Tinnitus and Hearing Loss Following Administration of Ototoxic Drugs in Humans: Results of a Large Prospective Study

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Introduction

Certain therapeutic drug treatments cause damage to the inner ear, resulting in tinnitus, hearing loss, and dizziness [1]. There is ample evidence that these symptoms adversely affect post-treatment quality of life. For example, there is a link between the presentation of ototoxic symptoms and increased clinical complaints of stress, pain, and neuropsychiatric disorders [2]. While hearing loss incidence has been reported for numerous ototoxic drugs, comparatively little is known about the incidence of other ototoxic symptoms. The archival literature lacks a large prospective study of ototoxicity-induced tinnitus and the relationship between drug-related changes in tinnitus and hearing status.

This poster reports results of a large prospective study that is part of a Veteran's Affairs Rehab R&D project to develop methods for early detection and monitoring of ototoxicity-induced hearing loss. The veteran population includes a higher proportion of individuals compared to the general population who are older and have a history of noise exposure, tinnitus and hearing loss. These factors may influence ototoxicity rates [3, 4]. The primary goal of this study was to determine the incidence of ototoxicity-induced tinnitus onset and hearing loss in veterans treated with the platinum-based chemotherapy agents cisplatin and carboplatin or with certain aminoglycoside antibiotics. A secondary goal was to determine the temporal relationship between drug-induced changes in hearing sensitivity and tinnitus status.

Methods

A. Subjects

Data from 35 female and 453 male adults (962 ears) were included in this study. *Experimental subjects* were adult in-patients and out-patients receiving cisplatin (CDDP group) or carboplatin (Carbo group) or specified antibiotics including the aminoglycosides amikacin, tobramycin and gentamicin, or the antibiotic vancomycin (AMG group) at one of three VA Participating Sites: VA Medical Centers at Portland, OR; Nashville, TN; and West Los Angeles, CA. *Control Subjects* were recruited from hospitalized patients at the sites who were prescribed non-ototoxic antibiotics including ceftriaxone, ampicillin, clindamycin or nafcillin, and had no pathology consistent with fluctuating hearing loss.

◆ ***Inclusion Criteria.*** Subjects (1) received at least one chemotherapeutic treatment of cisplatin or carboplatin, or more than 3 days of antibiotic medication; (2) had no active or recent history of middle ear pathology; (3) had no history of retrocochlear or Meniere's disease; (4) were able to respond reliably to behavioral pure tone audiometry based on repeated measures within the individualized sensitive frequency range (SRO) [5].

B. Procedures

Behavioral hearing thresholds were measured through 20,000 Hz and were compared to results of ear-specific tinnitus surveys. Audiometric and survey data were obtained prior to, during, and following drug treatment.

◆ ***Baseline Evaluation.*** Baseline evaluations provided the reference from which all further tests were compared and included: (1) case history, noise exposure and tinnitus history; (2) otoscopy; (3) tympanometry; (4) pure-tone thresholds (0.5 to 8 kHz in 1/2-octave steps and 9 to 20 kHz in 1/6th- octave steps); and (5) identification of uppermost frequency with a threshold of ≤ 100dB SPL followed by the adjacent six lower frequencies in 1/6th octave steps (SRO).

◆ ***Baseline Recheck.*** The baseline evaluation was repeated within 24 hours or as soon as possible, to determine intersession reliability. Subjects were excluded from the study if test-retest differences exceeded 5 dB.

◆ ***Monitor Evaluations.*** CDDP and Carbo subjects were tested within 24 hours of each dose. AMG and Control subjects were monitored every 2 to 3 days throughout the treatment course. Monitor evaluations included: (1) tinnitus questionnaire; (2) otoscopy; (3) tympanometry; and (4) puretone thresholds.

◆ ***Immediate Post-treatment and Follow-up Evaluations.*** Immediate post-treatment evaluations were obtained as soon as possible after the medication was discontinued and follow-up evaluations were obtained at one, three, and six months following treatment using the same procedure as monitor evaluations.

We calculated hearing change separately for ears with and without tinnitus at baseline in order to (1) assess whether ears with pre-existing tinnitus were more likely to show ototoxic hearing change; and (2) define ototoxic change by *both* hearing and tinnitus onset in ears free from tinnitus at baseline. Tinnitus onset could be reliably reported by subjects, whereas change in existing tinnitus was difficult to quantify and qualitative descriptions lacked internal consistency.

C. Criteria for Tinnitus

We analyzed responses to two questions on the tinnitus questionnaire that were repeated at each evaluation: (1) Does the subject have tinnitus? (2) If so, in which ear? Audiologists administering the questionnaire explained to subjects that an affirmative answer was appropriate when tinnitus was present most of the time, whether it was an intermittent or constant sound.

D. Criteria for Hearing Change

Subjects served as their own control for hearing change, which was relative to their baseline evaluation. ASHA 1994 guidelines for identifying ototoxic hearing change [6] were used, which include one of three criteria: (1) ≥ 20 dB change at any one test frequency; (2) ≥ 10 dB change at any two consecutive test frequencies; or (3) loss of response at three consecutive test frequencies where responses were previously obtained. The guidelines further stipulate that hearing change by any of these criteria must be confirmed by retest.

Results

Does exposure to ototoxic drugs cause tinnitus?

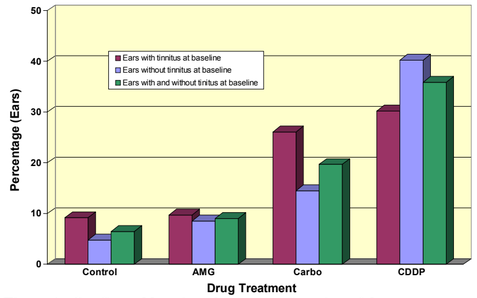

Figure 1. Confirmed hearing change as a function of drug-treatment group. Percentages were calculated for each treatment group (green bars) and separately for ears with (red bars) and without tinnitus (purple bars) at baseline. Hearing change was determined relative to baseline measures and present on two consecutive audiograms.

- Confirmed hearing change in ears with and without tinnitus at baseline (Fig. 1, green bars) was significantly different from Controls and therefore attributable to ototoxicity for each ototoxic-drug treatment group.
- For Control and Carbo groups, hearing change rates were greater for ears with tinnitus (red bars) compared to ears without tinnitus (purple bars) at baseline.

Table 1. Group information for ears with and without pre-existing tinnitus. Number of ears and baseline tinnitus rates are shown for each treatment group. T = ears with tinnitus at baseline; No T = ears tinnitus-free at baseline. Group means and standard deviations are given for age, high-frequency pure-tone average, HF PTA (1, 2 and 4 kHz in dB SPL), and the highest-frequency behavioral threshold able to be obtained (equipment limits were 110-115 dB SPL, depending on frequency).

Treatment Group	Baseline	N	% T at Baseline	Age in Years mean (SD)	HF PTA in SPL mean (SD)	Highest Fq in kHz mean (SD)
CDDP	T	162	44%	59.6 (9.2)	43.8 (17.2)	10.6 (3.3)
	No T	206	56%	60.9 (10.6)	38.0 (16.2)	11.3 (3.2)
	Total	***368***		***60.3 (10.0)***	***40.5 (16.9)***	***11.0 (3.3)***
Carbo	T	69	45.4%	64.5 (11.2)	48.4 (17.4)	9.5 (3.6)
	No T	83	54.6%	62.5 (9.1)	38.8 (19.0)	10.5 (3.3)
	Total	***152***		***63.4 (10.1)***	***43.2 (18.8)***	***10.1 (3.4)***
AMG	T	102	42.3%	55.0 (10.8)	39.7 (18.9)	11.9 (3.0)
	No T	139	57.7%	55.7 (10.7)	34.4 (15.1)	10.7 (3.5)
	Total	***241***		***55.3 (10.7)***	***36.6 (17.0)***	***11.4 (3.3)***
Control	T	76	37.8%	54.7 (12.0)	38.3 (19.5)	11.42 (3.4)
	No T	125	62.2%	53.1 (12.3)	30.7 (16.7)	12.3 (3.1)
	Total	***201***		***53.7 (12.1)***	***33.6 (18.1)***	***12.0 (3.3)***
Grand Total	T	409	42.5%	58.5 (11.0)	42.6 (18.4)	10.6 (3.5)
	No T	553	57.5%	57.9 (11.4)	35.5 (16.7)	11.5 (3.2)
	Total	***962***		***58.1 (11.2)***	***39.2 (18.0)***	***11.1 (3.3)***

- Baseline tinnitus rates across groups were high (37.8 to 45.4%) compared to the general population (10 to 15%) [7], and somewhat higher than tinnitus rates reported for individuals over age 65 (30%) [8]. This may be explained in part by the sample consisting primarily of sick patients, who tended to be older individuals with pre-existing hearing loss and a history of noise exposure.
- Baseline tinnitus rates and HF PTA were similar for groups receiving ototoxic drug treatment.
- Subjects free from tinnitus bilaterally at baseline were used to provide evidence for a link between administration of ototoxic drugs and tinnitus.

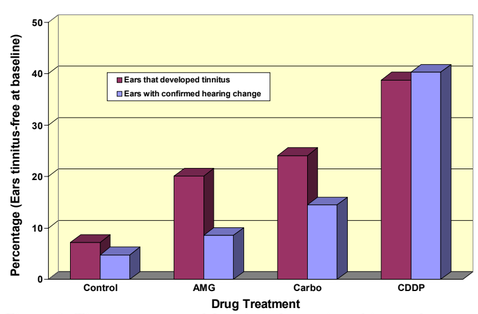

Figure 2. Tinnitus onset and hearing change in subjects who were tinnitus-free at baseline. Hearing change (purple bars) was re-plotted from Fig. 1.

- Tinnitus developed in a significantly greater proportion of CDDP, Carbo, and AMG ears compared to Controls.
- CDDP treatment resulted in tinnitus onset more often than treatment with Carbo or AMG. Differences in ototoxicity rates across treatment groups could not be attributed to age or baseline hearing sensitivity.
- For CDDP ears, tinnitus onset and hearing change occurred with similar frequency. In contrast, tinnitus onset rates were higher than hearing change rates for Carbo and AMG ears. This effect also is evident when data are re-analyzed to show ototoxic symptoms in subjects, rather than ears (see Fig. 3).

For subjects who did not have tinnitus at baseline, is drug-induced tinnitus correlated with drug-induced hearing loss?

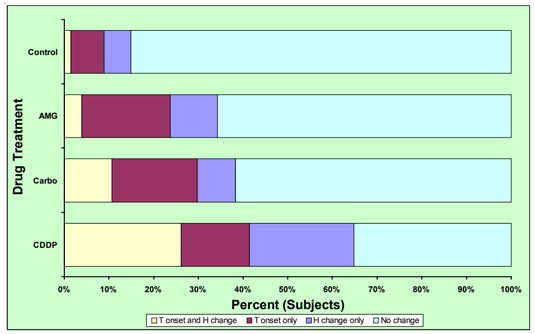

Figure 3. Ototoxic symptoms in subjects tinnitus-free at baseline. Percent of subjects that developed tinnitus and/or experienced hearing change in at least one ear.

- Only 14.9% of hospitalized Controls developed tinnitus and/or experienced hearing change compared to 34.2% of AMG-, 38.3% of Carbo-, and 64.9% of CDDP subjects.
- These data can be used to estimate the relative risk for developing ototoxic symptoms for patients treated with ototoxic drugs (incidence in ototoxic-drug treatment group divided by incidence in the Control group). The risk of developing tinnitus and/or hearing loss in at least one ear is 2.3 times greater (34.2/14.9=2.3) for AMG patients, 2.6 times greater (38.3/14.9=2.6) for Carbo patients, and 4.4 times greater (64.9/14.9=4.4) for CDDP patients compared to hospitalized patients receiving non-ototoxic drugs. Relative risk is less when calculated using hearing change alone and may underestimate ototoxicity.
- Tinnitus and hearing loss did not always co-occur. In ears tinnitus-free at baseline, CDDP subjects developed hearing loss alone with about the same frequency as tinnitus and hearing loss combined, and at a slightly greater rate than tinnitus alone. In contrast, subjects who received Carbo and AMG were more likely to develop tinnitus alone than hearing loss alone or tinnitus and hearing loss in combination. The latter result highlights the importance of tinnitus monitoring as part of any ototoxicity-monitoring program.

In ears without tinnitus at baseline, where both tinnitus and hearing loss develop, is tinnitus an early indicator of ototoxic hearing loss?

- Data from a subset of 56 cisplatin and carboplatin-treated ears that developed both tinnitus and hearing loss were used to determine whether there was a consistent pattern in the development of these two symptoms. 16 ears (28.6%) developed tinnitus before behavioral change occurred; 23 ears (41.1%) developed tinnitus after the behavioral change and in 17 ears (30.3%) the change occurred concurrently.
- These preliminary data do not suggest ototoxicity-induced tinnitus proceeds hearing loss. However, further analysis is required to verify this result.

Conclusions

Ototoxic drugs cause tinnitus. Ototoxic symptoms of tinnitus and/or hearing change occurred in 34% of AMG-, 38% of Carbo-, and 65% of CDDP subjects. Ototoxic agents are commonly used therefore ototoxicity has a large impact on tinnitus and hearing loss occurrence.

Cisplatin appears to be more ototoxic compared to carboplatin or aminoglycoside antibiotics, consistent with previous findings [1].

Tinnitus onset and hearing change occurred with similar frequency for cisplatin-treated subjects, but the incidence of tinnitus onset was higher than the incidence of hearing change following carboplatin and aminoglycoside treatment. The latter result indicates that tinnitus monitoring should be included in ototoxicity-monitoring protocols.

Further analysis of our sample with an emphasis on hearing and tinnitus changes that persist following cessation of drug treatment is warranted.

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Acknowledgements

Work supported by the Department of Veterans Affairs RR&D Service (grants C3213R and E3239V) and the VA RR&D National Center for Rehabilitative Auditory Research, Portland, OR.