Cisplatin Ototoxicity, Increased DPOAE Amplitudes, and Magnesium Deficiency

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Abstract

Outer hair cell (OHC) metabolism is blocked by cisplatin. Concurrent changes in the renal handling of magnesium occur because of the damage cisplatin causes to the renal proximal tubule cells within the thick ascending loop of Henle. Although there is no evidence of cisplatin within the OHCs, there are significant levels of intracellular calcium, the antagonist to magnesium at the cell membrane. The OHC motile response is dependent on intracellular calcium. When the calcium current is suppressed by an antagonist, the extracellular OHC microphonic potential decreases. Magnesium deficiency is known to produce hyperexcabililty within the central nervous system, including fatal audiogenic seizures. In addition, increases in the amplitude of the auditory brainstem response wave V occur with aminoglycoside therapy and magnesium deficiency. This paper illustrates the amplitude growth of distortion product otoacoustic emissions in two patients treated with cisplatin and explores the possible underlying reasons why this may be related to magnesium metabolism.

Key Words: Cisplatin chemotherapy, distortion product otoacoustic emissions, magnesium deficiency, outer hair cells, transient evoked otoacoustic emissions

Abbreviations: DPOAEs = distortion product otoacoustic emissions, OAEs = otoacoustic emissions, OHC = outer hair cell, TEOAEs = transient otoacoustic emissions

Cisplatin is ototoxic (Waters et al, 1991) and nephrotoxic (Dickerson and Brown, 1985; Lam and Adelstein, 1986). The damaging effects of this agent result in both hearing loss and hypomagnesemia (Lam and Adelstein, 1986). The paired sites of damage are the outer hair cells (OHC) within the cochlea and the renal proximal tubule cells within the thick ascending loop of Henle in the kidney. Although cisplatin blocks OHC metabolism, there is no evidence of intracellular cisplatin in the OHC (Saito and Aran, 1994). Rather, there are significant levels of intracellular calcium in the OHC after cisplatin administration (Comis et al, 1986). Likewise, there are no defects in the renal handling of electrolytes other than magnesium following the related nephrotoxicity seen with the administration of cisplatin (Lam and Adelstein, 1986). Since magnesium is an antagonist to calcium at the cell membrane, the hearing loss associated with cisplatin therapy may be influenced by a magnesium-related factor.

Since magnesium is an antagonist to calcium at the cell membrane (Seelig, 1994), the loss of intracellular magnesium increases plasma membrane permeability to an influx of calcium (al-Ghamdi et al, 1995). Increased intracellular calcium is associated with cellular death if the energy requirements to lower its level in the cytoplasm exceed production (Cheung et al, 1986). Likewise, when the calcium current is suppressed by an antagonist, the extracellular OHC microphonic potential decreases with a depolarization of the membrane potential (Nakagawa et al, 1992). The slow OHC motile response is considered to be dependent on intracellular calcium and adenosine triphosphate (Nakagawa et

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al, 1992). Since OHCs produce much of the summating potential, calcium antagonists decrease the summating potential (Bobbin et al, 1990). Antithetically, the loss of the calcium antagonists affects an increase of the summating potential.

Past and recent studies indicated that a deficiency of magnesium can have pervasive effects on peripheral and central auditory function. The importance of magnesium in the perilymph is underscored by a study that demonstrated a negative correlation between susceptibility to noise-induced hearing loss and perilymph magnesium concentration (Joachims et al, 1983). Animals with diets low in magnesium showed greater noise-induced hearing loss than those on a magnesium-rich diet. Interference with either the active transport of nutrient materials or the ionic composition of perilymph could also affect hair cells and afferent nerve endings, leading to a loss of hearing (Brown and Feldman, 1978). Oral magnesium intake was shown to reduce permanent hearing loss induced by noise exposure in healthy and normal-hearing recruits who underwent 2 months of military training (Attias et al, 1994).

Magnesium deficiency has been associated with an increase in auditory excitability. Small decreases in brain magnesium are accompanied by marked alterations in auditory excitability, including fatal audiogenic seizures (Bac et al, 1994). Magnesium-depleting drugs, such as furosemide and gentamicin, and a low magnesium diet are associated with increased wave V amplitudes of auditory brainstem responses (Cevette et al, 1989).

Reddel et al (1982) found in a prospective study that 47% of 32 patients receiving cisplatin developed a sensorineural hearing loss of 15 dB or greater after receiving a mean cumulative dose of 203 mg/m². The hearing loss is usually irreversible and high frequency, accompanied by transient or persistent tinnitus. Interestingly, case studies have shown continued deterioration of hearing loss after cessation of cisplatin administration (Aguilar-Markulis et al, 1981; Fausti et al, 1984; Sweetow and Will, 1993). Moreover, otoacoustic emissions (OAEs) change prior to behavioral pure-tone thresholds for both transient and distortion production (Plinkert and Krober, 1991).

One method of investigating the effects of ototoxicity on auditory function is the use of OAEs (Kujawa et al, 1992; Probst et al, 1993; Furst et al, 1995). Evoked OAEs are low levels of acoustic energy that are measured from the external ear canal in response to auditory stimulation (Kemp, 1978). The source of this energy is thought to be an active micromechanical process generated by the OHC of the organ of Corti (Brownell, 1990; Dallos, 1988). Stimuli are presented through a transducer in a probe fitted to the patient's ear. These emissions are present in nearly all humans with normal hearing sensitivity (Bonfils et al, 1988) but are absent in mild-to-moderate or greater cochlear hearing losses (Probst et al, 1987).

Distortion product OAEs (DPOAEs) are acoustic energy produced by the ear in response to tonal stimuli. The distortion products occur at frequencies other than those used to stimulate the ear. They are thought to be generated by the nonlinear movement of the basilar membrane in response to sound and can be recorded in essentially all normal-hearing individuals (Kemp et al, 1986). The largest DPOAE occurs at the $2f_1-f_2$ frequency, where f_1 and f_2 represent the frequencies of the input tones (Whitehead et al, 1992). Because DPOAEs are thought to provide frequency-specific information about OHC function, they may be ideally suited to study the early effects of magnesium on cisplatin ototoxicity.

Various investigators have demonstrated that DPOAE amplitudes are relatively stable over periods of 4 to 6 weeks (Franklin et al, 1992; Roede et al, 1993). Figure 1 demonstrates the consistency of amplitudes over a 6-month period in a normal-hearing individual. The mean change in amplitude of $2f_1-f_2$ with repeated measurements over several time intervals was 1.8 dB (SD = 1.8 dB) with stimuli at 70 dB SPL (Roede et al, 1993). Under relatively stable test conditions and with removal and replacement of the probe, changes exceeding 5.4 dB (mean + 2 SD)
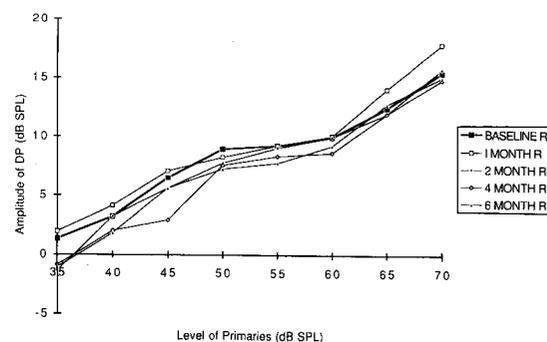

Figure 1 DPOAE growth functions at 5000 Hz for a subject with normal hearing over a 6-month period of time, who received daily magnesium supplementation after baseline testing.

for 70 dB SPL can be interpreted as clinically relevant changes within the cochlea for frequencies above 1000 Hz and below 8000 Hz (Roede et al, 1993). These data are consistent with another study (Franklin et al, 1992) that showed that DPOAE amplitudes are highly reliable over 4 weeks (test–retest correlation coefficient above 0.97 at 6000 Hz for primary tone levels of 65 and 75 dB SPL).

Amplitude increases of both transient evoked OAEs (TEOAEs) and DPOAEs during and after ototoxic amikacin treatment in an animal (chinchilla) model has been shown (Kakigi et al, 1998). The investigators noted that as a basal cochlear lesion progresses apically, there is often a transient increase in a frequency-specific OAE before it decreases or is lost. Their findings suggest that the increase in OAE amplitudes precedes the expression of detectable cochlear pathology. In addition, localized damage to the apical or middle turn may be accompanied by an increase in OAE measured from the adjacent apparently normal cochlea (Raveh et al, 1998).

The present case studies illustrate that significant fluctuations in amplitudes of DPOAEs are evident following the initiation of cisplatin chemotherapy. That is, clinically significant increases in amplitude are evident as well as the loss or decrease in amplitudes previously reported. The relationship of these findings to audiologic, serum magnesium, calcium, and creatinine testing is discussed.

METHOD

T wo patients and one control subject were seen for baseline, 1-month, 2-month, 4-month, and 6-month hearing assessments that included behavioral pure-tone air-conduction threshold testing (250–12000 Hz), tympanometry, and DPOAE input-output functions at 5000 Hz bilaterally. All subjects had hearing baseline thresholds better or equal to 25 dB HL for the frequencies from 250 Hz through 6000 Hz. None of the subjects had been treated previously with chemotherapy. Serum magnesium, calcium, and creatinine values and chemotherapy treatment were conducted the same day as hearing testing. All subjects received magnesium supplementation (one 500 mg tablet orally of magnesium chelated three times daily) for 6 months. This dosage provided 400 mg of elemental magnesium, which met the present recommended daily allowance for magnesium intake.

DPOAEs were measured using the Otodynamics Otoacoustic Analyzer ILO88XP module and software controlled by an IBM PC. A DPOAE input-output function at 5000 Hz was measured using levels from 35 to 70 dB SPL in 5-dB steps for f_1 and f_2 with an f_2/f_1 ratio of 1.22.

CASE STUDIES

Patient A

Medical History

The patient was a 30-year-old male who in July 1994 noted a left testicular nodule. Pathology reported a nonseminomatous germ cell tumor most consistent with an embryonal carcinoma. There was no definite teratoma. The diagnosis was stage III (left supraclavicular node) small-volume testicular embryonal cell carcinoma with rising serum markers. The primary lesion was surgically resected, and he subsequently received four monthly cisplatin chemotherapy treatments (75 mg/m^2 as a one half-hour infusion) from October 1994 through January 1995. He received magnesium supplementation of 400 mg daily for 6 months following the beginning of cisplatin treatment.

Audiologic Findings

Hearing thresholds (Table 1) were within 5 dB of baseline throughout the duration of the study, aside from an improvement at 6000 Hz from 25 dB to 10 dB HTL in the right ear from baseline to 1-month testing. Subsequent thresholds at this frequency for this ear did not change for the remainder of the study.

DPOAE amplitudes fluctuated throughout the study and are shown in Figure 2 (A and B).

Table 1   Audiometric Thresholds at 6000 Hz over 6 Months

6000 Hz	Test Date (Mo)	Normal Subject	Patient A	Patient B
Right ear	Baseline	5	25	20
	1	0	10	75
	2	–5	10	70
	4	5	10	75
	6	5	10	75
Left ear	Baseline	5	0	15
	1	5	5	80
	2	10	5	70
	4	0	5	75
	6	15	5	70

The largest change was seen in the left ear from baseline to 1 month, which showed a 15.8-dB increase in amplitude. In addition, there was a significant decrease in amplitude of 12.7 dB from 2-month to 4-month test dates. This was followed again by an increase of the DPOAE of 11.5 dB at the 6-month test. Significant increases in DPOAE amplitudes are also seen in the right ear. The largest increase in amplitude (5.6 dB) occurred from 1-month to 2-month testing, followed by a significant decrease in amplitude (13.2 dB) from 2 to 4 months. At 6 months, there were no measurable DPOAEs for the right ear. Calcium, magnesium, and creatinine serums levels remained within normal limits throughout the 6-month duration of the study (Fig. 3).

Patient B

Medical History

This patient was a 64-year-old female who presented with a left renal mass in September 1994. On September 29, 1994, she underwent a left radical nephronectomy for a 13 × 10 × 7 cm grade 2 cell carcinoma. In April 1995, she was subsequently found to have a large right pleural effusion with a 1.8 × 2.5 cm mass in the right apex, a 1.5 × 1.3 cm pleural-based lesion in the right lower lobe of the lung, and multiple nodules in both lungs. Testing revealed grade 3 metastatic adenocarcinoma. She was treated with mitomycin, velban, and cisplatin and completed five cycles of the treatment by October 31, 1995. She received a 400 mg daily supplement of magnesium for 6 months during and following chemotherapy.

Audiologic Findings

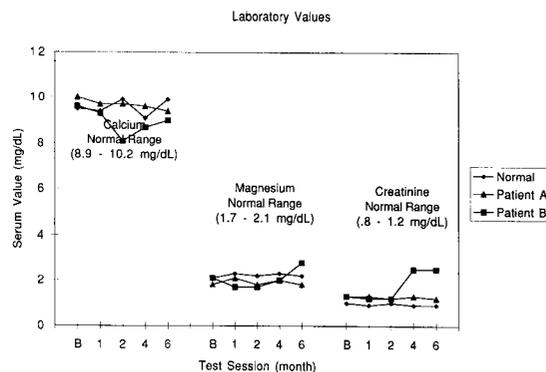Patient B demonstrated significant changes in hearing during the study. Threshold shifts

Figure 3 Calcium, magnesium, and creatinine serum levels (mg/dL) for normal control, patient A, and patient B over 6 months.

from baseline ranged from 15 dB to 65 dB at 6000 Hz for both right and left ears after baseline testing, with the greatest hearing loss noted above 2000 Hz (see Table 1).

Figure 4 (A and B) shows that slight increases in amplitudes of the DPOAEs for both ears were noted from baseline to 1-month testing. There were no measurable DPOAEs for either ear following 1-month testing. There was no change in serum magnesium during the study (see Fig. 3). The patient showed a decrease in serum calcium at 2 months and an increase in creatinine at 4 months beyond the normal range (0.6–1.2 mg/dL) for these serum values.

DISCUSSION

The present study demonstrated the variations in DPOAE amplitudes with and without concomitant changes in hearing thresholds over a 6-month period for cisplatin-treated patients supplemented with magnesium. Although loss of DPOAE amplitudes associated
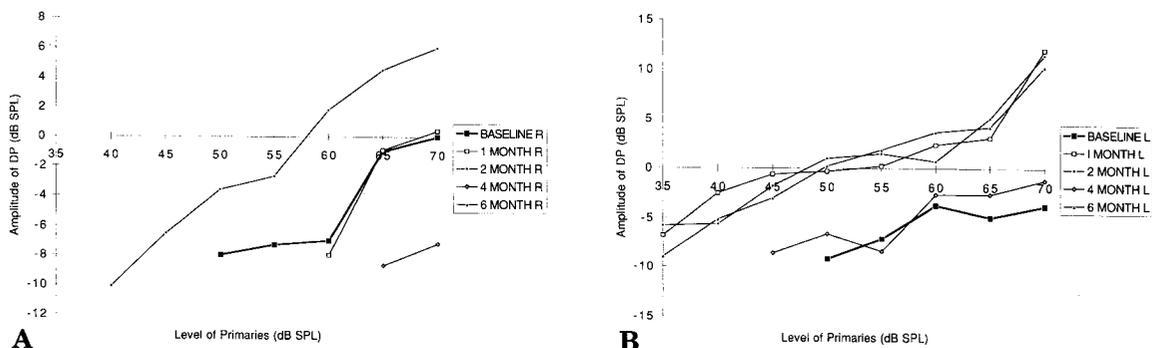

Figure 2 A, right ear; B, left ear. DPOAE growth functions at 5000 Hz for patient A, who was treated with cisplatin chemotherapy. The patient was supplemented daily with magnesium following baseline testing.
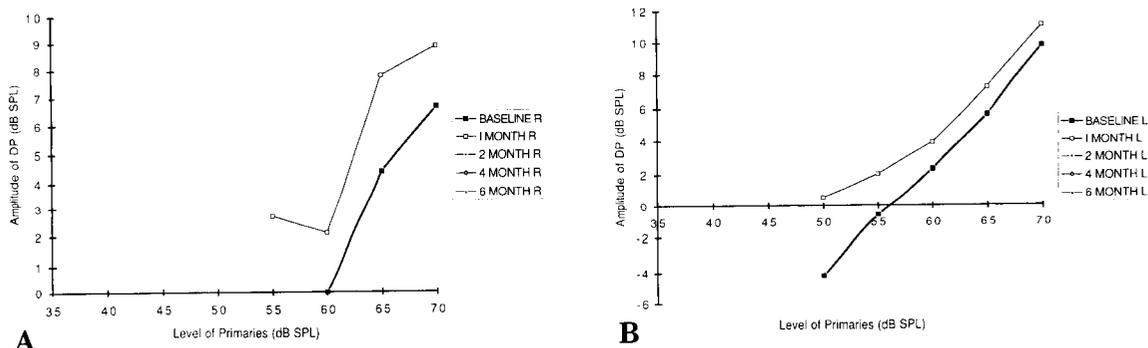
Figure 4 *A*, right ear; *B*, left ear. DPOAE growth functions at 5000 Hz for patient B, who was treated with cisplatin chemotherapy. The patient was supplemented daily with magnesium following baseline testing.

with loss of hearing is well known, increases in amplitudes of DPOAEs during cisplatin treatment in humans have not been reported previously.

The observations of significant fluctuations in DPOAE amplitudes of patients undergoing cisplatin treatment and normal controls supplemented with magnesium warrant further investigation. Laboratory measurements continue to remain a poor index of magnesium status (Seelig, 1981). If cisplatin ototoxicity is a magnesium-dependent phenomenon, then supplementation prior to, during, and after treatment may prove to be beneficial. The permanent changes in kidney function may play a role when further decreases in hearing loss are seen after the ototoxic drug has been discontinued. It is well known that patients with kidney disease are more susceptible to hearing loss associated with ototoxic drugs than those with normal kidney function.

There was no consistent relationship between hearing thresholds, DPOAE amplitudes, and serum magnesium, calcium, or creatinine that can be drawn from the two case studies. However, the longitudinal data showing the increases and decreases in these measures on a case-by-case basis are important. First, DPOAE amplitudes can increase and decrease independently of hearing thresholds, as seen in patient A. Second, increased levels of creatinine and decreased levels of serum calcium were associated with large changes in hearing thresholds and the loss of DPOAEs, as seen in patient B. Finally, hearing thresholds changed following similar patterns of fluctuation month to month in a normal-hearing patient who was supplemented with magnesium.

Amplitude increases of both TEOAEs and DPOAEs during and after ototoxic amikacin

treatment in an animal (chinchilla) model have been shown (Kakigi et al, 1998). The investigators noted that as a basal cochlear lesion progresses apically, there is often a transient increase in a frequency-specific OAE before it decreases or is lost. Their findings suggested that the increase in OAE amplitudes precedes the expression of detectable cochlear pathology. In addition, localized damage to the apical or middle turn may be accompanied by an increase in OAE measured from the adjacent apparently normal cochlea (Raveh et al, 1998).

The underlying mechanism responsible for these observed changes remains elusive. There are several important features of cisplatin therapy and auditory function that suggest that changes in magnesium metabolism, and subsequently calcium metabolism, may be underlying factors:

- Cisplatin treatment causes a severe loss of magnesium most likely due to nephrotoxicity (Daugaard et al, 1988).
- Cisplatin causes hearing loss by blocking OHC metabolism (McAlpine and Johnstone, 1990).
- Magnesium deficiency increases plasma membrane permeablity of the OHC to an influx of calcium and sodium (Brusilow and Gordes, 1973; Feldman and Brusilow, 1976).
- Chemical changes following cisplatin administration show a significant increase in the levels of intracellular calcium, sulfur, and phosphorus in abnormal hair cells (Comis et al, 1986).
- The OHC resting membrane potential is determined by a Ca_{2+}-activated K_+ conductance at the base of the OHC (Ashmore and Meech, 1986).

- Increased cytosolic calcium is associated with cellular death (Trump et al, 1984; Cheung et al, 1986).
- Small decreases in brain magnesium are accompanied by marked alterations in the auditory excitability of the brain (Chutkow and Grawbow, 1972; Chutkow, 1980).
- Hyperacusis has been associated with elevated serum calcium levels (Klein et al, 1990).

The anecdotal data from these case studies represent a preliminary report of magnesium supplementation over a 6-month period. As investigators evaluate the use of DPOAEs in monitoring ototoxicity, it may be important to examine the relationship between magnesium deficiency and hearing loss. The changes in the handling of electrolytes in cisplatin are well known. There is much that is known about the changes in OHC transduction. It may be equally important to consider that fluctuations in DPOAEs may be related to magnesium and calcium metabolism. Perhaps further clinical investigations in magnesium and calcium metabolism may provide the additional insight into the underlying mechanisms responsible for hearing loss in ototoxicity.

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