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REVIEW ARTICLE

Audiological monitoring for ototoxic tuberculosis, human immunodeficiency virus and cancer therapies in a developing world setting

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Abstract

Ototoxic drugs are widely used in the developing world, without audiological monitoring. Epidemiological data on ototoxic deafness are lacking for developing countries. The public health aspect of ototoxicity is often overlooked, to the detriment of the individual patient. This paper reviews ototoxic hearing loss, particularly in sub-Saharan Africa, and also assesses the impact of treatments for tuberculosis, cancer and human immunodeficiency virus (the latter including highly active antiretroviral therapy) on ototoxic hearing loss. The paper also discusses obstacles to audiological monitoring for ototoxicity in the developing world, and the potential of audiology screening using applications for mobile devices.

Key words: Ototoxicity; Aminoglycosides; Cisplatin; Highly Active Antiretroviral Therapy; HAART; Developing World; Audiology; Screening Programs; Mobile Devices; Iphone

Introduction

The World Health Organization's (WHO's) global estimate for disabling hearing impairment (defined as more than 40 dB HL impairment) has more than doubled from 120 million people in 1995 to at least 278 million in 2005.[1] A total of 364 million people worldwide have mild hearing impairment, while 624 million are estimated to have some level of hearing impairment; 80 per cent of the people live in developing countries.[1] The consequences of hearing impairment, such as inability to communicate, delayed language acquisition in children, educational and economic disadvantages, and social isolation, are amplified in developing world countries because of the lack of rehabilitation and social services.

Over 130 drugs are ototoxic. Injectable aminoglycosides are by far the most common cause of ototoxic hearing impairment.[2] Cancer is an increasing problem in developing countries, and chemotherapy-associated hearing loss is associated with the use of platinum agents, specifically cisplatin and high-dose carboplatin. Most information on cisplatin-induced hearing loss comes from developed countries, with only limited data from developing countries.

The UNAIDS organisation has estimated that, at the end of 2009, 33.3 million people were living with human immunodeficiency virus (HIV) infection, with Eastern and Southern Africa most affected.[3] An increased incidence of hearing loss among HIV-positive patients has been reported.[4–6] Understanding the effects of HIV, acquired immunodeficiency syndrome (AIDS) and highly active antiretroviral therapy (HAART) on the auditory system is therefore important, particularly in the developing world.

Furthermore, as tuberculosis (TB) and HIV often occur together in developing countries, HAART and ototoxic TB drugs are often given simultaneously, compounding the potential for ototoxicity.

Although monitoring for ototoxicity should be a standard part of therapeutic management, audiology services are virtually non-existent in many developing countries and hearing loss goes undetected.[7] Even in the face of limited resources, the value of monitoring patients without providing rehabilitation for those who develop hearing impairment might be questioned. However, at the very least, patients do have the right to be educated about the risks of ototoxic hearing loss; this should be part of the process of obtaining informed consent.

Aminoglycoside-induced ototoxicity

In 1995, the WHO stated that aminoglycoside ototoxicity was a 'major concern', and highlighted the lack of epidemiological data on ototoxicity and hearing

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impairment in both developed and developing countries.[8] Compared to developed countries, where there has been a dramatic reduction in the use of aminoglycosides, these drugs are still widely used in developing countries due to their low cost and broad antimicrobial spectrum.[8] The reported prevalence of aminoglycoside ototoxicity among deaf individuals in developing countries ranges from 3 to 30 per cent.[8]

Multidrug-resistant TB, defined as resistance to both isoniazid and rifampicin, requires prolonged treatment for up to 18–24 months with injectable aminoglycosides such as kanamycin and amikacin.[9] Due to the global upsurge of multidrug-resistant TB, aminoglycoside use is on the increase, placing many people at risk of ototoxicity.[9] In sub-Saharan Africa, where HIV contributes to the burden of TB, the prevalence of multidrug-resistant TB is five to six times higher than that in China and India.[9,10]

Cisplatin-induced ototoxicity

Cisplatin is an antineoplastic drug often used to treat various tumours, including head and neck, oesophageal, and small and non-small cell lung cancers, as well as Hodgkin's and non-Hodgkin's lymphomas and sarcomas. Ototoxicity is a dose-limiting side-effect of the drug.[11] Bokemeyer *et al.* showed that patients with sensorineural hearing loss or chronic noise exposure prior to chemotherapy had a threefold risk of ototoxicity.[12] Other risk factors for cisplatin-induced ototoxicity include increased dosage, depleted nutritional state (with low serum albumin levels and anaemia) and cranial irradiation.[13] Patients with nasopharyngeal carcinoma appear to be very susceptible to the interaction of cisplatin and cochlear irradiation.[14]

Human immunodeficiency virus treatment and ototoxicity

Patients who are HIV-positive have an increased incidence of hearing loss: 21–49 per cent will develop sensorineural hearing loss, predominantly in the high frequencies.[4,6,15]

Human immunodeficiency virus positive patients are at greater risk of hearing loss, due to otitis media, opportunistic central nervous system infections (e.g. toxoplasmosis, cytomegalovirus, TB and cryptococcosis), malignancies (including Kaposi's sarcoma and lymphoma), HIV-1 infection, ototoxic drug treatment and other causes.[15–19] In addition, HIV may directly affect auditory function due to neurotropism of the virus.[20]

Long-term antiretroviral therapy also has significant metabolic side effects.[21] The metabolic side effects of nucleoside reverse transcriptase inhibitor, a drug used in HIV treatment, may be related to mitochondrial toxicity.[22,23] Cross-sectional studies have demonstrated an association between this drug and hearing loss.[24–26] To date, prospective studies have not examined the long-term effects of antiretroviral drugs on the auditory system. However, Khoza-Shangase recently published a study which monitored the auditory status of adults with AIDS and receiving HAART, compared with a control group, over a period of six months. Initially, both groups had normal pure tone audiograms; however, after six months the HAART-treated AIDS patients showed subclinical hearing changes together with clinically significant changes in distortion product otoacoustic emissions.[27]

More recently, an animal study showed that while antiretroviral drugs may not be directly ototoxic, they may act synergistically when combined with other stressors (e.g. noise) due to effects on outer hair cell mitochondria.[28] This may have implications for HIV-positive patients receiving HAART, in terms of noise exposure and noise-induced hearing loss.

In South Africa, as in many sub-Saharan countries, TB treatment is one of the most frequently administered therapies for HIV-AIDS patients. The combined effects of aminoglycosides and HAART on the auditory system have yet to be determined. While there is very limited information on possible HAART ototoxicity, it is clear that HIV-positive individuals are potentially at high risk of ototoxic hearing loss, as they are often prescribed ototoxic medication for the treatment of opportunistic infections (e.g. amphotericin B) or cancer (e.g. cisplatin).[4–6,18]

Human immunodeficiency virus positive patients have an increased risk of malignancy.[29] Treating cancer in HIV-positive patients is challenging because of drug interactions, compounded side effects, and the potential effects of chemotherapy on HIV-1 viral load. To date, there are no published reports assessing the combined effects of chemotherapy (particularly platin-based chemotherapy) and HAART on the hearing status of HIV-positive patients.

Audiological monitoring for ototoxicity

Early identification of ototoxic hearing loss due to cisplatin therapy provides physicians with an opportunity to adjust the drug therapy in order to minimise or prevent hearing loss.[30] However, multidrug-resistant TB is a more immediately life-threatening disease, both to the patient and their community, and aminoglycosides often have to be continued despite ototoxic hearing loss. Even so, screening and monitoring for ototoxic hearing loss is still important for patients with multidrug-resistant TB, as this enables audiologists to counsel patients and their families regarding ototoxicity-induced hearing loss, tinnitus, communication strategies, and the synergistic effects of noise and ototoxic damage. It also identifies patients who may benefit from appropriate rehabilitation after completion of treatment.

There are no universally accepted protocols for monitoring ototoxicity. In the UK, there is wide variation in screening practices for ototoxicity related to multidrug-resistant TB.[31] The guidelines of the American Speech-Language-Hearing Association for audiological management of individuals treated with ototoxic drugs

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are based on large clinical studies, and recommend that patients should undergo a baseline evaluation before treatment is initiated. The frequency of monitoring depends on the particular drug regimen. For patients undergoing cisplatin chemotherapy, monitoring is usually performed prior to each dose; for those receiving ototoxic antibiotics such as aminoglycosides, it is done once or twice a week. Because ototoxic hearing loss can occur up to six months following drug exposure, post-treatment evaluation is required to confirm that hearing has stabilised.[30]

Initially, ototoxic drug exposure typically affects the basal end of the cochlea and the vascular striae and causes hearing loss in the high frequencies; however, continued exposure affects progressively lower frequencies which are important for understanding speech.[11,30] Therefore, detecting changes in pure tone thresholds using serial ultra-high frequency audiometry (up to 18 kHz) is an effective indicator of ototoxic hearing loss. High frequency audiometry and distortion product otoacoustic emission testing have been shown to be the most reliable means of detecting early cochlear outer hair cell damage. However, abnormal middle-ear function and baseline hearing loss of greater than 40 dB HL may preclude effective monitoring using otoacoustic emissions. Auditory brainstem evoked response testing may be more appropriate in such cases.[30]

Obstacles to audiological monitoring in the developing world

Developing countries have financial pressures on their health systems and competing budgetary demands from life-threatening and/or communicable diseases. In addition to these general constraints, the provision of audiology services in developing world countries is subject to additional challenges, exemplified in the Western Cape region of South Africa.[32] These challenges include: a heavy concentration of services at central hospitals, with few or no services available in smaller facilities; a need to decentralise audiological screening to peripheral hospitals where community-based multidrug-resistant TB treatment is commenced;[2,33] a shortage of staff and skills at regional hospitals, as well as at specialised TB hospitals (where multidrug-resistant TB patients should be screened and monitored for ototoxicity);[32] and inadequate facilities and equipment for delivery of audiology services.[32]

Fagan and Jacobs conducted a survey of ENT services in sub-Saharan Africa and found an alarming paucity of audiology services, with several countries having no audiology services at all.[7] In most of the countries surveyed, the majority of people depended on state services. In countries where ENT services were available, they were restricted to major cities.

Therefore, at this stage it is unrealistic to implement in developed countries the international audiological monitoring protocols that are considered to represent an acceptable standard of care as regards ototoxicity screening and monitoring.

Cost-effective, affordable monitoring of ototoxicity

We need to develop and validate ototoxicity screening and monitoring tools which are commensurate with the financial, infrastructural and audiology service constraints of developing world countries.

Telephonic and telemedicine audiology tools are already being used. More than 50 per cent of the world's mobile phones are in the developing world. This presents an opportunity to develop applications for mobile devices – tools of media and communication which are easy to use and readily available despite educational and socio-economic barriers.

The Apple computer company, together with Oticon, a hearing aid company, have devised uHear, a software program freely available for downloading onto Apple iPhone devices. uHear is a self-testing application that performs pure tone audiometric assessments. Its accuracy has not yet been validated in published studies.

However, in 2011 a pilot study assessing iPhone uHear as a screening tool for detecting hearing loss was conducted at Groote Schuur Hospital in Cape Town (S Peer, unpublished data). Twenty-five patients were tested using uHear, in three different settings: a waiting room, a quiet room and a soundproof room. The results were compared to a formal audiogram. There was good accuracy for high frequencies in a quiet setting and a soundproof room, and fair-to-moderate correlation for low frequencies.

Although this study was only a pilot study, its results suggest that audiology applications for mobile devices hold promise as cheap, mobile screening and monitoring tools for ototoxicity in developing world settings.

Conclusion

In order for ototoxicity monitoring programmes to be successfully implemented in the developing world, protocols must be applicable in this setting and context-sensitive. This requires sound ototoxicity research data, both epidemiological and clinical, from developing world populations, in order to inform local guidelines on screening practices. It is important that researchers investigate the ototoxic effects of HAART, both when used alone and when interacting synergistically with other drugs. Mobile devices are widely available in the developing world. This presents researchers with an opportunity to develop audiology applications for mobile devices which permit cheap, mobile screening and monitoring for ototoxicity, thus overcoming the scarcity of specialised audiology services.

References

1 Olusanya BO, Newton VE. Promoting a global health agenda for permanent childhood hearing impairment. *Journal of Community Ear and Hearing Health* 2007;**4**:5–27

https://doi.org/10.1017/S0022215112000357 Published online by Cambridge University Press

2 World Health Organization. *Report of an Informal Consultation on Strategies for Prevention of Hearing Impairment from Ototoxic Drugs*. Geneva: World Health Organization, 1994
3 UNAIDS, Global Report. In: http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2007 [30 Jul 2010]
4 Birchall MA, Wight RG, French PD, Cockbain Z, Smith SJ. Auditory function in patients infected with the human immunodeficiency virus. *Clin Otolaryngol* 1992;**17**:117–21
5 Lalwani AK, Sooy CD. Otologic and neurotologic manifestations of acquired immunodeficiency syndrome. *Otolaryngol Clin North Am* 1992;**25**:1183–97
6 Soucek S, Michaels L. The ear in the acquired immunodeficiency syndrome: II. Clinical and audiologic investigation. *Am J Otol* 1996;**17**:35–9
7 Fagan JJ, Jacobs M. Survey of ENT services in Africa: need for a comprehensive intervention. *Global Health Action* 2009;Mar 19:2
8 Saunders JE, Greinwald JH, Vaz S, Guo Y. Aminoglycoside ototoxicity in Nicaraguan children: patient risk factors and mitochondrial DNA results. *Otolaryngol Head Neck Surg* 2009;**140**:103–7
9 World Health Organization. *Global Tuberculosis Control 2008: Surveillance, Planning, Financing*. Geneva: WHO Report, 2008
10 World Health Organization. *Multidrug and extensively drug resistant TB (M/XDR-TB). 2010 Report on Surveillance and Response*. Geneva: World Health Organization, 2010
11 Rybak LP, Whitworth CA. Ototoxicity: therapeutic opportunities. *Drug Discov Today* 2005;**10**:1313–21
12 Bokemeyer C, Berger CC, Hartmann JT, Kollmansberger C, Schmoll HJ, Kuczyck MA *et al*. Analysis of risk factors for cisplatin-induced ototoxicity in patients with testicular cancer. *Br J Cancer* 1998;**77**:1355–62
13 Rybak LP, Whitworth CA, Mukherjea D, Ramkumar V. Mechanisms of cisplatin-induced ototoxicity and prevention. *Hear Res* 2006;**226**:157–67
14 Huang E, Teh BS, Strother DR, Davis QG, Chiu JK, Lu HH. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. *Int J Radiat Oncol Biol Phys* 2002;**52**:599–605
15 Chandrasekhar SS, Connelly PE, Brahmbhatt SS, Shah CS, Kloser PC, Baredes S. Otologic and audiologic evaluation of human immunodeficiency virus-infected patients. *Am J Otolaryngol* 2000;**21**:1–9
16 Michaels L, Soucek S, Liang J. The ear in the acquired immunodeficiency syndrome: I. Temporal bone histopathologic study. *Am J Otol* 1994;**15**:515–22
17 Meynard JL, el Amrani M, Meyohas MC, Fligny I, Gozian J, Rozenbaum W *et al*. Two cases of cytomegalovirus infection revealed by hearing loss in HIV-infected patients. *Biomed Pharmacother* 1997;**51**:461–3
18 Little JP, Gardner G, Acker JD, Land MA. Otosyphilis in a patient with human immunodeficiency virus: internal auditory canal gumma. *Otolaryngol Head Neck Surg* 1995;**112**:488–92
19 Grimaldi LME, Luzi L, Martino GV, Furlan R, Nemni A, Antonelli N *et al*. Bilateral eighth cranial nerve neuropathy in human immuodeficiency virus infection. *J Neurol* 1993;**240**:363–6
20 McArthur JC. Neurological manifestations of AIDS. *Medicine* 1987;**66**:407–37
21 Moore JM, James IR, Nolan D, Upton RP, McKinnon EJ, Mallal SA. Chronic hyperlactatemia in HIV-infected patients taking antiretroviral therapy. *AIDS* 2001;**15**:717–23
22 Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. *Lancet* 1999;**354**:1112–15
23 Anuurad E, Semrad A, Berglund L. Human immunodeficiency virus and highly active antiretroviral therapy-associated metabolic disorders and risk factors for cardiovascular disease. *Metab Syndr Relat Disord* 2009;**7**:401–9
24 Marra CM, Wechkin HA, Longstreth WT, Rees T, Syapin CL, Gates GA. Hearing loss and antiretroviral therapy in patients infected with HIV-1. *Arch Neurol* 1997;**54**:407–10
25 Simdon J, Watters D, Bartlett S, Connick E. Ototoxicity associated with use of nucleoside analog reverse transcriptase inhibitors: a report of 3 possible cases and review of the literature. *Clin Infect Dis* 2001;**32**:1623–7
26 McNaghten AD, Wan PT, Dworkin MS. Correspondence: prevalence of hearing loss in a cohort of HIV-infected patients. *Arch Otolaryngol Head Neck Surg* 2001;**127**:1516–18
27 Khoza-Shangase K. Highly active antiretroviral therapy: does it sound toxic? *J Pharm Bioallied Sci* 2011;**3**:142–53
28 Bektas D, Martin GK, Stagner BB, Lonsbury-Martin BL. Noise-induced hearing loss in mice treated with antiretroviral drugs. *Hear Res* 2008;**239**:69–78
29 Silverberg MJ, Chao C, Leyden WA, Xu L, Horberg MA, Klein D *et al*. HIV infection, immunodeficiency, viral replication, and the risk of cancer. *Cancer Epidemiol Biomarkers Prev* 2011;**20**:2551–9
30 Fausti SA, Helt WJ, Gordon JS, Reavis KM, Phillips DS, Konrad-Martin D. Audiologic monitoring for ototoxicity and patient management. In: Campbell KC, ed. *Pharmacology and Ototoxicity for Audiologists*, 1st edn. New York: Thomson Delmar Learning, 2006;230–48
31 Sturdy A, Goodman A, José RJ, Loyse A, O'Donoghue M, Kon OM *et al*. Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice. *J Antimicrob Chemother* 2011;**66**:1815–20
32 Swart S. *Draft Report. Modernisation of Audiology Services*. Cape Town: Western Cape Department of Health, 2010
33 DOTS-Plus for Standardised Management of Multidrug-resistant Tuberculosis in South Africa – Policy Guidelines. In: http://www.sahealthinfo.org/tb/mdrtbguidelines.pdf [17 November 2011]

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