deviations in 6 patients. The mean of those below 1 standard deviation was 1.4 ml/s per 1.73 m^2, the lowest being 1.0 ml/s per 1.73 m^2. However, serum creatinine was within the normal range in all patients, and the renal impairment therefore was considered slight. The reduced glomerular filtration may be caused by tobramycin, except in one patient, who 5 years previously had a dicloxacillin-induced interstitial nephritis. This patient was excluded from the group of possible tobramycin-associated nephrotoxicity.

Acute nephrotoxicity. Thirty-seven patients were evaluable for acute nephrotoxicity, and none (95% confidence limits, 0 to 9%) fulfilled the criteria for nephrotoxicity. No correlation was found between the change in glomerular function from day 1 to day 13 and the total dose of tobramycin in the current course. The mean pre- and posttherapy levels of creatinine clearance were 1.68 ± 0.37 and 1.51 ± 0.44 ml/s per 1.73 m^2, respectively.

Chronic ototoxicity. Of 42 patients, 2 (5%; 95% confidence limits, 1 to 15%) had a hearing deficit which might be drug related. One patient who had received a cumulative tobramycin dose of 5,100 mg/kg had no measurable hearing above 8 kHz. The speech reception threshold was normal and her renal function was normal as well, but she did not participate in the vestibular testing. She had previously, for a total of 84 days, inhaled neomycin sulfate, which is a well-known ototoxic agent (23), and therefore, tobramycin was not likely to be the only cause of hearing loss. The other patient had previously received 3,300 mg of tobramycin per kg and was unable to hear at 18 and 20 kHz. No other causes than tobramycin treatment were found to explain the hearing loss. Thus, 1 of 42 (2%; 95% confidence limits, 0 to 13%) had a probable tobramycin-related high-frequency hearing deficit.

Furthermore, a slight dip at 4 kHz was observed in three patients who had been exposed to noise. Additionally, three patients had a slight conductive hearing loss caused by middle ear infections. In the remaining patients hearing was excellent.

TABLE 2. Results of *t* test performed to illustrate changes in hearing thresholds with conventional audiometry and HFA in CF patients receiving tobramycin (10 to 20 mg/kg per day for 2 weeks)

Method	Frequency (kHz)	*t* value
Conventional audiometry	0.125	3.080[a]
	0.25	4.395[a]
	0.5	3.086[a]
	1	2.439[a]
	2	3.356[a]
	4	4.128[a]
	8	0.265
HFA	4	2.003
	8	0.980
	10	0.277
	12	1.278
	14	3.346[b]
	16	2.629[b]
	18	4.105
	20	3.687

[a] Significantly improved hearing ($P < 0.05$).
[b] Significantly reduced hearing ($P < 0.05$).

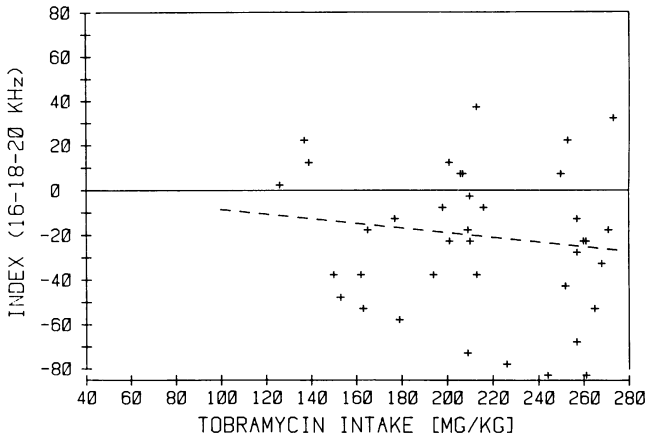

FIG. 2. Index of HFA in CF patients receiving 10 to 20 mg of tobramycin per kg per day for 2 weeks for chronic *P. aeruginosa* lung infection. For definition of HFA index, see text.

Acute ototoxicity. First, individual results from 38 patients were evaluated. Only one patient had a 15-dB threshold decrease in the conventional audiogram at two frequencies (right ear, 1 kHz; left ear, 8 kHz). This patient had a middle ear pressure of −100 mm water at the second examination, and the impaired conduction may explain the observed change in threshold. Therefore, the hearing loss is not likely to be due to drug-induced ototoxicity. Thus, 0% (95% confidence limits, 0 to 9%) suffered hearing loss in the conventional frequency range. HFA showed that 12 patients of 38 (32%; 95% confidence limits, 18 to 49%) had a deterioration of hearing between 15 and 30 dB at two or more frequencies by the second examination, which is between 1 and 2 standard deviations from the age- and sex-matched normal values.

Second, overall results were calculated, and a significant improvement of hearing during tobramycin therapy was found in the conventional frequency range up to 4 kHz. A statistically significant lower threshold in HFA performance at 14 to 20 kHz was observed after 2 weeks of treatment, but this remained within normal limits (Table 2). An index of the change in HFA was calculated as:

$$\text{Index}_{\text{HFA}} = \frac{\Delta Th}{16\text{ kHz}} + \frac{\Delta Th}{18\text{ kHz}} + \frac{\Delta Th}{20\text{ kHz}}$$

where ΔTh is the change in decibels in the threshold level from the first to the last examination. No correlation was found between HFA index and the total dose of tobramycin during the current course of therapy ($r = 0.14$) (Fig. 2).

Chronic vestibulotoxicity. No chronic impairment of vestibular function was seen, and all patients had a sum of responses within normal limits at day 1 (Fig. 3).

Acute vestibular toxicity. Although 9 of 32 patients (28%; 95% confidence limits, 14 to 47%) had a fall in vestibular response greater than 25% of the initial value, and overall the sum of responses was significantly lower on day 13 (Fig. 3), all changes remained within normal limits. This indicates mild acute damage to vestibular function, which was clinically unimportant since no symptoms of vestibulotoxicity were noted. The fall did not correlate with the total dose of tobramycin given during the current course of therapy.

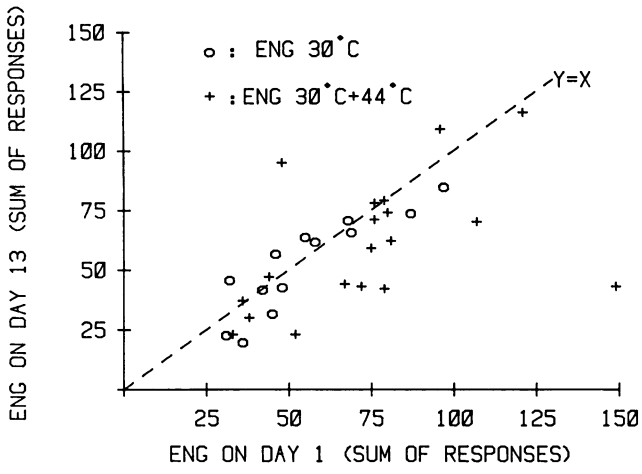

FIG. 3. Chronic (day 1) and acute (day 13) vestibular toxicity, measured by ENG in CF patients with chronic *P. aeruginosa* lung infection. The mean sum of response at 30°C = 47 units on day 1 and 41 units on day 13. Mean sum at 30 ⊕ 44°C = 74 units on day 1 and 60 units on day 13.

DISCUSSION

The value of tobramycin in the treatment of chronic *P. aeruginosa* lung infection in CF is well documented (7, 8, 13, 14, 22, 38, 42). Because of a low ratio between therapeutic and toxic levels, a major limitation in the use of aminoglycosides is the development of nephro- and acousticovestibular toxicity (3, 17).

The recommended dose of tobramycin in the treatment of CF patients is usually higher than in other patients for several reasons. The aminoglycoside pharmacokinetics differ in CF patients as they show faster excretion and a greater volume of distribution than other patients (10, 18, 19). The aminoglycosides do not penetrate readily into the bronchial secretions (2), and the best response to tobramycin treatment in CF is seen when high doses are used (12, 31) and when sputum concentrations are high (22).

The combination of high-dose aminoglycoside treatment repeated every 3 months at our clinic and improved prognosis (37) results in massive cumulative doses of tobramycin in the individual patient. There is, therefore, considerable concern about toxic side effects of repeated aminoglycoside therapy. However, to distinguish between pure tobramycin reactions and other causes of nephro- and ototoxicity is not simple as most CF patients have received many other drugs, e.g., methicillin, ampicillin, cephalosporins, and neomycin, which may cause side effects similar to those of tobramycin (21, 23).

CF patients meet several of the reported risk factors for development of acute aminoglycoside toxicity, i.e., high total dose, long duration of therapy, high antibiotic concentrations, and previous therapy with ototoxic drugs (24, 25). The incidence of acute toxicity in this study is in accordance with the figures cited for tobramycin whether given to non-CF patients or CF patients (17, 20, 25, 36).

A surprising finding was the observation of a significant improvement in hearing in the conventional frequency range after 2 weeks of aminoglycoside therapy. This may reflect the fact that the general condition of the patients improves considerably during therapy and that the first measurement is impaired because of diminished alertness level, a phenomenon also observed by Gatell et al. (11), or because of noisy respiration. However, the preferential damage by aminoglycosides to reception of the highest frequencies (6) is evidenced by the reduction in hearing thresholds in that frequency range. We are aware that the appearance of ototoxic damage is sometimes delayed (11, 31), but it was not within the scope of this investigation to test for this type of reaction.

Whereas the literature on acute toxicity is abundant (17, 41), not much literature is available on the toxicity of repeated exposure to tobramycin, although it is generally believed to be a risk factor for the development of acute toxicity. Rabin et al. (31) gave 38 courses of therapy to 19 CF patients and found no nephrotoxicity, but 1 patient had high-frequency hearing loss presumed to be caused by the aminoglycoside, and there were four cases of reversible vestibular toxicity. Thomsen et al. (38) found only one CF patient with reversible high-tone hearing loss and no sign of renal involvement in a group of 53 patients receiving 170 courses of tobramycin.

No clinically significant cumulative damage to hearing or vestibular function which could be considered to be induced by tobramycin alone was found. One patient had a slight high-frequency hearing loss which may have been caused by tobramycin. The practical consequence of high-frequency hearing loss is uncertain, but it might evoke early presbyacusis and affect the ability of a person to understand conversation in a noisy environment (6; R. E. Brummett, Proc. 13th Int. Congr. Chemother., p. 35/14–35/17, 1983).

In our study each of the patients had on the average received 20 courses of tobramycin, and it was most disturbing that we found that nearly 40% of the patients had a creatinine clearance below normal levels. This finding seems to support the histopathological study of Abramowsky and Swinehart (1), who found morphological evidence of chronic tubulointerstitial disease consistent with gentamicin nephrotoxicity in 26 of 34 autopsies of CF patients. However, the results cannot be directly compared since several of their patients suffered from renal failure and also because the only aminoglycoside our patients received was tobramycin, which in comparative clinical trials has been found to be less nephrotoxic than gentamicin (17, 36).

No clinically overt chronic nephrotoxicity was observed since serum creatinine remained within the normal range. It has been found that the concomitant administration of penicillins and cephalosporins with tobramycin results in a low frequency of nephrotoxicity (5, 40). Furthermore, it has been shown in experimental animal models that carbenicillin reduces gentamicin-induced nephrotoxicity (4) and that ticarcillin attenuates tobramycin toxicity (9). No similar data are available for the combination of tobramycin with the broad-spectrum cephalosporins, which are used extensively in our clinic. Despite the very high tobramycin dose given, the absence of apparent nephrotoxicity in our patients may, in part, be due to these concurrent medications. We found no dose-dependent correlation between total cumulative dose of tobramycin and glomerular filtration (Fig. 1). Instead, an individual variation in susceptibility to the toxic effects of tobramycin may determine whether development of chronic nephrotoxicity subsequently occurs. Therefore, we conclude that the benefits of tobramycin in the treatment of chronic *P. aeruginosa* infection outweigh the risk of chronic nephrotoxicity, and we continue to use tobramycin in high daily doses. Our data cannot rule out a possibility of development of renal failure in later years, and we plan to monitor prospectively the side effects of long-term tobramycin therapy. Excretion of casts or β-2-microglobulin and

enzymuria cannot predict development of renal damage (33, 35), and simple maintenance of tobramycin levels in the safe range does not exclude development of nephrotoxicity (35). Damage to the cochlea is usually irreversible (3), and by the time damage is observed with conventional audiometry it must have been sustained for a long time. Because of the unknown preferential damage of aminoglycoside to the outer hair cells in the cochlea responsible for high-frequency hearing, HFA may be an aid as monitoring audiometry in preventing ototoxic effects from the damage has extended to the conversational frequency range.

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