

Audiologic Monitoring of Multi-Drug Resistant Tuberculosis Patient on Aminoglycoside Treatment with Long Term Follow -Up

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Abstract

Objective: Early identification of ototoxic hearing loss provides physicians the opportunity to adjust the therapeutic treatment in order to minimize or prevent hearing loss requiring rehabilitation, depending on a patient's overall treatment picture

Method: About fifty newly patients of MDR-TB who are to be treated by second line drug will be enrolled to the purposed study.-Hearing status of these patient would be advised to undergo evaluation of their audiometry status before the commencement of the treatment.The auditory status evaluation comprising of tuning fork test pure tone audimatory would be performed at the interval of 1month.

Results:Hearing loss of 15 decibels (dB) at two or more frequencies, or at least 20 dB hearing loss at at least one frequency, was found in 18% of our total population treated with aminoglycosides (amikacin, kanamycin and/or streptomycin). In the group treated with kanamycin this percentage was 15.6. None of the factors sex, age, treatment duration, total aminoglycoside doses or first serum creatinine concentration, was found to be associated with hearing loss.

Conculsion:Aminoglycosides used in MDR-TB patients may result in irreversible hearing loss involving higher frequencies and can become a hearing handicap as speech frequencies are also involved in some of the patients thus underlining the need for regular audiologic evaluation in patients of MDR-TB during the treatment

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I. Introduction

Tuberculosis is major global health problem and is the second biggest cause of death from infectious disease after HIV .Tuberculosis is a communicative disease which is caused by mycobacterium infection in lungs .Tuberculosis is one of the oldest human disease and is the main cause of death in many countries. Incidence of active pulmonary tuberculosis is estimated to as high as 8 million new cases per year worldwide as well as approximately 2million death per year. In addition ,developed countries are experiencing a resurgence of tuberculosis, whereas tuberculosis has been major challenge for health care providers in developing countries for long time. Emergence of resistance to drug used to treat tuberculosis and particularly multidrug resistant has become an obstacle to effective global TB control . Incomplete and inadequate treatment is most important factor leading to its development. Inappropriate treatment results in unacceptably low cure rates and continued spread of tuberculosis in the community because of selection of M tuberculosis isolates that are resistant to antitubercular drug. There are several chemotherapeutic agent that exit to treat multidrug resistant mycobacterial infection. However the necessity of utilization of multidrug regimen has been associated with increased incidence of side effect.A crucial issue related to long-term administration of the injectable group is toxicity. Ototoxicity and nephrotoxicity are well recognized as dose-related adverse effects of aminoglycosides. Ototoxicity and nephrotoxicity have been of major concern because of the narrow therapeutic range of these agents and the wide variability in pharmacokinetics among patients]. Amikacin is a semi-synthetic aminoglycoside and shows excellent activity against Mycobacterium tuberculosis and atypical mycobacteria and has been used in the treatment of disseminated atypical Mycobacterium infection in AIDS patients.Kanamycin, an antibiotic elaborated by Streptomyces kanamyceticus has shown activity against Mycobacterium tuberculosis. But as the therapy of this disease is protracted and involves the administration of large total doses of the drug, with the risk of ototoxicity and nephrotoxicity, kanamycin should be used only in infection with organisms that are resistant to the more commonly used agents. It is more toxic to cochlea with

well documented ototoxicity but is still being commonly used in clinical settings like ours (in developing countries) for MDR-TB where cost considerations are a major factor in patient compliance. Capreomycin is an antimicrobial cyclic peptide elaborated by *Streptomyces capreolus* and is effective both in vitro and in experimental tuberculosis. It has proven to be of value in the therapy of 'resistant' or treatment failure tuberculosis when given with ethambutol or isoniazid]. The toxicity profile of capreomycin is similar to that of aminoglycosides and has been discussed along with aminoglycosides in the present study. Cost of therapy with capreomycin is quite high compared to amikacin and kanamycin and is used only in few patients of MDR-TB showing resistance to amikacin and kanamycin. Initial ototoxic drug exposure typically affects cochlear regions coding the high frequencies. Continued exposure results in spread of damage to progressively lower frequencies. Early identification of ototoxic hearing loss provides physicians the opportunity to adjust the therapeutic treatment in order to minimize or prevent hearing loss requiring rehabilitation, depending on a patient's overall treatment picture. The present study was conducted to study the effect of second line aminoglycosides (amikacin, kanamycin and capreomycin) on the hearing status in patients of MDR-TB after long term use as a part of multi-drug therapy. Aminoglycoside used in MDR TB patients may result in irreversible hearing loss. Hearing loss may be sensorinural..

II. Material & Method

The present study has been conducted in the Department of Otorhinolaryngology and Department of T.BandChest, J.L.N.M.C.H,Bhagalpur from May 2016 to April 2017. Ninty Six patients of MDR T.B were registered for study. Four patients died during patient and twenty patients failed to complete this study.

The objective to study

1. To investigate occurrence of hearing loss among the patient with MDR T.B who underwent chemotherapy.
2. Compare pre and postTreatment hearing status.

The study involved 72 patients who received treatment for MDR T.Bfrom fromMay 2016 to April 2017..All patients agreed to undergo hearing test and all provided written consent for participation in this study.

Inclusion Criteria

1. Newly diagnosed patients of MDR T.B who gave their consent for enrolment in the study.

Exclusion Criteria

1. Patients who did not give consent.
2. Patient with severe hearing loss .
3. Patient having active ear disease.
4. Patient who had tumour invasion into ear.

1. Assessment of Patients

Patients were assessed by taking detailed history and clinical examination as per performa .

In all patient investigation was done at our central and their diagnosis was confirmed prior to enrolment in the study.

Audiological Assessment

- After ruling out any pathology in External/Middle ear a baseline pure tone audiometry was done for every patient at the time of enrollment.
- 2nd PTA was done just after 2month starting of Treatment
- 3rd PTA was done after 4month starting of Treatment.
- 4th PTA was done after 6 month starting of Treatment.
- 5th PTA was done after 8 monthcomplete of treatment
- 6th PTA after 10 months of aminoglycoside use
- 7THPTA after complete of treatment

For audiological assessment only PTA was used and all PTA were carried out by at our center using an ALPS advanced digital audiometer – AD 2100.

Evaluation of Audiograms

- Each ear was treated as an unit.
- In Bone conduction: The average of hearing thresholds at 250, 500, 1000, 2000 and 4000 was taken. If there was No response at 2/4 KHz then 69 dB was substituted for calculation purpose.
- In Air Conduction: The average of hearing thresholds at low frequencies (250, 500, 1000, 2000) and high frequencies (4000, 8000 KHz) were taken.
- Where there was no response at 4/8 KHz then 125 dB was substituted for calculation for each no

response for particular frequency 4/8 KHz .

For objective post treatment audiological assessment □

- Difference of ± 5 dB at particular frequency between the audiograms was considered as no change.
- Difference of $\pm 6 - 15$ dB was considered mild objective hearing loss or hearing improvement.
- Difference of $> \pm 15$ dB was considered moderate objective hearing loss (HL)/ hearing improvement (HI).

For Statistical Analysis

The average change in air conduction thresholds at low (250-2000 Hz) and high (4000-8000 Hz) frequencies and bone conduction threshold (250 to 4000 Hz) before treatment were compared with values obtained during treatment and at the time of last follow up, i.e. 6 months after start of treatment. Whenever there was a difference in the mean hearing threshold, a paired t- test was done using SPSS (Statistical Package for Social Sciences).

III. Result

All the patients in this study were in the age group of 17 to 65 years (mean age = 39.9 ± 13.5 years). Overall male predominated and male : female ratio is approx. 7 : 1. Most of the patients (65.3%) were from rural area while (34.7%) were belonged to urban area. Rural urban ratio is equal to 1.88 : 1. Majority (65.6%) of the patients were from low socio-economic status. Overall incidence of HFL was 18.75% while incidence of FLAT loss was 6.25% in the present study. The mean duration of therapy was 20.3 ± 0.25 months after smear/culture conversion (range was 18–24 months) while aminoglycosides were continued for 6 months (180 days) post conversion in the initial phase. Total duration of aminoglycoside use was 233.3 ± 106.6 days while duration of audiologic follow-up after discontinuation of aminoglycoside use was 376.7 ± 42 days. Seven patients (20.6%, n = 34) of group I (amikacin) showed sensorineural hearing loss (SNHL) involving the higher frequencies (HFL). Amikacin was stopped on the first report of hearing loss and patient shifted to another of the second line drug. Follow-up audiogram showed development of FLAT loss in two (5.9%, n = 34) of these patients, (Subject # 2) at six months (pure tone audiogram at 6 months, PTA6) and (Subject # 4) at 10 months (pure tone audiogram at 10 months, PTA10) (Table 1). Duration of aminoglycoside use in group I was 235 ± 40 days (n = 34) while duration of aminoglycoside use in seven patients of group I which developed ototoxicity (n = 7) was 163 ± 45 days (as amikacin was discontinued on first report of hearing loss).

Table 1

Audiometry findings, present regimen and length of aminoglycoside use in group I (n = 7) and II (n = 4) patients showing audiological evidence of hearing loss.

Sr. No. (Group)	Length of treatment (Days)	Present regimen (Drugs)	PTA0	PTA2	PTA4	PTA6	PTA8	PTA10	PTAc
1 (I)	180	A, F, E, P, Py	N	N	N	HFL	HFL	HFL	HFL
2 (I)	60	A, F, E, P, Py	N	HFL	HFL	HFL	FLAT	FLAT	FLAT
3 (I)	180	A, F, E, P, Py	N	N	N	HFL	HFL	HFL	HFL
4 (I)	180	A, F, E, P, Py	N	N	N	HFL	HFL	FLAT	FLAT
5 (I)	180	A, F, E, P, Py	N	N	N	HFL	HFL	HFL	HFL
6 (I)	180	A, F, E, P, Py	N	N	N	HFL	HFL	HFL	HFL
7 (I)	180	A, F, E, P, Py	N	N	N	HFL	HFL	HFL	HFL
8 (II)	120	K, F, E, P, Py	N	N	N	HFL	FLAT	FLAT	FLAT
9 (II)	180	K, F, E, P, Py	N	N	N	HFL	HFL	HFL	HFL
10 (II)	180	K, F, E, P, Py	N	N	N	HFL	HFL	FLAT	FLAT
11 (II)	180	K, F, E, P, Py	N	N	N	HFL	HFL	HFL	HFL

A = amikacin, F = fluoroquinolone, E = ethionamide, P = Para-amino salicylic acid, Py = Pyrazinamide, K = kanamycin, Days = days of aminoglycoside use in present regimen, PTA0 = baseline pure tone audiogram, PTA2 = pure tone audiogram after 2 months of aminoglycoside use, PTA4 = pure tone audiogram after 4 months of aminoglycoside use, PTA6 = pure tone audiogram after 6 months of aminoglycoside use, PTA8 = pure tone audiogram after 8 months of aminoglycoside use, PTA10 = pure tone audiogram after 10 months of aminoglycoside use, PTAc = pure tone audiogram after completion of therapy for

MDR-TB, N = Normal, HFL = High frequency loss (hearing loss involving frequencies of 4000, 6000 and 8000 Hz), FLAT = Hearing loss involving frequencies in range of 250–3000 Hz along with involvement of 4000, 6000 and 8000 Hz (Criteria for hearing loss as defined in methods section)..

Four patients (15.4%, n = 26) of group II (kanamycin) had SNHL involving higher frequencies (HFL). In two (7.7%, n = 26) patients lower frequencies were also involved (FLAT) even when Subject # 8 had injectable drug stopped at 4 months while Subject # 10 had the drug stopped on report of high frequency loss at 6 months (Table 1). Duration of aminoglycoside use in group II was 237 ± 34 days (n = 26) while duration of aminoglycoside use in four patients of group II which developed ototoxicity (n = 4) was 165 ± 30 days (as kanamycin was discontinued on first report of hearing loss).

One of the patients of group III (25.0%, n = 4) developed sensorineural hearing loss involving high frequencies (HFL) at 4 months (Table 2) and capreomycin was substituted with other second line drug based on drug sensitivity testing. Mean duration of aminoglycoside use in group III was 215 ± 64 (n = 4) days. Duration of capreomycin use in single patient with HFL (Subject # 12) was 120 days. None of the patients had any recovery in pure-tone thresholds after stopping the injectable treatment. Group-wise mean loss shown by patients with ototoxic threshold shift (Group I, n = 7; Group II, n = 4, Group III, n = 1) at different frequencies tested in the present study is shown in Table 3. Mean loss (average decrease in pure tone threshold from baseline at each frequency tested in patients with ototoxic threshold shift in each group) in seven patients of group I fulfilled the criteria (ASHA' 1994) for ototoxic threshold shift in frequencies range of 4000–8000 Hz (HFL) but not in the frequency range from 250–3000 Hz. Mean loss in four patients of group II fulfilled the criteria for ototoxic threshold shift in both the frequency ranges i.e. 4000–8000 Hz (HFL) and 250–3000 Hz. As sample size for group III was small, the data was not further analyzed but a note of ototoxic threshold shift in 4000–8000 Hz range was made. Studies with larger number of patients using capreomycin are required but higher cost of the therapy with capreomycin limits its use in large number of patients in our setting.

Table 2 Audiometry findings, present regimen and length of aminoglycoside use in all four patients using capreomycin (Group III).

Sr. No.	Length of treatment (Days)	Present regimen (Drugs)	PTA0	PTA2	PTA4	PTA6	PTA8	PTA10	PTAc
1	247	C, F, E, P, Clo	N	N	N	N	N	N	N
2	254	C, F, E, P, Clo	N	N	N	N	N	N	N
3*	120	C, F, E, P, Clo	N	N	HFL	HFL	HFL	HFL	HFL
4	240	C, F, E, P, Clo	N	N	N	N	N	N	N

C = capreomycin, F = flouroquinolone, E = ethionamide, P = Paraminosalicylic acid, Clo = Clofazimine, Days = days of aminoglycoside use in present regimen, PTA0 = baseline pure tone audiogram, PTA2 = pure tone audiogram after 2 months of aminoglycoside use, PTA4 = pure tone audiogram after 4 months of aminoglycoside use, PTA6 = pure tone audiogram after 6 months of aminoglycoside use, PTA8 = pure tone audiogram after 8 months of aminoglycoside use, PTA10 = pure tone audiogram after 10 months of aminoglycoside use, PTAc = pure tone audiogram after completion of therapy for MDR-TB, N = Normal, HFL = High frequency loss (hearing loss involving frequencies of 4000, 6000 and 8000 Hz), FLAT = Hearing loss involving frequencies in range of 250–3000 Hz along with involvement of 4000, 6000 and 8000 Hz (Criteria for hearing loss as defined in methods section). * Patient in group III with audiological evidence of hearing loss

Table 3 Mean loss in patients with ototoxic threshold shift in group I (n = 7), group II (n = 4) and group III (n = 1) at different frequencies tested

Group	250 Hz	500 Hz	1000 Hz	2000 Hz	3000 Hz	4000 Hz	6000 Hz	8000 Hz
I	3 ± 5.7	2 ± 5.7	3 ± 3.8	5 ± 5	8 ± 8.6	17 ± 12.5	29.3 ± 9.3	34.3 ± 8.5
II	2.5 ± 5	5 ± 7.1	10 ± 9.1	16.25 ± 10.3	20 ± 14.7	27.5 ± 10.4	30 ± 7.9	33.75 ± 16
III	-	-	5	5	10	30	35	45

IV. Discussion

MDR-TB is a growing problem throughout the world. The selection of drug resistant *M. tuberculosis* depends on the frequency of the specific drug-resistant mutants in the initially drug-susceptible bacterial population. As a consequence, the chance of selecting such mutants is highest in the case of mono-therapy 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 monotherapy. 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. A large literature exists on the adverse effects of anti-tuberculosis medications, which range from minor to life threatening.

The main constraint to the administration of aminoglycosides are risks of nephrotoxicity and ototoxicity. 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]. The other major limitation to the clinical use of aminoglycosides continues to be concern for the development of nephrotoxicity. Nephrotoxicity has been defined as an increase in the baseline serum creatinine concentration of 0.5 mg/dl or a 50% increase, whichever is greater, on two consecutive occasions any time during therapy or up to 1 week after the cessation of therapy. Evidence from studies with animals and humans has demonstrated a correlation between the nephrotoxic effect of aminoglycosides and the accumulation of these drugs in the cortex of kidney.

The present study evaluates the effect of parenteral second line aminoglycosides namely amikacin, kanamycin and capreomycin on hearing status of MDR-TB patients. We report a hearing loss documented by pure tone audiometry in 18.75% patients of MDR-TB using a single parenteral second line aminoglycoside involving higher frequencies (4000 to 8000 Hz) to start with and progressing to involve lower frequencies (500, 1000, 2000 and 3000 Hz) in 6.25% thus affecting the speech comprehension of the patient (n = 64). Speech comprehension can also be affected with hearing loss in the 4000 Hz range and may adversely affect communication especially in situations like environments with back ground noise. The loss once developed has been found to be irreversible and none of the patients in the present study showed any improvement after stopping the therapy.

Ototoxicity is determined by comparing baseline data, ideally obtained prior to ototoxic 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]. Monitoring audiological evaluations after the baseline evaluations have been recommended 1–2 times per week for patients receiving ototoxic antibiotics. Other approaches to audiological monitoring for ototoxicity are high frequency audiometry and otoacoustic emissions.

In the present study, pure tone audiometry was performed every other month for each patient until the completion of therapy. Because aminoglycoside ototoxicity can progress after discontinuation of the drug [13], we also performed audiometric follow-up in all patients for an average of over one year after drug discontinuation. This long term follow-up confirmed that all aminoglycoside-induced hearing loss in this patient population was permanent and not reversible. Persistence of toxicity of sera has been reported up to one year in patients using aminoglycosides even after stopping the ototoxic drug. Twice weekly audiograms as recommended were not performed in the present study 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. It is not common to find equipment for audiometry as well as trained staff at peripheral centers in developing country like ours. Conventional frequency range (250–8000 Hz) was used in the present study as only conventional audiometers with frequency range between 125 and 8000 Hz are available with us owing to low cost compared to high frequency equipment.

Different studies have reported hearing loss as an adverse drug reaction in patients of MDR-TB ranging from 6–18%. The finding that higher frequencies are involved before the lower frequencies may be used as a monitoring procedure for the detection of ototoxicity and has the potential for minimizing irreversible communication deficits in patients receiving aminoglycoside therapy. In all the patients showing hearing loss, the aminoglycoside was stopped and changed to another second line drug done. Incidence of hearing loss may have been reduced because the aminoglycoside was stopped immediately at the outset of ototoxicity and substituted with another second line drug. All the patients included in the present study completed the remaining part of the therapy. Other authors have also reported changing to other second line drugs and completion of full therapy [].

A number of otoprotective agents are being investigated for protection against hearing loss induced by cisplatin, carboplatin, aminoglycosides or noise exposure. 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].

There is evidence that aminoglycoside accumulation in the kidney may be related to the dosing schedule i.e. administration of larger doses less frequently may reduce the level of drug accumulation in the kidney and has been prospectively shown to reduce the nephrotoxic potentials of aminoglycosides].

Conventional multiple daily dosing is being gradually abandoned in favor of once daily dosing and results from meta-analysis of randomized clinical trials show diminished or comparable nephrotoxicity, better] or comparable] efficacy and comparable] ototoxicity with once daily dosing among adults. Once daily dosing has been used in all the patients in the present study but individualized dosing based on monitoring of serum levels of aminoglycosides has not been used in present study.

Individualized aminoglycoside dosing guided by targeted peak and trough concentrations in serum on the basis of the patient's individual pharmacokinetics parameters and standard equations has been related to decreased toxicity. An association of ototoxicity with nephrotoxicity and with an elevated mean trough aminoglycoside serum level has been observed in patients treated with aminoglycosides]. Because of economic constraints and the non-affordability by the patients, serum levels of aminoglycosides during the therapy were not measured in the present study. But with individualized dosing based on patient's individual pharmacokinetic monitoring guided by targeted peak and trough concentrations, side effects could probably be avoided in some cases.

First row outer hair cells (OHCs) in the basal turn tend to be affected earlier than inner apical cells and type I cells are affected before type II cells. The progression of hair cell loss in cochlea tends to be from basal to apical and from OHCs to inner hair cells (IHCs) to supporting cells to more central neural structures like spiral ganglion cells. This stepwise progression of damage explains the clinical findings of high frequency hearing loss occurring first with ototoxic drugs

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