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Ototoxicity and Irradiation: Additional Etiologies of Hearing Loss in Adults

George T. Mencher*
George Novotny†
Lenore Mencher*
Mark Gulliver*

Abstract

A brief review of the effects of the seven groups of substances and chemicals known to affect hearing and/or the vestibular system is followed by a more detailed discussion of cisplatin (cisplatinum). An illustrative case study is included that exemplifies a recent finding of some recovery of hearing following withdrawal of cisplatin chemotherapy. Some suggestions for reducing the potential for ototoxicity are also presented. The article continues with a discussion of the effects of irradiation on hearing and the ear and an illustrative case study. Included are some reported results from patients in the Ukraine who were exposed to excessive radiation as a result of the Chernobyl nuclear disaster. A discussion of the effects on the ear and the vestibular system caused by the interaction between chemotherapy and irradiation treatment is followed by the warning that, with the recent successes these treatments have had in the war against cancer, more patients with hearing loss triggered by these techniques will be seen in audiology clinics. These factors are now one of the newest and more frequent etiologic factors for hearing loss in adults in this decade.

Key Words: Cisplatin, irradiation, ototoxicity

One of the chief goals of medical research is the discovery of a successful treatment for disease. For neoplasms, the primary treatment outside of surgery is chemical therapy and/or irradiation. There is, unfortunately, accumulating evidence that either or both of these treatments can result in hearing loss. In fact, these iatrogenic determinants probably represent two of the more frequent etiologic factors in hearing loss in adults today. Obviously, if the choice is hearing impairment or death, use of techniques that may result in hearing loss is more understandable. However, a keen awareness of acceptable levels of exposure is necessary to reduce risk, limit any actual loss, and facilitate management of the patient whose hearing is affected. Clearly, with each new drug and each new treatment, there is potential for a new etiologic factor for hearing loss.

*Nova Scotia Hearing and Speech Clinic, Halifax, Nova Scotia, Canada; †Dalhousie University, Halifax, Nova Scotia, Canada

Reprint requests: George T. Mencher, Nova Scotia Hearing and Speech Clinic, Fenwick Place, 5599 Fenwick St., Halifax, Nova Scotia, Canada B3H 1R2

CHEMOTHERAPY/OTOTOXICITY

There are seven groups of substances and chemicals known to affect hearing and/or the vestibular system:

1. Antibiotics;
2. Diuretics;
3. Analgesics and antipyretics;
4. Antimalarial agents;
5. Antineoplastic agents;
6. Miscellaneous drugs, including antihepatinizing agents, anticonvulsive drugs, and beta blocking agents; and
7. Chemicals (mercury, lead, alcohol, etc.)

Chief among the symptoms associated with these agents are sensorineural hearing loss, vertigo, nausea, and tinnitus. The first sign is usually a complaint about tinnitus and a muffling of speech. The type and extent of loss and the reported symptoms vary significantly with the drug used, dosage, method of administration,

renal function, individual susceptibility, previous hearing loss, and other factors.

Recently, antineoplastic agents, most specifically, cisplatin (cisplatinum), have come to our attention as potentially ototoxic. Chemotherapy regimens utilizing cisplatin have been reported to cure 60–100 percent of patients with advanced germ cell tumors affecting the head and neck, ovaries, and other soft tissue areas. The ear appears to be most affected by single, high-dose injections, but the cumulative effect of repeated low-dose treatments has also been noted.

Van der Hulst et al (1988) reported incidence rates for hearing loss ranging from 4–91 percent, but noted that variability is a function of the terminology utilized to define ototoxic change. The hearing loss is usually bilateral and permanent, primarily affecting 4000 Hz and above, although lower frequencies have been affected in some patients. It has also been suggested that patients might develop a "base" amount of hearing loss, which is unspecified and remains constant no matter what the dosage or how long it is prolonged. There are also reports of partial recovery of hearing following termination of drug therapy (Skinner et al, 1990). A case from our center may further illustrate that phenomenon.

Table 1 illustrates the audiometric results for the right ear of a 2.5-year-old male with a diagnosed neuroblastoma. The patient demonstrated identical patterns of loss in both ears; however, we are presenting only one side to facilitate interpretation. Throughout all testing, tympanometry was normal, that is, normal static compliance and pressure. Furthermore, acoustic reflex thresholds were within expected levels. Speech reception threshold remained at 10 dB or better on all tests, and speech discrimination scores remained at 92 percent. Because of the age and delicate nature of the child, we did not attempt tests of central function. Note the decrease in high-frequency response over time and with continued treatment of cisplatin. What is of interest are the results obtained 3 months following completion of cisplatin therapy. Note the decrease at 2000 Hz, but the small increase in audiometric response "recovery" at some higher frequencies. Unfortunately, the child died and we were unable to confirm the degree and progress of this initial recovery.

Individual susceptibility to ototoxic effect has been an area of detailed study. As with other ototoxic substances, pre-existing hearing loss, age,

Table 1 Audiometric Results of a Male with a Stage IV Neuroblastoma Treated with Cisplatin Chemotherapy

	Hearing Level (Hz)				
Status	*500*	*1000*	*2000*	*4000*	*8000*
Start of treatment	15	10	15	10	10
3 mo later	15	10	15	30	No test
3 mo later	15	10	15	50	65
End of treatment	15	10	20	65	80
3 mo later	15	10	30	55	70

and kidney function have been shown to be confounding variables in determination of cisplatin ototoxicity (Laurell and Skedinger, 1990). There seems to be some disagreement about any correlation between hearing loss and patient age (Kretschmar et al, 1990; Laurell and Jungnelius, 1990; Skinner et al, 1990). Increased dosage and increased age, combined, seem to be critical factors.

Recently, Schwan et al (1992) suggested that there may be other physiologic risk factors. They divided 42 head and neck cancer patients undergoing cisplatin chemotherapy into two groups: those resistant and those susceptible to hearing loss following treatment. Utilizing prechemotherapy blood chemistry work-ups, the authors found statistically significant differences (< 0.05) between resistant and susceptible hearing loss groups for the factors albumin, hemoglobin, red blood cell count, and hematocrit. They concluded that the albumin results reflect poor nutritional and physical condition, something known to occur in head and neck cancer patients. This implies that poorer general health is associated with greater risk for cisplatin-induced hearing loss. They suggested that lower plasma albumin levels may have resulted in higher levels of active cisplatin in plasma, because only that fraction of the cisplatin not bound by plasma proteins is considered to be active in toxicity. The authors also concluded that red blood cell count, hemoglobin, and hematocrit results in the susceptible group suggest relatively poorer oxygen transport capabilities. This could mean that intervention by blood transfusion, general nutritional support, and administration of supplemental oxygen could potentially reduce the risk of cisplatin-induced hearing loss.

Clearly, if this susceptibility model is accurate and was to be applied to other potentially ototoxic drugs, it could be a valuable tool in preventing hearing loss. Further research with all

Table 2 Effect of Irradiation Therapy on Hearing*

Authors	Number of Patients (N = 275)	Rad Level	Type of Hearing Loss			Patients Affected %
			Conductive	Sensorineural	Unknown	
Borsanyi et al	14	4000–6000		X		100
Leach	56	3000–12000		X		36
Dias	29	1000–18000		X	X	50
Moretti	13	6000–24000		X		54
Kupperman et al	100	?		X		9
Thibadoux et al	61	2400			X	0
Coplan et al	1	5000		X	X	100
Talmi et al	1	24000		X		100
Shidlovckaya	?	.25–1.0 Gy		X		42
Mean						55.4

*Based upon Talmi et al (1989).

These results relate to complete body exposure to radiation, which is not easily directly comparable to a pinpointed specific dosage delivered under controlled circumstances. A radiologist can be exposed to 5.0 Gy over a year and still be within acceptable levels of safety.

types of drugs should be encouraged along these lines.

Audiometric monitoring for ototoxicity is the most common method for tracking hearing loss. Since changes in the audiogram only occur after ototoxicity has begun and the hair cells are damaged, this is a bit like closing the barn door after the cattle are out. However, audiometric monitoring can still be an effective method of preventing further deterioration if the loss can be detected before it reaches the critical speech frequencies. Recently, it has been suggested that the audiometric criteria for monitoring ototoxicity should involve multiple-frequency averaging above 8000 Hz (Simpson et al, 1992). Fausti et al (1992) have reported a five-frequency screening test, specific to each individual's hearing threshold configuration, as highly sensitive to early ototoxic change. The authors suggest examining the highest frequency at which each subject's threshold is at ≤100 dB SPL and the next four lowest frequencies. Usually, at least three of the test frequencies will be above 8000 Hz. Any change of 20 dB or more in one frequency, 10-dB change in two consecutive frequencies, loss of response at any three consecutive frequencies, or consistent change over at least two test sessions should be considered a sign of ototoxic change and the appropriate actions taken.

IRRADIATION

In addition to chemotherapy, focal irradiation is often a treatment of choice for patients with carcinoma. Adverse effects depend upon the amount of radiation absorbed and on the quantity delivered. For example, damage is almost always present following doses higher than 6000 Rad, but doses of 3000 Rad may or may not affect hearing. The basic reaction to irradiation, which may implicate the middle or inner ears, is an inflammation of the endothelium of the blood vessels leading to vasodilation and then destruction of the vascular lumen. The result is soft tissue that is injured or prone to injury, as well as being highly susceptible to infection. It is not uncommon for the effects of radiation treatment to be delayed for months or years after exposure. Schuknect and Karmody (1965) describe changes due to soft tissue irradiation, including inflammatory changes in the skin of the auricle and external auditory canal and in the mucosal membrane of the middle ear, atrophy of the organ of Corti, destruction of hair cells, and atrophy of the basilar membrane, spiral ligament, and stria vascularis. If irradiation absorption is sufficient enough to implicate bony structures, the effect might be delayed in onset, but the result would include death of osteocytes, alteration in new bone formation, and loss of marrow substance. A necrosis of the outer and middle ear structures including the ossicles is not uncommon. Because the focus of the irradiation and the dosage level can vary so significantly, there is no specifically defined hearing loss one would expect to see in these cases. Talmi et al (1989) summarized a large portion of the literature concerning irradiation. Table 2 is primarily based upon their work.

A case we have been following at the clinic clearly illustrates the difficulties faced with these patients (Table 3). The case study involves a 5′2″ female of normal weight, blood pressure, gait, and neurologic behavior. Cranial nerves, with the exception of factors related to hearing

Table 3 Case Study of a Female with a Right Acoustic Neuroma

Treatment	Cobalt radiation for 6 wk — dosage unknown (1965); incomplete excision of 1979 — tumor crossed midline.
Pertinent History	Original diagnosis was incomplete with tentative label of demylinating disease; necrotized otitis externa, keratin debris and exposed portion of left canal floor; post surgery: Right VII N paralysis.
Visit 1: January 19/84	Right Ear: No response. Left Ear: 45 dB 500, 1000, 2000, and 4000 Hz within normal limits, 35 dB 8000 Hz. No PIPB rollover. 98% disc, reflex, and impedance within normal limits. ABR: Waves I and III within normal limits. Wave V extended causing interpeak latencies to be abnormal (I–V = 4.80). Recommendations: Otologic/neurologic evaluation. There was very limited follow-up.
Visit 2: October 4/85	Left Ear: Patient to emergency room with sudden onset of HL 60–70 dB HL across all frequencies, SN/flat 24% disc, recruitment present, impedance within normal limits, no reflex. Patient complains of left hemiparesis or paraesthesia. Admitted to hospital; CT scan, ABR scheduled. Treatment: 80 mg of prednisone (3 days).
Visit 3: October 6/85	Left Ear: 40 dB 500, 1000, 2000, and 4000 Hz within normal limits, 45 dB 8000 .92% disc, reflex and impedance within normal limits. ABR: Waves I and III within normal limits. Wave V extended causing interpeak latencies to be abnormal (I–V = 5.08). Diagnosis: CAT scan with enhancement, results within normal limits. Undetermined diagnosis.
Visit 4: November 23/85	Left Ear: Patient to emergency room with sudden onset of HL. 1-day transient episode previous week. No CNS or visual symptoms. No response to auditory stimuli. Admitted to hospital; ENT suspects hydrops. Treatment: 80 mg of prednisone (3 days).
Visit 5: November 24/85	Left Ear: 40 dB 500 Hz, 20 dB 1000 and 2000 Hz, 30 dB 4000 Hz, 50 dB 8000 Hz. 88% disc, reflex and impedance within normal limits. Diagnosis, repeat CAT scan within normal limits. Neurology/ENT staffing and consultation.
Visit 18: March 20/92	Left Ear: 50 dB 500 Hz, 25 dB 1000 and 2000 Hz, 45 dB 4000 Hz, 90 dB 8000 Hz. 88% disc, reflex ?, impedance within normal limits; attempting a hearing aid. Necrosis of ear canal and occasional ME infection. Status: No further emergency SNHL problems. Drug therapy as recommended.

CNS = central nervous system, ME = middle ear, SNHL = sensorineural hearing loss.

loss and a facial nerve (C VII) paralysis, are within normal limits. Diagnosis of this case was very difficult. First, the question of demyelinating disease, such as multiple sclerosis, was considered as the etiology of her hearing loss. However, this was ruled out because anyone who had such a disease over the 20 years of this case would have many additional signs, and there were none. By the same logic, a generalized collagen vascular disease was ruled out by our neurologist, as he would have expected to find some other symptoms or signs. There were none.

The patient's hearing loss does include a low-frequency component and a 1–2 kHz peak suggestive of Meniere's disease. While Meniere's disease or hydrops is a possibility, the neurologist disagreed, arguing that the audiometric and behavioral patterns seen in this patient ruled out that etiology. He suggested that the fluctuating hearing loss was due to vascular insufficiency secondary to postradiation necrosis at the brain stem, probably involving vessels coming off the basilar artery and/or both vertebrals. This area was in the stream of radiation at the time of the episode in 1965. He recommended that the patient should be on a low-dose steroid to see if further difficulty could be prevented. He also suggested putting her on entrophen as an antiplatelet preparation to ease the flow of blood through the damaged area. He instructed the woman to avoid salt, alcohol,

cheese, red wine, and the chocolate complex, all of which are known to affect people with migraines by enhancing vessel spasms.

We are pleased to report that the latest information regarding this lady indicates that the diagnosis and treatment seem to have been correct.

IRRADIATION THERAPY AND CHEMOTHERAPY COMBINED

The synergistic effect of these two treatment regimes is quite important to consider. Skinner et al (1990) described two children in whom aural radiotherapy prior to exposure to cisplatin yielded similar results; that is, a severe hearing loss. Walker et al (1989) and Sweetow and Will (1993) discussed the question and concluded that there is a synergistic effect, but it may be limited in direction. That is, if a patient has received irradiation prior to chemotherapy, there may be enhanced ototoxicity. Conversely, if the patient has been given ototoxic drugs first and then has been irradiated, the probability of a significant hearing loss is less likely. Obviously, this latter conclusion is mitigated by the age of the patient and the dosage. The question of directionality is an interesting one, and perhaps the young woman described in the case from our clinic offers some insight into its basis. Initial drug therapy acts on an otherwise healthy system. However, drug therapy applied to a system that has received prior irradiation acts on damaged tissue, weakened blood supply, and an already disturbed environment. It is possible that the effects may simply be accumulative, but it is more likely that the irradiation has provided a "predisposition" to damage.

RECENT EVENTS

Shidlovckaya of the Kiev Research Institute of Otolaryngology has been studying a group known as the "Liquidators," those individuals charged with the clean-up following the Chernobyl nuclear power plant disaster. There is no question that those unfortunate people have been exposed to excessive levels of radiation. The difference between them and those patients discussed earlier is, of course, that the patients have been exposed to specific and focal irradiation of controlled dosages, while the Chernobyl Liquidators have been exposed to full-body radiation in uncontrolled amounts.

Shidlovckaya (1992) reports that her patients have evidenced a number of serious disorders (Table 4), including hearing loss. Hearing impairments involved all aspects of the auditory mechanism, sensory and conductive. When Shidlovckaya divided her population into three groups — Liquidators, who worked directly at the disaster site; residents of Narodichi district, a community nearby; and residents of Ivankov district, a community some distance from the disaster site — an interesting pattern in the auditory results emerged. Even though hearing impairment appeared in only 42.2 percent of the Liquidators, objective analysis indicated that, in 100 percent of those examined, there are disturbances or abnormalities of the acoustic reflex, and of the brain stem and cortical evoked potential tracings. This is true even when hearing is normal. Furthermore, the greater the individual's distance from the disaster site (e.g., lesser radiation exposure), the less likely it was that these deviations would be present (Table 5).

Table 4 Disorders Noted as a Result of Chernobyl Nuclear Plant Disaster

	Patients Affected (%)
Headaches	82.3
Memory impairment	58.3
Vertigo	91.3
Nausea	97.8
Equilibrium disorder	81.3
Tinnitus	46.8
Hearing impairment	42.2

From Shidlovckaya (1992).

Unfortunately, other than to comment that the wave I–V interpeak latency value was important in detecting alteration of the brain stem due to irradiation, Shidlovckaya did not specify precise details about exact values and specific latencies. Obviously, this is an important area of further research and could have a significant impact on our reaction to patients who have been exposed to radiation treatment.

While the work of the group from Kiev may initially appear to be tangential to a discussion

Table 5 Reported Abnormalities of the Auditory System (%)

Group	*Acoustic Reflex*	*ABR*	*Cortical Evoked Response*
Liquidators	100	100	100
Narodichi district	43	78	85
Surrounding area	21	34	20

of new etiologies of hearing loss, it does have a specific relevance. It is evident from the results reported earlier by Talmi et al (1989), as well as that reviewed by Schuknect and Karmody (1965), that any hearing loss associated with irradiation may be gradual in development and slow in onset. The outcome is a function of dosage, absorption, susceptibility, etc. By the same token, the work of Shidlovckaya suggests there may be a predictor of that outcome through an early view of auditory brainstem response (ABR), cortical, and acoustic reflex test results.

Early abnormal ABR results and tracings, even in the face of normal hearing, may point to the impending onset of a hearing loss (Lau et al, 1992). Armed with that information, the clinician should monitor irradiated patients in the same fashion as those undergoing chemotherapy are monitored. As Shidlovckaya suggested, we can use these results as an objective criterion for revealing early preclinical disturbances of the acoustic analyzer.

Obviously, if the choice is severely limited, use of a therapeutic technique that may result in hearing loss is more understandable. A keen awareness of acceptable levels of exposure is necessary to reduce risk, limit any actual loss, and facilitate management of the patient whose hearing is affected. Supposedly, there is now careful monitoring of those exposed to ototoxic drugs and, perhaps, to radiation therapy, although there does seem to be some doubt about this latter factor. On faith, then, we might accept the notion that we must be controlling the side effects of drug therapy and minimizing the number of people who become ototoxic cases. On the other hand, because treatments such as cisplatinum and irradiation have proven to be effective in limiting the growth and spread of carcinomas, we know that they are in more widespread use and, consequently, more patients are living longer. This has to mean that it is highly likely that more patients are being left with a hearing loss. However, it is hard to prove exact prevalence or incidence figures because ototoxicity/radiation statistics are not well kept or easily interpreted and, in many cases, hearing loss is not considered relevant in the face of life-threatening disease. This is further compounded by the fact that many patients do not survive, and, consequently, their hearing losses are unrecorded. The result of all this is that we do not know how much ototoxicity and radiation-based hearing loss there really is. We believe that ototoxicity and radiation therapy are much larger etiologic factors in adult hearing loss than has been suspected, and should clearly be recognized as major factors in the etiology of adult hearing disorders. It is vital that these patients be monitored routinely for hearing loss, and that every possible step be taken to ensure that the prolonged life now possible has richness and quality as well as quantity.

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