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Gentamicin-induced ototoxicity in hemodialysis patients is ameliorated by *N*-acetylcysteine

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Aminoglycoside (AG) antibiotics are associated with several side effects, including a reversible nephrotoxicity and a permanent ototoxicity. Oxidative stress is thought to contribute to the pathophysiology of both conditions. We studied the possible protective effect of the antioxidant *N*-acetylcysteine (NAC) in gentamicin-induced hearing loss in hemodialysis patients. This study includes 53 hemodialysis patients scheduled to receive gentamicin for dialysis catheter-related bacteremia that were randomized to receive the antibiotic with or without NAC. Hearing function was assessed by the standard technique of pure-tone audiograms over a range of frequencies. Audiometric evaluations were performed at baseline, 1 week and at 6 weeks after the completion of gentamicin therapy. A total of 40 patients completed the study protocol with a mean duration of therapy of almost 15 days. At both 1 and 6 weeks after the completion of antibiotic therapy, there were significantly more patients exhibiting ototoxicity in the control group compared with the group receiving NAC. Additionally, significantly more patients in the control group had bilateral ototoxicity. The greatest otoprotective effect of NAC was noticed in the high audiometric tone frequencies. Taken together, our study suggests that NAC treatment may ameliorate gentamicin-induced ototoxicity in hemodialysis patients.

Kidney International (2007) **72,** 359–363; doi:10.1038/sj.ki.5002295; published online 25 April 2007

KEYWORDS: hemodialysis; gentamicin; *N*-acetylcysteine; ototoxicity

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Received 16 December 2006; revised 21 February 2007; accepted 8 March 2007; published online 25 April 2007

Aminoglycoside (AG) antibiotics are important drugs in the treatment of several life-threatening infections, especially those caused by Gram-negative bacteria.[1] Sixty years after their introduction, AGs remain the drugs of choice in many circumstances, including bacterial endocarditis, peritonitis, and line sepsis.[1] Unfortunately, AGs are associated with several side effects, including nephrotoxicity and ototoxicity.[2] The renal toxicity is generally reversible, whereas the damage to the cochlear and the vestibular systems may lead to permanent loss of hearing and balance, respectively.[3]

The prevalence of AG-induced ototoxicity is 3–25%.[4] However, when high-frequency audiograms were performed, the prevalence was as high as 62%.[5] Hemodialysis patients are a special vulnerable group, frequently requiring AG therapy due to vascular access infection or line sepsis. Because 99% of AG is excreted by the kidneys, patients with end-stage renal disease (ESRD) have increased risk of AG ototoxicity.[6] Several measures have been proposed to prevent AG ototoxicity, including monitoring of plasma blood levels with subsequent dose adjustment, once-daily dosing schedule, or shortening duration of therapy if clinically appropriate.[1,7,8] Unfortunately, none of these measures have proved to be effective.[7,8]

The most promising hypothesis, explaining AG ototoxicity, is based on reactive oxygen species damage to the inner ear.[9] In animal studies, co-administration of antioxidant therapy ameliorated AG ototoxicity.[10] Recently, Sha *et al.*[11] have demonstrated that aspirin may have a protective effect against AG-induced ototoxicity. *N*-acetylcysteine (NAC), a thiol-containing antioxidant, has been used successfully to ameliorate the toxic effects of a variety of substances on liver, heart, kidney, and lung.[12–15] NAC may prevent hearing loss associated with bacterial meningitis[16] and auditory hair cell damage from cisplatin.[17] NAC can also ameliorate gentamicin-induced nephrotoxicity.[18] The aim of this study was to evaluate the protective effect of NAC against gentamicin-induced ototoxicity in ESRD patients treated with hemodialysis.

RESULTS

Fifty-three patients were enrolled in the study and underwent baseline otologic examination (Figure 1). Twenty-six patients were in the NAC-treated group and 27 in the control group. Thirteen patients did not complete the study protocol: one

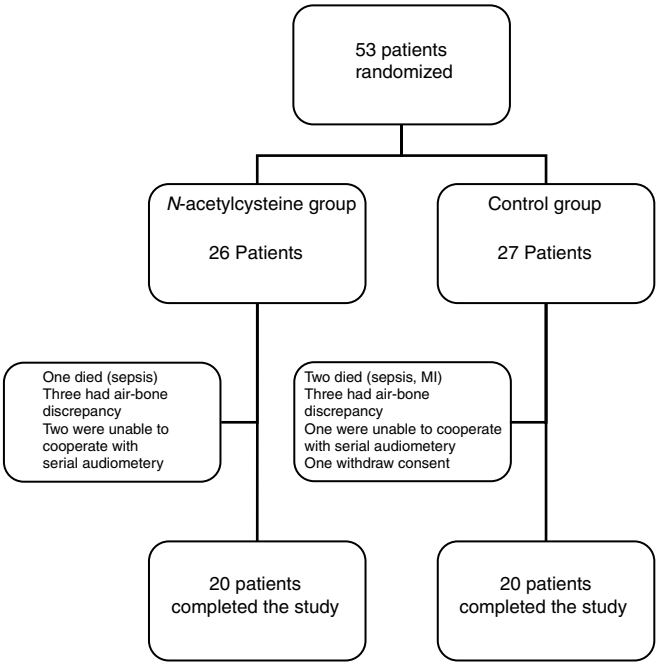

Figure 1 | Study design.

patient in each group died from sepsis; one patient from control group died from acute coronary event; six patients had an air-bone difference >10 dB; three were unable to cooperate with serial audiograms; and one withdrew his consent. Forty patients completed the study protocol, 20 patients in each group. There was no statistically significant difference between the groups in any of the baseline patients' clinical characteristics, as well as in the baseline hearing threshold levels on audiometric examination (Table 1). All uncuffed catheters had been removed immediately in case of suspected line-related bacteremia.

The characteristics of the present gentamicin course were similar in both groups (Table 1). Mean duration of therapy with gentamicin was 14.75±3.82 days in the NAC-treated group and 14.28±5.76 days in the control group ($P=0.76$). The cumulative gentamicin dose was 675.5±242.02 mg in the NAC-treated group and 694.5±249.02 mg in the control group ($P=0.81$). The cumulative dose corrected for patients' weight was 9.78±3.55 mg/kg in the NAC-treated group and 9.6±4.11 mg/kg in the control group ($P=0.88$). Mean predialysis blood level of gentamicin was 3.02±0.62 mcg/ml in the NAC group and 2.87±0.64 mcg/ml in the control group ($P=0.46$). Clinical effect of antibiotic therapy did not differ between the groups. There were no side effects that could be related to NAC therapy during the follow-up period.

The results of the otologic evaluation are summarized in Table 2. During the study period, ototoxicity developed in 12 patients (60%) from the control group and in five patients (25%) from the NAC group; 41.6% risk reduction ($P=0.025$). At the early follow-up examination (7±3 days after completing gentamicin therapy), 11 patients (55%) in the control group and four patients (20%) in the NAC group fulfilled the ototoxicity criteria ($P=0.022$). At the late follow-up examination (42±3 days after completing gentamicin therapy), 11 patients (55%) in the control group and two patients (10%) in the NAC group still fulfilled the ototoxicity criteria ($P=0.002$). One patient (5%) from the NAC group and six patients (30%) from the control group had bilateral ototoxicity ($P=0.037$).

The maximal change in hearing threshold in the control group, as well as the most significant benefit in the NAC group, were noticed in the high audiometric frequencies, PTA-3 (Table 2, Figure 2). The mean change in PTA-3 at early follow-up was 5.83±5.14 dB in the control group and 2.00±3.8 dB in the NAC-treated group ($P=0.011$). The

Table 1 | Patients characteristics

	N-acetylcysteine (n=20)	Control (n=20)	P-value
Age (years)	65.8±12.5	59.8±11.5	0.12
Gender, female (%)	8 (40%)	7 (35%)	0.50
Weight (kg) (post dialysis)	72.4±19.1	74.5±18.0	0.71
Months on dialysis	28.6±32.6	27.6±39.8	0.93
Hemodialysis adequacy (K_t/V)	1.26±0.28	1.15±0.23	0.19
Cuffed catheter, patients (%)	12 (60%)	14 (70%)	0.507
Systolic BP (mmHg)	145.35±25.0	133.25±20.8	0.11
Diastolic BP (mmHg)	73.35±10.77	71.35±9.2	0.53
Fever >38°C, patients (%)	15 (75%)	13 (65%)	0.46
Respiratory rate per minute	22.30±3.45	20.80±3.636	0.189
Hb (g/l)	105.3±16.6	107.6±13.3	0.68
WBC ($\times 10^3/\mu l$)	15.4±2.8	14.9±2.6	0.64
Albumin (g/l)	35.7±4.6	34.0±3.78	0.19
Renal disease, patients			
Diabetic nephropathy	8 (40%)	9 (45%)	0.50
Hypertension	7 (35%)	3 (15%)	0.137
Chronic glomerulopathy	1 (5%)	2 (10%)	0.50
Polycystic kidney	2 (10%)	2 (10%)	1.0
Obstructive uropathy	2 (10%)	1 (5%)	0.50
Other/unknown	0 (0%)	3 (15%)	0.115
Diabetes mellitus, patients	9 (45%)	11 (55%)	0.376
Present smoker, patients	4 (20%)	6 (30%)	0.36
Previous AG therapy, patients	8 (40%)	6 (30%)	0.37
Present gentamicin course			
Duration (days)	14.75±3.82	14.28±5.76	0.76
Cumulative dose (total mg)	675.5±242.02	694.5±249.02	0.81
Cumulative dose (mg/kg)	9.78±3.55	9.6±4.11	0.88
Blood predialysis level (μg/ml)	3.02±0.62	2.87±0.64	0.46
Bacteriological data, patients			
Pseudomonas sp	4 (20%)	6 (30%)	0.36
Enterobacteriaceae	6 (30%)	7 (35%)	0.45
Other Gram-negative	4 (20%)	2 (10%)	0.331
Enterococcus sp	4 (20%)	2 (10%)	0.331
Culture-negative	2 (10%)	3 (15%)	0.50
Baseline hearing level, dB			
PTA-1	28.5±11.3	28.3±10.23	0.92
PTA-2	45.16±19.59	39.9±15.08	0.35
PTA-3	66.58±20.49	59.33±16.71	0.23

AG, aminoglycoside; BP, blood pressure; PTA, pure-tone average hearing threshold; PTA-1, PTA at frequencies 250, 500, and 1 000 Hz; PTA-2, PTA at frequencies 2 000, 3 000, and 4 000 Hz; PTA-3, PTA at frequencies 6 000, 8 000, and 12 000 Hz.

Table 2 | Effect of *N*-acetylcysteine on otologic outcomes

	N-acetylcysteine (*n*=20)	Control (*n*=20)	*P*-value
Audiologic toxicity, patients (%)			
Total	5 (25%)	12 (60%)	0.027
Early[a]	4 (20%)	11 (55%)	0.024
Late[b]	2 (10%)	11 (55%)	0.003
Bilateral	1 (5%)	6 (30%)	0.01
Tinnitus, patients (%)	5 (25%)	4 (20%)	0.50
Vertigo, patients (%)	4 (20%)	8 (40%)	0.15
Mean hearing loss at early follow-up (dB)			
PTA-1	−1.83±4.11	1.33±3.73	0.015
PTA-2	−0.58±4.46	2.08±4.64	0.072
PTA-3	2.00±3.80	5.83±5.14	0.011
Mean hearing loss at late follow-u, (dB)			
PTA-1	−0.75±4.27	2.25±6.56	0.095
PTA-2	0.16±4.32	4.33±8.36	0.055
PTA-3	2.08±5.18	7.00±8.15	0.029

PTA, pure-tone average hearing threshold; PTA-1, PTA at frequencies 250, 500, and 1 000 Hz; PTA-2=PTA at frequencies 2 000, 3 000, and 4 000 Hz; PTA-3=PTA at frequencies 6 000, 8 000, and 12 000 Hz.
[a]7±3 days after completing gentamicin therapy.
[b]42±3 days after completing gentamicin therapy.

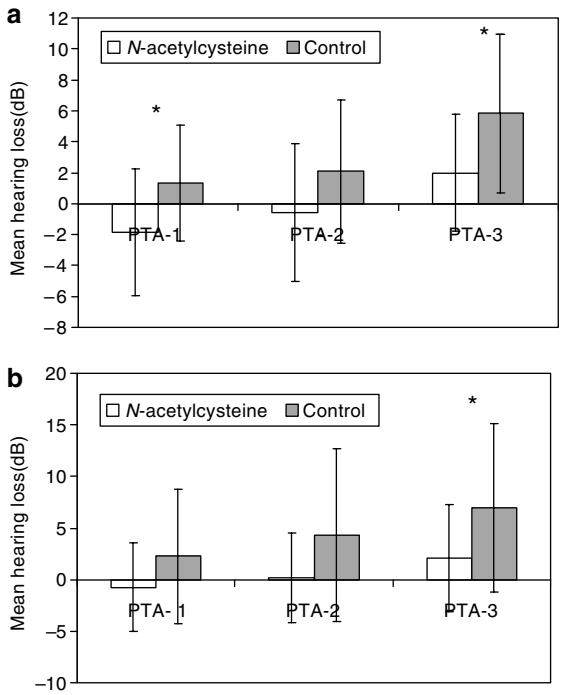

Figure 2 | Mean change from baseline in air conduction threshold (mean hearing loss). (**a**) Mean hearing loss at early follow-up (7±3 days after completing gentamicin therapy). (**b**) Mean hearing loss at late follow-up (42±3 days after completing gentamicin therapy). *$P<0.05$. PTA = pure-tone average hearing threshold. PTA-1 = PTA at frequencies 250, 500, and 1 000 Hz. PTA-2 = PTA at frequencies 2 000, 3 000, and 4 000 Hz. PTA-3 = PTA at frequencies 6 000, 8 000, and 12 000 Hz.

mean change in PTA-3 at late follow-up was 7.00±8.15 dB in the control group and 2.08±5.18 dB in the NAC-treated group ($P=0.029$).

Four patients (20%) in the control group and five patients (25%) in the NAC-treated group had tinnitus during the follow-up period ($P=0.705$). Eight patients (40%) from the control group and four patients (20%) in the NAC-treated group had any vertigo sensation during the follow-up period ($P=0.168$).

DISCUSSION

Hearing loss is a major complication of AG therapy. This study evaluated the protective effect of NAC against AG-induced hearing loss in the high-risk group of hemodialysis patients. In the NAC-treated group, there was a significant reduction of ototoxicity compared to the control group (41.6% reduction, $P=0.025$). NAC exerted its protective effect mainly in the high audiometric frequencies (6 000–12 000 Hz). No adverse events related to NAC therapy were recorded during the follow-up period.

Sixty years after their discovery, AGs remain an important tool in the armamentarium of anti-infectious drugs. AGs are part of the standard therapy used for bacterial endocarditis, sepsis, and peritonitis.[1] Moreover, the use of AG is increasing in at least three groups of patients: patients suffering from bronchiectasis, including those with cystic fibrosis;[19,20] patients suffering from multidrug-resistant TB;[21] and line sepsis or peritonitis in the constantly growing group of dialysis patients.[22,23] AGs have several advantages over other antibiotics with the same antibacterial spectrum, as newer β-lactams and fluoroquinilones: the prevalence of bacterial resistance against AG remained relatively low; allergic reactions are rare, and the cost is low.[1] In this study, AG therapy was given as part of the routinely used antibiotic therapy for central line-related bacteremia in hemodialysis patients.

Several measures such as drug levels monitoring, once-daily administration, and audiometric tests have been traditionally used to prevent AG ototoxicity.[7,8] Unfortunately, they are not free of some caveats. Careful monitoring of serum concentration is important; however, ototoxicity can occur within the recommended therapeutic range.[7] Once-daily administration of AG has not proved to diminish ototoxicity and is not suitable for patients with subacute bacterial endocarditis.[8] The benefit of widely recommended audiometric testing is even less certain. Indeed, early detection of ototoxicity may lead to discontinuation of AG, but ototoxicity may develop or progress well after their cessation.[7] AG can be retained in the cochlea for as long as 11 months after the drug administration and is known to cause delayed hearing loss.[24] Additionally, the clinical condition of many seriously ill patients precludes performance of full audiologic examination. Enormous cost and effort required for such testing makes it unpractical for routine clinical use.

The beneficial effect of NAC on cochlear function in the special context of AG-induced ototoxicity observed in this

study might be explained by its antioxidant properties. NAC, a thiol-containing antioxidant, has been used originally as a mucolitic drug in a variety of pulmonary diseases. Further, it became the drug of choice for acute acetaminophen poisoning.[12] Recently, it has been used successfully in several models of ischemic and toxic injuries to the heart, kidney, liver, and lung.[13–15,18] In each of these syndromes, it is thought that the activity of NAC is mediated, at least in part, by its antioxidant properties.

In a study performed by Farr *et al.*[25], using animal model, it was found that NAC crosses the blood–brain barrier and accordingly may exhibit its protective effect directly within the central nervous system. In healthy volunteers, the absorption of orally administrated NAC is rapid ($t_{max} = 1.4 \pm 0.7$ h), and after administration of 800 mg/m^2/day the mean C_{max} was 8.9 ± 4.9 μg/ml.[26] Unfortunately, currently, there are insufficient data regarding the pharmacokinetics of NAC in patients with ESRD, and it may be possible that higher doses or other routes of administration (e.g. intravenously) would be more effective.

The investigation of the possible otoprotective effect of NAC therapy in this special group of dialysis patients is, in our opinion, especially important. ESRD patients treated by hemodialysis are subjected to enhanced oxidative stress due to increased reactive oxygen species generation (uremic syndrome, chronic inflammatory state, bioincompatibility of dialysis membranes and solutions) and decreased antioxidant ability (vitamin C and E deficiency, reduced activity of glutathione system).[27] Elevated oxidative stress in patients with ESRD is associated with increased cardiovascular risk.[27–29] Although antioxidants were generally ineffective in preventing cardiovascular events in general population,[30] in two recent trials in hemodialysis patients, antioxidant therapy (vitamin E and NAC) reduced cardiovascular risk.[28,29] On the basis of the free radical theory of AG ototoxicity, it is logical to suggest that NAC would be more beneficial in ESRD patients than in the general population.

The study has several limitations. First, the initial hearing examination was performed during acute sepsis. Acute illness may affect the audiometric examination and accordingly lead to underestimation of the baseline hearing levels. Second, this study did not address either laboratory investigation of vestibular ototoxicity by electronystagmography or evaluation of cochlear function by otoacoustic emissions measurement. These instrumental tests were considered to be too distressing for seriously ill septic patients. Third, this is a single-center trial and further studies are needed in a larger cohort of patients.

In conclusion, our data suggest that NAC may be used as a simple, effective, and safe drug for prevention of AG ototoxicity in hemodialysis patients. Further studies are needed to investigate the possible otoprotective effect of NAC in other clinical conditions associated with increased oxidative stress such as diabetes mellitus, chronic inflammation, and malnutrition.

MATERIALS AND METHODS

Study population

The study included patients with ESRD treated with hemodialysis, aged 18 years or older, who were candidates for gentamicin treatment due to dialysis catheter-related bacteremia, in Assaf Harofeh Medical center, between 1 July 2002 and 1 July 2005. We defined suspected dialysis catheter-related bacteremia as fever more than 38°C and/or shaking chills in a patient with a dual-lumen (either cuffed or uncuffed) catheter for whom no other source of infection was obvious. Clinically suspected bacteremia was considered to be sufficient for immediate initiation of empirical antibacterial therapy without waiting for its bacteriological confirmation. Patients were excluded if they were treated with AG within the previous 3 months; had known allergy to AG, mechanical occlusion of external ear by wax or foreign body; signs of disturbed integrity of tympanic membrane on otoscopy or tympanometry; inability to undergo audiometric studies in the first 72 h after the start of the gentamicin therapy or to cooperate with serial audiograms; air-bone gaps of greater than 10 dB at any audiometric frequency for exclusion of a conductive component of hearing loss; treatment by NAC for other reasons or by any other known antioxidants, including herbal medications, simultaneous therapy with other potentially ototoxic drugs such as vancomicin, furosemide, or more than 100 mg of acetylsalicylic acid per day. The study was approved by the local Helsinki Committee of Assaf Harofeh Medical Center (Israel), and all patients signed an informed consent before their inclusion in the study.

Study design

This is a prospective randomized controlled open label study. After enrollment, patients were randomly assigned to receive either gentamicin (Gentamicin®; Teva, Petah-Tikva, Israel) with NAC (Siran® tablets; Temmler Pharma GmbH&Co. KG, Marburg, Germany) 600 mg twice daily (treatment group) or gentamicin alone (control group). Two venous blood cultures (one from the central line and another from the peripheral vein) were obtained immediately before therapy. The initial empirical therapy for line sepsis included intravenous infusion of 2 mg/kg of gentamicin over 30 min together with 2 g of cephazolin after dialysis until specific pathogens were isolated.

Blood gentamicin levels were measured with the use of fluorescence polarization immunoassay before each consecutive hemodialysis session. Subsequently, gentamicin dose was administered to keep therapeutic trough predialysis level of 2–4 mcg/ml. Blood gentamicin level measurements and appropriate dosage changes were supervised by staff physicians on call, not involved in study process. Duration of treatment was at the discretion of the patient's physician according to the patient's condition, including blood culture results, clinical course of bacteremia, removal or preservation of dialysis catheter. Treatment with NAC was continued until the first follow-up otologic examination, 1 week $\pm$ 3 days after completing gentamicin therapy. Compliance with oral therapy using NAC was ascertained by tablet's count in the drug package during each dialysis session.

Ototoxicity evaluation

Within 72 h after the initiation of gentamicin therapy, all patients underwent otoscopic examination and baseline tympanometry and speech audiometry. Patients' otologic complaints, such as tinnitus and dizziness, were recorded. Pure-tone audiometry was performed by a certified audiologist in the audiologic laboratory of Assaf

Harofeh Medical Center with GSI 16 Audiometer (Grason-Stadler Inc., Milford, NH 03055-3056, USA) using a standard technique of pure tone air and bone conduction thresholds measurement at frequencies of 250, 500, 1 000, 2 000, 3 000, 4 000, 6 000, 8 000, and 12 000 Hz. Only patients with high level of audiometric reliability, as assessed by an audiologist, were included in the study. The measured frequencies were gathered in three groups and the pure-tone average (PTA) was calculated: 250, 500, and 1 000 Hz (PTA-1); 2 000, 3 000, and 4 000 Hz (PTA-2); and 6 000, 8 000, and 12 000 Hz (PTA-3). Follow-up otologic examinations were carried out 7 ± 3 days ('early' follow-up) and 42 ± 3 days ('late' follow-up) after completing gentamicin therapy. Audiometer was calibrated in accordance with American National Standards Institute (ANSI) specifications and was recalibrated every 6 months during the study period. Hearing impairment was evaluated by using the criteria of the American Speech-Language-Hearing Association (ASHA 1994).[31] Auditory toxicity was defined as an increase in the auditory threshold by at least 20 dB at any one test frequency or at least 10 dB at any two adjacent frequencies or loss of response at three consecutive frequencies between the baseline and follow-up studies in the worse ear. Neither the audiologist nor the study's contributor who analyzed the audiograms was aware of the patient's group allocation.

Baseline data collections

Baseline blood pressures were recorded and blood samples were collected before dialysis session. Adequacy of hemodialysis was estimated using fractional clearance of urea as a function of its distribution volume (K_t/V) and was determined by the K_t/V natural logarithm formula.[32] The most recent K_t/V obtained within 1 month before inclusion to this study was referred as baseline K_t/V.

Statistical analysis

Continuous baseline variables were compared between the treatment groups by an unpaired *t*-test and by a paired *t*-test within each group. Categorical parameters were compared by the Fisher's exact test. The effect of NAC treatment on auditory function at baseline, 1 week ± 3 days and 6 weeks ± 3 days after the end of gentamicin therapy, was compared between the groups by a general linear model repeated measures analysis of variance (ANOVA). The statistical software SPSS (version 10.0, SPSS Inc., Chicago, IL, USA) was used for all analyses. All tests were two-tailed. *P*-values <0.05 were considered significant. Data are expressed as mean $\pm$ s.e.m.

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