OTOTOXICITY AMONG PATIENTS RECEIVING MULTIDRUG-RESISTANT TUBERCULOSIS TREATMENT; EXPERIENCE FROM A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) is an increasing challenge to health services globally. Although new drugs are in development, current guidelines still recommend prolonged use of injectable antimicrobials (usually Amikacin, Kanamycin or Capreomycin).

Methods: We conducted a retrospective study of patients initiating treatment for MDR-TB at Programmatic Management of Drug Resistant TB unit, Lady Reading Hospital (PMDT-LRH) Peshawar between January 2012 and December 2013.

Objective: Objective of the present study is to find out the incidence of ototoxicity (defined both clinically and on audiological testing), its associated factors and its effects on final outcome.

Results: The choice of injectable antimicrobial varied. Total of 543 patients treated with injectable antimicrobials for MDR-TB were included in the analysis. Of 543 MDR-TB patients, 476 (87.7%) received amikacin and 67 (12%) received capreomycin. All the patients received baseline screening by audiometry at the time of registration for MDR-TB treatment and 36.83% had more than one audiogram.

Among 543 patients, 200 (36.83%) patients showed evidence of ototoxicity. Most of the male patients (p= 0.010), age between 25 to 44 (p= 0.012), comorbidity (p= 0.023), duration of illness (p=0.010), past TB treatment outcome (p= 0.047) and use of amikacin (p= 0.031) were significantly associated with ototoxicity.

Conclusions: Long-term morbidity from injectable treatment is significant in this setting, and the data suggest capreomycin might be associated with less ototoxicity when compared with amikacin. There is a need for more high-quality clinical data to inform future guidelines for treatment and monitoring.

Keywords: Aminoglycosides; Capreomycin; Drug toxicity; Peshawar; Pakistan

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is caused by strain of Mycobacterium tuberculosis (MTB) that is resistant to at least two of the most powerful 1st line anti TB drugs i.e. isoniazid (INH, H) and rifampicin (RMP, R). Because of emergence of resistant strains, tuberculosis adopted more dreadful nature in the form of MDR-TB, which poses a serious threat to ongoing national TB

control programmes.[1] World Health Organisation (WHO) estimates that 5% of all tuberculosis cases are now multidrug-resistant tuberculosis (3.3% of new and 20% of previously treated TB cases) and that these numbers are likely to increase in the coming years.[2] Patterns of international migration mean that MDR-TB will be an increasing challenge in both resource-rich and -poor settings.[3] Current treatment duration of MDR-TB is at least 24 months and during this high side effected second line drugs (SLD's) are used and its cure rate is low as compared to Drug-Susceptible TB.[4] The aminoglycoside family of antimicrobials or the mechanistically similar cyclic peptide antibiotic capreomycin are recommended to form part of all MDR-TB treatment regimens.[5,6] Injectable antimicrobials are likely to remain a key part of treatment for the foreseeable future. WHO guidelines advise the use of amikacin or kanamycin initially, with capreomycin in resistant cases, and streptomycin is to be avoided due to widespread resistance, although opinions differ.[7,8] All four agents are injectable, with the suggested duration of treatment being at least 6 months.[9] Therefore MDR-TB patients often receive a very large cumulative dose of injectable agents with significant toxicity. Ototoxicity and nephrotoxicity are both well-recognized adverse effects of injectable treatment. Ototoxicity can present with either hearing disturbance or vestibular symptoms. Hearing loss is classically irreversible, bilateral and high frequency, progressing to the lower frequencies in some patients, and is often accompanied by tinnitus.[10,11] Both patient and drug factors influence ototoxicity.[12]

Different factors, such as lack of adequate audiological testing technology and lack of standards for hearing loss, which consider different auditory thresholds for ototoxicity, emerge a need for further investigations. To our knowledge, this is one of the first studies that investigates the relationship between patients' characteristics and the incidence of the ototoxicity in MDR-TB from this area. The aim of this study was to investigate the incidence of ototoxicity and study the risk factors that would influence this toxicity among all patients, registered at PMDT unit, Lady Reading Hospital Peshawar from January 2012 to December 2013 who received a second line therapy for MDR-TB.

METHODS

A retrospective study was carried out at PMDT-LRH Peshawar, Pakistan. Eligible cases were culture-proven MDR-TB patients treated between 1 January 2012 and 31 December 2013 and receiving an injectable agent for 2 weeks. For each patient, the following baseline demographics were collected: age at the start of treatment, gender, co-morbidities, past TB treatment duration of illness and the choice of injectable. total dose and the reason for stopping injectable treatment were identified. Total dose of drugs was calculated from the weight of the patient. Duration was defined as the number of days from initiation of injectable treatment until its withdrawal. For patients who received more than one injectable during treatment, the duration and dose are the combined total for both compounds. Data were collected from routine clinical records and anonymized, thus ethical approval was not required. All audiograms were collected and analysed. Audiograms were recorded using standard British Society of Audiology guidelines.[13] Patient-reported hearing loss or tinnitus at any point was recorded with the date first reported and whether symptoms persisted after treatment. Outcome variables were defined as cases with evidence of ototoxicity and cases without. Two definitions of ototoxicity were used: an audiogram-based definition and a clinical definition. Ototoxicity on audiogram was defined as a 20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies.[14] An audiogram was defined as a true baseline result if it was taken within 2 weeks of the commencement of treatment. If there was no baseline, the first audiogram taken during treatment was used as the baseline.[15] The clinical definition used was cases with hearing loss or tinnitus without available audiograms.

Ototoxicity associated with injecables were investigated using chi square ($\chi 2$). Factors associated with ototoxicity were analyzed by using univariate analysis to investigate the ototoxicity associated with age, gender, co-morbidity, duration of illness, past TB treatment and MDR treatment outcome. p-values less than 0.05 were considered statistically significant. All Statistical analysis was performed using SPSS software for windows (version 20).

RESULTS

Demographics

Total of 543 patients treated with injectable antimicrobials for MDR-TB were included in the analysis. Baseline characteristics of patients treated in 2012 to 2013 at this center are described in Table 1. Mean age of the study cases were 30.34 $\pm$ 14.93 years; 297 (54.7%) were female. Duration of past TB treatment was more than one year for 269 (49.5%) patients, while duration of less than one year was 270 (50.5%). Most of the patients 262 (48.3%) were previously treated with category I and 228 (42.0%) with CAT II and 53 (9.8%) were new patients. Most of the patients 364

(63.0%) had unsuccessful previous TB treatment outcome and successful MDR-TB treatment outcome 394 (72.6%).

Injectable agent choice

Four hundred and sixty-seven (87.7%) of the MDR-TB patients received amikacin and 67 (12.3%) capreomycin as the first choice of injectable (Table 2) with 5% patients switching from amikacin to capreomycin (3.5% due to ototoxicity, 1% due to pregnancy and 1% skin rashes). A number of patients (28%) had their initial dosing regimen changed at least once over the course of treatment due to drug levels, toxicity concerns or partial difficulties.

Screening

All of the patients 543 (100%) received audiogram at baseline. Using the definition of 'baseline' as an audiogram taken at the time of registration for MDR-TB treatment. More than 1 audiogram received by 200 (36.83%) patients after the report of symptoms.

Ototoxicity outcomes

Two hundred (36.83%) patients showed evidence of ototoxicity. None of these patient is recorded as having reported symptoms before treatment began. Of the 200 patients with audiogram evidence of ototoxicity, 59 were found with hearing loss, 69 tinitus

Table 1. Baseline Demographic characteristics of MDR - TB patients (N=543)

Characteristics	No. of patients (%) N= 543
Gender	
Male	246 (45.3)
Female	297 (54.7)
Age (Years) Mean age ±SD	30.34± 14.93
Age Groups	
5-14 15-24 25-34 35-44 45-54 55-64 65+	27 (5) 201 (37) 129 (23.8) 75 (13.8) 47 (8.7) 46 (8.5) 18 (3.3)
Duration of Ilness	
≥ 1 Year < 1 Year	269 (49.5) 270 (50.5)
Comorbidity	
Yes No	128 (23.6) 415 (76.4)
Previous TB Treatment Category	
CAT I CAT II New	262 (48.3) 228 (42.0) 53 (9.8)
Previous TB Treatment Outcome	
Successful treatment outcome Unsuccessful treatment outcome New	124 (22.8) 364 (63.0) 55 (9.5)
MDR Treatment Outcome	
Successful treatment outcome Unsuccessful treatment outcome	394 (72.6) 149 (27.4)

Table 2. Injectable use by MDR - TB Patients (N=543)

Injectbles	N(%)
Am	476 (87.7%)
Cm	67 (12.3%)

Am: Ami kacin; Cm: Capreomycin

Table 3. Audiogram screening by MDR-TB Patients

Total Number of AG's	MDR -TB Patients
Number receiving BL	543 (100%)
Number receiving ≥1 AG	200 (36.83%)
Mean AGs received	1.63 ± .483

AG: Audiogram; BL: Baseline

Table 4. Ototoxicity Outcome by injectable used

Outcome	Am	Cm	P-value ($\chi 2$)	Odd ratio
Ototoxicity	182	18	0.031	2.179
No Ototoxicity	294	49		

Am: Amikacin; Cm: Capreomycin

and 73 with both. One hundred and eighty-two (91%) had ototoxicity with receiving amikacin injection and 18 (9%) with capreomycin injection. Ototoxicity were statistically found to be significant (p = 0.031, Odd Ratio = 2.179) with injectable (amikacin and capreomycin). Co-morbidity were also found to be statistically significant (p = 0.023) with ototoxicity.

Factors associated with Ototoxicity

Table 5 shows the outcome of the analysis of variables for the ototoxicity group compared with the non-ototoxicity group. Gender, age, duration of illness, past TB treatment and MDR-TB treatment outcome were significantly associated with ototoxicity on analysis. Among 543 MDR-TB patients 200 (36.83%) were observed with ototoxicity with MDR-TB treatment. Of the 200 patients who had ototoxicity, most of the patients 120 (60%) age were lies between 25-44 years found to be statistically significant (P= 0.012). One hundred and five (52.50%) male patients and duration of illness greater than one year 106 (53%) were found to be highly statistically significant with ototoxicity (P = 0.010). Past TB treatment with unsuccessful outcome 131 (65.5%) and MDR-TB treatment outcome were significantly associated with ototoxicity (P = 0.049)

DISCUSSION

Occurrence of resistant MTB among susceptible TB patients creates problems against TB control programme throughout the world. Among Drug resistant-TB, MDR-TB is serious one. MDR-MTB is become a growing problem throughout the world.[16] Treatment for DR-TB is long, difficult and with side effects. The selection of drugs for resistant M. tuberculosis depends on the frequency of the specific drug-resistant mutants in the initially drug-susceptible bacterial population. As a consequence,

Table 5. Univariate analysis of variables associated with ototoxicity in MDR-TB patients (N=543)

Variables	Ototoxicity (%) N= 200	No Ototoxicity (%) N=343	P-value
Gender			
Male	105 (52.50)	141 (41.10)	0.010
Female	95 (47.50)	202 (58.89)	
Age (Years)			
5 -14	7 (3.5)	20 (5.83)	
15-24	71 (35.5)	130 (37.90)	
25-34	49 (24.5)	80 (23.32)	
35-44	34 (17)	41 (20.5)	0.012
45-54	22 (11)	25 (7.29)	
55-64	14 (7)	32 (9.33)	
65+	3 (1.5)	15 (4.37)	
Duration of illness			
1≥ Year	106 (53)	164 (47.81)	0.010
< 1 Year	94 (47)	179 (52.19)	
Comorbidity			
Yes	58 (29)	70 (20)	0.023
No	142 (71)	273 (80)	
Previous TB Treatment Category			
CAT I	101 (50.5)	160 (46.65)	0.657
CAT II	81(40.5)	147 (42.86)	
New	81 (40.5)	36 (10.50)	
Previous TB Treatment Outcome			
Successful treatment outcome	51 (25.5)	73 (21.28)	0.047
Unsuccessful treatment outcome	131 (65.5)	233 (67.93)	
New	18(9)	37 (10.79)	
MDR Treatment Outcome			
Successful treatment outcome	155 (77.5)	239 (69.68)	0.049
Unsuccessful treatment outcome	45 (22.5)	104 (30.32)	

the chance of selecting such mutants is highest in the case of mono-therapy[17] and this is the rationale of combination chemotherapy both in case of drug-susceptible as well as MDR-TB even at the cost of adverse drug reactions so that mutants resistant to a single drug are not easily selected by mono-therapy. Adherence to treatment is a critical factor in the management of MDR-TB and adverse events associated with second line drugs could have a severe impact on adherence because long term use of second line drugs is required in MDR-TB ranging from 18–24 months.[18] A large literature exists on the adverse effects of anti-tuberculosis medications, which range from minor to life threatening.[19-22]

Aminoglycosides are also used during MDR-TB treatment and the main problems with the administration of aminoglycosides are risks of development of nephrotoxicity and ototoxicity.[23] Ototoxicity is the major irreversible toxicity of aminoglycosides. Cochlear damage can produce permanent hearing loss, while damage to vestibular apparatus results in dizziness, ataxia and/or nystagmus. Aminoglycosides appear to generate free radicals within the inner ear, with subsequent permanent damage to sensory cells and neurons resulting in permanent hearing loss.[24]

The present study conducted to know the effect of second line aminoglycosides namely amikacin,

kanamycin and capreomycin on hearing status of MDR-TB patients and any possible relations with final outcomes of the patients. We report ototoxicicty documented by pure tone audiometry in 36.83% patients of MDR-TB using a single parenteral second line aminoglycoside. This rate of ototoxicity is slightly in comparison some other study conducted in different areas of the world.[19,23,25-27] Whereas some other studies have reported hearing loss as an adverse drug reaction in patients of MDR-TB ranging from 6–18% which is lower as compared to our study.[20,28,29]

The present study also suggests age, gender and treatment time along with aminoglycoside as predictors for ototoxicity. Also the present study pointed out negative effect of Amikacin was more as compared to Capreomycin. Another important point of the present study is that ototoxicity negatively affect the good outcome of the disease. This is because due to this side effect, medication of injectables changed or lower the dose or dose changed to alternative days.

Ototoxicity is determined by comparing baseline data, ideally obtained prior to drug administration, to the results of subsequent monitoring tests. Detecting changes in pure tone thresholds directly using serial audiograms is considered the most effective indicator of ototoxic hearing loss, particularly when ultra-high frequency thresholds are included.[30,31] In the present study, audiometry was performed every other month or when patient complain for any problem and continue until the completion of intensive phase of therapy. Ideally audiograms is recommended twice a week but at PMDT-LRH twice weekly audiograms were not performed because of cost involved and the inability of the patients from far distant places to report twice weekly at our center where facilities for conventional assessment of hearing are available.

In all the patients showing hearing loss, the aminoglycoside was not stopped and the only changed is its dose modification. All the patients included in the present study completed the remaining part of the therapy. This study also showed that if possible capreomycin should be added to treatment for the control of this ADR. Also there is a number of otoprotective agents are present. These agents delivered either before or in combination with ototoxic drugs may help to prevent ototoxicity. D-methionine as an otoprotective agent has shown protection against amikacin induced ototoxicity.[32]

CONCLUSION

In conclusion, MDR-TB is an increasingly common challenge in clinical practice and current injectable therapies can lead to substantial long-term ototoxicity. Better use of current treatment and monitoring strategies could reduce this. Besides this also administration of Capreomycin may help in the decrease of this ADR. More detailed prospective studies and randomized data comparing agents within this class are needed to improve our knowledge base, potentially within the context of trials of new agents.

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