Pediatr Nephrol (1993) 7: 178–181

Pediatric Nephrology

Original article

Aminoglycoside ototoxicity in pediatric patients receiving long-term peritoneal dialysis

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Received May 28, 1992; received in revised form and accepted October 13, 1992

Abstract. We evaluated 14 children on long-term peritoneal dialysis for ototoxicity associated with aminoglycoside (AG) therapy. Baseline evaluation of all patients and 7 controls included pure-tone audiometry (PTA) and click-evoked auditory brain stem response (ABR). Nine patients had repeat PTA and ABR evaluations and vestibular testing 1 year after study entry. Five patients had an additional assessment following intraperitoneal AG therapy. The baseline auditory function of the patients was significantly poorer than controls at 6.0 and 8.0 kHz by PTA ($P < 0.05$), whereas the results of ABR testing were not different. Of the 14 patients, 4 (28%) had hearing loss, 3 of whom had a history of intravenous AG therapy. In contrast, none of the patients who received intraperitoneal AG therapy only, or without a history of AG therapy, had hearing loss ($P < 0.005$). There was no evidence of progressive loss of hearing acuity with time or associated with intraperitoneal AG therapy. One patient had findings of vestibular dysfunction. We conclude that children receiving peritoneal dialysis are at risk of AG ototoxicity. While intraperitoneal administration of AG may be associated with less ototoxicity than intravenous administration, further study is necessary to verify this finding and close monitoring of AG levels remains mandatory irrespective of the route of administration. PTA rather than click-evoked ABR appears to be the best indicator of abnormal hearing acuity in this population.

Key words: Aminoglycoside – Peritoneal dialysis – Ototoxicity – Vestibular – Pure-tone audiometry – Auditory brain stem response

Introduction

Ototoxicity is defined as the tendency of certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner ear, in particular the end organs and neurons of the cochlear and vestibular divisions of the eighth cranial nerve [1]. The aminoglycoside (AG) antibiotics are a class of antibiotics active against gram-negative organisms and are known to have significant ototoxic potential. Studies by Jackson and Arcieri [2] have clearly demonstrated that the most dramatic potentiator of the ototoxic effects of AG is renal insufficiency. In patients receiving long-term peritoneal dialysis, the ease of administering AG therapy by the intraperitoneal route has made it a common practice in patients who require antibiotic therapy for the treatment of peritonitis or other systemic infections. While this approach to therapy produces a fairly constant plasma concentration of the AG, little information exists on the ototoxic potential of such therapy in adults or children [3, 4]. The present study was designed to evaluate children receiving long-term peritoneal dialysis for the presence of AG ototoxicity.

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Patients and methods

Fourteen patients aged 8.9 ± 4.0 years (range 3.3–16.7 years) undergoing automated peritoneal dialysis for 17.3 ± 15.1 months (range 1.0–43.0 months) were enrolled in the study. Seven pediatric patients without medical illness served as controls. The study was approved by the Institutional Review Board and informed consent was obtained in each case.

Upon entry into the study, historical information pertaining to AG usage was obtained for each patient from a review of their medical record. The hearing sensitivity of each subject was evaluated by conventional pure-tone audiometry (PTA) and the click-evoked auditory brain stem response (ABR) test. Hearing thresholds were determined over a range of frequencies from 250 to 8,000 Hz. We considered as evidence of acquired auditory toxicity an increase in the auditory threshold of 15 dB or more at any two frequencies or 20 dB at one or more frequencies when compared with the patient's baseline audiogram. The diagnosis of hearing loss upon entry into the study was based on a comparison of the patient's baseline audiogram and the audiogram of the control patients. The following criteria were used in characterizing audiometric losses [5]: 15–25 dB, not significant; 26–40 dB, slight loss; 41–55 dB, mild loss; 56–70 dB, marked loss; 71–90 dB, severe loss. The parameters studied with the ABR test were the wave V latency-intensity function and the interpeak latencies of wave intervals I–III, III–V, and I–V as measured

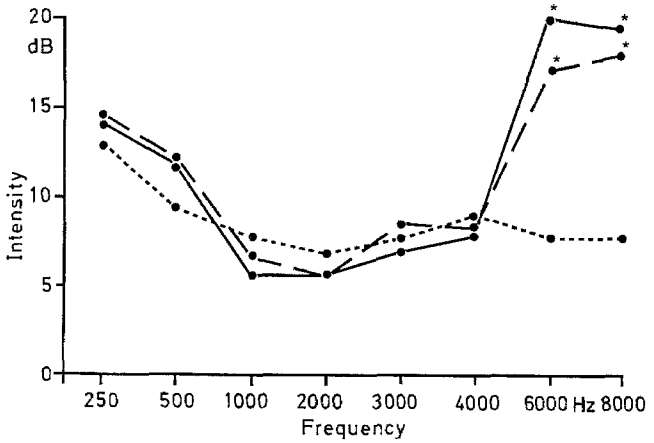

Fig. 1. Pure-tone hearing thresholds (0.25–8.0 kHz) of dialysis patients at study entry (——— ———), patients at 1-year evaluation (———), and of controls (– – – –). * $P \leq 0.05$ patients vs. controls

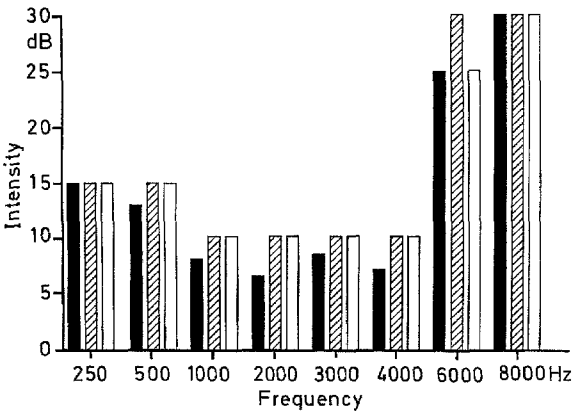

Fig. 2. Pure-tone hearing thresholds of patients who received intraperitoneal aminoglycoside therapy at initiation of therapy (■), at completion of therapy (▨), and 4–6 weeks later (□)

in milliseconds at 80 dBnHL (decibel normed hearing level) and recorded for each ear.

All 14 patients received baseline PTA and ABR evaluations. Five patients subsequently received kidney transplants and were removed from the study. The remaining 9 patients completed the entire study and had PTA and ABR evaluations repeated 1 year after entry into the study. Patients and controls also had tympanograms performed prior to each PTA evaluation to assess for possible conduction abnormalities. Abnormal tympanograms were followed by postponement of the PTA until the conduction abnormalities were corrected.

Of the 9 patients who completed the entire study, 5 had an additional PTA and ABR evaluation performed at the time of intraperitoneal AG therapy. The evaluations were conducted within 48 h of initiating therapy (baseline), within 48 h of completing therapy, and 4–6 weeks later (post therapy). In 4 of the cases, therapy with intraperitoneal tobramycin was designed to maintain a steady-state serum drug level of 4–6 μg/ml).

The vestibular function of the 9 patients who completed the entire study was evaluated 1 year after entry into the study using dynamic posturography (Neurocom Equitest, Clackamas, Ore., USA) and compared with control data. Movement coordination and the relative contributions of vision, proprioception, and vestibular sense to the ability to maintain postural control were assessed.

Chi-squared analysis with Yates' correction for small samples was used to determine the significance of the association between intravenous AG usage and abnormal hearing acuity. Analysis of variance and covariance with repeated measures and the Newman-Keuls multiple comparison tests were used to determine levels of significance among test variables. In each case, the results obtained from testing of the right and left ear were combined and averaged. Data are presented as mean ± SD and significance was accepted at the $P < 0.05$ level.

Results

The mean pure-tone thresholds at 6,000 Hz and 8,000 Hz, respectively for all 14 patients upon entrance to the study (18.0 ± 12.0 dB and 20.5 ± 20.2 dB) and for the 9 patients who completed the entire study, at baseline (17.2 ± 5.3 dB and 18.1 ± 11.8 dB) and at 1 year after study entry (20.0 ± 16.6 dB and 19.4 ± 18.0 dB) were significantly different from the thresholds of the control population (7.8 ± 4.7 dB and 7.8 ± 5.1 dB, $P < 0.05$) (Fig. 1). The differences in the mean pure-tone thresholds at 6,000 and 8,000 Hz between the larger and smaller patient groups were not significant. Of the 14 patients, 4 (28%) demonstrated abnormal pure-tone thresholds.

The severity of the hearing loss at 6,000 Hz was characterized as not significant in 3 of the patients and slight in 1. At 8,000 Hz, the hearing loss was slight in 3 patients and mild in 1 patient. In no case was the hearing loss clinically evident to the patient. In addition, there was no evidence of progressive hearing loss when evaluated by PTA, as the patient's mean pure-tone threshold values at all frequencies obtained at baseline and at 1 year were not significantly different and no additional patients developed evidence of abnormal hearing acuity.

Vestibular testing revealed normal performance in 8 of the 9 patients when compared with controls. One child, with a history of the hemolytic uremic syndrome and a cerebral vascular accident, demonstrated evidence of mild peripheral vestibular dysfunction. There were no significant differences noted between the ABR testing of the patients and controls when the results of the two groups were compared at baseline and at the follow-up assessment (Table 1).

Five patients received intraperitoneal AG therapy during the initial year of the study. Four cases of peritonitis and one case of pyelonephritis were treated with four courses of tobramycin and one course of kanamycin. The mean steady-state serum concentration of tobramycin was 4.2 ± 0.3 μg/ml with a dose of 8.3 ± 0.5 mg/l. The mean intraperitoneal dose of kanamycin and the steady-state serum drug level were 15 mg/l and 6.5 μg/ml, respectively. No significant differences were noted between the individual and group mean pure-tone threshold values obtained at baseline and following therapy (Fig. 2). In addition, there was no significant change noted in ABR testing in association with intraperitoneal AG therapy.

Finally, 4 of the 5 patients who received intravenous AG therapy prior to initiating dialysis therapy, with or without the subsequent use of intraperitoneal and/or intramuscular therapy, demonstrated hearing loss. Three of these 4 patients received two courses of intravenous gentamicin each, while 1 patient had received four courses of intravenous gentamicin and four courses of intravenous

Table 1. Brain stem auditory evoked responses of pediatric dialysis patients and controls

	I–III interval (ms)	I–V interval (ms)	III–V interval (ms)	Wave V				
				80 (dB)	70 (dB)	60 (dB)	50 (dB)	40 (dB)
Baseline								
Patients ($n = 14$)	2.2±0.2	3.9±0.3	1.7±0.2	5.8±0.2	5.9±0.3	6.2±0.2	6.5±0.3	6.9±0.5
Controls ($n = 7$)	2.1±0.2	3.9±0.2	1.9±0.2	5.6±0.1	5.9±0.2	6.2±0.3	6.5±0.3	6.9±0.3
Follow-up								
Patients ($n = 9$)	2.1±0.2	4.0±0.2	1.9±0.2	5.8±0.3	6.0±0.3	6.3±0.2	6.7±0.3	7.1±0.3

tobramycin. In contrast, none of the patients who received intraperitoneal AG therapy only (4 patients), or who had no history of AG therapy (5 patients), had impaired hearing acuity ($P < 0.005$). There was no significant correlation noted between the presence or severity of the hearing loss and either the plasma AG levels or the total dosage of AG as determined by chart review.

In 3 of the patients with hearing loss, there was a history of exposure to an additional ototoxic drug. Two patients received two 10-day courses each of intravenous vancomycin, 1 of whom also received a course of intravenous furosemide. The third patient had three courses of intravenous vincristine as part of a chemotherapeutic regimen for Wilms' tumor. Two of the patients with normal hearing and a history of intraperitoneal AG therapy received a single 10-day course of intravenous vancomycin.

Discussion

Ototoxicity is a potential complication of AG antibiotic usage and may affect both the auditory and the vestibular functions of the ear [1, 2, 5–9]. Laboratory detectable cochlear toxicity associated with gentamicin and tobramycin usage occurs in 3%–41% of patients [10]. Vestibular dysfunction probably occurs as commonly or more commonly than cochlear dysfunction and may manifest itself as dizziness, vertigo, or ataxia [5, 9].

Previous studies have suggested that factors which increase the risk of AG-related ototoxicity include: concomitant ototoxic drug use, increased duration of AG therapy and increased dosage of the AG, elevated plasma AG levels, advanced age, and noise exposure [11–16]. However, Jackson and Arcieri [2] and others have found that ototoxicity occurred with the greatest frequency in the presence of impaired renal function. While the exact mechanism of ototoxicity is not known, it has been suggested that it may be largely dependent on the AG levels present in the fluids of the inner ear, the perilymph and endolymph [5, 9]. These fluids are in direct contact with the vestibular and cochlear sensory hair cells. Animal studies have demonstrated rapid elimination of the perilymphatic AG with normal kidney function, while anephric animals maintain inner ear fluid AG concentrations at a higher level for a prolonged period of time [17, 18]. This may, in turn, alter the ionic concentration of the fluids predisposing to damage to the sensory hair cells.

Very little information exists on the audiovestibular function of the patient receiving long-term peritoneal dialysis [3, 4, 19]. It has been suggested that the use of intraperitoneal gentamicin and tobramycin, with a resultant constant plasma AG concentration, may be particularly risky in terms of the development of ototoxicity. While elevated peak and trough AG levels have variably been associated with ototoxicity, it has also been suggested that a closer correlation may exist between total exposure (the "area under the curve") and ototoxicity, making the continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis population particularly susceptible.

Nikolaidis et al. [3] recently studied 40 adult CAPD patients who received intraperitoneal tobramycin and were unable to demonstrate a consistent pattern of ototoxicity. While ototoxicity was diagnosed by PTA in 25% of the patients following treatment, hearing was inexplicably improved in 7 other patients. Chong et al. [19] described four cases of severe vestibular toxicity occurring in adult peritoneal dialysis patients treated with intraperitoneal gentamicin. Unfortunately, gentamicin levels were not followed closely in any of the patients.

In the only other pediatric study, Salmon and Arant [4] studied 25 children on dialysis and found that 7 (28%) had evidence of a neurosensory hearing loss when evaluated with PTA. In 6 of these 7 patients, there was a history of prior intravenous AG usage. The lack of follow-up testing in this study prevented any "long-term" assessment of the audiovestibular function and its relationship to intraperitoneal AG therapy.

Our study confirms the results of Salmon and Arant [4] that children with renal insufficiency are at risk of developing hearing loss, especially in the high frequency range. The baseline evaluation of our patients revealed significantly poorer auditory function at 6,000 Hz and 8,000 Hz when compared with the control population. High frequency hearing loss is characteristic of AG toxicity and is detectable audiometrically well before it involves the speech frequency range (e.g., 250–3,000 Hz) in which the abnormality can be detected by the patient. We also found, as did Salmon and Arant [4], that the majority of our

patients with evidence of neurosensory hearing loss had a history of intravenous AG therapy. This finding emphasizes the necessity of closely monitoring AG therapy in patients with preexisting renal insufficiency.

Acknowledging the limitations of our small sample size, none of our patients had evidence of a progressive high frequency hearing loss. In addition, and in contrast to the experience with intravenous therapy, in no case was intraperitoneal AG therapy alone associated with ototoxicity when evaluated with PTA and ABR. It should be noted that various drugs, when used in combination with AG therapy, can contribute to the development of ototoxicity in the dialysis population [8, 20]. Three of our patients with impaired hearing acuity had a history of exposure to an additional ototoxic drug. While these medications were given separate from AG, each may have adversely influenced hearing acuity.

Our assessment of vestibular function revealed that only 1 of the 4 patients with evidence of auditory abnormalities had an abnormal vestibular evaluation. In this patient, the history of a cerebral vascular accident makes it unlikely that the abnormal vestibular function was related to AG usage alone.

It is of interest that, despite the suggestion that ABR testing may improve the detection of AG ototoxicity, no abnormalities were noted by ABR in our patients [21]. This was most likely due to the fact that the click-evoked ABR primarily tests the frequency range between 2,000 and 4,000 Hz, frequencies which were outside the range in which abnormalities were detected during our evaluation.

On the surface, our study suggests that the hearing loss present in this population is not progressive and that intraperitoneal AG therapy, when closely monitored with serum drug levels, does not contribute to auditory or vestibular toxicity. However, it must be recognized that a far greater number of patients must be studied before such a conclusion can be reached and that close monitoring of AG therapy in the dialysis population remains mandatory. Future evaluations should use techniques such as ultra-high frequency pure-tone testing in the 10,000- to 16,000-Hz range as a means of detecting very early or subtle changes in hearing acuity. Only with the use of such investigative methods can we determine the most effective and least toxic approach to AG therapy in pediatric patients receiving long-term peritoneal dialysis [22].

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