Original Article

Ototoxicity: Scope and pattern in a tertiary hospital in Port Harcourt, Nigeria

Uju Matilda Ibekwe, Chibuike Nwosu, Jephtah Kpopene

Department of Otorhinolaryngology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria

Abstract

Background: Ototoxicity is a common cause of avoidable hearing loss in our environment. It is also an important factor of public health importance in developing countries. The aim of this study is to examine the pattern, note the prevalence and highlight the common medications implicated in ototoxicity in our environment.

Methods: This study is a 6-year retrospective review of patients diagnosed with ototoxicity that were managed at the otorhinolaryngology clinic from January 2011 to December 2016. The patients' case files and the clinical registries were the source of data. The data extracted for analysis were demographics, type of medication used, route of administration, duration, otologic symptoms, time of presentation and pure-tone audiometric findings. Data were analysed using SPSS software version 20.

Results: One hundred and thirty-six patients with ototoxicity were seen within the 6-year period, of which 71 had complete medical records and these were analysed. There were 37 males (52.1%) and 34 females (47.9%), giving a ratio of 1:1. The most common age group affected was 28–38 years. Unknown or unidentified medications (38%) were the most common cause of ototoxicity; among the known drugs, injection gentamicin (17%) and chloroquine (17%) were the most common implicated drugs, followed by quinine (12.7%). All the patients presented with hearing loss. Tinnitus was seen in 83.1%, whereas 22.5% had vertigo. Majority (56.3%) of the patients had severe-to-profound sensorineural hearing loss. There were more bilateral (80.3%) than unilateral (19.7%) cases. Majority (63.3%) of the patients presented after 2 weeks of the onset of symptoms.

Conclusion: Ototoxicity is still prevalent in our environment, with chloroquine and gentamicin being the most commonly implicated drugs. Most of the patients were found to have bilateral severe-to-profound sensorineural hearing loss.

Keywords: Hearing loss, ototoxicity, pure-tone audiometry

Address for correspondence: Dr. Uju Matilda Ibekwe, Department of Otorhinolaryngology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria.
E-mail: ibekwe_uju@yahoo.com

Received: 22.07.2018, **Accepted:** 17.12.2018

INTRODUCTION

Damage to the auditory and balance system of the inner ear caused by toxins is known as ototoxicity. The toxins from drugs and chemicals are more readily encountered; therefore, ototoxicity is often taken to be damages to hearing and balance as a result of medications. It means damage to the cochlea and/or the vestibular apparatus as

Access this article online	
Quick Response Code:	Website: www.phmj.org
	DOI: 10.4103/phmj.phmj_16_18

How to cite this article: Ibekwe UM, Nwosu C, Kpopene J. Ototoxicity: Scope and pattern in a tertiary hospital in Port Harcourt, Nigeria. Port Harcourt Med J 2018;12:111-6.

distinct from neurotoxicity which means damage to the cranial nerve VIII. These damages to the structures of the auditory and balance system are associated with hearing loss, tinnitus and disequilibrium. It is often bilateral and symmetrical but can also be asymmetrical. Ototoxicity is a common cause of avoidable hearing loss in our environment.[1] It is known to be on the increase and is one of the diseases of public health importance in developing countries.[1]

The damage can be irreversible; it initially affects the higher frequencies but can progress to the speech frequencies with continued exposure.[2] The high frequencies are required for speech discrimination or intelligibility; hence, even mild hearing loss in these frequencies will affect language acquisition and development, especially in children, therefore, impacting on their academia and integration into the general society.[3,4] Hearing impairment due to ototoxicity is said to account for 3%–4% of all deafness in children in developing countries.[5]

There are over 1000 classes of drugs that have been implicated. Quinine was amongst the first drugs known to be associated with tinnitus, hearing loss and dizziness; others include aminoglycosides and other antibiotics, calcium channel blockers, chemotherapeutics with platinum base, salicylates and loop diuretics.[6-8] While the aminoglycosides, by their action on the cochlea, generate free radicals that damage the hair cells beginning with the outer ones and then progressing to the inner hair cells,[9] others such as quinine in addition to causing loss of outer hair cells may affect blood flow to the cochlea by causing vasoconstriction of its small vessels.[10] The ototoxic effects of the aminoglycosides persist even when the therapy has been stopped.[11] The most common platinum-based chemotherapeutic cisplatin, although very effective in the treatment of cancers, has very high potential of ototoxicity and its effect is irreversible.[12] The damage with these kinds of drugs can be temporary or permanent; aminoglycosides and the chemotherapeutic agents tend to cause more permanent damages,[11] whereas others such as aspirin and quinine have a temporary ototoxic effect that reverses with discontinuation.[8] The resultant serious damage of permanent hearing loss and balance from ototoxicity are currently not able to be reversed by any available drug.[13] There is associated permanent sensorineural hearing loss.[14] Although ototoxicity appears to affect all age groups, the young people in their productive years appear to be more affected.[15] It may, therefore, be more prevalent than the literature suggests. This study, therefore, aimed to examine the pattern, note the prevalence and highlight the common medications implicated in ototoxicity in our environment.

METHODS

This study is a 6-year retrospective review of all patients diagnosed with ototoxicity that were managed at the otorhinolaryngology clinic from January 2011 to December 2016. However, patients that had previous hearing impairment from other otologic problems as well as children that could not undergo pure-tone audiometry due to their young age were excluded since this was the only investigative tool available at the centre at the time of the study. Also excluded were those without complete records for the analysis. The criteria for the diagnosis of ototoxicity were as follows: any patient with complaint of sudden or progressive hearing impairment with or without dizziness noticed during or within a period of <3 weeks of administration of a particular drug or drugs that have pure-tone audiometric findings suggestive of ototoxicity. The patients' case files and clinical registries were the source of data. The information extracted from these records for analysis included biodata, types of medications, site of administration, duration of use, otologic symptoms, time of presentation and pure-tone audiometric findings. A conventional audiometer with frequency between 125 and 8000 Hz was used.

Hearing loss was classified using the WHO classification; a pure-tone average calculated across the following frequencies in the better ear: 500, 1000, 2000 and 4000 Hz. Values lower or equal to 25 dB are taken as normal hearing, while values from 26 to 40 dB as slight/mild hearing loss, 41–60 dB as moderate, 61–80 dB as severe and 81 dB and above as profound loss. Ethical approval was sought and obtained from the hospital's Ethical Committee for the study.

Data were analysed using Statistical Package for the Social Sciences (SPSS Statistics, Version 20. IBM Corp., United States of America), and the results were presented in simple statistic tables.

RESULTS

One hundred and thirty-six patients with ototoxicity were seen out of a total of 2801 patients who presented at the clinic within the 6-year period under review, giving a prevalence of 4.9%. Seventy-one patients had complete medical records and these were analysed.

Patients' ages ranged from 7 to 68 years. The most common age group affected was 28–38 years (33.8%) [Table 1]. There were 37 males (52.1%) and 34 females (47.9%), giving a ratio of 1.1:1.

Unknown or unidentified medications (38.0%) were the most common cause of ototoxicity in this study; these were the drugs the patients did not know the names but were found responsible for their hearing loss. Among the known drugs, injection gentamicin (17%) and chloroquine (17%) were the most common implicated drugs [Figure 1].

All the patients presented with hearing loss; however, a total of 128 ears (90.1%) had hearing loss, whereas 14 ears (9.9%) were normal, 83.1% had tinnitus and 22.5% had vertigo. Majority (66.5%) of the ears had severe-to-profound sensorineural hearing loss, as shown in Table 2. There was more bilateral involvement (80.3%) than unilateral (19.7%). Majority of the patients presented later than 2 weeks after the onset of symptoms [Table 3] intramuscular route is the commonest method of drug administration recorded [Table 4].

The drug/pharmacy shops and the peripheral clinics were the most common places where these drugs were administered, with 36% and 32%, respectively [Figure 2].

Table 1: Age distribution

Age group (years)	Frequency (%)
6-16	5 (7.0)
17-27	14 (19.7)
28-38	24 (33.8)
39-49	14 (19.7)
50-60	10 (14.1)
61-71	4 (5.6)
Total	71 (100.0)

Table 2: Degree of hearing loss

Degree of hearing loss	Frequency (%)
Mild	4 (3.1)
Moderate	14 (10.9)
Moderately severe	25 (19.5)
Severe	45 (35.2)
Profound	40 (31.3)
Total	128 (100.0)

Table 3: Duration of onset of symptoms before presentation

Presented after	Frequency (%)
<4 days	1 (1.4)
4-7 days	11 (15.5)
1-2 weeks	14 (19.7)
2-4 weeks	15 (21.1)
4-12 weeks	22 (31.0)
>12 weeks	8 (11.3)
Total	71 (100.0)

Table 4: Method of drug administration

Route of administration	Frequency (%)
Intravenous	21 (29.6)
Intramuscular	36 (50.7)
Oral	14 (19.7)
Total	71 (100.0)

DISCUSSION

The most common age group affected in this study was the 28–38 years (33.8%). This makes a statement on the economic burden ototoxicity can have on our society as it is affecting predominantly the younger population. The age 28-60 years made up about 67.6% of the patients seen. this age range is makes up the majority of the adult workforce so ototoxicity invariably affects the economy. The possible explanation could be implied from the finding that antimalarial drugs were amongst the most common drugs implicated in ototoxicity in this study, and it is known that malaria has more serious effects on the young adults.[16]

There is a slight male preponderance in this study, similar to work by Salisu and Hasheem,[14] but contrary to that of Kokong *et al*. with female preponderance.[13]

The most common implicated drugs in this study were injection chloroquine and gentamicin (17%), followed by quinine (13.0%). In a similar study, the antimalarial drugs had a percentage of 23.7%.[14] This is not surprising as we live in a malaria-endemic area with a high rate of drug-resistant forms. Chloroquine is one of the drugs of choice in our environment that is cheap, affordable and easily available for the treatment of uncomplicated malaria. Moreover, there are some studies which postulate that the malaria parasite itself could be a cause of the damage to the hearing of these patients and not necessarily the antimalarial drugs.[17,18] The study also found gentamicin as one of the most common drugs involved in ototoxicity. This is a common drug used in the treatment of gynaecological problems and gastrointestinal infections and can be readily used topically as ear drops. Kokong *et al*. also had chloroquine as the most implicated drug followed by gentamicin, however the values he obtained 14.1% and 12.8% appear lower than that from this study.[13] A contrary finding was in a work done in Benin City by Obasikene *et al*., with quinine as the most common implicated medication

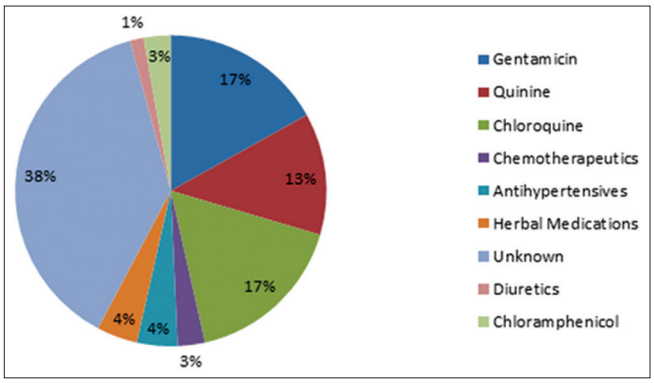

Figure 1: Ototoxic medications used

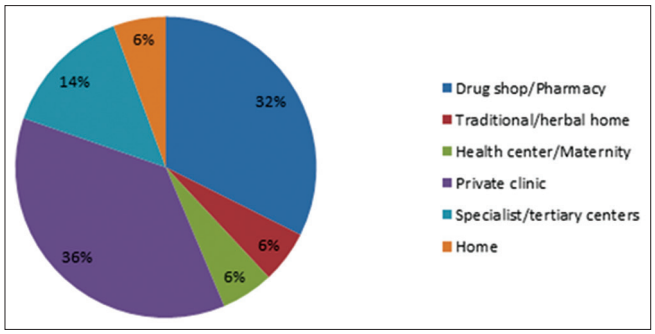

Figure 2: Places where ototoxic medications were given

and chloroquine and gentamicin at the 3rd and 4th positions, respectively.[15] However, an earlier study in the same Benin had chloramphenicol injection implicated instead.[19] The antimalarial drugs appear to be highly implicated.[20] In this study, the antimalarial drugs when combined together have the highest percentage, 30%.

It is of note that the administration of unnamed pharmaceutical agents or agents patients could not identify was the most common cause of ototoxicity in our environment. This finding is also documented by other researchers, however, with higher values[13,15] pointing to the challenges likely to be encountered in setting up protocols for prevention.

Majority of the affected ears in this work had severe-to-profound sensorineural hearing loss from the pure-tone audiogram, with 80.3% of the patients having bilateral hearing loss. This shows the high level of disability that can be associated with ototoxicity. The prevalence of 4.9% in this study appears low; however, the sensorineural hearing loss documented compares with that in other studies (66.5%), where Salisu and Hasheem in Kano found 50%–85%.[14]

In this environment, most drugs are available over the counter often without proper prescription; therefore, patients and the general public could be exposed to drugs that they have no knowledge of the pharmacokinetics, and hence are at the risk of its toxicity. This study shows that the majority of the cases had the drugs administered in the drug shops and peripheral clinics. The incidence of ototoxicity, therefore, may be higher than it appears[21] because some of the affected population may not readily present to the ENT clinic.

The route and the dosage of the drugs are important. Adverse reactions of drug can increase with the dose, frequency and continued exposure.[22] For the antimalarial drugs, it is more likely to have increased plasma concentration of these drugs faster with parenteral than oral administration. Therefore, it is possible that adverse effects could be more with parenteral route. The intramuscular route was the highest in this study. Kharkheli *et al*. studied gentamicin ototoxicity with respect to the route of administration and reported an incidence of 7%–10% with intramuscular administration.[23] In contrast, Indudharan *et al*. had an incidence of 7%–42% of the same drug with topical administration.[24] In our society, patient's preference is often the main determinant of the route of administration of medications and often will opt more for parenteral, especially the intramuscular route. Using the intramuscular route is easier, requiring less skill especially in the drug shops which these patients often frequent. This may explain the 50.7% of the intramuscular route recorded. The parenteral route delivers the drugs faster to the bloodstream; therefore, it is more likely to cause severe side effects since ototoxicity may be dose dependent.[21] Moreover, some of these drugs are often administered by the untrained that has no knowledge of the dosage and possible side effects of such drugs.

With the resurgence of tuberculosis (TB) and HIV, especially the multidrug-resistant TB that requires the use of second-line drug treatment, there could be an increase in ototoxicity. This is because the aminoglycosides, especially kanamycin and streptomycin, constitute the major part of this regime. These are still very much in use in the developing countries due to their low cost and wide antibacterial coverage.[25,26] They are often given without monitoring yet they are known to be a major cause of preventable deafness worldwide.[27] In the developing countries, the choice of treatment depends mainly on the affordability rather than the safety. In this particular study, we did not record any case of ototoxicity from this group of aminoglycosides possibly because these patients are managed at a special centre that is outside the general hospital environment.

It is known that ototoxicity is better prevented. However, in developing countries, resources are scarce and incomes are low; therefore, attention is paid more to sustaining the available health system and little to interventions.[28] Early detection is therefore key. This could be done by monitoring patients on drugs with known potentials for ototoxicity with at least pure-tone audiometry before and during the treatment. According to the American Speech–Language–Hearing Association (ASHA) recommendations, there should be a baseline evaluation of every patient on ototoxic drugs before and during the treatment based on the particular drug.[29] At the slightest sign of ototoxicity, either have the drug changed to an alternative or have the dose adjusted if there is no

alternative. The lowest effective and safe dosage of such drugs should be used. In this study, the patients were monitored using the conventional pure-tone audiometer with frequency from 0.25 to 8 kHz. The ideal audiometer would be the ultra-high-frequency audiometer that tests beyond 8 kHz; this detects early hearing loss in the ultra-high-frequency region, 10–20 kHz, which is the hallmark of ototoxicity.

The treatment of ototoxicity, especially when there is late presentation, has poor result. Most of these patients presented more than 2 weeks after the onset of symptoms (63.4%). This could explain why majority of these patients are often lost to follow-up (62.0%), this is similar to the finding of other researchers.[13-15] Moreover, some of the damage and therefore hearing loss are irreversible.

Limitations

In this study, the conventional pure-tone audiometer was the only available tool and was used. The ultra-high-frequency audiometer is preferred because it will test the very-high frequencies beyond 8000 Hz which are the first to be affected in ototoxicity. There were also no tools for objective tests such as otoacoustic emission which would have been ideal, especially for the very young.

A good number of the patients could not identify the offending drugs due to the fact that they were often administered in the chemists, drug shops and peripheral clinics and were often not given the names.

The clinical registries and records were the source of data and hence lack of complete records excluded a good number of these patients.

CONCLUSION

Ototoxicity may be more common than it appears in our environment. Some of the commonly used drugs in our environment, especially the antimalarials, may be implicated. It seems to affect the young adults more and being associated with significant hearing loss may have potential for possible disability in this group. The pharmacy shops and peripheral clinics appear to be the main places where these drugs are administered.

Recommendations

There is, therefore, a need to adopt properly laid down protocols on the use of these drugs and to monitor closely patients on any of these potentially ototoxic drugs. The administration of these potentially ototoxic drugs should be prescribed strictly by the advice of the physician. Efforts at early detection are recommended. The use of quinine and gentamicin, especially in children and the very young, should be reconsidered and safer alternatives should be adopted. Rehabilitation and reintegration of the severely hearing impaired into the general population so as to improve their quality of life is advocated.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Smith AW. The World Health Organisation and the prevention of deafness and hearing impairment caused by noise. Noise Health 1998;1:6-12.
2. Fausti SA, Henry JA, Schaffer HI, Olson DJ, Frey RH, McDonald WJ, *et al.* High-frequency audiometric monitoring for early detection of aminoglycoside ototoxicity. J Infect Dis 1992;165:1026-32.
3. Petersen LO, Rogers C. Aminoglycoside induced hearing deficits – A review of cochlear ototoxicity. South Afr Fam Pract 2015;57:77-82.
4. Stelmachowicz PG, Pittman AL, Hoover BM, Lewis DE, Moeller MP. The importance of high-frequency audibility in the speech and language development of children with hearing loss. Arch Otolaryngol Head Neck Surg 2004;130:556-62.
5. World Health Organization. Programme for the Prevention of Deafness and Hearing Impairment. Report of an Informal Consultation on Strategies for Prevention of Hearing Impairments from Ototoxic Drugs, WHO/PDH/95.2. Geneva: World Health Organization; 1995. Available from: http://www.who.int/iris/handle/10665/62065. [Last accessed on 2012 Jun 16].
6. Buszman E, Wrzenisck D, Matusinki B. Ototoxic drugs. Aminoglycoside antibiotics. Wiad Lek 2003;56:254-9.
7. Hayes DM, Cvitkovic E, Golbey RB, Scheiner E, Helson L, Krakoff IH, *et al.* High dose cis-platinum diammine dichloride: Amelioration of renal toxicity by mannitol diuresis. Cancer 1977;39:1372-81.
8. Jung TT, Rhee CK, Lee CS, Park YS, Choi DC. Ototoxicity of salicylate, nonsteroidal antiinflammatory drugs, and quinine. Otolaryngol Clin North Am 1993;26:791-810.
9. Rybak LP, Ramkumar V. Ototoxicity. Kidney Int 2007;72:931-5.
10. Lee CS, Heinrich J, Jung TT. Quinine induced ototoxicity: Alterations in cochlear blood flow. Otolaryngol Head Neck Surg 1992;107:233.
11. Schacht J, Talaska AE, Rybak LP. Cisplatin and aminoglycoside antibiotics: Hearing loss and its prevention. Anat Rec (Hoboken) 2012;295:1837-50.
12. Bokemeyer C, Berger CC, Hartmann JT, Kollmannsberger C, Schmoll HJ, Kuczyk MA, *et al.* Analysis of risk factors for cisplatin-induced ototoxicity in patients with testicular cancer. Br J Cancer 1998;77:1355-62.
13. Kokong DD, Bakari A, Ahmad BM. Ototoxicity in Nigeria: Why it persists. Ear Nose Throat J 2014;93:256-64.
14. Salisu AD, Hasheem MG. Pattern of ototoxicity in a Nigerian teaching hospital. Niger J Med 2010;19:320-3.
15. Obasikene G, Adobamen P, Okundia P, Ogusi FO. Prevalence of ototoxicity in university of Benin teaching hospital, Benin city: A 5-year review. Niger J Clin Pract 2012;15:453-7.
16. Maude RJ, Dondorp AM, Faiz MA, Yunus EB, Samad R, Hossain A, *et al.* Malaria in Southeast Bangladesh: A descriptive study. Bangladesh Med Res Counc Bull 2008;34:87-9.
17. Zhao SZ, Mackenzie IJ. Deafness: Malaria as a forgotten cause. Ann

Trop Paediatr 2011;31:1-10.
18. Dunmade AD, Segun-Busari S, Olajide TG, Ologe FE. Profound bilateral sensorineural hearing loss in Nigerian children: Any shift in etiology? J Deaf Stud Deaf Educ 2007;12:112-8.
19. Ogisi FO. Chloramphenicol induced hearing loss. Niger J Surg Res 2001;3:75-80.
20. Mukherjee DK, Mukherjee K. Ototoxicity of commonly used pharmaceutical preparations. Niger Med J 1979;9:52-7.
21. Bisht M, Bist SS. Ototoxicity: The hidden menace. Indian J Otolaryngol Head Neck Surg 2011;63:255-9.
22. Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. BMC Ear Nose Throat Disord 2007;7:5.
23. Kharkheli E, Kevanishvili Z, Maglakelidze T, Davitashvili O, Schacht J. Does Vitamin E prevent gentamicin-induced ototoxicity? Georgian Med News 2007;146:14-7.
24. Indudharan R, Valuyeetham KA, Raju SS. Role of glucocorticoids in ototopical antibiotic-steroid preparations in the treatment of chronic suppurative otitis media. Arch Med Res 2005;36:154-8.
25. Harris T, Peer S, Fagan JJ. Audiological monitoring for ototoxic tuberculosis, human immunodeficiency virus and cancer therapies in a developing world setting. J Laryngol Otol 2012;126:548-51.
26. Grohskopf LA, Huskins WC, Sinkowitz-Cochran RL, Levine GL, Goldmann DA, Jarvis WR, *et al*. Use of antimicrobial agents in United States neonatal and pediatric intensive care patients. Pediatr Infect Dis J 2005;24:766-73.
27. Schacht J, Hawkins JE. Sketches of otohistory. Part 11: Ototoxicity: Drug-induced hearing loss. Audiol Neurootol 2006;11:1-6.
28. Olusanya BO, Newton VE. Global burden of childhood hearing impairment and disease control priorities for developing countries. Lancet 2007;369:1314-7.
29. American Speech-Language-Hearing Association. Audiologic management of individuals receiving cochleotoxic drug therapy. Guidelines for audiologic management of individuals receiving cochleotoxic drug therapy. ASHA 1994;36 (Suppl 12):11-9. Availabe from: www.asha.org. [Last accessed on 2017 Jun 07].