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# Ototoxicity Associated With The Usage Of Injectable Kanamycin In Multi-Drug Resistant Tuberculosis Patientsduring Intensive Phase Of Category IV Treatment On DOTS-Plus Therapy.

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***Abstract:***
***Context-****Drug-Resistant Tuberculosis(DR-TB) patients have to undergo long duration of treatment which has severe adverse drug reactions and even leads to change of treatment regimen and discontinuation of treatment.*
***Aim-****To document the Kanamycin induced Ototoxicity in DR-TB Patients(Category-IV Eligible) during Intensive phase of Treatment on DOTS-Plus Therapy.*
***Setting and Design-****A Prospective follow up study on 100 confirmed DR-TB patients diagnosed by CBNAAT at DR-TB centre, Surat. Patients were followed up monthly during Intensive Phase of treatment.*
***Methods and Material-****A pre-tested standardized semi-structured questionnaire was used. Pure Tone Audiometry(PTA) was done on patients to establish ototoxic effect of Kanamycin. Data was collected and extrapolated in tables and graphs.*
***Results-****Out of 100 patients enrolled in the present study, 37 patients (36 hearing loss only, 1 hearing loss & Vertigo both) developed ototoxicity.Out of them, 24 were male and 13 were female. Hearing loss was of sensori-neural type and bilateral in most of the patients. Majority,25(67.6%) developed ototoxicity due to Kanamycin within one month of treatment, which shows the early toxic effects of the drug.*
***Conclusion and Recommendation****-Early recognition of adverse drug reactions, necessary laboratory and other investigations like regular PTA help to identify irreversible hearing loss, which can be prevented by taking appropriate measures and proper counselling of the patient.*
***Keyword****- Drug-Resistant Tuberculosis, Kanamycin, Ototoxicity, Sensori-neural, Category-IV eligible.*

## I. Introduction

Tuberculosis is increasingly being recognised as a cause of major global health concern. It is currently the leading cause of death among the curable infectious diseases. With the emergence of Drug-resistance, Tuberculosis is being recognised as a global threat and a huge obstacle to effective Tuberculosis control.

Multi-drug Resistant Tuberculosis (MDR-TB)[1] is defined as TB resistance to at least Isoniazid and Rifampicin. In the patients of MDR-TB, DOTS strategy fails to provide acceptable cure rates. Long regimen with multiple second line Anti-Tubercular drugs is the necessity for effective chemotherapy of Drug- resistant Tuberculosis. However, MDR-TB is very difficult to treat as the second line drugs are less effective, more toxic, more expensive and need to be given for longer duration. Long term use of these drugs increases the possibility of adverse drug reactions in patients under treatment. The occurrence of Adverse Drug Reactions has raised concerns on the adherence of treatment in cases of MDR-TB, thus signifying the importance to the management of Drug- Resistant Tuberculosis.A vast literature exists on the adverse drug reactions of Anti-tubercular medications, ranging from minor to life threatening drug reactions. In severe drug reactions, it may lead to discontinuation of the culprit drug.

In India, management of Tuberculosis is carried out under standardized treatment Strategy by the Revised National Tuberculosis Control Programme (RNTCP). Management of Drug Resistant Tuberculosis is under DOTS-Plus programme according to Programmatic Management of Drug Resistant Tuberculosis (PMDT) guidelines.[1]Multi-Drug Resistant Tuberculosis (MDR-TB) is treated under Category IV Regimen which comprises of Intensive Phase of 6-9 months depending on the Culture Conversion of infected sample and Continuation Phase of 18 months with dose adjustment according to the weight of patient. In the Intensive Phase 6 drugs are given viz. Kanamycin (6 days/week) while Levofloxacin, Ethionamide, Ethambutol, Pyrazinamide and Cycloserine are given daily. In the continuation phase, 4 drugs are given viz. Levofloxacin, Ethionamide, Ethambutol and Cycloserine on daily basis. Under RNTCP, Category IV eligible patients are those patients whose infected specimen isfound to be Rifampicin Resistant by CBNAAT.

Kanamycin is a bactericidal second line Injectable Aminoglycoside Anti-Tubercular drug which inhibits protein synthesis by irreversibly binding to 30S ribosomal subunit. Kanamycin is not metabolized in the liver and is excreted unchanged in the urine. The optimal dose is 15 mg/kg bodyweight, usually 500 mg to 1 g given daily, by deep intramuscular injection. Under RNTCP, dose of Kanamycin for patients under 16 kg is calculated as 15 mg/kg body weight, 16-25 kg and 26-45 kg weight bands are administered 5oo mg (6 days/week), 46-60 kg weight bands are administered 750 mg (6 days/week) while more than 60 kg patients are administered 1 gm (6 days/week) by intramuscular route.Kanamycin has been shown to suppress cochlear activity irreversibly, resulting in increased incidence of ototoxicity.[1]This study provides an insight into the Ototoxic Adverse Reactions due to administration of Kanamycin during Intensive Phase of treatment of MDR-TB patients under DOTS-Plus Programme.

## II. Aims

To document the Ototoxicity in MDR-TB patients receiving Kanamycin during Intensive Phase of Category IV treatment under DOTS Plus programme.

## III. Objectives

To study the Pattern, Time of onset and Severity of Ototoxicity on patients on kanamycin during Intensive Phase of Category IV treatment under DOTS Plus programme.

## IV. Subjects And Methods

The present study is a prospective Cross-Sectional study (case series) carried out in a teaching hospital during the year 2013-2014 at the DOTS Plus Site of Pulmonary Medicine Department, Government Medical College, Surat. The study was approved by Human Research Ethics Committee of Government Medical College, Surat.

All the patients studied were confirmed cases of MDR-TB who were enrolled in DOTS Plus–Category IV Regimen after diagnosis by CBNAAT at District Tuberculosis Center, Surat. A detailed history of previous treatment and comorbidities was taken and a thorough clinical examination was done. Pre-treatment evaluation was carried out and all the patients with pre-existing comorbidities were excluded. They were then evaluated for the development of Adverse Drug Reactions over the period of 6 months (Intensive phase of treatment). Monthly follow-up during Intensive Phase of CAT-IV regimen of all the patients was done to assess ototoxic effects, during which a pretested standardized semi-structured questionnaire was used and patients were subjected to Pure Tone Audiometry.

**Inclusion Criteria:**

1) All patients eligible for Category IV regimen enrolled and admitted for initiation of treatment in the DOTS Plus Site, Surat.
2) Patient willing to participate in the study.

**Exclusion Criteria:**

1) Patients under 12 years of age.
2)Patients eligible for category IV regimen with pre-existing co-morbid conditions viz. renal, hepatic, vestibular or auditory impairment, peripheral neuropathy etc.
3) Pregnant and lactating females
4) History of Hypersensitivity to Aminoglycosides, rashes etc.
5) Significant family history to ototoxicity.
6) Prolonged use of certain drugs predisposing to Aminoglycoside toxicity viz. loop diuretics, nephrotoxic drugs, muscle relaxants etc.

100 patients fulfilling the above criteria were registered for the study from April 2013 to January 2014 and were monthly observed for a period of 6 months for the development of Ototoxicity. All enrolled patients were admitted for initiation of treatment in the DOTS Plus Site, Surat. A detailed history of previous treatment and comorbidities was taken and a thorough clinical examination was done. Pre-treatment evaluation was carried out and all the patients evaluated for pre-existing comorbidities. The particulars of the patients like age, sex, previous admission and treatment, diagnosis, details of clinical examination, previous adverse reactions and investigations including x-rays chest, hemogram, liver function test, Renal function test, Audiometry, fundus examination, ECG, USG and serum biochemistry were recorded. Data entry and analysis was done with the help of MS excel 2003.

Monthly follow up of these patients was done for 6 months at the out-patient department. At each follow up a detailed pretested standardized semi-structured questionnaire was used along with detailed clinical examination and Pure Tone Audiometry performed and their findings recorded for the development of ototoxicity.

During the study period once, patient develop adverse drug reaction, offending agent were identified and removed from the regimen, necessary modification also done in the regimen in case of intolerance, remaining adverse drug reaction were corrected with supportive medication and treatment completed.

Being a Cross sectional study, the study was Interview Bias, Selection Bias. Since sampling technique was convenient sampling which is being a non probability sampling, so the findings of this study cannot be generalised which is the limitation of the study.

## V. Result

### 5.1.Characteristics of Study Participants:

Out of 100 patients enrolled during the study, 61(61%) were male and 39(39%) were female. Majority of the patients (89/100) were in the reproductive age group of 15-45 years(89%). All patients were sero-negative for HIV testing. Majority of the patients (80/100), were undernourished with BMI of less than 18.5(80%). Of these, 16 were primary MDR-TB cases while rest 84 were Acquired MDR-TB cases. (Table 1)

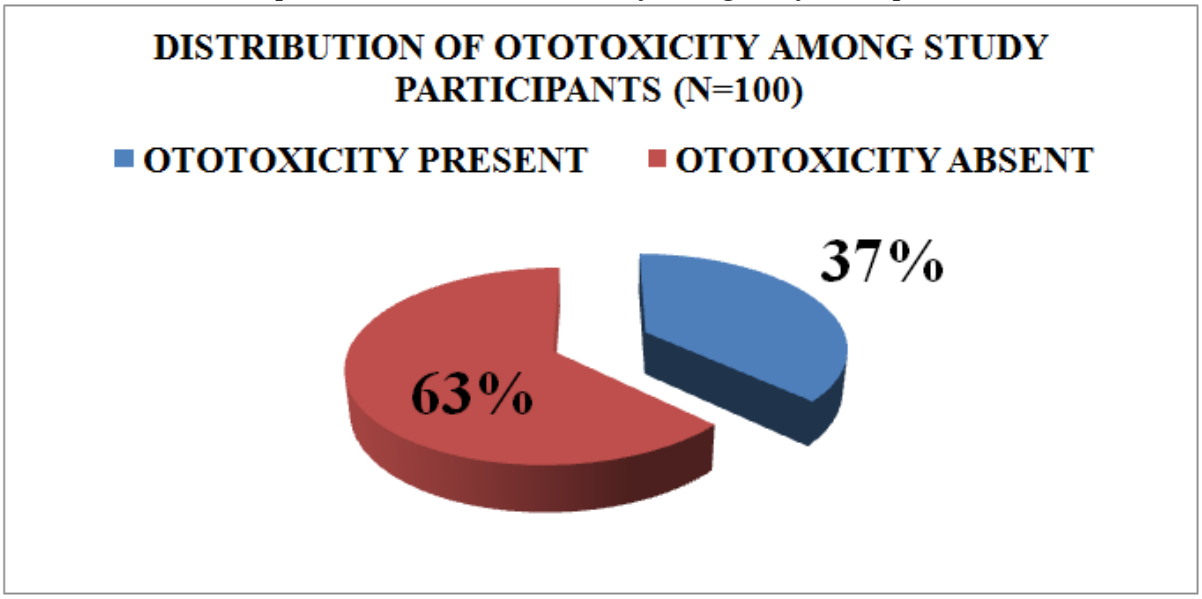
**Table 1:- Characteristics of Study Participants**

| Sr.no. | Characteristic | | Study Participants(n=100)N |
|---|---|---|---|
| 1 | Gender | Male | 61 |
| | | Female | 39 |
| 2 | Age group(Years) | ≤15 | 3 |
| | | 16-30 | 60 |
| | | 31-45 | 29 |
| | | 46-60 | 8 |
| 3 | Body Mass Index ($Kg/m^{2)}$ | <18.5 | 80 |
| | | 18.5-22.9 | 17 |
| | | 23-24.9 | 1 |
| | | ≥ 25 | 2 |
| 4 | Type of MDR-TB | Primary MDR-TB | 16 |
| | | Acquired MDR-TB | 84 |

### 5.2. Distribution of Ototoxicity among Study Participants:

Out of these 100 patients, 37 patients developed symptoms of Ototoxicity. All patients had complaints of hearing loss. Only 1 of these patients had vertigo along with hearing loss. On the basis of evaluation of Pure Tone Audiometry, 35 patients had mild Sensori-neural hearing loss while 2 patients had moderate Sensori-neural hearing loss.36 of these patients had bilateral hearing loss. (Graph 1)

**Graph 1:- Distribution of Ototoxicity among Study Participants.**




### 5.3. Characteristicsof Patients developing Kanamycin Induced Ototoxicity:

Out of 37 patients having hearing loss, 24(64.8 %) were male and 13(35.2%) were female.33(89.2%) of the patients were in the reproductive age group of 15-45 years.29(78.4%) of the patients were undernourished

with BMI of less than 18.5, 7(18.9%) had BMI in normal range while 1 was over-weight with BMI more than 25.

Weight band distribution revealed 18(48.6%) out of 37 patients had weight in the range of 26-45 kg who were receiving 500 mg Kanamycin (6 days/week) and 19(51.4%) out of 37 patients had weight in the range of 46-60 kg who were receiving 750 mg Kanamycin (6 days/week).3(8.1%) out of 37 were Primary MDR-TB cases while 34(91.9%) were Secondary MDR-TB cases.

At the end of 6 months of Intensive phase, 3(3/100) patients did not show culture conversion and the intensive phase had to be extended. Out of these 3 patients, 2 had ototoxicity and kanamycin had to be replaced by PAS. (Table 2)

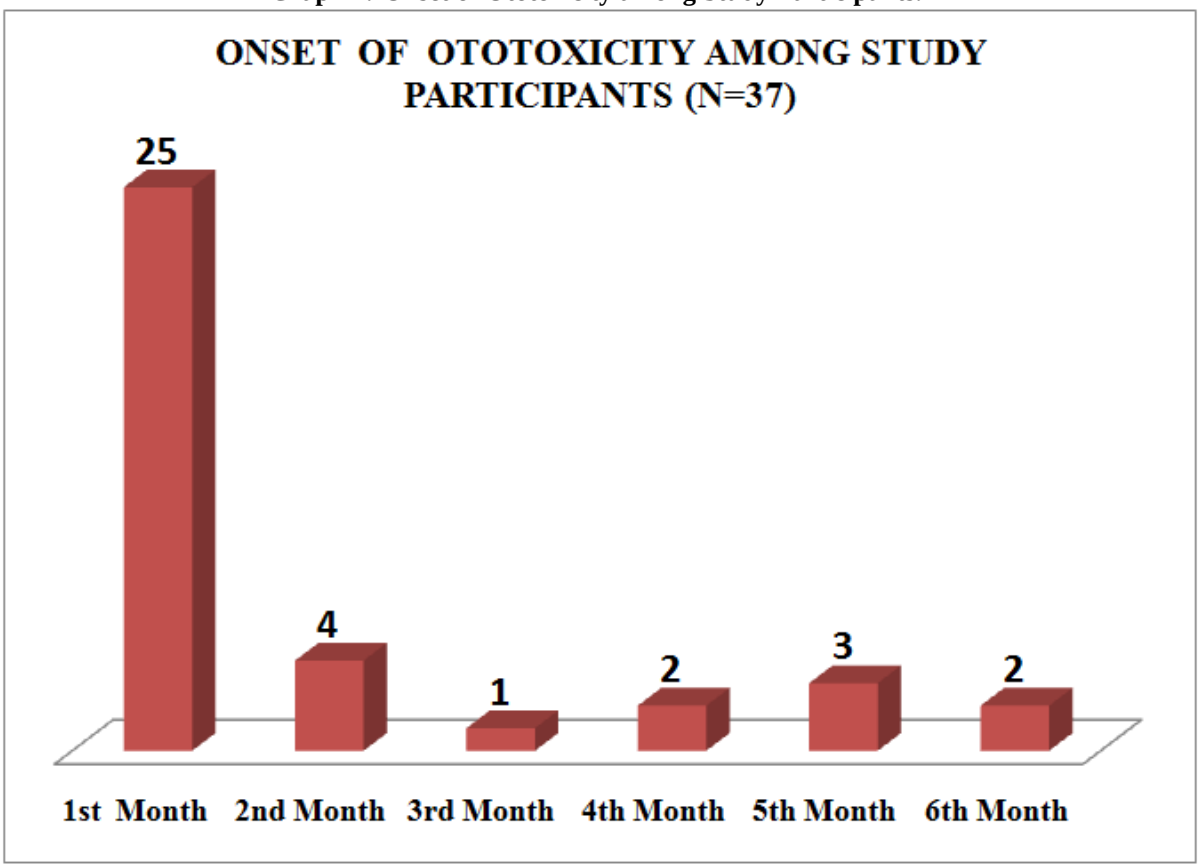
**Table 2:-Characteristics of Patients developing Kanamycin Induced Ototoxicity**

| Sr.no. | Characteristic | | Study participants(n=37)N (%) |
|---|---|---|---|
| 1 | Gender | Male | 24(64.9) |
| | | Female | 13(35.1) |
| 2 | Age group(Years) | <15 | 2(5.4) |
| | | 16-30 | 21(56.8) |
| | | 31-45 | 11(29.7) |
| | | 46-60 | 3(8.1) |
| 3 | Body Mass Index ($Kg/m^{2)}$ | <18.5 | 29(78.4) |
| | | 18.5-22.9 | 7(17.9) |
| | | 23-24.9 | 0 |
| | | ≥ 25 | 1(2.7) |
| 4 | Type of MDR-TB | Primary MDR-TB | 3(8.1) |
| | | Acquired MDR-TB | 34(91.9) |

**5.4. Onset of Ototoxicity among Study Participants:**

25 (67.6%) of these patients developed symptoms during the first months of treatment, 4 (10.8%) during second month, 1 (2.7%) during third month, 2 (5.4%) during fourth month, 3 (8.1%) during fifth month and 2 (5.4%) during sixth month. (Graph 2)

**Graph 2:-Onset of Ototoxicity among Study Participants.**



## VI. Discussion

In the present study we found that out of 100 patients on Category IV Anti-tubercular treatment, 37% (37/100) had hearing loss while among them 1% had vertigo also.

A Study by J. J. Furin et al[2] conducted in year 1996-99 three districts of northern Lima, Peru, with sample size of 60 showed hearing impairment in 4(6.7%) of patients.

Similarly a study by Study by R. Prasad et al[3] in year 1998-2004 with sample size of 46 showed the development of Hearing impairment in 4(8.6%) of patients.

Study by Aleyamma Thomas et al[4] in year 1999-2003 in the study area is a sub-district (predominantly rural) of Tiruvallur district, in south India, with sample size of 66 showed development of giddiness in 5(13%) of patients.

Study by E. Nathanson,R. Gupta et al [5]in year 1998-2002 conducted in Estonia, Latvia,Peru (Lima), the Philippines (Manila) and the Russian Federation (Tomsk Oblast) with sample size of 818 patients showed development of Dizziness in 117(14.3%), Hearing Loss 98(12.0%)and Tinnitus 42(5.1%) of patients.

Study by M. R. Masjediet al[6] in year 2002-2006 conducted in Iran with sample size of 43 showed development of hearing loss in 20(46%) patients along with Tinnitus in 2.3% of patients.

A Study by V.K Aroraetal[7]in year 2002-2005 with sample size of 66 patients showed that three (4.5%) patients developed hearing loss/giddiness.

Thus, we see that the occurance of ototoxicity in different studies varied from 6.7% in the study by J. J. Furin et al to 46% in an Iran Study by M. R. Masjedi et al. The present study shows Ototoxicity due to Kanamycin in 37% of the patients which is comparable to the Studies by E. Nathanson and byM. R. Masjedi et al while it is quite high compared to other studies.

## VII. Conclusion

Cat–IV Regimen Drugs have various serious adverse drug reactions and ototoxicity is found with the usage of Injectable Kanamycin in significant number of patients. Out of 37 patients, 25 (67.6%) developed ototoxicity due to kanamycin within one month of treatment, which shows the early toxic effects of the drug. With the continued occurrence of ototoxicity during the latter months, the cumulative effect of Kanamycin dosage is also suggested.

All the patients should be regularly screened by Pure Tone Audiometry in pre-treatment evaluation as well as during the monthly follow up of intensive phase.Early and prompt intervention can be done with substitution of Aminoglycosides with Reserve Cat IV drugs to prevent progression to irreversible hearing loss even before development of symptoms.

Due to severe and irreversible Adverse Drug Reactions, an increasing number of patients may default the treatment, so proper counselling of the patient needs to be done regarding at the initiation of the treatment as well as during each and every follow up.Most of the patients of MDR-TB were found to be undernourished (BMI<18.5%) due to long term illness. Under the current guidelines, dosage of Kanamycin is fixed according to weight bands not taking into consideration the overall health status of the patient. Dose of long term use of Kanamycin should be individualized based on the Body Mass Index and the General Health Condition of the patient, not on the basis Weight only.

Moreover many Secondary MDR-Tb cases were already on other Aminoglycosides viz. Streptomycin, so cumulative effect of other Aminoglycosides should also be taken into consideration. Since most of the studies regarding adverse drug reactions are carried out on small sample size, the results can not be generalized to the whole population, so more data is required before a consensus can be reached.

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