Tinnitus Onset Rates from Chemotherapeutic Agents and Ototoxic Antibiotics: Results of a Large Prospective Study

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Abstract

Background and Purpose: To report on the incidence and relative risk of tinnitus onset from a variety of drug therapies known to be ototoxic. Two main questions were asked: (1) What is the prevalence and incidence of tinnitus among patients treated with cisplatin, carboplatin, or ototoxic antibiotic therapies? (2) Do commonly reported treatment or subject factors confound or modify the incidence of tinnitus onset?

Data Collection and Analysis: A prospective observational study design was used to evaluate occurrence of significant otologic changes in 488 veterans (962 ears) receiving chemotherapeutic agents (cisplatin, carboplatin), ototoxic antibiotics (primarily aminoglycoside), or nonototoxic drugs (control medications). A subset of 260 veterans lacking tinnitus prior to drug exposure was used to compare rates of tinnitus onset. Subjects were tested prior to, during, and following their treatment. Planned comparisons using logistic regression, analysis of variance (ANOVA), and χ^2 statistics were made among groups by the type of medication taken, age, presence of preexisting hearing loss, days on drug, and cumulative dose of drug.

Results: Baseline tinnitus rates were high (nearly 47%) relative to the general population of a similar age. Subjects with exposure to ototoxic medications had significantly increased risk for developing tinnitus. Those on chemotherapeutic agents were found to have the greatest risk. Cisplatin elevated the risk by 5.53 times while carboplatin increased the risk by 3.75 over nonototoxic control medications. Ototoxic antibiotics resulted in borderline risk (2.81) for new tinnitus. Contrary to other reports, we did not find that subject factors (increased age or pre-existing hearing loss) or treatment factors (days on drug or cumulative dose) contributed to rates of tinnitus onset during treatment.

Conclusions: This large prospective study confirms that new tinnitus during treatment is associated with chemotherapy and with certain ototoxic antibiotic treatment. Cisplatin and carboplatin were found to be the most potent ototoxic agents causing tinnitus at much greater numbers than the other drugs studied. Implications for counseling and audiological resource allocation are discussed.

Key Words: Ototoxicity, ototoxicity monitoring, tinnitus, veterans

Abbreviations: PTA = pure-tone average; RR = relative risk; SRO = sensitive range for ototoxicity

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Certain chemotherapeutic (e.g., cisplatin, carboplatin) and antimicrobial (e.g., gentamicin, tobramycin, vancomycin, and amikacin) drugs necessary for the treatment of cancer and serious infection are toxic to the inner ear structures and can result in tinnitus, hearing loss, and vestibular dysfunction (Brummett, 1980; Govaerts et al, 1990; Shotland et al, 2001). Of particular interest are the effects to the cochlea, the sensory organ responsible for hearing. These side effects, termed "ototoxicity," can decrease psychosocial, physical, and overall quality of life for patients during and after treatment (Mulrow et al, 1990). For example, hearing loss can impair speech understanding at a time when communication with family members and health-care providers is vital. Tinnitus can cause strong emotional reactions and can interfere with sleep and concentration (Dobie, 2003; Sindhusake et al, 2003). While incident, or new, cases of hearing changes are commonly reported in the literature, few studies have reported the incidence of tinnitus resulting from ototoxic medication administration.

Chemotherapeutic agents such as cisplatin and carboplatin are generally regarded as the most ototoxic. Because of its well-known ototoxicity, hearing change during cisplatin chemotherapy is often reported. Further, there are reports that tinnitus can be as common as hearing changes with some reports that tinnitus may be the earliest noticeable sign of ototoxicity (Lesar, 1993; Seligmann et al, 1996). In a quality-of-life study following cisplatin treatment for testicular cancer, at 2 yr postchemotherapy, persistent tinnitus continued to be reported in 20–25% of these primarily younger cancer survivors, and "worsened hearing" was reported in 21% (Fossa et al, 2003).

Other studies have found similar rates of persisting and often irritating tinnitus. Bokemeyer et al, (1998) reported on 86 patients treated with cisplatin for testicular cancer followed for at least 12 mo after completion of treatment. They found that nearly 20% (17 subjects) complained of persisting ototoxic symptoms (persistent hearing shift or tinnitus). Ten (12%) of those 17 complained of tinnitus only, and another four (5%) complained of both tinnitus and hearing shift while three (3%) complained of persistent hearing shifts only. Of the 14 subjects with tinnitus complaints, 10 described their symptoms as "very disturbing" or "moderately annoying." Rybak (2005) reported on the incidence of tinnitus from cisplatin exposure and found that 15–38% reported persistent tinnitus with or without concurrent hearing change 1–2 yr after cessation of treatment. Arora et al (2009) found 10.7% of subjects reported tinnitus during cisplatin treatment for head and neck cancers while Biro et al (2006) similarly found rates of 15%. Finally, both Kopelman et al (1988) and Hallmark et al (1992) commented that their study subjects had complaints of tinnitus, but unfortunately neither study quantified the incidence.

Ototoxic antibiotic use has been declining in the United States but is still widespread in the developing world (Dobie, 2008). Aminoglycosides, used in the treatment of serious infections in the United States, are now thought to be less ototoxic than previously believed (Brummett and Morrison, 1990; Schmuziger et al, 2004). This reduction in ototoxicity is due to a variety of factors including changes in the administration of these drugs to reduce their potential toxicity, recognition of familial predispositions for aminoglycoside ototoxicity, and the identification of drug interactions that can increase the potency of some aminoglycosides (Rizzi and Hirose, 2007). Recent reports suggest the incidence of hearing change resulting from aminoglycosides ranges between 2 and 5% (Contopoulos-Ioannidis et al, 2004; Rizzi and Hirose, 2007). Unfortunately, unlike the incidence of hearing change, tinnitus incidence is often not included in reports of comorbid conditions during ototoxic antibiotic treatment.

The lack of published results highlighting the risk of tinnitus resulting from ototoxic medication administration impedes the assessment of associated risk factors. While the relationship between increasing ototoxic drug dosages and hearing change is widely accepted in the literature, the dose-toxicity relationship between increasing drug dose and tinnitus onset has not been discussed. Though not as widely accepted as the increasing risk of hearing change with increasing dosage, previous reports have suggested that individuals toward the ends of the age spectrum (very young and elderly) and individuals with poorer hearing at baseline are at increased risk for ototoxicity and may confound the dose-toxicity relationship. Although this has been investigated for hearing change, it has not been studied for the onset of tinnitus and a gap in the literature remains.

The failure of some studies to report or quantify tinnitus as an ototoxic symptom may be because it does not have the same level of urgency as hearing loss. However, the negative impact of tinnitus on the quality of life during and following cancer treatment motivates this study. A further motivation is that having incidence and risk ratios for new tinnitus in the armamentarium of counseling tools available to an audiologist is important.

This article reports results of a large prospective study that was part of a Veterans Affairs Rehabilitation Research and Development (VA RR&D) Service project to develop methods for early detection and monitoring of ototoxic hearing change. The primary purpose of this report was to determine the prevalence of tinnitus (or how many people in a defined population have tinnitus) in hospital-treated veterans and compare the incidence (or new onset) of tinnitus across a variety of drug therapies known to be ototoxic. Further, we wanted to explore potential confounders (age, preexisting hearing loss) and effect modifiers (drug dose and duration) related to incident cases of tinnitus.

METHODS

Subjects

Subjects were recruited from VA Medical Centers located in Portland, Oregon; Nashville, Tennessee; and West Los Angeles, California; and from Vanderbilt Medical Center. Behavioral results have been reported previously for many of these subjects (Fausti et al, 1999, 2003b; Vaughan et al, 2002). The present report describes tinnitus data obtained in 488 subjects, 35 female and 453 males (962 ears).

Experimental subjects were drawn from inpatients and outpatients receiving potentially ototoxic drugs that were among those prescribed most frequently at the participating medical centers. These drugs included the antineoplastic, chemotherapeutic agents: cisplatin (Cisplatin Group) and carboplatin (Carboplatin Group) prescribed as treatment for several types of cancer; the aminoglycoside antibiotics: amikacin, gentamicin, and tobramycin, and the glycopeptide antibiotic vancomycin given as treatment for serious infection (Ototoxic Antibiotic Group). Experimental subjects received a minimum of one chemotherapeutic treatment of cisplatin or carboplatin or at least three days of ototoxic antibiotic administration. Therapeutic regimens (drug dosages, treatment schedules, and length of treatment) varied within treatment groups in order to best serve the therapeutic needs of each patient.

An important aspect of this work was the selection of a control group in which factors affecting test-retest variability would be similar to that of subjects undergoing medical treatment with ototoxic drugs. Thus, the Control Group comprised hospitalized subjects receiving widely used nonototoxic antibiotics including ceftriaxone, ampicillin, clindamycin, or nafcillin. Further, the Control Group was not administered any other known ototoxic substances and was comprised mainly of VA subjects.

All subjects met the following additional inclusion criteria: subjects (1) had not received a potentially ototoxic drug within the previous 30 days; (2) had measurable pure tone thresholds in at least one ear; (3) had no active or recent middle ear pathology; (4) had no history of retrocochlear or Ménière's disease. Informed consent was obtained from each subject prior to participation following the guidelines of each participating hospital's institutional review board, and subjects were compensated for their time.

Test Protocol

A baseline evaluation was performed within the week prior to or within 24 hr following initial treatment with a chemotherapy agent and within 72 hr of the first antibiotic treatment for both the Ototoxic Antibiotic Group and the Control Group. Baseline evaluations included a hearing evaluation, done as a part of the larger prospective study, a brief tinnitus questionnaire, and counseling. The hearing evaluation included otoscopy, tympanometry, and pure-tone air conduction threshold testing (0.5–20 kHz) including the individualized sensitive range for ototoxicity (SRO) determined as the uppermost frequency at which threshold is 100 dB SPL or better and the next six consecutively lower frequencies in 1/6-octave steps. The tinnitus questionnaire was aimed at determining prevalence of tinnitus prior to drug exposure (Question: Do you have ringing, buzzing or other noise in your head? Answer: Yes/No). Subjects comprising the Cisplatin, Carboplatin, and Ototoxic Antibiotic Groups received counseling regarding the effects of the study medication on the auditory system. The baseline evaluation provided the reference with which all further findings were compared.

Follow-up evaluations mirrored the baseline evaluations including tinnitus questions and occurred within 24 hr of the treatment date for cisplatin or carboplatin administration. Subjects receiving antibiotics (both ototoxic antibiotics and control antibiotics) were followed weekly throughout the treatment course. When possible, evaluations were also performed immediately after treatment had been discontinued and at one, three, and six months after treatment. In addition to the tinnitus prevalence question noted above, a question targeted at determining tinnitus incidence was now included (Question: Have you noticed any ringing, buzzing or other noise in your head since you started treatment? Answer: Yes/No).

Tinnitus Questionnaire

Tinnitus has proven to be a difficult percept to quantify. An important first step in measuring tinnitus incidence would be to choose a parameter of tinnitus, such as onset, that can be more reliably quantified and is time efficient. For the purposes of this report, only two questions were considered for analysis: (1) Question: Do you have ringing, buzzing, or other noise in your head? Answer: Yes/No; and (2) Question: Have you noticed any ringing, buzzing, or other noise in your head since you started treatment? Answer: Yes/No. If the subject reported tinnitus, a follow-up question was asked whether one or both ears were involved. The questions were scripted and asked the same each time.

Tinnitus assessment, including definition and questions, must be worded carefully because prevalence and incidence will vary greatly depending on how lax or how strict the definition of tinnitus. More general definitions will capture both transient and chronic tinnitus sufferers; whereas strict questions and definitions of tinnitus will capture only the chronic tinnitus sufferers and/or chronic tinnitus sufferers who are

bothered by their tinnitus. Since the larger prospective study was aimed at early detection and monitoring, the more general tinnitus definition was established (i.e., duration and rate of recurrence was not relevant) with the known but circumscribed possibility of overreporting tinnitus prevalence and incidence.

Tinnitus questionnaires such as the Tinnitus Handicap Inventory or the Tinnitus Handicap Questionnaire are often related to the self-perceived handicapping nature of tinnitus. These questionnaires presume tinnitus is present. The purpose of this paper was to ascertain a causal relationship between ototoxic medication administration and the onset of tinnitus.

Statistical Analysis

Descriptive statistics for groups were compared using one-way analysis of variance (ANOVA). Chi-square analyses were utilized to compare categorical variables among groups. Statistical significance was achieved if *p value*s were less than 0.05.

Prevalence and incidence are both reported. Prevalence in this report is defined as the proportion of veterans with tinnitus during the baseline evaluation among those enrolled in the study. Incidence is the proportion of veterans reporting the new onset of tinnitus during a period of time following study entry. The incidence proportion can be reported for those exposed (Cisplatin, Carboplatin, and Ototoxic Antibiotic Groups) and for those unexposed (Control Group). The tinnitus incidence proportion in the exposed veterans relative to the incidence proportion in the unexposed veterans yields a risk (incidence proportion) ratio and provides an estimate of the relative risk (RR).

RR is the underlying relationship of interest between the "true" risk of ototoxicity in the exposed group in comparison to the "true" risk of ototoxicity in the unexposed group. It is reported as the number of times greater (or less) risk in the exposed relative to an unexposed population. An RR of 1.0 implies no increased risk with exposure. An RR <1.0 implies decreased risk with exposure, and conversely, an RR >1.0 implies an increased risk with exposure. Associated 95% confidence intervals (CI) are also reported and represent the 95% likelihood that the true RR falls between the lower and upper portion of the 95% CI. If the 95% CI includes 1.0, it is generally accepted that the drug exposure is not statistically associated with the outcome (new tinnitus).

Finally, logistic regression was used to determine if age, pre-existing hearing loss, total cumulative drug dose, or total drug duration was associated with an increased risk of new tinnitus and to determine which confounded or modified any observed association. Main effects were considered to be significant at the .05 level and interactions at the .10 level.

RESULTS

Study Sample

A total of 9853 adult subjects were screened for eligibility through medical record review over a period of 6 yr. Subjects were excluded for a variety of reasons including severe illness, less than three days on medication (for the antibiotic groups only), hospital discharge before enrollment, receipt of a potentially ototoxic medication within the previous 30 days, mentally incompetent to provide consent, or refusal to participate. Of this group approximately 607 subjects and 1214 ears met the inclusion criteria. Of these 1214 ears, an additional 21 ears were excluded because hearing loss was too severe, 198 ears had baseline hearing test data only with no follow-up testing done, and 33 ears had no baseline tinnitus data recorded. Thus, data from a total of 488 subjects (962 ears) with two or more behavioral hearing tests and corresponding tinnitus data were included in this study. Data for both ears were included except for 12 males and 2 females from which only monaural data were obtained.

Group information for subjects stratified by medication type is given in Table 1. Just over half (54.1%) of the 488 subjects included in the study sample belonged to the chemotherapy group (cisplatin and carboplatin). Hospitalized subjects being treated with potentially ototoxic antibiotics constituted 25.6% of the study sample, and hospitalized subjects receiving control medications constituted 20.3% of the study sample.

There were significant differences found between the treatment groups in their age. Results of an ANOVA showed a significant main effect of age among the treatment groups ($F = 17.2$, *p value* <0.001). Subjects receiving cisplatin and carboplatin were older compared to subjects receiving ototoxic antibiotics (Bonferroni adjusted p-value <0.001 for both comparisons). However, cisplatin- and carboplatin-treated subjects did not differ with respect to age (p-value = 0.22). Neither was age significantly different between subjects receiving ototoxic antibiotics and control subjects (*p value* = 1.0). Table 1 also shows comparisons regarding the mean PTA (pure-tone average) and SRO thresholds. Overall, there were no significant differences among subjects between treatment group in terms of hearing abilities at the pre-exposure baseline audiogram ($F = 1.76$, *p value* = .16).

Tinnitus Prevalence (Prior to Treatment)

Prior to this report, there have been no publications that we are aware of reporting the prevalence of tinnitus among veterans in general. We found that the prevalence of veterans who reported tinnitus in at least one

Table 1. Group Information for Subjects by Medication Type

	Treatment Group					
	Cisplatin	Carboplatin	Ototoxic Antibiotic	Control	Total	*p value*
N	186	78	125	99	488	–
Tinnitus Prevalence	47.3%	51.3%	46.4%	42.4%	46.7%	.70
Age	60.3 (10.0)	63.4 (10.1)	55.2 (10.8)	53.9 (12.1)	58.2 (11.2)	<.001
PTA	44.9 (20.0)	48.6 (22.3)	38.5 (19.6)	34.5 (20.2)	41.7 (20.8)	<.001
SRO Average	72.4 (14.2)	73.8 (14.0)	69.8 (13.2)	70.5 (15.0)	71.6 (14.1)	.16

Note: Prevalence of tinnitus at baseline with means and SD for age, high-frequency pure-tone average (PTA = 2, 3, 4 kHz), and SRO average threshold (highest octave of hearing) for each medication type. Associated *p value*s were derived from χ^2 analysis for tinnitus prevalence and by one-way ANOVA for both age and SRO average threshold.

ear was high, 46.7% (228/488 subjects). Of the 14 subjects contributing monaural data, 6 reported tinnitus. Of the remaining 474 subjects contributing binaural data, 41 (8.6%) reported unilateral tinnitus and 181 (38.2%) reported bilateral tinnitus. Further, the prevalence was similar across all study groups as seen in Table 1 (Pearson $\chi^2 = 1.417$, $p\ value = 0.78$). Since the subjects in this study were primarily veterans with some preexisting hearing loss and a likely history of significant noise exposure, we conclude that this prevalence, while high, may be normal for this population. The remaining 260 subjects without tinnitus at the (pre-exposure to drug) baseline visit (8 contributing monaural data and 252 contributing binaural data) were used to evaluate and quantify the incidence of tinnitus during the study period. Subjects contributing data from both ears but who had tinnitus in one ear (but not the other ear) were not included in this group for analysis.

Tinnitus Incidence Proportions (during Treatment) and Relative Risk

The report of tinnitus (i.e., its presence or absence) was generally consistent across test sessions in control subjects in comparison to other subjective aspects of tinnitus (e.g., length of percept). Of the control subjects with and without tinnitus prior to their medication regimen, only 6% (6/99) reported a change in their tinnitus (onset or disappearance). Given this very small change, the subjective evaluation of tinnitus incidence was deemed reliable.

Table 2 provides a cross-tabulation of 260 subjects without tinnitus at the baseline (pre-exposure) evaluation who went on to develop tinnitus. Overall, the incidence proportion among veterans exposed to ototoxic medications was 30.0% (61/203), and the incidence proportion within the control group was 7.0% (4/57). Thus, among subjects, the RR of developing tinnitus in veterans exposed was 4.28 (95% CI: 1.63–11.27) times the risk of veterans unexposed to ototoxic medications.

When stratified by drug exposure, it is apparent that cisplatin was more likely to result in tinnitus onset (38.8%) than either of the other ototoxic medication groups. While carboplatin (26.3%) and ototoxic antibiotics (19.4%) are considerably less ototoxic, they still have relatively high incidence proportions when compared with the control group of hospitalized subjects on non-ototoxic medications (7.0%). In this study, the underlying risk of developing tinnitus for subjects exposed to cisplatin was 5.53 times (95% CI: 2.08–14.68) the risk in unexposed subjects. The risk of developing tinnitus with exposure to carboplatin or ototoxic antibiotics was 3.75 (95% CI: 1.27–11.09) and 2.81 (95% CI: 0.96–8.00) times greater, respectively, than the unexposed. With the exception of ototoxic antibiotics in which the 95% CI includes 1.0, the risk of tinnitus among those exposed is statistically higher compared to those unexposed. While a CI that includes 1.0 suggests no association, the χ^2 value ($p\ value = 0.046$) is borderline significant ($p\ value < 0.05$). This discrepancy is related to differences in how CIs and *p value*s are calculated. However, considering the direction and magnitude of the CIs, it is likely that subjects exposed to ototoxic antibiotics are at an increased risk for developing tinnitus compared to hospitalized subjects not receiving ototoxic agents. In general, veterans exposed to the study medications are at elevated risk for new tinnitus.

Potentially, the incidence could be elevated when considering subjects as the unit of analysis compared to ears as the unit of analysis. Therefore, incidence proportions and RR were determined among the 553 ears (504 ears from 252 subjects free of tinnitus in both ears, eight ears from subjects contributing monaural data, 41 ears from 41 subjects free of tinnitus in one of two ears) that were tinnitus free at baseline and contributing either one or both ears to the analysis. Of the 553 ears, 434 ears from subjects were administered an ototoxic medication and 119 ears comprised the subjects of the control group. Of ears exposed to potentially ototoxic medications, 128 developed tinnitus, representing an incidence of 29.5%. Among control subjects the incidence of tinnitus was 7.6% (9/119). When stratified by drug group, the RR of new tinnitus was nearly identical whether considering ear level or subject level data. The

Table 2. Incidence of New Tinnitus among the 260 Subjects without Tinnitus at Baseline

	No Tinnitus	Tinnitus	Total	Incidence*	RR†	95% CI	
						Lower Bound	Upper Bound
Cisplatin	60	38	98	38.8%	5.526	2.080	14.681
Carboplatin	28	10	38	26.3%	3.750	1.268	11.092
Ototoxic Antibiotics	54	13	67	19.4%	2.807	.955	8.009
Control	53	4	57	7.0%	–	–	–
Total	195	65	260	25%	–	–	–

*Tinnitus/Total

†Incidence in exposed/Incidence in unexposed (subject to rounding errors)

similar findings regardless of whether ear or subject level data were used in the analysis likely results from the overwhelmingly bilateral report from most subjects (80%). Table 3 reports the number of subjects who contributed binaural data at baseline that went on to report unilateral or bilateral new tinnitus. Due to the nearly identical results between ears and subjects, only subject data are reported.

Assessment of Potential Confounders and Effect Modifiers

Age

As described above in the "Study Sample" section, the chemotherapy treatment groups were generally older than either the Ototoxic Antibiotic Group or the Control Group; thus, it is possible the high rates of new tinnitus in the chemotherapy groups were influenced by the age of the subject. Table 4 presents tinnitus onset collapsed across treatment groups. There was no significant age difference (p *value* = 0.66) between those who experienced new tinnitus during treatment (mean = 58.4 yr) and those subjects who did not report the onset of tinnitus (mean = 57.7 yr). Therefore, increasing age was not associated with an increased risk of tinnitus onset. However, it is apparent from Table 4 that those subjects who report new tinnitus were, in fact, younger on average than subjects who remained tinnitus free. Conversely, subjects within the Control Group who experienced new onset tinnitus were older than their tinnitus-free counterparts. Therefore, age, drug group, and their interaction were assessed by a multivariate logistic regression. The interaction was not significant (p *value* = 0.24), and after adjusting for the medication type, there was no significant association between the age of a subject and the onset of tinnitus (p *value* = 0.35). Thus the age of a subject did not influence the onset of tinnitus.

Pre-exposure Hearing Levels

At baseline, the Ototoxic Antibiotic Group and the Control Group had better average hearing thresholds than the chemotherapy groups, likely related to the younger subjects who comprise those groups. A closer look at baseline hearing levels collapsed across treatment groups and stratified according to tinnitus onset is presented in Table 4. The baseline high-frequency PTA levels for those who experienced tinnitus during treatment (39.3 dB SPL) and for those subjects who did not report the onset of tinnitus (37.3 dB SPL) were not significantly different (ANOVA, p *value* = 0.48). When stratified by drug type, the baseline hearing levels within the chemotherapy groups who experienced tinnitus during treatment were better than the baseline hearing levels of their tinnitus-free counterparts. The reverse was observed within the antibiotic groups such that subjects experiencing tinnitus during treatment had poorer hearing than their tinnitus free counterparts. The multivariate logistic regression model including drug type, pre-exposure hearing level, and the interaction between the two was done. The interaction was not significant (p *value* = 0.33) and neither was pre-exposure hearing level after adjusting for drug type (p *value* = 0.27).

Another measure of hearing is the average SRO (highest octave) hearing thresholds. Among those

Table 3. Prevalence of New Tinnitus in Subjects Who Contributed Data from Both Ears

	Developed Unilateral Tinnitus	Developed Bilateral Tinnitus	Total
Cisplatin	5 (13.2%)	33 (86.8%)	38
Carboplatin	4 (40.0%)	6 (60.0%)	10
Ototoxic Antibiotic	3 (23.1%)	10 (76.9%)	13
Control	1 (25.0%)	3 (75.0%)	4
Total	13 (20.0%)	52 (80.0%)	65

Table 4. Development of Tinnitus: Patient and Treatment Factors

Drug	Developed Tinnitus		Pure-Tone Average	Age	Days Exposed	Total Cumulative Drug Dose
Cisplatin	*No Tinnitus*	Mean	43.7 (20.7)	61.8 (12.0)	44.6 (51.6)	440.2 (325.6)
		N	60	59	59	55
	Tinnitus	Mean	39.4 (17.5)	59.3 (8.5)	53.0 (72.1)	441.0 (282.3)
		N	38	38	38	37
	Total	Mean	42.1 (19.6)	60.8 (10.8)	47.9 (60.3)	548.7 (829.8)
		N	98	97	97	94
Carboplatin	*No Tinnitus*	Mean	44.7 (22.4)	63.0 (10.0)	49.4 (30.8)	1633.9 (1080.5)
		N	28	28	27	26
	Tinnitus	Mean	35.9 (21.7)	60.1 (7.0)	122.4 (105.5)	2804.0 (2354.0)
		N	10	10	9	8
	Total	Mean	42.4 (22.3)	62.2 (9.3)	67.7 (65.4)	1909.2 (1521.1)
		N	38	38	36	34
Ototoxic Antibiotic	*No Tinnitus*	Mean	34.6 (17.7)	55.6 (10.6)	27.3 (52.0)	21215.8 (28495.4)
		N	54	54	52	52
	Tinnitus	Mean	41.5 (21.2)	52.9 (11.6)	18.9 (26.3)	28030 (42440.9)
		N	13	13	13	13
	Total	Mean	35.9 (18.5)	55.0 (10.8)	25.6 (47.9)	22578.6 (31501.2)
		N	67	67	65	65
Control	*No Tinnitus*	Mean	28.9 (16.7)	52.4 (12.5)	6.7 (7.4)	22090.2 (22354.6)
		N	53	53	41	41
	Tinnitus	Mean	39.6 (19.8)	63.3 (9.2)	7.3 (2.5)	37266.7 (5154.0)
		N	4	4	3	3
	Total	Mean	29.7 (16.9)	53.2 (12.5)	6.7 (7.2)	23125.0 (21933.4)
		N	57	57	44	44
Collapsed across Treatment Groups	*No Tinnitus*	Mean	37.3 (20.1)	57.7 (12.2)	*	*
		N	195	194	*	*
	Tinnitus	Mean	39.3 (18.7)	58.4 (9.3)		
		N	65	65	*	*
	Total	Mean	37.8 (19.7)	57.8 (11.5)		
		N	260	259	*	*

** Since dosing regimens varied widely across treatment groups, no beneficial information can be derived from the mean data collapsed across all treatment groups.*

subjects without tinnitus at baseline, there was also no significant difference (ANOVA, $p\ value = 0.143$) in SRO average hearing between those subjects who experienced new tinnitus and those who did not. This was true even when stratified across drug treatment group and compared ($p\ value = 0.252$). Thus, there was no relationship found between pre-existing cochlear damage, measured as either high-frequency PTA or as average SRO hearing, and the development of tinnitus.

Cumulative Drug Dose

The effect of cumulative dose on an ototoxic medication was evaluated to determine if it modified the association with tinnitus onset. Again logistic regression was used to determine if there was a relationship between the cumulative drug dosage and the presence of new tinnitus for each treatment group, resulting in three univariate analyses. Interestingly, we did not find a relationship between total dose of any ototoxic drug and tinnitus. The overlap of dosages was large between the treatment groups with and without tinnitus onset (Table 4). The associated logistic regression *p value*s for the Cisplatin, Carboplatin, and Ototoxic Antibiotic Groups were 0.89, 0.09, and 0.49, respectively. This was somewhat surprising since ototoxic symptoms, particularly hearing shifts, are often linked in the literature with cumulative dose. However, there has not been as clear a link made between tinnitus onset and cumulative dose to date.

Number of Days Exposed

Table 4 also shows the number of days on average that each group of subjects was on their medication. Again logistic regression was used to determine if there was a relationship between the total number of days exposed and the presence of new tinnitus for each drug type, resulting in three univariate analyses. Results of the logistic regression *p value*s mirrored that of

cumulative drug dose for the Cisplatin (0.51) and Ototoxic Antibiotic (0.58) Groups, which were not significant. However, increasing time of exposure to carboplatin (p *value* = 0.02) was associated with the onset of tinnitus in subjects who were tinnitus free at baseline. An interesting pattern is observed within the Ototoxic Antibiotic Group in that subjects reporting the new onset of tinnitus received a larger cumulative dose of antibiotics over fewer days, suggesting tinnitus may be associated with more drug over shorter time periods, though no significant effects were found.

DISCUSSION

Summary

This large-scale study is the first to report the prevalence of tinnitus among veterans seeking hospital treatment. Prior to exposure to ototoxic drugs, veterans were asked if they had tinnitus. We found that the proportion of tinnitus among veterans is higher than in the general population and higher even than a subset of persons closer to their age range. Nearly 47% of veterans in our study reported tinnitus, which is high when compared with the prevalence of tinnitus in the general population (10–20%) (Bokemeyer et al, 1998; Davis and Rafie, 2000; Sindhusake et al, 2003). This rate was also high even when compared to individuals over 65 yr of age (30%) also from the general population (Sindhusake et al, 2003). When considering the degree to which we might be overestimating the incidence of new tinnitus among patients taking potentially ototoxic medication, we also believe error of the estimate is small. This study has used an appropriate control population of hospitalized patients on medications that have not been found to be ototoxic. The incidence of new tinnitus in this control group was 7%. Therefore, the estimated error in the report of new tinnitus using more general (lax) tinnitus questions is ±7% accuracy. This estimated error in our measurement suggests that the general questions used in this study about tinnitus change, which is a subjective percept and based on memory, are, in fact, remarkably reliable.

The main purpose of this large prospective investigation was to provide much-needed information on the incidence and relative risk of tinnitus onset among veteran subjects receiving ototoxic medications. Consistent with other reports, cisplatin was the most ototoxic agent in our study. While carboplatin was less ototoxic, it also resulted in high rates of new tinnitus. However, ototoxic antibiotics only marginally increased the risk for new tinnitus.

Subject-level information is provided in this study since it is the most relevant information for an audiologist to have when providing counseling prior to and during treatment. Cisplatin resulted in nearly 39% of subjects developing tinnitus during treatment. Taking cisplatin increased the risk for developing tinnitus by 5.53 times. Carboplatin also resulted in a significant increase in new tinnitus (26.3%) and higher RR (3.75).

It is noteworthy that the control group did experience some changes in tinnitus over the study period. While this occurred at a much lower incidence (7%) than for the treatment groups, it did occur and most likely reflects the degree to which health issues can affect the incidence (and report of) tinnitus. It is also important to recall that the current study did not address perceptual changes in tinnitus that might have occurred among those subjects with tinnitus at baseline. In our experience, these perceptual changes in tinnitus do occur. Further, subjects in this investigation were not followed beyond six months. We do not know if the tinnitus resolved after treatment, but the literature suggests that the percept in some can last longer than 1–2 yr.

Commonly reported in the literature is that older patients and those with preexisting hearing loss are at an increased risk for developing ototoxic symptoms. We did not find either of these contentions to be necessarily true. The mean age of veterans on chemotherapy was greater than those on ototoxic antibiotics or control medications. However, their age did not influence whether they would experience new tinnitus. The presence of a preexisting hearing loss, measured either as high-frequency PTA or average SRO thresholds, was also not a good predictor. Rather, it was the medication they took that was associated with new tinnitus.

We did not find that the cumulative dose of the drug had an effect on new tinnitus rates. This was surprising since cumulative dose is commonly found to be related to hearing shifts during treatment. We had large variation in the report of cumulative dose in our data. We attempted to approach cumulative dose comparisons another way by comparing the number of days a subject was on each medication across the drug treatment groups. An extended number of days on drug could be considered equivalent to a higher (cumulative) dose. Days on drug, we reasoned, might not have the same variability in report across centers. However, even using this metric, we did not find an association between the number of days on a drug and new tinnitus. It may be that the treatment factors commonly related to ototoxicity resulting in hearing change are different from the treatment factors that result in tinnitus onset. The lack of statistical significance in these comparisons means that we cannot rule out the possibility that these factors are important. Further research is needed to examine the risk factors associated with new tinnitus.

CLINICAL IMPLICATIONS

The results of this large prospective study may prove useful for treatment consideration when interacting with the medical team and for counseling patients

and their families. The majority of change associated with ototoxic medications was within the chemotherapy group. When facing life-threatening disease, social and clinical interactions become acutely important to the patient and family members. A tremendous impact toward well-being can be made by educating the patient and the medical team regarding what symptoms might be expected and what action to take should they occur. Knowing in advance that these symptoms can occur could help the patient avoid unnecessary anxiety and will alert the medical team to consider referrals to audiology should they occur.

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