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Research Article

DRUG INDUCED OTOTOXICITY IN PATIENT WITH TUBERCULOSIS

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ABSTRACT

Streptomycin is the most important aminoglycoside of antibiotic family, that usually employed TB and different advanced gram-negative microorganism infections. All aminoglycosides (AGs) have the potential to induce irreversible / reversible ototoxicity, neuromuscular blockage & nephrotoxicity. In this case study,37 years old man, weighing 53 kg was brought to the hospital with chief complains of tinnitus, hearing loss, fever (on/off), cough with expectoration and vertigo from last 5-6 days. He had a known case of relapsed smear positive pulmonary tuberculosis (PTB) and was taking regular IInd line anti-tubercular drugs therapy (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, and Streptomycin) in the last 1 month. Pulmonologist had stopped the Streptomycin 0.75g BD injection, because this drug was responsible for ototoxicity in patient, but other IInd line ATT medication was continued. Pulmonologists had found the provisional & final diagnosis of anti-tubercular drug (Streptomycin) induced ototoxicity on the bases of subjective and objective observation. Although there are many case reports already done previously, AGs induced ototoxicity particularly in TB patients, we come over the Ist case of AGs induced ototoxicity in TB patients. In this case patient condition was resolved only after discontinuation of streptomycin.

INTRODUCTION

Streptomycin is the most important drug in AGs antibiotics family. AGs can potentially cause ototoxicity (hearing impairment). The susceptibility to AGs increases in the presence of certain mitochondria gene mutations.[1,2] Streptomycin (an aminoglycoside) is part of the drug regimen in relapsed tuberculosis. Also, since streptomycin induced ototoxicity could adversely affect treatment adherence in tuberculosis patients. This case study could enable better pre-treatment counselling with subsequent better treatment adherence.[3] Patients on tuberculosis re-treatment will be recruited longitudinally from Direct Observation Therapy-Short (DOTS) course centres. Early detection of ototoxicity was determined using the American Speech and Hearing Association criteria and genetic analysis to determine relevant mitochondria gene mutations will be done[4]. Streptomycin is also used in many diseases like, Meniere; s disease & other advanced bacterial infections usually in the combination with the other antimicrobials; as it is pharmacologically less active then the other member of the AGs category[5]. streptomycin causes the damage to cochlear & vestibular portion of the inner ear. loss of the vestibular sensitivity causes difficulty walking and oscillopsia. Loss of hearing generally occurs after a short latent period (7-10 days) at 1 gm / days or higher doses & slowly worsens[6].

CASE STUDY

- A case of 37 years old male, weighing 53 kg was brought to hospital with chief complains of tinnitus, hearing losses, fever, cough with expectoration, and vertigo for last 5-6 days.
- On examination, the patient was conscious, at the time of general vital study pulse rate 96 beats per minute, blood pressure 120/80 mmHg, SPO_2 92% at the atmospheric air and cardiac sounds S1, S2 positive were noted.
- He had a past history of pulmonary tuberculosis (1 year back), but at that time patient was completed six months course of first line anti-tubercular DOTS therapy (CAT Ist).
- Patient had no past & family history of hypertension (HTN), diabetes mellitus (DM), thyroid disease and PTB.
- He had a social history of alcoholic & smoking. But patient had occasionally taking limited amount of alcohol and smoking, it means patient had not addicted for alcohol and smoking.
- He had a known case of relapse smear positive PTB & taking regular IInd line ATT (Isoniazid, Rifampicin,

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Pyrazinamide, Ethambutol and Streptomycin) for last 1 month.

- On the 25 days of the II[nd] line anti-tubercular drug treatment, patient was developed with the problems like tinnitus & hearing losses related problem.
- Pulmonologist had stopped the Inj. Streptomycin because; this drug is responsible for the ototoxicity in the long term used for the therapy. But other II[nd] line ATT medication (HRZE) was continued.
- Pulmonologist had advice the patient for routine laboratory investigation like CBCs, LFTs, KFTs, CXR, & viral serological marker (HHH) test. Patients had need to adequate prophylactic treatment of reduced the risk of active tuberculosis.
- On the same day, pulmonologist was prescribed the following medication to the patients after clinical observation:

1. Injection Pantoprazole 40 mg TDS
2. Injection Ondansetron 2 mg TDS
3. Hold only Injection Streptomycin 0.75 gm but other CAT II[nd]ATT medication therapy were continuing.
4. Tab Pyridoxine 20 mg OD
5. Injection Piperacillin + Tazobactam 4.5 mg TDS, IV
6. TabletMontelukast+ levocetirizineHS
7. Nebulization with Formoterol 6 mcg & budesonide 200mcg BD

On the second day, blood pressure was recorded as 130 / 70 mmHg & pulse rate was 88 bpm. Then laboratory investigation reports were collected, according to the laboratory reports patient LFTs, CBCs all count was normal limits. Viral markers for hepatitis including hepatitis A, B & C viruses & HIV all were negative. CXR diagnosed with pulmonary KOCH's. On the same day Fresh complain of Patient was constipation, vertigo, tinnitus (hearing losses); pulmonologist referred the patient to ENT department for the ototoxicity related problem.

ENT References

S.No.	Drugs Prescribed (Brand Name)	Generic Name	Dose	Indication
1.	Cap. Neurivigurd -XL	Vitamin B_{12}	300mg	OD
2.	Tab. Vertiline-8	Bitahistine	8mg	BD
3.	Syp. Mucaine gel	Aluminium hydroxide, Magnesium hydroxide, and Oxetacaine	4TSF	TDS
Stop	Inj. Streptomycin		Rx. Continue same treatment	

- On the 3rd day, BP was normal (120 / 70 mmHg), PR were 78 bpm & SPO2 concentration 97%. Patient fresh complaints of whole-body ache, fever (ON, OFF) and KFTs reports were collected. KFTs reports the uric acid levels were elevated in the normal limits. So, pulmonologist had prescribed with tablet paracetamol 500 mg SOS for the fever and body ache & tab febuxostat 40 mg BD for lowering the uric acid levels.
- On the 4[th]Day, patients complain loss of appetite, bitterin mouth & taste, pulmonologist had done the nutritional assessment of the patient was on soft liquid diets, moderate proteins & low-fat liquids a food diets with same treatment.
- On 5,6, 7,8,9 10[th] days, no fresh complaints were seen & temperature were normal, BP was 110 / 70 mmHg, RR was 22 bpm, PR was 78 bpm with SPO2 concentration 98%. Uric acid reports were normal and then tab febuxostat 40 mg was stopped.
- On the basis of subjective & objective observation, Pulmonologist had made a final diagnosis of ATT (Streptomycin) induced Ototoxicity.
- Staying 10[th] days in hospital, patient condition was improved & then tab Neurogurd-XL (Vitamin B_{12}) was stopped. Patient discharged with appropriate medication **(Table 1)** & patient counselling.

Table 1 Discharged Medication Chart

S. No.	Drugs Prescribed (Brand Name)	Generic Name	Dose	Indication
1.	Tab. AKT-4	Tab. Isoniazid Tab. Rifampicin Tab. Ethambutol Tab. Pyrazinamide	300 mg 450 mg 800 mg 1200 mg	OD- BBF
2.	Tab. Benadon	Tab. Pyridoxine	20 mg	OD-HS
3.	Tab. Pentop	Tab. Pantoprazole	40 mg	OD-BBF
4.	Tab. Dolo-650	Tab. Paracetamol	650 mg	SOS
Review once in a month to OPD with LFTs reports.				

DISCUSSION

Streptomycin is the most important drug for the group of aminoglycoside antibiotic family, it is used as IInd line therapy in the PTB and ototoxicity may occur after several weeks or months of its use, as in the present case. Ototoxicity is irreversible most of the time, & audiometric monitoring is preponderant before, during and after therapy.[1,2]

We read many case reports & short literature reviews on the mechanisms of drugs induced ototoxicity, their monitoring, prevention and control. Ototoxicity is an irreversible side effects of the AGs. The adverse effects is dose dependent and compounded by the narrow therapeutic range of AGs, and the wide inter-individual variability in the pharmacokinetics of the drugs (According to De Jager and Van Altena *et al* 2002)[7], and it could manifest as damage to the cochlea with permanent hearing loss or vestibular damage with dizziness, ataxia and / or nystagmus (According to Duggal and Sarkar *et al* 2007).

AGs enter the fluids of the inner ear of the organ of the cortii& induced the death of the sensory hair cells through the various cellular mechanisms. Disruption of mitochondrial protein production, changes in cell membrane potentials, interaction with transition metals, formation of free radicals, N-terminal c-Jun kinase (JNK), caspases and nucleases are some reasonable pathological mechanisms. AGs causes degeneration of the sensory cells in the cochlea; usually with the basal first, rotate before you get to the tip of the cochlea. This is the basis for the initial high frequency hearing loss followed by low frequency hearing loss. Therefore, hearing cannot be impaired in the early stages of the AGs toxicity. The inner ear and kidney are known to suffer collateral damage in many patients. The hearing loss can be conductive or sensorineural. Before hearing can be assessed, the condition of the ear canal and eardrum must be determined. This is done with a combination of otoscopy and tympanometry[9].

ROLE OF CLINICAL PHARMACIST

- The clinical pharmacist has a crucial role in early detection, management, prevention & control of the drugs related adverse effects.
- The role of a clinical pharmacist is more important to overcome the ATT drugs induced adverse effects. In this case, a discussion session could be done regarding the patient condition and ATT induced adverse effects.

- Upon discussion, clinicians along with health care professionals can design a prophylactic regime to treat the non-intentional effects in DOTS therapy. Multivitamins medication along with pyridoxine (vitamin B_6) and cyanocobalamin (vitamin B_{12}), can be given alongside the therapy with in definite intervals of 45-60 days for 7-8 days.
- Peripheral neuropathy, psychosis, hepatotoxicity & hypovitaminosis are the most important problems in TB patients. Multivitamins + pyridoxine along with ATT therapy can be prescribed to combat the unwanted side effects of these drugs.
- All the patients on regime with AGs should be monitored thoroughly up to six months after cessation of AGs therapy. Additionally, serum concentrations should be monitored during the treatment, due to its dose dependent adverse effects.
- Patients counselling should be carried out to acknowledge the patients for complete adherence of medication moreover, in accordance with the health care professionals, LFTs and KFTs should be done on proper time.
- As a clinical pharmacist, prescription review should also be done as, drugs containing B_6 and B_{12} both belong to vitamin B complex category, a combined drug should be given, additionally pantoprazole, a PPI drug should be indicated BD before meals rather than TDS so that to maintain the patient quality of life and bypassing drug related side effects, eventually PPIs (pantoprazole) shouldn't be given with INH as it reduces the effect of INH showing Drug-Drug Interaction.

CONCLUSION

Drug induced ototoxicity is the adverse effects seen in most of the TB patients; Although many case reports have been published on AGs induced ototoxicity but we encountered this first case in pulmonary isolation ward. On concluding, the ototoxicity induced by AGs is managed by providing supportive care and discontinuation of the particular drugs. Clinicians & Pulmonologist must take a prophylactic drive once every two months on patients indicated streptomycin. Medication review is the key process for a clinical pharmacist so as to avoid medication error, prescription error, dosing error etc. Patients with tuberculosis are very susceptible to other infections and other morbid condition so proper review, counselling and treatment should be given to the patients. It improves the diseased conditions as well as the patient's quality of life.

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