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ASSESSMENT OF PREVALENCE OF KANAMYCIN INDUCED OTOTOXICITY IN MDRTB PATIENTS IN TERTIARY CARE HOSPITAL, (INDIA)

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ABSTRACT

Background: Standard treatment of MDR-TB (multidrug resistant tuberculosis) consists Category IV regimen of RNTCP. Although this regimen is effective in treating MDR TB, it is associated with many adverse drug reactions (ADRs) Aim and objective: To assess incidence of ototoxicity in MDR-TB patients in tertiary care hospital and causality assessment of reported ADRs using suitable scales. Methods: In this prospective, observational study, patients selected from TB & chest OPD was evaluated for deafness before and after treatment. The nature of the ADRs, likelihood of association with the study medications and severity were evaluated. Result: kanamycin used in MDR-TB patients may result in mild to moderate bilateral sensorineuronal type hearing loss. Careful audiologic monitoring may help in limiting this damage which once developed is permanent.

KEYWORDS: MDRTB, Kanamycin, Hearing loss, ADRs.

INTRODUCTION

Tuberculosis is one of the leading infectious diseases in the world and is responsible for more than two million deaths and nine million new cases annually.[1] Emergence of resistance to drugs used to treat tuberculosis and particularly multi-drug resistant (MDR-TB) has become an obstacle to effective global TB control.[2]

MDR-TB was defined as a high-level resistance to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs. In Category IV regimen, RNTCP will be using a

standardized treatment regimen for the treatment of MDRTB cases under the program: The Intensive Phase will consist of 6-9 months of Km (Kanamycin, Ofx (Ofloxacin), Eto (Ethionamide), Cs (Cycloserine), Z (Pyrazinamide), and E (Ethambutol) and the Continuation Phase will consist of 18 months of Ofx, Eto, Cs, and E.[3] A crucial issue related to long-term administration of the injectable kanamycin is Ototoxicity and is well recognized as dose-related adverse effects of aminoglycoside[4] due to such as lack of adequate audiological testing technology and lack of standards for hearing loss, and different auditory thresholds for ototoxicity. Kanamycin has been shown to suppress cochlear activity irreversibly, resulting in increased incidence of ototoxicity than the vestibulotoxicity which leads to a permanent sensorineural hearing loss in human being.

Aim and objective

1. To assess incidence of ototoxicity in MDR-TB patients in Tertiary care hospital Surat, Gujarat.
2. To assess causality of reported ADRs using WHO-UMC criteria.
3. To assess severity using Naranjo algorithm and preventability of reported ADRs using suitable scales.

Method

In this prospective, observational study patients were selected from TB & chest OPD, Department of pulmonary Medicine, New civil hospital Surat, Gujarat. Study was conducted from January 2013 to May 2014. Study was approved by local institutional ethical committee. **Inclusion criteria was** MDR-TB patients whereas **exclusion criteria were t**hose patients with any pre-treatment evidence of hearing loss (congenital deafness, congenital abnormalities), patients with evidence of infective pathology in ear (meningitis, chronic otitis media, surgical procedures, concomitant use ototoxic drugs. 100 patients were enrolled and receive CAT-IV regimen (<45kg 500mg, >45kg 750mg) of intravenous kanamycin combined with the second- and third-line drugs for MDR-TB for six months. Pure tone audiometry (PTA)was performed on all patients before and monthly during the treatment. The onset of symptomatic ototoxicity was detected using questionnaire monthly.

The criteria used for determining ototoxicity: Threshold shifted from baseline audiogram were: (I) 20 dB or greater decrease at any one test frequency, (II) 10 dB or greater decrease at any two adjacent frequencies, or (III) loss of response at three consecutive frequencies.[5]

Baseline pure-tone audiograms between 250 Hz and 8000 Hz were performed for all the patients in an acoustic room.

RESULT

The incidence of mild to moderate bilateral sensorineuronal hearing loss observed in 35 (35%) patients (male=23, female=12) and 65 (65%) patients (Male=38,Female=27) without developing ototoxicity over the period of six months,who had confirmed MDR-TB from July 2013 to June 2014 in New civil hospital Surat, Gujarat. To investigate the relationship between the individual demographics and the incidence of ototoxicity, patients were divided in two groups: those with ototoxicity and those without ototoxicity (Table-1)

Table 1.: Demographic and clinical characteristics of MDR-TB Patients treated with anti-tubercular medication.

Sr.no	Characteristic	Patients (n =100)	Patients with ototoxicity (n= 35)	Patients without ototoxicity (n= 65)
1	Age	28.77±9.92	29.29±10.40	28.35±9.74
2	Sex (M/F)	61/39	23/12	38/27
3	Weight(kg)	44.57±7.94	44.66±7.50	44.34±8.15
4	Patients with Cat-I treatment	15 (15%)	3 (8.6%)	12 (18.46%)
5	Patients with Cat-II treatment	85 (85%)	32 (91.4%)	53 (81.53%)

Table 2. Relationship between onset of ototoxicity and administration of anti-Tuberculosis treatment (based on audiogram, n=35).

Onset of ototoxicity	1st month	2nd month	3rd month	4th month	5th month	6th month
No. of patients with (ototoxicity) (n=35)	22 (62.85%)	4 (11.4%)	1 (2.85%)	3 (8.57%)	3 (8.57%)	2 (5.71%)

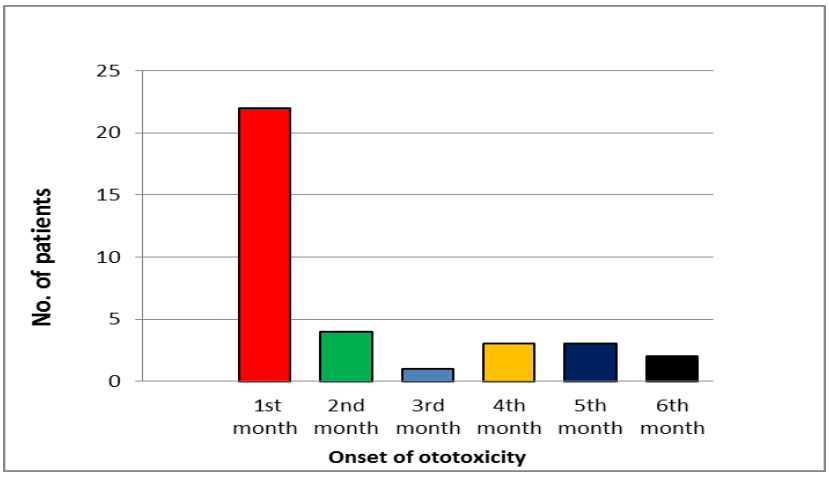

Figure 1. Onset of ototoxicity and administration of anti-Tuberculosis treatment (based on audiogram, n=35).

Table 3. Causality categories-wise distribution of adverse drug reactions (ototoxicity) reported at New civil Hospital, Surat.

Sr.no	WHO-UMC causality criteria[6]	Number of ADRs (%)	Naranjo algorithm [7]	Number of ADRs (%)	MODIFIED SCHUMOCK AND THRONTON PREVENTABILITY SCALE[8]	Number of ADRs (%)
1	Certain	4 (11.42%)	Definite	4 (11.42%)	DEFINITELY	0 (0%)
2	Probable	31 (88.57%)	probable	31 (88.57%)	PROBABLE	0 (0%)
3	Possible	0 (0 %)	possible	0 (0 %)	NOT preventable	35 (100%)
4	Unlikely	0 (0 %)	doubtful	0 (0 %)		
5	unclassified	0 (0 %)				
6	Unclassifiable	0 (0 %)				

DISCUSSION

Burden of MDR TB increasing in the society. MDRTB treatment regimen has potential for toxic ADRs. Number of studies shown list of ADRS related to anti-tubercular therapy. Laboratory test and many risk factors identify patients prone for serious ADRs.[9] But in some cases it's difficult to predict course of ADR in future. Present study was designed to indicate role of pure tone audiometry, seriousness of ototoxicity of kanamycine and causality assessment with standard WHO scales.

Ototoxicity is the major irreversible toxicity of Kanamycin.[10] 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.[11,12] In the present study, pure tone audiometry was performed every other month for each patient over the period of six month. Aminoglycoside ototoxicity can progress after discontinuation of the drug. This long term follow-up confirmed that Kanamycin induced hearing loss in this patient population was permanent and not reversible. Keeping in mind ototoxicity there is need for alternatives to kanamycin.

CONCLUSION

kanamycin used in MDR-TB patients may result in irreversible hearing loss Involving of mild to moderate bilateral sensorineuronal type. Audiologic changes have been reported in patients of MDR-TB using second line aminoglycoside kanamycin which can potentially affect the communication ability of the patient. But careful audiologic monitoring may help in limiting this damage which once developed is permanent.

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