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Protective effect of *N*-acetylcysteine from drug-induced ototoxicity in uraemic patients with CAPD peritonitis

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Abstract

Aim. Peritonitis is currently one of the leading complications of continuous ambulatory peritoneal dialysis (CAPD) treatment. Aminoglycosides and vancomycin are used in the treatment of CAPD peritonitis despite their potential risk for ototoxicity. *N*-acetylcysteine (NAC) is a molecule used in the treatment and prophylaxis of many diseases related to oxidative stress. The aim of this study was to examine whether ototoxicity due to antibiotics used in the treatment of CAPD peritonitis can be prevented by NAC.

Methods. Sixty patients, who first developed CAPD peritonitis attacks from February 2008 to April 2010 were included in this study. Patients were divided into two groups, those taking an additional NAC treatment ($n = 30$) and a control group ($n = 30$). Low- and high-frequency hearing function tests were performed on the two groups before treatment (baseline), at the end of the first (early follow-up) and the fourth week after the treatment (late follow-up). Total doses of vancomycin and amikacin were recorded.

Results. There was no statistically significant difference between the groups in terms of hearing functions at the beginning. However, patients taking NAC had better hearing function test results 4 weeks after the treatment compared with those of the control group ($P < 0.05$). There were no statistical differences between posttreatment low-frequency hearing function tests conducted at the baseline and the first and the fourth weeks in patients taking NAC. The first and the fourth week's low-frequency hearing functions worsened when compared with the baseline low-frequency results in the control group ($P < 0.001$). It was found that NAC had a protective effect against ototoxicity on low-frequency (0.25–8 KHz) hearing functions. The first and the fourth week's high-frequency hearing functions improved when compared with baseline high-frequency hearing functions in patients taking NAC ($P < 0.05$), while they worsened. The first and fourth week's high-frequency tests worsened when compared with the baseline high-frequency tests in the control group ($P < 0.001$).

Conclusions. The present study suggests that intraperitoneal aminoglycoside and vancomycin administration in CAPD patients may cause low- and high-frequency hearing loss, and this ototoxic effect is related to the dose given. It was found that when the antioxidant NAC is administered alone, it prevents ototoxicity, associated with intraperitoneal amikacin and vancomycin in patients with CAPD peritonitis. In addition, it was revealed that NAC may also have a curative effect on impaired high-frequency hearing functions.

Keywords: amikacin; CAPD peritonitis; NAC; ototoxicity; vancomycin

Introduction

Peritonitis is currently one of the leading complications of continuous ambulatory peritoneal dialysis (CAPD) [1–5]. It is not only a reason for technical failure, but it also leads to considerable morbidity and mortality. Its incidence varies

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from centre to centre, and it resulted in death in 3% of the episodes in our cohort [6]. Many patients are hospitalized due to peritonitis and may have to stop receiving CAPD therapy [7]. According to the recommendations of the International Society for Peritoneal Dialysis, as soon as a patient is diagnosed with peritonitis, cultures must be taken and empirical antibiotic therapy should be started without delay [8–11]. Empirical therapy has to cover both Gram-positive and Gram-negative microorganisms. Each peritoneal dialysis (PD) centre should determine which antibiotics should be used in empirical therapy by being aware of the efficacies and sensitivities of the microorganisms causing peritonitis in its own patient population. Gram-positive organisms may be covered by vancomycin or cephalosporin and Gram-negative organisms by a third-generation cephalosporin or aminoglycoside [11]. Although aminoglycosides and vancomycin are recommended for only short-term use because of the risk of ototoxicity [11], there is enough data regarding the correlation between the usage of aminoglycosides and the frequency of hearing loss even with short-term treatments. We have established that hearing loss is a much more overlooked complication during CAPD treatment in a recent study [12]. We found that PD patients with a history of peritonitis had significantly higher incidence of hearing loss according to the median hearing values for both lower and higher frequency sounds as compared to those PD patients with no history of peritonitis, and the administration of aminoglycoside antibiotic was directly associated with the development of the hearing loss [12]. The most frequently emphasized mechanism responsible for aminoglycoside and vancomycin ototoxicity is reactive oxygen types resulting in damage to the internal ear. In animal studies, coadministration of antioxidant therapy ameliorated aminoglycoside-induced ototoxicity [13]. *N*-acetylcysteine (NAC) is a molecule used in the treatment and prophylaxis of many diseases related to oxidative stress. It has been suggested that NAC might prevent hearing loss associated with bacterial meningitis [14] and auditory hair cell damage from cisplatin [15]. NAC has also been shown to ameliorate gentamicin-induced nephrotoxicity [16]. In this study, we aimed to examine whether ototoxicity due to antibiotics used in the treatment of CAPD peritonitis can be prevented by NAC.

Methods

This study was performed on monitored patients with CAPD in the Nephrology Department of the Medical Faculty of Erciyes University for a period of 26 months between February 2008 and April 2010. In the centre, the majority (~90%) of dialysis patients are on PD. Two hundred and sixty-four PD patients are currently being followed. In the study period, 164 new patients have started receiving PD, and 127 patients have dropped out from this population for several different reasons. Additionally, during the study, 191 peritonitis attacks were diagnosed (6779 patient-month/191 peritonitis attack, 1 peritonitis every 35 months in the centre) and 83 of these were having a first peritonitis episode.

From these 83 patients, a total of 60 CAPD patients were enrolled in the study. Three patients were excluded from the study due to a perforated tympanic membrane, and eight patients were rejected for enrollment in the study. Also, 12 patients applied after office hours and were excluded from the study because of the inability to perform audiometric tests at the admission. Patients >18 years of age with end-stage renal disease (ESRD), on CAPD therapy, experiencing their first peritonitis episode, and being treated with cephalozine or vancomycin and/or amikacin were included in the study. CAPD peritonitis was diagnosed when the peritoneal fluid white cell count was $\geq 100/mm^3$ and when $\geq 50\%$ of these cells were polymorphonuclear leucocytes. Patients with impaired tympanic membrane integrity were excluded. Each patient was queried in terms of complaints such as tinnitus, vertigo and dizziness, and their responses were recorded.

This is a prospective, randomized, controlled, open-label study. The patients were randomly assigned to receive treatment for CAPD peritonitis either with NAC (Asist®; Bilim Ilac Sanayi Ticaret A.S., İstanbul, Turkey) 600 mg twice daily (treatment group) or with treatment for CAPD peritonitis alone (control group). After the patient was informed and consent for the enrollment in the study was given he/she was requested to choose a sealed envelope in which 'NAC Group' or 'Control Group' was written. Thus, the groups were developed.

Threshold values for hearing were identified through 'pure-tone audiometry' measurements with the AC 40 Audiometer (Interacoustics, Assens, Denmark) using a standard technique of pure-tone air and bone conduction threshold measurements at frequencies of 250, 500, 1000, 2000, 3000, 4000, 6000, 8000, 10 000, 12 000, 14 000 and 16 000 Hz in the Audiology Laboratory in the Otorhinolaryngology Department. Recordings of the threshold hearing values obtained from the ear with lower hearing were retained for analysis. The measured frequencies were separated into two groups and pure-tone averages (PTA) were gathered as follows:

- lower frequencies, PTA-1: 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz,
- higher frequencies, PTA-2: 10 000, 12 000, 14 000 and 16 000 Hz.

Hearing function tests were performed on the two groups before treatment (baseline). Follow-up otologic examinations were carried out 8 ± 2 days (early follow-up) and 28 ± 2 days (late follow-up) after starting treatment for CAPD peritonitis. Hearing impairment was evaluated by using the criteria of the American Speech-Language-Hearing Association (ASHA 1994) [17]. Ototoxicity 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.

Statistical considerations

SPSS 15.0 software was used for the statistical analysis. The Kolmogorov–Smirnov test was used to determine the normality of variable distributions. Continuous variables with normal distribution were presented as mean ±SD. Where normal distribution was absent, the median value was used. Statistical analysis of the parametric variables was performed by a Student's *t*-test between two groups and by a one-way analysis of variance, with Scheffe's post hoc test among more than two groups. The Mann–Whitney *U*-test was used to compare nonparametric variables between the two groups. The Kruskal–Wallis test was used to compare nonparametric variables among more than two groups. Then, the Mann–Whitney *U*-test with Bonferroni correction was used to assess the differences among more than two groups. The correlation analysis was evaluated by the Pearson's correlation test for parametric variables and by the Spearman's correlation test for nonparametric variables. Qualitative variables were given as percentages, and the correlation between categorical variables was examined by the chi-square test. A P-value of <0.05 was considered to be significant.

Results

A total of 63 CAPD patients were enrolled in the study. Three patients were excluded from the study due to a perforated tympanic membrane. There were 30 patients in the NAC-treated group and 30 patients in the control group. There was no statistically significant difference between the groups in any of the patients' baseline clinical and demographic characteristics. The demographic and clinical characteristics of the patients are summarized in Table 1.

The most common cause of ESRD in patients in the study was diabetes mellitus. The causes of ESRD are summarized in Table 2.

The cultures from the peritoneal fluids were evaluated. No microorganisms grew in the peritoneal fluid cultures in 7 patients in the NAC-treated group, whereas 11 in the

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Table 1. Demographic, biochemical, clinical and audiometric parameters in all patients[a]

Parameters	NAC-treated group	Control group	P
Age (year)	45.0 ± 13.2	49.9 ± 15.2	0.19
Duration of CAPD (month)	31 (13.50–68.25)	40 (15.5–72.0)	0.51
Body surface area (m^2)	1.68 ± 0.24	1.68 ± 0.18	0.97
Blood WBC (mm^3)	7960 ± 2558	8410 ± 2276	0.47
Haemoglobin (g/dL)	9.5 ± 1.0	9.2 ± 1.2	0.33
Albumin (g/dL)	2.9 ± 0.4	3.0 ± 0.4	0.17
Residual urine volume (mL/day)	125 (0–700)	100 (0–787)	0.80
Cumulative cephazolin dosage (g)	14 (10–28)	18 (10–28)	0.15
Cumulative amikacin dosage (g)	1.5 (1–1.5)	1.25 (1.0–1.6)	0.66
Cumulative vancomycin dosage (g)	4 (1.5–6)	4 (0–6)	0.70
Peritoneal fluid WBC (mm^3)	3175 (1547–5325)	2350 (1700–4225)	0.09
Kt/V_{urea}	2.34 ± 0.46	2.46 ± 0.75	0.48
D/P creatinine	0.72 ± 0.13	0.79 ± 0.11	0.06
Baseline hearing level, dB			
PTA-1	27.5 ± 13.2	24.4 ± 12.1	0.36
PTA-2	48.7 ± 17.5	38.3 ± 17.7	0.06

[a]WBC, white blood cell.

control group had no microorganisms. Table 3 summarizes the causative microorganisms in the peritoneal fluid cultures.

When the treatment and the control groups were compared, late follow-up test results of low- and high-frequency hearing functions showed a statistically significant difference (Table 4).

At the early follow-up, low-frequency (PTA-1) examination, three patients (10%) in the control group and one patient (3.3%) in the NAC group, and in the high-frequency (PTA-2) examination, nine patients (30%) in the control group and one patient (3.3%) in the NAC group fulfilled the criteria for ototoxicity ($P = 0.11$ and $P = 0.021$, respectively). At the late follow-up, low-frequency (PTA-1) examination, 15 patients (50%) in the control group and 1 patient (3.3%) in the NAC group, and in the high-frequency (PTA-2) examination, 21 patients (70%) in the control group and 1 patient (3.3%) in the NAC group fulfilled the criteria for ototoxicity ($P < 0.001$).

The mean change in PTA-1 at early follow-up was 3.16 ± 6.25 in the control group and 1.36 ± 5.85 in the NAC-treated group ($P = 0.25$), while in PTA-2 at early follow-up, it was 5.43 ± 8.56 in the control group and −4.73 ± 7.40 in the NAC-treated group ($P < 0.001$). As for the mean change in PTA-1 at late follow-up, it was 12.76 ± 6.22 in the control group and −1.86 ± 5.98 in the NAC-treated group ($P < 0.001$). Finally, the mean change in PTA-2 at late follow-up was 16.93 ± 8.10 in the control group and −5.96 ± 8.89 in the NAC-treated group ($P < 0.001$) (Tables 5 and 6).

There was no statistically significant difference between the groups in terms of hearing functions at the beginning. However, patients taking NAC had better hearing function test results at the end of the fourth week after treatment compared with those of the control group ($P < 0.05$). There were no statistical differences between the baseline low-frequency hearing function tests and the first and the fourth week's low-frequency results tests in patients taking NAC. The first and the fourth week's low-frequency hearing functions worsened compared with the baseline low frequency tests in the control group ($P < 0.001$). It was seen that NAC had a protective effect against ototoxicity on low-frequency (0.25–8 KHz) hearing functions. The comparison

Table 2. Underlying causes for ESRD

Causes of ESRD	NAC-treated group ($n = 30$)	Control group ($n = 30$)	Total ($n = 60$)
Diabetic nephropathy	9 (30%)	11 (36.7%)	20 (33.3%)
Hypertension	6 (20%)	6 (20%)	12 (20%)
Glomerulonephritis	0 (0%)	2 (6.7%)	2 (3.3%)
Polycystic kidney disease	1 (3.3%)	0 (0%)	1 (1.7%)
Amyloidosis	3 (10%)	1 (3.3%)	4 (6.7%)
Others/unknown	11 (36.7%)	10 (33.3%)	21 (35%)

Table 3. Causative organisms isolated from peritoneal effluent fluid[a]

Microorganisms	NAC-treated group ($n = 30$)	Control group ($n = 30$)
Gram positive		
Staphylococcus epidermidis	5 (16.6%)	4 (13.3%)
MSSA	4 (13.3%)	3 (10.0%)
MRSA	3 (10%)	4 (13.3%)
CNS	5 (16.6%)	2 (6.7%)
Enterococcus	0 (0%)	2 (6.7%)
Gram negative		
Pseudomonas	3 (10%)	1 (3.3%)
E. coli	1 (3.3%)	2 (6.7%)
Others	1 (3.3%)	1 (3.3%)
Fungus	1 (3.3%)	0 (0%)
Culture negative	7 (23.3%)	11 (36.7%)

[a]MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus. aureus*; CNS, coagulase-negative *Staphylococcus*.

Table 4. Early and late follow-up hearing levels between groups

Hearing function test (dB)	NAC-treated group ($n = 30$)	Control group ($n = 30$)	P
Early follow-up			
PTA-1	28.8 ± 12.0	27.6 ± 14.1	0.71
PTA-2	44.0 ± 14.9	43.8 ± 19.2	0.95
Late follow-up			
PTA-1	25.6 ± 11.6	37.2 ± 13.8	<0.05
PTA-2	42.8 ± 14.7	55.3 ± 17.1	<0.05

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Table 5. Mean hearing loss at early and late follow-up

	NAC group ($n = 30$)	Control group ($n = 30$)	P
Early follow-up			
PTA-1	1.36 ± 5.85	3.16 ± 6.25	0.25
PTA-2	−4.73 ± 7.40	5.43 ± 8.56	<0.001
Late follow-up			
PTA-1	−1.86 ± 5.98	12.76 ± 6.22	<0.001
PTA-2	−5.96 ± 8.89	16.93 ± 8.10	<0.001

Table 6. Number of patients who developed ototoxicity

	NAC group ($n = 30$)	Control group ($n = 30$)	P
Early follow-up			
PTA-1	1 (% 3.3)	3 (% 10)	0.11
PTA-2	1 (% 3.3)	9 (% 30)	<0.05
Late follow-up			
PTA-1	0 (% 0)	15 (% 50)	<0.001
PTA-2	1 (% 3.3)	21 (% 70)	<0.001

between the first and the fourth week's high-frequency hearing functions and the baseline high-frequency tests yielded that the former improved in patients taking NAC ($P < 0.05$) and worsened in the control group ($P < 0.001$) (see Figure 1). Correlation between hearing loss and total antibiotics dosage in control groups is shown in Figure 2.

This results suggest that NAC may have a curative effect on impaired hearing functions in addition to a protective effect on high-frequency hearing functions.

Discussion

Aminoglycosides have been used in the management of peritonitis in patients with CAPD despite a well-known ototoxicity risk. In spite of their side effects, the absence of safe alternatives to aminoglycosides is the main cause for using these antibiotics. On the other hand, aminoglycosides are highly advantageous drugs since they are inexpensive, their bacterial resistance lower, and the allergic reactions rare [18]. In patients with CAPD, aminoglycosides are frequently used in peritonitis therapy through the intraperitoneal route. The correlation between usage of intraperitoneal aminoglycosides and ototoxicity in patients with CAPD has been frequently studied in patients treated with tobramycin and gentamicin [19–23].

In one of the early studies on this issue, Nikolaidis *et al.* [19] suggested that the administration of intraperitoneal tobramycin in patients with CAPD peritonitis did not lead to any increase in hearing loss. A possible reason for failure to determine the specific ototoxicity related to aminoglycosides in that study may be due to limited frequency range measurements (i.e. between 250 and 10 000 Hz only).

Similarly, by measuring serum drug levels in the patients with CAPD, Gendeh *et al.* [20] suggested that the treatment with intraperitoneal gentamicin did not increase ototoxicity risk. However, it should be emphasized that only ordinary frequencies (128−8000 Hz) were examined in that study. In another study, the same researchers reported that repeated intraperitoneal gentamicin administration increased the risk of ototoxicity [23].

Mars *et al.* [21] reported no hearing loss in the study in which they performed audiogram tests at the start of intraperitoneal aminoglycoside treatment (within the first 24 h of administration) and after the completion of therapy (within 17 days on average) in patients with CAPD. This study was conducted on only six patients although it had a prospective design. Another study performed on 19 patients with CAPD indicated that clinical ototoxicity occurred even if gentamicin blood levels did not specifically increase after intraperitoneal administration [22].

This study revealed that hearing loss was observed particularly at higher frequencies. Gendeh *et al.* [24] found that vancomycin could produce hearing impairment in CAPD patients when administered in combination with aminoglycoside. It has been suggested that ototoxicity may be attributable to the possible synergistic effect of the two drugs. Taking into consideration that hearing loss can negatively affect quality of life, unnecessary repetitive usage of aminoglycoside antibiotics should be avoided, and therapy should be stopped as soon as possible. Patients with CAPD who are treated with ototoxic drugs should be followed up in terms of complaints regarding hearing loss such as tinnitus, dizziness or vertigo.

Of the mechanisms that are held responsible for aminoglycoside ototoxicity, the most frequently emphasized mechanism is the reactive oxygen type, which results in damage to the internal ear [25]. NAC, a thiol-containing antioxidant, was originally used as a mucolytic drug in a variety of pulmonary diseases. Later, it became the drug of choice for acute acetaminophen poisoning [26]. Recently, it has been used successfully in several models of ischaemic and toxic injuries to the heart, kidney, liver and lung [16, 27–29]. In each of these conditions, it is presumed that NAC activity is mediated, at least in part, by its antioxidant properties.

On the basis of the free radical theory of Aminoglycosides (AG) and vancomycin-induced ototoxicity, it is logical to suggest that NAC would be more beneficial in uraemic patients than in the general population, because uraemia is associated with a high level of oxidative stress.

In the study carried out by Okur *et al.* using the animal model, carboplatin-induced ototoxicity was evaluated. Carboplatin was applied to the rats, and it was shown that carboplatin-induced hearing loss by increasing nitric oxide (NO) levels. It was reported that NAC, which was applied 30 min before the carboplatin application, had protective effects by decreasing NO production [30]. In a study performed by Theneshkumar *et al.* [31], using an animal model, it was shown that intraperitoneally administered NAC prevented cisplatin-induced ototoxicity.

Thomas Dickey *et al.* reported that the protective effects of infusion of NAC and isotonic saline infusion against cisplatin-induced ototoxicity were compared and it was observed in the group to which NAC was applied that the results were better at low-frequency audiometric examinations on the 7th day than baseline auditory examinations. These data show that treatment with NAC can prevent cisplatin-induced ototoxicity in rats

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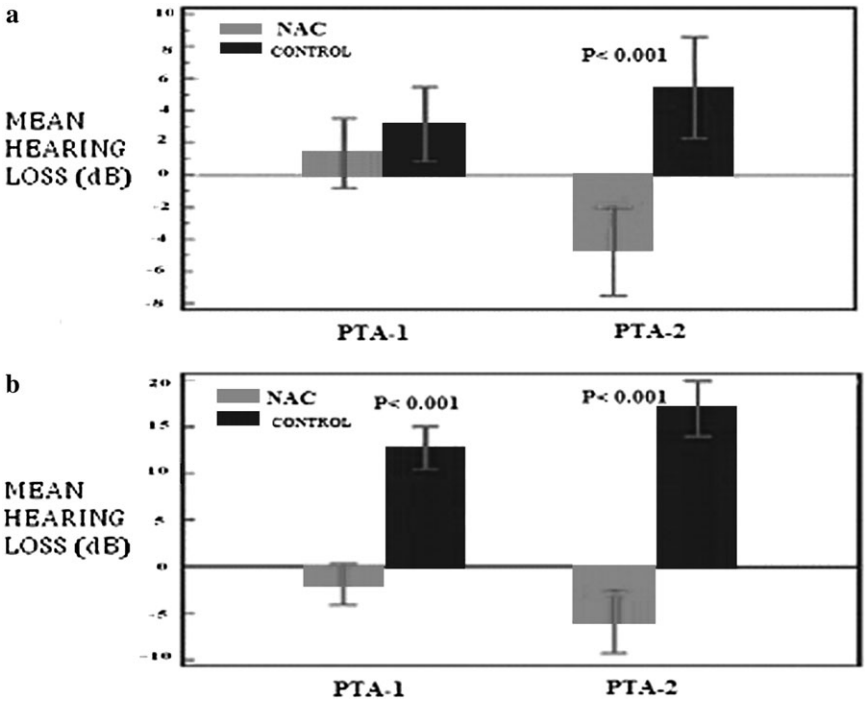

Fig. 1. Comparison of mean hearing loss between control and NAC groups.

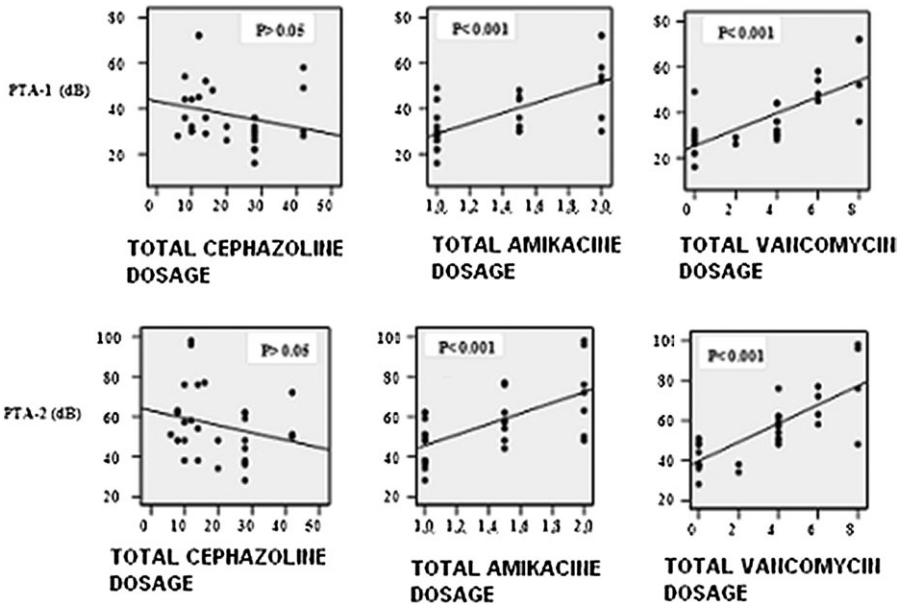

Fig. 2. Correlation between hearing loss and total antibiotics dosage in control groups.

[32]. Additionally, Sinswat and *et al.* [13] designed a study in guinea pigs and intraperitoneal coadministration of antioxidant therapy recovered intraperitoneal AG-induced ototoxicity.

In a study performed by Low *et al.* [33], radiation-induced ototoxicity was evaluated in patients who were on radiotherapy because of head–neck cancer and it was found that NAC significantly reduced both cochlear cell apoptosis and the production of free oxygen radicals in the inner ear after the radiation. It was shown by the flow cytometry method that cochlear cell death was reduced with the addition of NAC at 72 h after the radiotherapy. It was found that the use of NAC was safe and effective, and it reduced hearing loss in radiotherapy patients because of head–neck cancer. In another study performed by Feghali *et al.*, the protective effects of NAC on cisplatin-induced ototoxicity was evaluated. It was shown that NAC was protective against both cisplatin-induced damage to auditory neuronal cells and to auditory hair cells [15].

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One of the most important recent studies showed that antioxidant therapy using NAC was otoprotective in patients undergoing haemodialysis. Feldman *et al.* investigated the possible protective effect of the antioxidant NAC in gentamicin-induced hearing loss in 53 haemodialysis patients. These patients were randomized consecutively, depending on whether or not they received NAC; hence, the demographic, biochemical and clinical features of both groups were similar. In consequence, the otoprotective effect of NAC was established in the high audiometric tone frequencies [34].

In conclusion, our data suggest that NAC may be used as a cheap, effective and safe drug for the prevention of AG and vancomycin-induced ototoxicity in CAPD patients.

The present study has several limitations. First of all, blood AG and vancomycin levels were not measured. Also, the study did not address either laboratory investigation of vestibular ototoxicity by electronystagmography or evaluation of cochlear function by otoacoustic emissions measurement. Additionally, this was a single-centre trial and further studies examining the protective effect of antioxidant therapy against ototoxicity are required in a larger cohort of CAPD patients.

Acknowledgements. This study is registered with a name of 'Prevention of Drug-Induced Ototoxicity in PD Patients by NAC' on ClinicalTrials.gov and its ClinicalTrials.gov identifier number is NCT01131468.

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Conflict of interest statement. None declared.

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