

## Absence of Cochleotoxicity Measured by Standard and High-Frequency Pure Tone Audiometry in a Trial of Once- versus Three-Times-Daily Tobramycin in Cystic Fibrosis Patients

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We undertook assessment of hearing in patients with cystic fibrosis who were taking part in a large randomized controlled trial of once- versus three-times-daily tobramycin for pulmonary exacerbations of cystic fibrosis (the TOPIC study). All patients were eligible to have standard pure tone audiometry performed across the frequency range of 0.25 to 8 kHz. High-frequency pure tone audiometry over 10 to 16 kHz was also performed with a subset of patients. Audiometry was undertaken at the start of tobramycin treatment, at the end of a 14-day course of treatment, and at follow-up 6 to 8 weeks later. We enrolled 244 patients, of whom 219 (125 children and 94 adults) completed treatment. Nineteen patients were excluded from analysis due to abnormal baseline audiometry. Complete pre- and posttreatment standard audiological data were obtained for 168/219 patients. We found no significant differences in hearing thresholds when they were assessed at the baseline, at the end of treatment, and at follow-up 6 to 8 weeks later were compared. In addition, no significant differences in hearing thresholds were detected between treatment regimens. Similar results were obtained for the subset of 63/168 patients who underwent high-frequency audiometry. We conclude that for a single 14-day course of tobramycin treatment in patients with cystic fibrosis with no preexisting auditory deficit, no measurable effect on hearing was apparent with either once- or three-times-daily treatment. Estimation of the cumulative cochleotoxic risk in cystic fibrosis patients due to repeated aminoglycoside therapy, as evidenced by the patients excluded from this study due to hearing loss, also requires further characterization.

There has been a growing body of evidence in the literature supporting the use of once-daily over three-times-daily dosing with aminoglycosides for treatment of gram-negative bacterial infections (7, 21). The majority of evidence comparing these dosing regimens has, however, been obtained from non-cystic fibrosis (non-CF) patient groups with disparate disease states (21, 24). Comparatively, non-CF patients often require lower doses of aminoglycosides for shorter periods than those required by CF patients for treatment of pulmonary exacerbations (26). Additionally, there are important differences in aminoglycoside pharmacokinetics in CF patients. There is an increased volume of distribution (although this is accounted for by differences in the body surface area of CF patients compared with those of control individuals) and more rapid elimination of aminoglycosides (28). The relevant therapeutic profile outcome can also differ, with eradication of *Pseudomonas aeruginosa* difficult or impossible to achieve in CF patients. This makes extrapolation of the findings from the once-daily studies conducted with the disparate non-CF groups inappro-

appropriate (26, 28). This is further compounded by the absence in many of these studies of well-defined therapeutic and toxicological end points (7, 25).

A paucity of studies have investigated the balance of therapeutic efficacy and toxicity with respect to the dosing regimens of tobramycin in CF patients. This has recently been addressed by an adequately powered, randomized, double-blind trial (the TOPIC study) carried out in 21 CF centers across the United Kingdom and completed in 2003. The results of the TOPIC study have been published elsewhere in summary form (25).

The primary therapeutic end point in TOPIC was the equivalence in improvement of the forced expiratory volume at 1 s obtained with once- and three-times-daily dosing. In terms of therapeutic efficacy, once-daily dosing was clearly found to be equivalent to three-times-daily dosing. The report also briefly summarized the absence of any evidence of serious side effects, including clinically marked hearing loss and nephrotoxicity, in either treatment arm. Within the study protocol, hearing loss was defined in terms of a loss that would be evident clinically and was defined as a consistent elevation of any two pure tone audiometry (PTA) thresholds above 20 dB hearing level (HL) over 2 to 8 kHz (16, 22).

In this report, a more detailed and sensitive analysis of pre- and posttreatment auditory thresholds is presented. This covers standard audiometric frequencies up to 8 kHz and extends

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up to 16 kHz in the higher frequencies, where aminoglycoside ototoxicity is typically first manifest (5). The primary aims of this more detailed analysis were to establish whether there were any subtle changes in auditory thresholds over a 2-week course of tobramycin treatment and whether any difference in the incidence of cochleotoxicity was apparent between the two treatment arms. The secondary aim in a study with a subgroup of patients who attended a third audiometric test session was to establish if any changes in audiometric threshold were apparent at 6 to 8 weeks after the completion of tobramycin therapy.

## MATERIALS AND METHODS

**Ethical approval and data monitoring.** The study was submitted to and approved by the Trent Multicenter Research Ethics Committee and the local research ethics committee of each of the 21 centers around the United Kingdom that agreed to take part in the TOPIC study. During the course of the study an independent data monitoring committee scrutinized the data collection and monitored the occurrence of any adverse events.

**Patient recruitment.** Patients were first identified by the treating clinician at outpatient clinics as presenting with an exacerbation of their *P. aeruginosa* infection that required aminoglycoside therapy.

Before formal written informed consent was obtained, the clinician explained the TOPIC study to the patient or, in the case of children, the child's parents or caregiver. No child was recruited unless he or she gave his or her clear verbal assent. After consent was obtained, the patient was entered into the TOPIC study. Following entry into the study, the patient's general practitioner was informed and asked to inform the CF clinician of any audiovestibular disturbance experienced by the patient following entry into the study. Patient recruitment was carried out from February 1999 to April 2003.

Patients were first identified by the treating clinician at outpatient clinics as presenting with an exacerbation of their *P. aeruginosa* infection that required aminoglycoside therapy for treatment of their symptoms. With additional consent, the patient's general practitioner was also informed of the patient's participation. The general practitioner was also asked to inform the TOPIC team of any audiovestibular disturbance experienced by their patients following their participation in the TOPIC study.

**Inclusion and exclusion criteria.** The inclusion criteria were as follows: the patient had to have a diagnosis of CF defined by a positive sweat test or genotyping, patients over 5 years of age had to be able to perform lung function assessments reliably, the patient had to have had a pulmonary infection with *P. aeruginosa* on at least one occasion, the patient had to have experienced a pulmonary exacerbation that required 10 to 14 days of intravenous antibiotic therapy, and the latest isolate of *P. aeruginosa* had to be sensitive to tobramycin and/or ceftazidime (all patients received ceftazidime as a second antibiotic).

Exclusion criteria were primarily based on grounds of patient safety. These were a history of an adverse reaction to tobramycin or ceftazidime, established pulmonary infection with *Burkholderia cepacia* complex, established renal damage (serum creatinine levels outside the normal range), established hearing deficit (thresholds of >20 dB at two or more frequencies between 2 and 8 kHz on at least two or more assessments), and pregnancy. With regard to auditory function, it was considered unethical to include patients with preexisting hearing loss when the effects of the once-daily treatment on this patient group had yet to be fully evaluated.

Patients were requested to report any noticeable change in hearing or balance to their treating physicians during their participation in the study. If changes were apparent and were considered to be sufficiently marked by the treating clinician, the patient was withdrawn from the study.

**Sample size calculation.** The original power calculations used to derive the sample size for the study were based on the use of the respiratory parameter forced expiratory volume at 1 s, in line with the primary therapeutic rationale of the TOPIC study. This returned a total figure of 220, with 110 patients to be included in each treatment arm of the study. Changes in pure tone audiometric threshold were included to provide a secondary toxicological end point in the study. Previous reports showed that the means and variance of PTA thresholds in CF patients not presenting with hearing loss appeared to be directly comparable to those of the audiometrically healthy non-CF population (18).

Depending on the frequency of testing, the repeat testing of standard PTA thresholds within individuals usually varies with a standard deviation of 5 to 10 dB (23). Depending on the type of ototrauma experienced by an individual and the degree of any preexisting hearing loss, a consistent increase in threshold at two or more frequencies of 10 dB or above could be considered clinically relevant

(16, 22, 23). Other studies have used a criterion for aminoglycoside-induced cochleotoxicity of increases in two or more PTA thresholds of at least 15 to 20 dB HL (8, 12, 14).

The standard deviation of repeated threshold measurement within individuals for high-frequency pure tone audiometry (HFPTA) is also reported to be about 5 to 10 dB sound pressure level (SPL) (11). Currently, there is no consensus on what changes in HFPTA thresholds are of clinical use.

Based on the numbers for audiometric testing obtained in this study, retrospective power calculations returned a value of at least 90% power to detect a 5-dB difference in standard PTA thresholds.

**Randomization to once- versus three-times-daily treatment.** Patients were randomly assigned to a once- or three-times-daily treatment arm by use of a computerized randomization program. A permuted block randomization schedule was used by the clinical trials pharmacist at Nottingham City Hospital (NCH) to blind the study coordinator and the patients to their treatment arms. Treatment allocation was stratified by center and age. Patients were grouped as adults or children aged 5 to 16 years, and the centers involved were those for either adult or pediatric patients. Each center had its own randomization schedule, with equal numbers in each treatment group used to avoid selection bias.

**Administration of treatment.** All patients received of a combination of intravenous ceftazidime and tobramycin as their antibiotic treatment for 10 to 14 days, with all patients receiving intravenous ceftazidime three times daily. Total daily doses equivalent to those previously received by patients (three times daily) during routine treatment were used. If a patient had not previously had tobramycin, then a dose of 10 mg/kg of body weight per day was prescribed.

**(i) Once-daily dosing.** Patients randomized to the once-daily tobramycin dosing schedule received three infusions every 24 h at intervals of 8 h. Only one contained the total daily dose combined with 0.9% sodium chloride solution. The remaining two infusions contained only 0.9% sodium chloride solution.

**(ii) Three-times-daily dosing.** Patients randomized to the three-times-daily tobramycin dosing schedule received three infusions administered every 24 h at intervals of 8 h. Each infusion contained a third of the total daily dose combined with 0.9% sodium chloride solution.

**Analysis sampling and adjustment of plasma tobramycin concentration.** Tobramycin concentrations were measured by fluorescent polarization immunoassays immediately before the fourth infusion and 30 min after the end of the fourth infusion (19). For patients on the once-daily regimen, the fourth infusion (on day 2) contained the second active dose; for those having three-times-daily treatment, this infusion contained the fourth active dose. The target concentrations of tobramycin for the once-daily regimen were 1 mg liter<sup>-1</sup> or less (trough) and 20 to 30 mg liter<sup>-1</sup> (peak). For the three-times-daily regimen, these values were 2 mg liter<sup>-1</sup> or less and 5 to 12 mg liter<sup>-1</sup>, respectively. If the trough concentration was higher than the target range, the patient was withdrawn from the study. If the peak concentration was outside the target range, a 10% increase or a 10% reduction in the dose was made, as appropriate.

**Audiological screening by questionnaire otoscopy and tympanometry.** Prior to the study, all patients were screened by questionnaire to exclude hearing loss attributable to prior aminoglycoside exposure or other possible causes. These included birth trauma; familial deafness; diseases implicated in hearing loss, e.g., meningitis; a history of chronic middle ear disease or ear surgery; concurrent or previous use of other known ototoxic agents, e.g., loop diuretics; a significant history of noise exposure; and nonorganic hearing loss (18). During the study, the concurrent medications that the patient took were also recorded, including those associated with reports of ototoxicity.

Prior to each audiometric test session all subjects underwent otoscopy to establish a patent ear canal and whether there was scarring/perforation of the tympanum. Tympanometry was then performed to establish normal middle ear function, as determined by the presence of a normal type A tympanogram (4).

**Standard PTA and HFPTA.** All patients entering the study underwent a standard PTA performed over 0.25 to 8 kHz with Kamplex KD-29 audiometers and TDH 39P headphones fitted with audiocups (P. C. Werth, Balham, United Kingdom). Care in headphone placement was taken to reduce the effects of suboptimal positioning on the subject's estimation of higher-frequency thresholds (4 to 8 kHz) in the standard PTA (10).

HFPTA was used to measure thresholds at 10, 12, 14, and 16 kHz by using ER-2 insert earphones (Etymotic Research). These were calibrated, according to the manufacturer's specification, with a Zwislocki coupler (DB 100; Etymotic Research). When driven with a 1-V root mean square signal, the ER-2 earphones generated 100 ± 2 dB SPL over 10 to 16 kHz within the coupler. Signals over 10 to 16 kHz, to a maximum of 1 V root mean square, were delivered by a function generator (TG 230; RS Components, Corby, United Kingdom) via the external input of the KD-29 audiometer. HFPTA was performed only with those patients participating at two centers: NCH and Birmingham Heartlands Hospital.

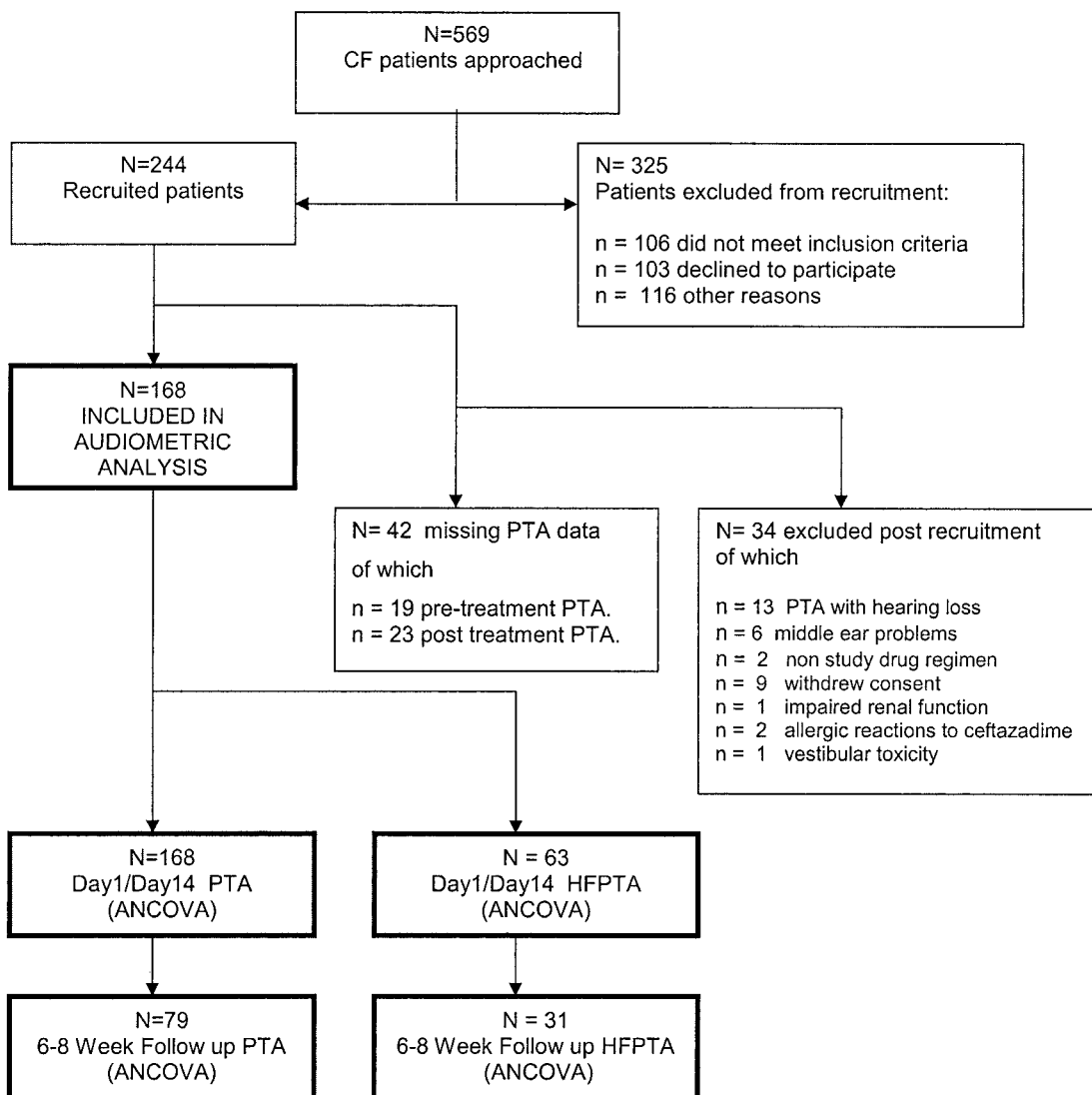


FIG. 1. Flow diagram summarizing the numbers of patients completing audiometric test procedures within the TOPIC study.

Prior to the beginning of the audiometry, the subjects were first familiarized with the test protocol. For both PTA and HFPTA, threshold values at each frequency were obtained to within 5 dB, according to a recognized protocol (1, 2). Testing was carried out in standard soundproof rooms of hospital audiology departments or in quiet rooms. These locations satisfied the criteria for ambient noise levels during audiometric testing (9). In cases of marked unilateral hearing loss, narrow-band masking noise was delivered to the contralateral ear (i.e., the threshold at a test frequency  $\geq 40$  dB above the threshold in the contralateral ear) (3).

PTA thresholds were measured before commencement of TOPIC medication administration and at the end of therapy. Similarly, HFPTA at NCH and Birmingham Heartlands Hospital was performed at these times. A subgroup of participants was assessed again at 6 weeks after the end of their course of treatment to see if there was any evidence of delayed cochleotoxic effects.

**Poststudy criteria of cochleotoxicity.** A clinical hearing deficit following testing was defined as a persistent increase in the PTA threshold above 20 dB HL in either ear at any two frequencies in the standard audiogram between 2 and 8 kHz (16, 22). Changes in hearing thresholds over 10 to 16 kHz were not considered primary evidence of aminoglycoside cochleotoxicity. They were, however, considered secondary experimental evidence of clinical cochleotoxicity.

**Statistical analysis.** All data was first entered and formatted in Microsoft Excel spreadsheets (version 2000), and formatted data sets were then entered into SPSS software (version 11). The assumption of normality for each frequency and time point was then checked and confirmed. Prior to the start of therapy, a baseline

comparison of the mean thresholds between the two treatment arms was carried out by the unpaired *t* test. After treatment, the paired Student *t* test was first used to see whether tobramycin therapy alone had any effect on auditory thresholds. More detailed multiple regression analysis was performed by using analysis of covariance (ANCOVA). The use of ANCOVA adjusts for any potential confounding effects of baseline variables which differed to any degree between the two treatment groups. In the ANCOVA model, the postthreshold dB HL value was specified as the outcome variable. Age and prethreshold dB HL values were specified as independent covariates. Sex and treatment were categorical and were specified as factors within the model. PTA thresholds for each frequency at 14 days and at 6 to 8 weeks after entry into the TOPIC study were then compared between those on the once-daily treatment regimen and those on three-times-daily treatment regimen. A *P* value  $<0.05$  was considered significant throughout.

## RESULTS

**Recruitment and exclusion.** Recruitment of patients into the TOPIC study was carried out in 21 CF centers across the United Kingdom. Figure 1 summarizes the flow of patients through the study who eventually went through to complete the audiometric measurement in this study.

Of the initial entry of 244 patients who began treatment within the TOPIC study, 168 had sufficiently complete sets of before-and-after standard PTA data for analysis. Of the original 244 entrants, 34 were excluded from this analysis. Most notably, 13 of these had evidence of clearly elevated PTA thresholds at the baseline. A further 19 did not attend their first PTA measurement. In this group, follow-up audiometry at day 14 returned unremarkable PTA thresholds. A further 23 patients did not attend their 14-day follow-up PTA. At the follow-up 6 to 8 weeks later, 79 patients attended for PTA assessment. HFPTA measurements were completed by 63 patients on study entry and on day 14. At the 6- to 8-week follow-up, 31 attended to complete assessment of their HFPTA thresholds.

**Tobramycin dosing and plasma tobramycin concentrations attained in the once- and three-times-daily treatment groups.** Data on the dose/kg were obtained for a total of 137 (87%) patients who had completed two audiograms, performed at enrollment and on day 14. Of these 137 patients, 70 received tobramycin once daily and 67 received tobramycin three times daily.

The total daily doses received by the two groups were found to be directly comparable. The mean  $\pm$  standard deviation (SD) dose for those receiving tobramycin once daily was  $9.4 \pm 1.8$  mg kg<sup>-1</sup>, and that for those receiving tobramycin three times daily was  $3.1 \pm 0.6$  mg kg<sup>-1</sup>. When each mean  $\pm$  SD dose was summed for the three-times-daily group, the total daily dose came to  $9.3 \pm 1.7$  mg kg<sup>-1</sup>, which was not significantly different from the mean daily dose for the once-daily group.

As reported previously (24), detailed pharmacokinetic modeling was performed for 108 patients who completed treatment according to the protocol for 51 patients in the once-daily group and 57 patients in the three-times-daily group. The mean  $\pm$  SD peak tobramycin concentration for the once- and three-times-daily treatments were  $28.4 \pm 5.07$  mg liter<sup>-1</sup> and  $9.9 \pm 1.4$  mg liter<sup>-1</sup>, respectively.

**Effects of once- versus three-times-daily tobramycin on PTA thresholds at day 14.** PTAs were completed before and after treatment for 168 patients; 95/168 patients (57%) were male and 83/168 patients (49%) received the once-daily treatment; The 168 patients comprised 66 adult patients and 102 pediatric patients. The paired *t* test comparison of PTA thresholds before and after treatment returned no evidence of any significant increases in threshold due to tobramycin therapy alone.

Before the commencement of treatment, comparison of the baseline mean PTA thresholds by unpaired *t* tests between the once- and the three-times-daily treatment groups revealed no significant differences across all frequencies. Baseline PTA thresholds in both treatment arms over 1 to 8 kHz fell between 4 and 8 dB HL. Mean thresholds at the lower frequencies of 0.25 to 0.5 kHz were slightly higher at 10 to 13 dB HL.

Following therapy, there was no evidence of differences in PTA thresholds with once- or three-times-daily dosing. Over both ears, the values for differences in treatment regimen returned by ANCOVA did not reveal any marked difference between posttreatment PTA thresholds at day 14. Figure 2 illustrates the clinically unremarkable threshold means obtained for each treatment arm in both ears after treatment. The PTA thresholds for both treatment arms at day 14 over 1 to 8 kHz were between 4 and 8 dB HL. Over the lower fre-

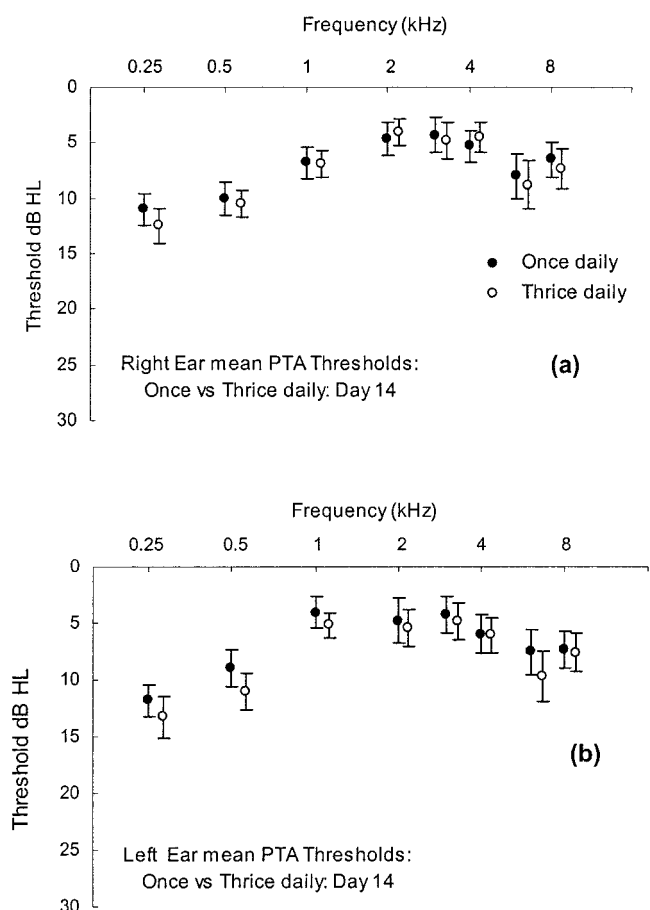


FIG. 2. Standard PTA threshold means  $\pm$  95% confidence intervals on day 14 for the (a) right and (b) left ears ( $n = 168$ ) for once-versus three-times-daily treatments. Across all frequencies, these were found to be directly comparable to each other. No changes between these values and standard PTA thresholds on entry at day 1 were apparent when they were analyzed by ANCOVA.

quencies of 0.25 to 0.5 kHz, the mean thresholds were slightly higher at 10 to 13 dB HL. At all frequencies, the means for each treatment arm were directly comparable to those obtained at the baseline. There were no clinically or statistically significant differences between those receiving treatment once and those receiving treatment three times daily for both ears, with or without adjustment for baseline thresholds, age, and sex.

**Effects of once- versus three-times-daily tobramycin on PTA thresholds 6 to 8 weeks after treatment.** Of the 79 patients who returned to complete their 6- to 8-week follow-up audiometry, 41/79 were male (51%) and 43/79 (54%) were treated with the once-daily regimen. At the follow-up at 6 to 8 weeks, this group divided into 33 adult patients and 46 pediatric patients.

The analysis performed on the PTA thresholds at 6 to 8 weeks posttreatment returned results largely comparable to those obtained at the end of TOPIC study therapy on day 14. PTA thresholds at 6 to 8 weeks in both treatment arms were again found to be directly comparable to each other, falling over the threshold range described above. Figure 3 shows the



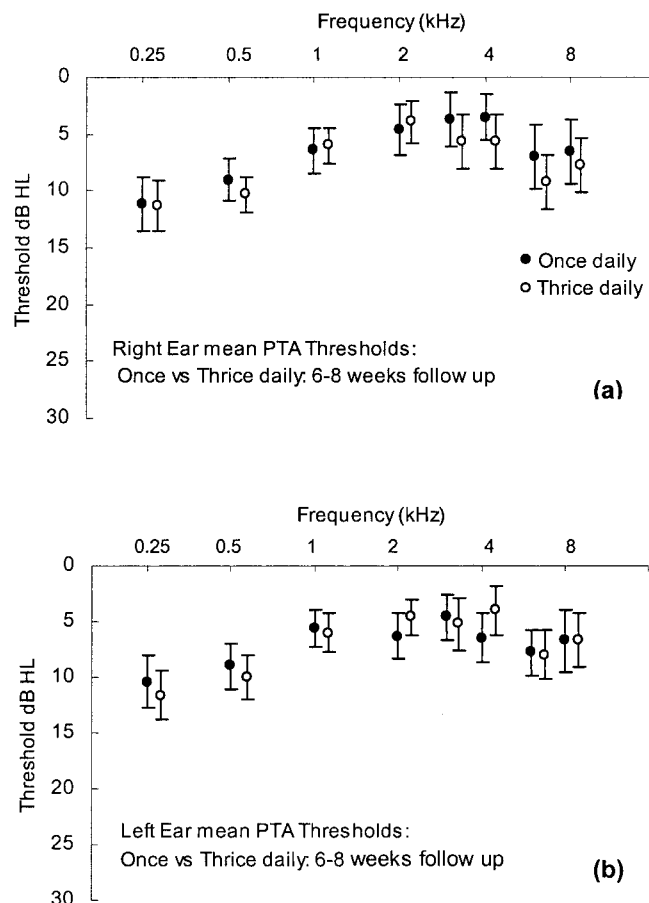


FIG. 3. Standard PTA threshold means  $\pm$  95% confidence intervals for once- versus three-times-daily treatments at 6 to 8 weeks after entry into TOPIC for (a) right and (b) left ears ( $n = 79$ ). No difference in treatment means were evident at 6 to 8 weeks and day 1 when they were analyzed by ANCOVA.

threshold means for both treatments measured at 6 to 8 weeks in both ears.

**Effects of once- versus three-times-daily tobramycin on HFPTA thresholds on day 14.** The potential numbers of patients able to be assessed by HFPTA was limited to the two main recruitment centers. A total of 63 patients completed the pre- and posttreatment testing, with 34/63 (54%) of these patients being males and 33/63 (52%) patients having received the once-daily treatment. In contrast to the proportion of adult patients to pediatric patients performing standard PTA, adult participants predominated, with 43 being adult patients and 20 being pediatric patients.

As for the PTA thresholds before the start of treatment, comparison of the baseline HFPTA thresholds between the once- and three-times-daily treatment groups revealed no significant differences at the four HFPTA frequencies. Unlike standard PTA thresholds, HFPTA thresholds are expressed in dB SPL and increase with increasing frequency. The mean baseline thresholds in both treatment groups fell between 25 and 75 dB SPL over 10 to 16 kHz.

Comparison of the day 1 and day 14 HFPTA thresholds by paired *t* test showed that tobramycin therapy alone did not

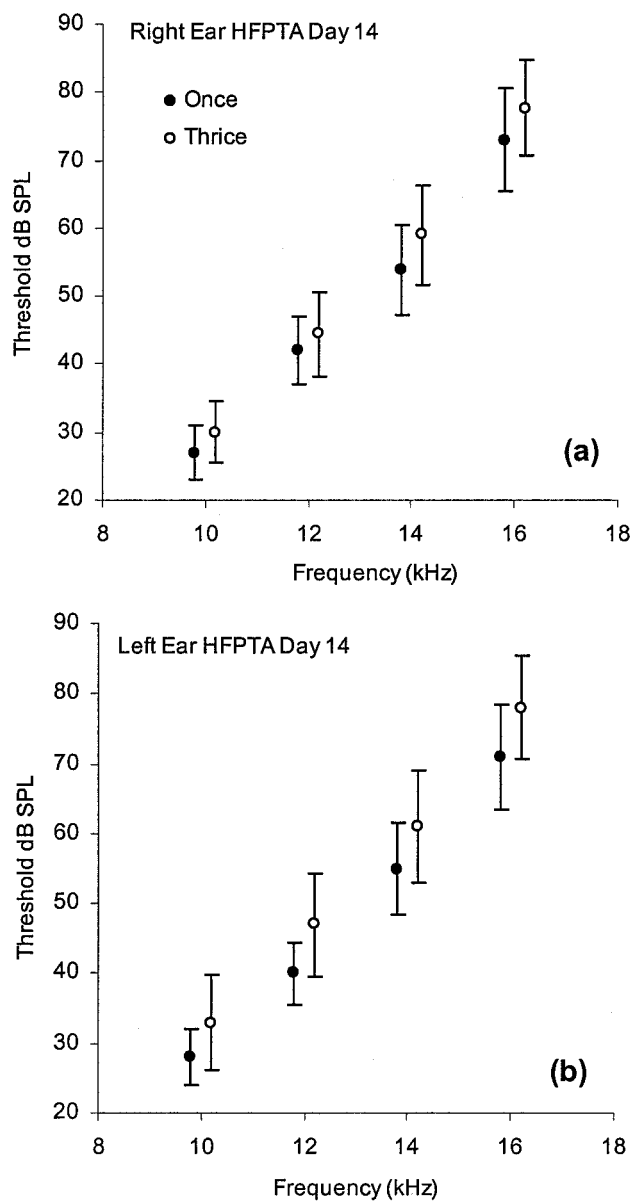


FIG. 4. HFPTA threshold means in dB SPL  $\pm$  95% confidence intervals for once- and three-times-daily treatments on day 14 after entry into TOPIC for the (a) right and (b) left ears ( $n = 63$ ). There were no differences between the HFPTA means at day 14 and on entry day 1 when they were analyzed by ANCOVA.

result in any significant threshold elevation at day 14. The mean thresholds at day 14 in both treatment groups fell between 25 and 75 dB SPL over 10 to 16 kHz. Comparison of the once- versus three-times-daily HFPTA day 14 thresholds, as shown in Fig. 4, did show some evidence of an apparent trend in small differences in the mean thresholds between the once- and the three-times-daily treatment groups at all frequencies ranging from 3 to 7 dB. However, analysis by ANCOVA at day 14 did not return any significant difference between groups for both ears and at all frequencies.

**Effects of once- versus three-times-daily tobramycin on HFPTA thresholds 6 to 8 weeks after treatment.** The total

numbers of patients who completed HFPTA measurement at 6 to 8 weeks after treatment had reduced further to 31. Of these, 18/31 (58%) were male and 18/31 (58%) had received the once-daily treatment. The numbers of adult and pediatric patients completing the follow-up evaluation were 22 and 9, respectively. Based on the results for these 31 patients, there was no evidence by paired *t* test that tobramycin therapy alone resulted in any longer-term change in HFPTA thresholds.

Even with the reduced number of patients, there was still some evidence of a trend, shown in Fig. 5, of slightly increased thresholds between 4 and 9 dB in the three-times-daily treatment group compared to that in the once-daily treatment group. This was seen over 12 to 16 kHz in the right ear, but the trend was no longer apparent in the left ear by HFPTA. Again, by ANCOVA there was no evidence of any significant changes in the mean HFPTA threshold values in either ear from the baseline to 6 to 8 weeks after treatment for either treatment group.

**Concurrent medication associated with reports of ototoxicity.** Apart from the aminoglycosides, which present the primary risk of ototoxicity in the treatment of CF patients, a number of other drugs that are used to treat CF patients have been associated with reports of ototoxicity. In this study, the concurrent treatments included the macrolide azithromycin (6), the nonsteroidals ibuprofen and naproxen (6), and the polymyxin colistin (13). Two patients, one in each treatment arm, received azithromycin. Seven patients received nonsteroidal therapy orally; this consisted of ibuprofen in six cases and naproxen in one case. By chance, six of these patients, including the one taking naproxen, were in the once-daily arm. These were prescribed only at the lower doses for analgesia and were not prescribed at the higher doses normally used to slow the decline in lung function in these patients (15). The audiograms of these patients were unremarkable.

As a constituent in otic preparations, colistin has been shown to be associated with a risk of ototoxicity (17). In this study, only nebulized colistin was prescribed concurrently in 79 patients (38 in the once-daily arm and 41 in the three-times-daily arm). There is no evidence in the literature that nebulized colistin is associated with ototoxicity (13, 27).

## DISCUSSION

Overall, the results of this study comprehensively describe the absence of acute and medium-term cochleotoxicity in CF patients with no preexisting hearing loss entered into the TOPIC study. This is as judged by the use of both standard and high-frequency pure tone audiometry. These results show that there is no evidence that tobramycin therapy alone results in threshold elevation. Neither was any difference apparent across all thresholds between the once- and three-times-daily dosing groups. This was apparent at day 14 and at the follow-up 6 to 8 weeks later. This absence of a significant difference between dosing regimens was also apparent, albeit with a smaller sample size in those patients who underwent HFPTA.

The interest in whether once-daily dosing is as efficacious and safe as a three-times-daily dosing regimen is common to all patient groups receiving tobramycin. In contrast to most previous studies, the TOPIC study was designed to answer these questions by use of a large, single, well-defined patient group. With regard to safety, this component of the TOPIC study with

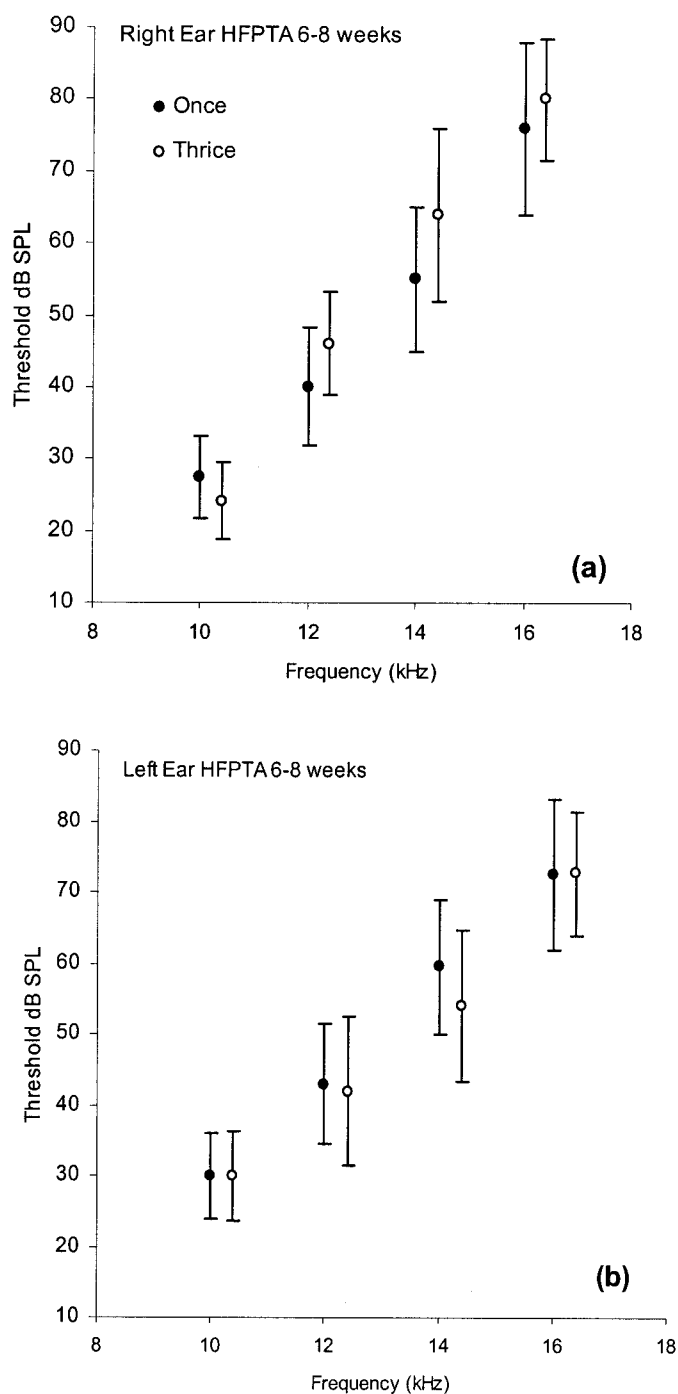


FIG. 5. HFPTA threshold means in dB SPL  $\pm$  95% confidence intervals for once- versus three-times-daily administration at 6 to 8 weeks after TOPIC entry for the (a) right and (b) left ears ( $n = 31$ ). There were no differences between treatment means at 6 to 8 weeks and day 1 when they were analyzed by ANCOVA.

the numbers of patients recruited also allowed greater resolution of any subclinical cochleotoxic effect. Analysis for signs of any significant subclinical effect does not appear to have been performed in many previous clinical studies of aminoglycoside cochleotoxicity (8, 12).

The important issue of the incidence of cochleotoxicity arising from cumulative exposure was not addressed directly by this part of the TOPIC study. Inclusion of those patients with preexisting hearing loss raised ethical issues about a possible increase in hearing deficit subsequent to the completion of therapy within the TOPIC study. This was a serious consideration in those with already marked hearing loss. This arose with 13 patients who initially entered the TOPIC study, but after completion of the baseline audiogram they were withdrawn. These patients were sent for independent confirmation of suspected iatrogenic hearing loss by an ear-nose-throat specialist. Following confirmation, their treating clinician made further decisions about the treatment of their pulmonary exacerbation outside of the TOPIC study. These patients were then included in an additional study investigating the cumulative risk of aminoglycoside cochleotoxicity in CF patients.

The findings of this investigation of the incidence of cochleotoxicity judged by the standard PTA in CF patients are in contrast to those of previous reports with non-CF patient groups. In these groups, it appears that the median incidence of clinically recognized cochleotoxicity following a single course of tobramycin treatment (typically three times daily) is 7.5% (8, 12, 14). Moreover, these groups also require a lower dose of aminoglycoside therapy of a shorter duration than that required for the treatment of pulmonary exacerbations in CF patients. In non-CF patients groups, this typically amounts to 3 to 8 mg/kg/day for 7 to 10 days (8, 12, 14). This is in contrast to a typical course for pulmonary exacerbation in CF patients of 10 mg/kg/day over 14 days (24, 26). These data show that in comparison with non-CF patient groups, the per-course exposure to tobramycin is greater by a factor of between 2 and 4. The results presented here are in line with those of previous reports of lower-than-expected acute and chronic cochleotoxicity in CF patients (18, 20). The observations reported here may be explained either by the more rapid clearance of aminoglycosides in CF or, possibly, by the fact that the CF condition actually confers some protection against aminoglycoside-induced cochleotoxicity (18).

In summary, the relevance of the results presented here to clinical practice is that for a single course of tobramycin, there is no difference between once- and three-times-daily dosing in terms of the incidence of cochleotoxicity. While the study findings provide positive support for a change to a practically simpler once-daily dosing regimen with tobramycin, it does not cover assessment of the incidence or the risk of cochleotoxicity with repeated therapy in CF patients. This would require further long-term audiometric follow-up in this patient group.

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