ORIGINAL ARTICLE

Prevalence of ototoxicity in University of Benin Teaching Hospital, Benin city: A 5-year review

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Abstract

Background: Ototoxicity refers to damage of the cochlea and/or vestibular apparatus from exposure to chemical substances, resulting in hearing impairment and or disequilibrium. An earlier study carried out at University of Benin Teaching Hospital (UBTH) in 2000 implicated chloramphenicol as the commonest ototoxic drug, followed by antimalarials (Quinine).
Aim: To identify the commonly implicated drugs in patients diagnosed with ototoxicity in Ear, Nose and Throat (ENT) Clinic of UBTH.
Materials and Methods: One-hundred and three patients' case notes, diagnosed as having ototoxicity, between June 2005 and July 2010 at the ENT Clinic of UBTH were reviewed. Seventy-nine cases met the criteria for diagnosis of ototoxicity in this study.
Results: Intravenous quinine (19.0%) was the commonest implicated drug, followed by oral chloroquine (6.3%), antihypertensive drugs (nifedipine, moduretics, artenolol [6.3%]), native herbal medicine (13.9%), chloramphenicol (1.3%), and unidentifiable drugs accounted for 53.2%. Most patients had severe to profound hearing loss at 4000 Hz and at 8000 Hz. Tinnitus was found in 84.8% of the patients.
Conclusion: Quinine is still the commonest implicated ototoxic drug in this part of the country.

Key words: Hearing loss, ototoxicity, prevalence

Date of Acceptance: 23-Jan-2012

Introduction

Ototoxicity refers to damage of the cochlea and/or vestibular apparatus from exposure to chemical substances, resulting in hearing impairment and/or disequilibrium. Ototoxicity may be reversible or irreversible. It is different from neurotoxicity where the site of action of the drug is on the central nervous system (i.e. on the cranial nerve VIII). Ototoxicity came to forefront in 1944 when streptomycin was discovered to have caused hearing and vestibular disequilibrium in patients where it was used to treat tuberculosis (Kahlmet 1984).[1] Quinine therapy was also found to be associated with hearing loss, tinnitus, and disequilibrium for more than two centuries.[2] Since then, other drugs like aspirin, calcium channel blockers, moduretic, cisplatin, etc, were added onto the ototoxic drug list.[3-6] [Table 1]. The mechanism of oto- and vestibular toxicity has been elusive. Mechanisms for acute and chronic toxicity may be different. Blood quinine levels of 0.2 mg/mL found in pilots who died in aviation accidents suggested that quinine toxicity may have played a causative role.[7] Ototoxic effect of quinine is due to vasoconstriction in the small vessels of the cochlea and stria vascularis. Prolonged administration of high-dose quinine in many patients led to loss of outer hair cells. There may also be an effect on cochlear blood flow.[8]

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Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/1119-3077.104527

PMID: 23238197

Aminoglycosides cause selective destruction of the outer hair cells, starting from the basal coil and progressing onto the apex of the cochlea. The incidence of clinical and functional hearing loss due to aminoglycosides has been significantly diminished because some of the newer derivatives have lower ototoxic potential and, perhaps, efficient monitoring of serum levels of drugs has allowed for better dosing schedules. However, the problem is a significant one as they are still widely used in the treatment of serious gram-negative infections as pointed out by Schacht.[9] In 1979, Mukhajee and Mukhajee reported antimalarials as the commonest cause of ototoxicity.[10] However, there is paucity of literature on the prevalence of ototoxicity in Nigeria. In 2000, F. O. Ogisi in a prospective study of 49 patients with ototoxicity at ENT Clinic of University of Benin Teaching Hospital (UBTH) reported that chloramphenicol was the commonest ototoxic drug, incriminated in 43% of their patients.[11]

Aim of the study

To identify the ototoxic drugs currently responsible for ototoxicity at UBTH.

Materials and Methods

This study was a review of patients who presented at UBTH with a history of hearing loss following drug intake. The patients were assessed based on the type of drugs they took and/or were taking within the 3 weeks he or she noticed the hearing loss. The route and the length of period the drug was being taken were also considered. The patient's type and degree of hearing loss were obtained where possible because infants less than 4 years could not give a reliable PTA (pure tone audiometry) response. The illness that resulted in the intake of the accused drug was also reviewed. Out of 6420 patients seen in ENT Clinic of UBTH between June 2005 and July 2010, 103 patients were diagnosed as having ototoxicity. Out of the 103 patients diagnosed as having ototoxicity, only 79 of them met the criteria for this study. Inclusion criteria for this study include patients who presented with sudden or progressive hearing loss of less than 3 weeks' duration following drug intake for any illness and patients who did pure tone audiometry following the hearing loss. However, children below 5 years of age were assessed using distraction test because most of them could not give a reliable pure tone audiometric response. Patients with previous history of hearing impairment from any other cause and patients with incomplete data were excluded from the study.

Results

The results of 79 patients were analyzed. There were 40 males and 39 females. The age ranged from 6 months to

Table 1: List of drugs causing hearing impairment and/or balance problems

Aminoglycosides	Gentamicin, streptomycin, kanamycin, amikacin, tobramycin, neomycin, netilmicin, polymyxin-B
Macrolides	Erythromycin, azithromycin, clarithromycin
Loop diuretics	Furosemide, bumetanide, ethacrinic acid
Salicylates	
Antimalarials	Quinine, chloroquine (high dosage)
Non-steroid anti-inflammatory drugs	Naproxen, indomethacin (no definite findings)
Anti-neoplastic drugs	Cisplatin, bleomycin, carboplatinum
Chelating agents	Desferoxamine
Topical otological preparations	Antibiotic solutions
	Anti-inflammatory
	Antiseptic
	Acidifying
	Neomycin
	Aminoglycosides
	Polymyxin-B
	Chloramphenicol
	Fosfomycin
	Propylene-glycol, hydrocortisone
	Chlorohexidine, povidone-iodine (?)
	2% acetic acid solution (?)
Chemical agents	Heavy metals
	Solvents
	Others
	Mercury, lead (Industrial pollution, cosmetics).
	Toluene, styrene
	Arsenic, cobalt, cyanides, benzene,
	propylene-glycol, potassium bromide

70 years, with a mean age of 31–40 years and STD ± 1.89. The commonest affected age group was 20–30 years (21.5%) while the least affected age was less than 1 year (1.3%) [Figure 1]. Majority of the patients (84.8%) had tinnitus. Others stated either they did not have tinnitus (3.8%) or could not say whether they have tinnitus or not (11.4%). The treatment outcome showed that 82.3% absconded from treatment and 10.1% had no improvement while only 7.6% got better. The commonest implicated drug was quinine (19%) followed by native herbal medicine drugs (13.9%). Other implicated drugs were chloroquine (6.3%), antihypertensives (6.3%), chloramphenicol (1.3%), and others (53.2%). All the patients had severe-to-profound hearing loss on both high and low frequencies.

Discussion

The study showed that almost all age groups were affected but people in their most productive years of life (15–49 years) had the highest (51.9%) incidence of ototoxicity, followed by children below 10 years old [Table 2].[12] The elderly patients and infants below 1 year were the least affected though assessing the type and degree of hearing loss in patients of less than 4 year was difficult, especially without otoacoustic emission. In this study, children of less than 4 years were assessed by verbal speech and distraction method.

The commonest illness that necessitated the intake of the offending drug was malaria, followed by febrile illness. However, most of the diagnoses and treatment were made in peripheral hospitals and by non-experts. All patients in this study live in a malaria endemic area. Young adults are known to suffer drug-resistant malaria compared to infants).[13] Other studies also showed that young adults are worst hit by malaria.[14,15] It has been documented that about 95–99% of the adult population carry the malaria parasite with less than 30% of this number coming down with illness.[16] This could partially explain the higher incidence of ototoxicity seen in young adults. The commonest implicating substance in our study was intravenous quinine [Table 3]. In 2000, a similar study by Ogisi *et al.* in the same center revealed quinine to be the 2nd most common cause of ototoxicity after chloramphenicol.[11] During that period, typhoid fever was treated most commonly with chloramphenicol. Today, because of the awareness of the ototoxicity and other side effects of the drug, it has been replaced by ciprofloxacin and other safer antibiotics.

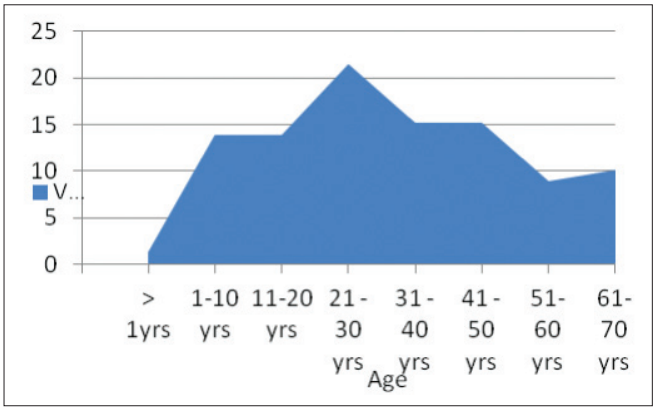

Figure 1: Age histogram

This study, however, found quinine to be the commonest offending drug, which is not unexpected in a malaria endemic area like Nigeria, especially where quinine is mostly used in the treatment of resistant and cerebral malaria.[17] Tinnitus was present and bilateral in 84.8% of all the patients [Table 4]. Tinnitus is one of the commonest side effects of quinine, which is the most common drug used in treatment of drug-resistant malaria. Because only 19% of patients in this study took quinine, other drugs are also implicated for this high percentage of tinnitus noted in the study.

One of the major determinants for choice of treatment is the most affordable drugs, usually not the safest.[18] Quinine being one of the most available and affordable drugs, when other cheap drugs for resistant malaria have failed, will

Table 2: Age frequency

Age in years	Frequency	Percent
<1 yr	1	1.3
1–10 yrs	11	13.9
11–20 yrs	11	13.9
21–30 yrs	17	21.5
31–40 yrs	12	15.2
41–50 yrs	12	15.2
51–60 yrs	7	8.9
61–70 yrs	8	10.1
Total	79	100.0

Table 3: Frequency of implicated drugs

Suspected drugs	Frequency	Percent
Chloroquine	5	6.3
Quinine	15	19.0
Chloramphenicol	1	1.3
Antihypertensives	5	6.3
Native herbal medicine	11	13.9
No idea	42	53.2
Total	79	100.0

Table 4: Frequency of tinnitus

	Frequency	Percent
Tinnitus	67	84.8
No tinnitus	3	3.8
Not clear	9	11.4
Total	79	100.0

Table 5: Treatment outcome Frequency

After treatment	Frequency	Percent
Improvement	6	7.6
No improvement	8	10.1
Absconded	65	82.3
Total	79	100.0

continue to dominate in the hands of non-medical experts for treatment of resistant malaria. It has also been reported that sub-standard drugs are readily available. In a study in two developing countries for instance, of 96 samples of chloroquine collected from Nigeria and Thailand for analysis, the results indicated that 36.5% were sub-standard.[19] Not only does this imply discrepancies in clinical studies, but this may, in itself, be a cause of ototoxicity in developing countries. The 53% who had no idea of the drugs given to them and could not fix their hearing loss to any cause may be due to the problems of a developing country [Table 5]. This problem includes low or no education, which denies an individual the power to know, lack of funds or facility to diagnose or seek medical attention, and patients having little or no knowledge of the drugs given to him.[20-22] 13.9% were on native herbal medicine. Herbal medicine was introduced into National Health Service (NHS) many years ago. It started when the Royal London Homeopathic Hospital (RLHH), founded in 1849, joined the National Health Service (NHS) at its inception in 1948 and became part of University College Hospitals NHS Foundation Trust (UCLH), one of the UK's leading academic medical centers, in 2003. Despite its title, it offers a range of complementary medicine (CM) services, not only homeopathy. Until around 1980, it was a small general hospital with a specialist homeopathic department. The surgical and other facilities were replaced by a range of CM services including the NHS's first complementary cancer (1960), acupuncture (1977), autogenic training (1986), musculoskeletal (1993), herbal medicine services (2008), and others.[23] Many people mistakenly think that all medicinal herbs, being natural, are generally safe and free from undesirable side effects while acting as an effective agent. However, very often, herbs may interact with medications that result in adverse effects. The use of herbal medicine is still poorly understood by the public. Nowadays, toxicity and safety of medicinal herbs is one of the most discussed topics as herbal products have become popular in the developed and developing countries.

More research work is needed on ototoxic drugs, especially among the 53% who had ototoxicity but were not able to identify the drugs they were given. 6.3% of both antihypertensives and chloroquine and the 1.3% of the chloramphenicol are equally of great importance, considering the population on these drugs and at the risk of developing ototoxicity. These drugs are also in the ototoxic drug list.[24] Over 80% of patients were lost to follow-up; this could be because they were not getting better or that they could not afford the cost of their treatment. The severe-to-profound hearing loss seen in all the patients could also be attributed to the problems of the developing world where medical attention is not sort on time because of lack of funds and unavailability of specialists in many places.

Conclusion

Quinine has been found to be the commonest ototoxic drug in our environment. As part of a health campaign to prevent quinine ototoxicity, quinine should be prescribed with caution, and if possible, with audiometric and quinine serum level monitoring. There should be a drug policy guiding the dosage prescription and potency of herbal drugs. Above all, the side effects of herbal drugs must be specified on the drug container. There should be an unrelenting effort to get the best alternative to drugs with unavoidable severe side effects and a health policy that can give everybody the opportunity of receiving good health care, irrespective of the patients' financial status. Also, a massive health campaign on side effects of drugs and herbal medicine should be made to all primary healthcare providers, patent medicine dealers, herbalists, homeopaths, and pharmacists.

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How to cite this article: 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.
Source of Support: Nil, **Conflict of Interest:** None declared.