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 and their related changes affect post-treatment quality of life. For example, there is a link between the presentation of ototoxic symptoms and increased clinical symptoms of pain, stress, and psychiatric disorders [2]. While hearing loss incidence has been well documented for ototoxic drugs, comparatively little is known about the incidence of other ototoxic symptoms. The archival literature lacks a large retrospective study of toxicity-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 ototoxic-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 as 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 specific 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 history consistent with fluctuating hearing loss.

Inclusion Criteria: Subjects (1) received at least one chemotherapy treatment of cisplatin or carboplatin, or more than 50 days of antibiotics, had been opioid naive or 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 (SRQ) [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 were performed from the reference from which all further tests were compared and included: (1) case history and ototoxicity history, (2) otoscopy, (3) tympanometry at baseline, (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 any asymmetry in hearing or tinnitus.

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

- **Monitor Evaluations**: Cisplatin and Carboplatin subjects were tested within 24 hours of each dose. AMG and Control subjects were monitored every 2 to 3 days throughout the treatment course. Monitoring evaluations included: (1) tinnitus questionnaire; (2) otoscopy; (3) tympanometry; and (4) pure-tone 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 6 months following the procedure 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 ototoxicity due to tinnitus and hearing changes in at least one ear.

C. Criteria for Tinnitus

We analyzed responses to two questions on the tinnitus questionnaire that were repeated at each evaluation: (1) Do you have a constant or variable hearing. (2) If so, in which ear? Audiolists 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 were used to identify: (1) 20 dB change at any test frequency; (2) a 20 dB change at any two consecutive test frequencies; or (3) any three consecutive test frequencies where responses were consistent.

The guidelines further stipulate that hearing change by any of these criteria must be confirmed by retest.

Results

Table 1. Group information for Tinnitus and Hearing Loss Following Administration of Ototoxic Drugs in Humans: VA RR&D National Center for Rehabilitative Auditory Research, Portland, Oregon

<table>
<thead>
<tr>
<th>Drug Treatment</th>
<th>Control</th>
<th>AMG</th>
<th>Carbo</th>
<th>CDDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ears</td>
<td>409</td>
<td>139</td>
<td>162</td>
<td>83</td>
</tr>
<tr>
<td>Ears with tinnitus at baseline</td>
<td>162</td>
<td>162</td>
<td>162</td>
<td>83</td>
</tr>
<tr>
<td>Ears that developed tinnitus</td>
<td>115</td>
<td>83</td>
<td>112</td>
<td>75</td>
</tr>
<tr>
<td>Total</td>
<td>277</td>
<td>252</td>
<td>274</td>
<td>158</td>
</tr>
</tbody>
</table>

- **Baseline**: Baseline tinnitus rates across groups were high (37.4% to 45.4%) compared to the general population (10% to 15%) [6], 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 healthy patients, who tended to be older individuals with pre-existing hearing loss and a history of noise exposure.

- **Baseline tinnitus rates in ears with and without tinnitus**: Number of ears and baseline tinnitus rates were shown for each treatment group. T = ears with tinnitus at baseline. N = total number of ears. Tinnitus-free at baseline. Group means and standard deviations were given for age, high-frequency pure-tone average, HT PA (1, 2, and 4 kHz in dB SPL), and the highest-frequency pure tone able to be obtained (behavioral limits were 10-15 dB SPL, depending on frequency).

- **Confirmed hearing change in ears with and without tinnitus**: Confirmed hearing change in ears with and without tinnitus at baseline. Hearing change was determined relative to baseline tinnitus-free and present on two-consecutive audiograms.

- **For Control and Carbo groups**: Hearing change rates were greater for ears with tinnitus than for ears without tinnitus (p-value < 0.001).

- **For CDDP subjects**: Tinnitus developed in a significantly higher rate than hearing change in at least one ear.

- **Only 14.9% of Hospitalized Control subjects developed tinnitus as experienced hearing change compared to 32.4% of AMG, 38.3% of Carbs, and 64.9% of CDDP.

These data can be used to estimate the relative risk for developing ototoxic effects for patients treated with ototoxic drugs.

![Figure 1. Confirmed hearing change as a function of drug-treatment group.](image1)

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

- **Do not have tinnitus at baseline**: Percent of subjects that developed tinnitus and hearing change in at least one ear.

Conclusions

Otic toxic drugs cause tinnitus. Tinnitus of ototoxicity and/or hearing loss occurred in 34% of CDDP, 38% of Carboplatin, and 32% of AMG subjects. These differences were attributed to age or baseline hearing loss amplitude. The primary result is that tinnitus monitoring is an important tool in detecting ototoxic symptoms.

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

- **CDDP 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 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 deep tinnitus alone than hearing loss alone or tinnitus and hearing loss combination. The last result highlights the importance of tinnitus monitoring as part of any ototoxicity-monitoring program.

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

References


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