

RESEARCH ARTICLES

Hearing Loss among Multi-Drug Resistant Tuberculosis patients on Kanamycin in Ndola Teaching Hospital, Zambia: Study of ototoxicity and practice

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Multi-drug resistant tuberculosis is of public health importance. The purpose of this study was to determine the magnitude of hearing loss among multi-drug resistant TB patients being treated with kanamycin in Ndola Teaching Hospital, Zambia. This was a one year prospective descriptive study conducted among 38 MDR TB patients who received kanamycin injection for a maximum of eight months and tested by high frequency audiometer for at least two times. Out of 38 patients, 11 (29.0 %) were female and 73.7% were aged between 15 and 44 years. Of the 38 patients, 29 (76.0%) were HIV positive. Altogether, 35 (91.1%) patients on kanamycin had abnormal hearing assessment, 30 (86.0%) had clinical hearing loss and the other 5 (14.0%) only had high frequency loss on the audiogram without functional hearing impairment. No significant association was observed between gender and ototoxicity ($p=0.861$). Among patients with clinical hearing loss, 2 (7.0%) had mild, 5 (17.0%) had moderately severe, 16 (53.0%) had severe and 7(23.0%) profound hearing loss. A total of 11 (29.0%) patients were not aware of possible hearing loss. The study has shown a significant proportion of patients who get MDR TB treatment end up with significant hearing loss.

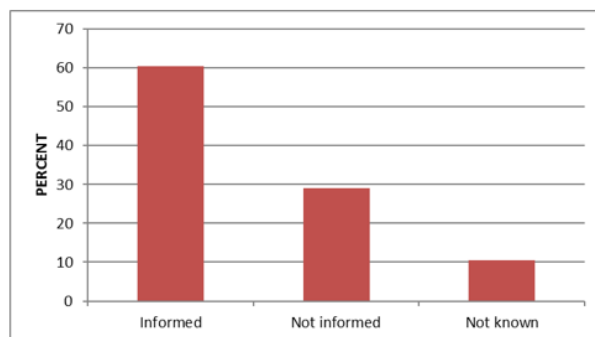
Introduction

Tuberculosis has remained a challenge to both global and Zambia public health. There is significant progress in treating Tuberculosis (TB) both globally and in Zambia, however the number of drug resistant TB has also been significantly increasing globally [1]. Zambia had the incidence of TB of 545/100,000 by the year 2006 with prevalence of 1.8% and 2.3% drug resistant Tuberculosis (DR-TB) in new and previously treated TB, respectively, based on 2001 drug resistance survey. This translates to approximately 265 new cases of multidrug resistant Tuberculosis (MDR-TB) [2] and it was reported that the MDR-TB cases were

the most frequent accounting for 49% of the total DR-TB [1].

Ototoxicity is defined as medication-induced auditory and/or vestibular system dysfunction those results in hearing loss or loss of balance [3]. Current international DR-TB guidelines and expert opinion provide limited detailed advice regarding the monitoring, classification and management of hearing loss.

Figure 1. Proportional of patients informed of possible hearing loss before commencing kanamycin



A consensus is lacking. The World Health Organization (WHO) simply states that hearing loss should be documented and compared with baseline results if audiometry is available. If hearing loss is detected, options include changing from an aminoglycoside to capreomycin, decreasing the frequency/dose, or discontinuing the suspected agent if this can be performed without compromising the regimen. No mention is made in the guidelines of how hearing should be tested, how frequently it should be performed or what classifies as hearing loss [2,4].

Incidence of ototoxicity ranges from 7 to 90% in different regions of the world [5-16]. The wide variation observed in several studies is attributed to the different methodology, ways of measuring hearing, aminoglycosides used and guidelines used to identify hearing loss.

The main ototoxic drugs in Ndola Teaching Hospital used for the treatment of drug-resistant TB are kanamycin and capreomycin for a length of eight months. Despite the wide use of kanamycin to the patients with multi drug resistant Tuberculosis patients in Zambia, no study has been done before to assess the burden of hearing loss or guidelines put in place for the patient receiving treatment of multi drug resistant to assess their hearing. Hence, the objective of the study was to determine prevalence of ototoxicity and associated factors among multi drug resistant TB patients treated at Ndola Teaching Hospital.

Methods

This was a hospital prospective descriptive study conducted among MDR tuberculosis patients who received initial dose of kanamycin for eight months. The patients were tested for at least two phases. Phase one was before or within two weeks of use of kanamycin and the phase two were after

several months of using kanamycin at Ndola Teaching Hospital Tuberculosis Ward.

Audiometry findings were considered under three categories; 'normal' defined by patients with pure tone audiograms showing air-conduction thresholds up to 20 ± 5 dB HL at all the tested frequencies from 125 Hz to 8000 Hz with air-bone gap of ≤ 10 dB; 'high frequency loss' (HFL) was defined by (1) a 20 dB or greater decrease at any of the five frequencies; 4000, 6000, 8000, 10,000 and 12,000 Hz, (2) 10 dB or greater decrease at any two adjacent frequencies in above range, (3) loss of response at all the three frequencies (4000, 6000, 8000, 10,000 and 12,000 Hz) where responses were previously obtained; and 'flat' (FLAT) when in addition to HFL, above criteria will be also fulfilled in the frequencies ranging from 250 to 3000 Hz basing on American Speech-Language-Hearing Association guideline (ASHA). All the pure tone threshold shifts were recorded at each frequency tested with reference to the baseline pure tone threshold at the same frequency. All the patients in MDR TB treatment were tested for renal function and HIV per hospital protocol.

Ndola Teaching Hospital is a third level hospital which serves almost half of the country. It is one of the two Multi drug resistant TB treatment centers in Zambia.

Convenient sampling was used to recruit patients from the patient registries at Ndola Central Hospital treatment center on a daily basis during the whole time of the study. The duration of recruitment of subjects was one year. A structured questionnaire was used to collect information on socio-demographic characteristics, ototoxic drug(s) used, HIV status, history of dizziness, loss of balance and vertigo, tinnitus, hearing loss, otoscopic examination findings, tympanogram and audiogram. These activities were done by the Principal investigator and the qualified audiology technician.

In determining the knowledge of the TB health workers, a questionnaire comprising the following questions was used: knowledge of drug used in the management of multidrug resistant TB; Ototoxic drugs used in the MDR-TB management; Ear disorder symptoms; When to refer a patient to audiologist; Protocols and regulation that are in place to monitor the ototoxicity; and Involvement of Audiologist in The TB management Team.

Data were analyzed using STATA version 14. The categorical variables were summarized in frequencies with respective percentages. The Chi-squared test was used to assess association between exposure

factors and the outcome at the 5% significance level.

Inclusion and exclusion criteria

All patients who were confirmed by culture and sensitivity to have multi drug resistant TB and on treatment or scheduled to start treatment with kanamycin were included in the study. Patients who were excluded from the study included: patients who had used the aminoglycoside for a month or more in the past six month prior to the start of study, patients with renal failure, patients with hearing loss prior to the start of the study, patients who received concomitant administration of other ototoxic drugs, patient with other ear pathology like otitis media which can affect hearing of a patient and uncooperative patients.

Ethical consideration

The investigator introduced himself to each individual patient and gave explanation on what the study was about before asking the patient to participate in the study. Only patients who gave written/verbal consent were enrolled for the study. Patient interview was conducted privately with only the investigator and the patient. All the otoscopic examinations, tympanometry and audiometry tests did not harm patients. These tests were done to any patient with suspected hearing loss per Ndola Teaching Hospital treatment

protocol. The patients' information and results were handled confidentially. Patients who were found to have otology problems during the study, they were managed per existing Ndola Teaching Hospital and Ministry of Health Protocol.

The proposal was reviewed by the Scientific, Technical and Advisory Committee Tropical Diseases Research Centre (TDRC). Ethical clearance was granted by the TDRC Research Ethics Committee, Ndola, Zambia.

Results

A total of 38 patients were recruited in the study of whom 11 (29.0%) were female. Half (50.0%) of the participants were in the 35-44 years' age group (Table 1).

Table 1: Baseline characteristics of study participants (n=38)

Factor	Frequency	Percent
Sex		
Female	11	28.9
Male	27	71.1
Age (years)		
16-34	9	23.7
35-44	19	50.0
45+	10	26.3
HIV status		
Positive	29	76.3
Negative	9	23.7
Total	38	100

Out of the 38 drug resistant TB patients enrolled for this study and screened for hearing loss, 35 (92.1%) had hearing loss.

In this study, we found that about 46.0% of the participants had severe hearing loss, and

up to 20.0% with profound hearing loss. Altogether, 80.0% of patient with ototoxicity had severity between moderately severe to profound (Table 2).

Table 2: Severity of hearing loss

Severity	Frequency	Percent
High frequency hearing loss (HFL)	5	14.3
Mild (21-40DB)	2	5.7
Moderately severe (41-60DB)	5	14.3
Severe (61-90DB)	16	45.7
Profound (>90DB)	7	20.0
Total	35	100

Out of the 38 patients who were enrolled for this study, only 23 (60.5%) were informed of the risk of ototoxicity prior to commencement of kanamycin (Figure 1).

In this study, none of the factors included in the analysis was found to be significantly associated with hearing loss (Table 3).

Through observation on the practice on the treatment of MDR TB, we found that not all patients were assessed for baseline audiometry. Also, we observed that incase of hearing loss the dose was reduced to acceptable lower dose. The minimum score in the questionnaire given to health workers to assess their knowledge on ototoxicity was 75.0%.

Discussion

In the present study, we found that 35 (92.1%) patients who were on kanamycin

injection developed hearing loss. The proportion of patients who developed hearing loss in this study is higher than most of the studies done in Africa and outside Africa [5-16]. The difference observed could be attributed to the difference in audiology test used whereby some study only used convention audiometry which only tests frequencies from 125 Hz to 8000 Hz leading to miss patients with hearing loss in frequencies above 8000 Hz. Also in our study only kanamycin was used throughout the treatment of MDR TB patients while in other studies the less ototoxic drugs like capreomycin and akamacin were used. In our study we had a large proportion more than 76.0% of HIV patients compared to most of the studies which on its own is a risk factor of developing hearing loss. Other risk factors which we couldn't rule out like genetic predisposition could influence the number of patients with hearing loss.

Table 3: Factors associated with hearing loss

Variable	Hearing status (Ototoxicity)		P-value
	With (n)	Without (n)	
Age group			0.371
18-34	8	1	
35-44	17	2	
45+	10	0	
Sex			0.861
Male	10	1	
Female	25	2	
HIV status			0.108
Positive	28	1	
Negative	7	2	

Health workers who were assessed for knowledge on ototoxicity due to MDR TB treatment, all of them had at least 75.0% of knowledge about MDR Treatment ototoxicity. However, when MDR TB patients interviewed, more than 28.0% did not get any kind of information of possible hearing impairment as a result of medication for MDR TB before the commencement of treatment. All the time the audiologist was consulted in case of MDR TB patient suspected to have hearing loss, tinnitus or loss of balance and the option of reduction of dose of aminoglycoside in all cases that confirmed to have ototoxicity. NTH MDR TB center only use Kanamycin as a treatment of MDR TB for the reason that it is a cheapest ant MDR TB drug despite being the most ototoxic. Because of that, it is impossible to follow the recommendation by WHO of changing Kanamycin to a lesser toxic ant MDR TB drug like capreomycin to patients

with hearing loss. Also, it was found that Baseline audiological evaluation, which is supposed to be done prior to commencement of kanamycin, was not consistently done as well there were no protocol in place for regular check-up of hearing status of patients once commenced kanamycin.

In conclusion, the study has shown a significant proportion of patients who get MDR TB treatment ends up with significant hearing loss, insufficiency protocol on monitoring hearing status of patients, lack of other anti MDR TB drugs to opt in case of ototoxicity and inconsistency in informing patients of possible hearing and balance loss due to the medication.

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