ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 16, Issue 12, 2023

Online - 2455-3891
Print - 0974-2441

Case Report

CLINICAL PHARMACIST INTERVENTIONS ON MILIARY KOCH'S PATIENT WITH ANTITUBERCULAR THERAPY-INDUCED HEPATOTOXICITY AND PSYCHOSIS: A RARE CASE REPORT

ROHIT BANGWAL*

Department of Pharmacy Practice, Shree Dev Bhoomi Institute of Education Science and Technology, Dehradun, Uttarakhand, India.
***Corresponding author: Rohit Bangwal; Email-rohitbangwal93@gmail.com**

Received: 07 June 2023, Revised* and *Accepted: 20 July 2023

ABSTRACT

Psychosis and hepatotoxicity are the dangerous side effects of the antitubercular drugs directly observed treatment short course (DOTS) therapy. Hematological spreading of tubercular bacteria in the lungs is also known as miliary tuberculosis. In this case study, 45-year-old man, weighing 55 kg was brought to the hospital with the chief complaints of vomiting (multiple episodes), fever, pain in abdomen, difficulty in breathing, mucoid cough, and disturbed sleep for the past 1 week. He had a known case of smear-positive pulmonary tuberculosis (in the past 1 month), but at that time, patient was not taking regular antitubercular treatment (ATT) medications (DOTS therapy). After 3th week of irregular antitubercular drug treatment, patient developed with the problems such as vomiting (multiple episodes), fever, pain in abdomen, difficulty in breathing, cough with expectorations, disturbed in sleep, and delirium. Pulmonologists had found the provisional and final diagnosis on the bases of subjective and objective observations miliary KOCH'S with antitubercular drugs induced hepatotoxicity and psychosis. Patients recovered from psychosis and hepatotoxicity withdrawn the first line ATT medication and tablet pyridoxine, antipsychotic medicines, and modified ATT were added in the therapy. Psychotic in a patient on ATT can be one of the complications of tablet isoniazid. As a clinical pharmacologist, we prevent and minimize drugs-induced complications and adverse drug reactions. Proper patients counseling and patients' education are important for the better management of patients.

Keywords: Antitubercular drug therapy, Directly observed treatment short course, Psychosis, Miliary tuberculosis, KOCH'S.

 DOI: http://dx.doi.org/10.22159/ajpcr.2023v16i12.48098. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Tuberculosis is also known as KOCH'S. It is a granulomatous disease. Hematological spreading of tuberculosis bacteria in the lungs is also known as miliary tuberculosis. Antitubercular drug therapy is generally used in the tuberculosis, this therapy is also known as directly observed treatment short course (DOTS) therapy [1-3]. Antitubercular treatment (ATT) drugs therapy is mainly responsible for the irreversible/reversible hepatotoxicity, hepatitis, ototoxicity, neuromuscular blockage, neuropathy, ophthalmopathy, thrombocytopenia, and nephrotoxicity. Several antitubercular medications are known to cause neuropsychiatric adverse reactions such as delirium, depression, mania, psychosis, seizure disorder, and hepatotoxic adverse drug reactions (ADRs) such as nausea, vomiting, gastritis, and abdomen pain. [4,5]. Psychosis and hepatotoxicity are the known complication of the isoniazid (INH) and other antitubercular drug therapy. Neuropsychiatric ADRs usually appear during the initiation of the treatment or while changing from a previously prescribed regimen [6,7]. Isoniazid is the first-line antitubercular agent for the treatment of tuberculosis. Tuberculosis is the life-threading public health problem [8]. Although there are many case reports already done previously, INH induced psychosis and hepatotoxicity particularly in tuberculosis (TB) patients, in this case, patient's condition was resolved only after discontinuation of the DOTS therapy and started the modified ATT therapy [9,10].

CASE STUDY

- A case of 45-years-old male, weighing 55 kg was brought to the hospital with chief complaints of vomiting (multiple episodes), fever, pain in abdomen, difficulty in breathing, mucoid cough, disturbed sleep, delirium for the past 1 week with no past and family history of hypertension, diabetes mellitus, thyroid disease, mental disorder, and pulmonary tuberculosis (PTB).
- Patient was an ex-smoker, ex-alcoholic, and prefentially non-vegetarian.
- At the time of general vital study pulse rate (PR)-93 bpm, blood pressure (BP)-120/90 mmHg, oxygen saturation (SPO_2) 94% at the atmospheric air, abdomen examination was soft and non-tender and cardiac sounds S1, S2 positive were noted.
- He had a known case of smear-positive PTB (in the past 1 months), but at that time, patient was not taking regular ATT medications (DOTS therapy).
- After 3rd week of irregular antitubercular drug treatment, patient developed with the problems such as vomiting (multiple episodes), fever, pain in abdomen, difficulty in breathing, cough with expectorations, disturbed in sleep, and delirium.
- Pulmonologist had advised the patient for routine laboratory tests such as complete blood counts (CBCs), liver function tests (LFTs), kidney function tests (KFTs), Chest X-ray (CXR), high-resolution computed tomography (HRCT), and magnetic resonance imaging (MRI) brain.
- On the same day, pulmonologist prescribed the following drugs to the patient after examination:
  1. Injection Pantoprazole – 40 mg TDS
  2. Tablet Akurit-4 (3 Tab) OD
  3. Tablet Pyridoxine 40 mg ½ OD
  4. Injection Ondansetron TDS
  5. Injection Piperacillin + Tazobactam 4.5 mg TDS, IV
  6. Syrup Mucaine Gel 4 TSF TDS
  7. Tablet Heptagon OD

- On the 2nd day, BP was recorded as 130/80 mmHg and PR was 92 beats/min. According to the laboratory reports, patient laboratory investigations in the report LFTs, CBCs, CXR, HRCT, and viral marker are show many abnormalities. Chest X-ray was seen the miliary KOCHS. Viral markers for hepatitis, including hepatitis A, B, and C viruses, and human immunodeficiency virus all were negative (Table 1 and Fig. 1).
- Pulmonologist was on hold of previous antitubercular drug therapy. Although it was started with modified antitubercular drugs

(Streptomycin 0.75 g, Levofloxacin750 mg, Ethambutol 800 mg) therapy, along with hepatoprotective agents.

Table 1: Clinically investigational findings

Parameter	Test value (Day-1)	Test value (Last Day)	Reference value
LFTs			
SGOT	349	66	17–59 IU/L
SGPT	248	59	9–52 IU/L
GGT	175	51	12–43 IU/L
Total Bilirubin	1.6	0.8	0.2–1.3 mg/dL
Direct Bilirubin	1.2	0.2	0.0–0.8 mg/dL
ALP	233	133	38–126 IU/L
CBCs			
Neutrophils	96	72	40–80%
Lymphocytes	66	34	20–40%
Monocytes	18	12	02–10%
TLC	20413	7156	4000–11000 cell/cumm
Viral markers	**Reactive/Non-reactive**		
Hepatitis A	Non-reactive		
Hepatitis B	Non-reactive		
Hepatitis C	Non-reactive		
HIV virus	Non-reactive		
Radiological Markers	**Impression's**		
Chest X-ray	s/o Miliary KOCH'S		
HRCT	Finding a case of suggestive of acute infective airway disease pulmonary KOCH'S. Clinicopathological correlations.		
MRI brain	Acute impact and cerebral atrophy.		

LFT: Liver function test, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamate pyruvate transaminase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase, CBCs: Complete blood counts, TLC: Total leucocyte count, HIV: Human immunodeficiency virus, HRCT: High-resolution computed tomography, and MRI: Magnetic resonance imaging

Table 2: Neurology references

S. No.	Drugs prescribed (brand name)	Generic name	Dose	Indication
1.	Tab Lanzep	Lorazepam	2 mg	OD
2.	Inj. Haloperidol	Haloperidol	10 mg	OD
3.	Tab Benadon	Pyridoxine	20 mg	OD
4.	Start modified ATT medications			
	Tab L-Cin	Levofloxacin	750 mg	OD
	Tab Combutol	Ethambutol	800 mg	OD
	Inj. Streptomycin	Streptomycin	0.75 gm	OD
	HoldATT medication	Rx. Continue same treatment		

ATT: Antitubercular treatment

- Pulmonologist monitored the laboratory investigations in the reports LFTs, KFTs, CBCs, CXR, MRI brain, and HRCT shown abnormalities.
- On 2nd day, fresh complains of patient were vertigo, insomnia, psychosis, and headache pulmonologist referred the patient to neurology department for the psychosis-related problem (Table 2).
- On the 3rd and 4th day, BP was normal, that is, 120/70 mmHg and PR was 86 beats/min with SPO_2 concentration 96%. Patient no fresh complaints on day 4.
- On 5th day, patient complains loss of appetite, on brief discussion of pulmonologist with a clinical pharmacologist, counseling, along with diet assessment was done of patient.
- Patient was advised to take proper fluid, high protein, and diet rich in fibers. Pomegranate juice was advised to be avoided.
- Pulmonologist stopped the tab lorazepam and haloperidol on the consult of neurology doctors. He started Tab Quetiapine 50 mg/day, Tab Risperidone 4 mg/day and find the diagnosis INH-induced psychosis.
- On 6th, 7th, 8th, and 9th days, no fresh complaints were seen, and all vitals and laboratory's reports were normal.
- On the basis of subjective and objective observation, pulmonologist had made a final diagnosis of Miliary KOCH'S with ATT Induced Hepatotoxicity and Psychosis.
- After staying 10 days in hospital, the patient condition was improved and then Tab Quetiapine and Risperidone were stopped.
- On normalization of patient's conditions, pulmonologist started first-line antitubercular drug therapy containing Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol with continued liver tonics.
- Patient discharged with appropriate medication (Table 3) and patient counseling after advising review once in a month with LFTs reports.

DISCUSSION WITH CLINICAL PHARMACOLOGIST INTERVENTIONS

ADR analysis

On the basis of ADRs analysis on the Naranjo Scale, possible hepatotoxicity and psychosis induced by ATT has found probable and found to be the major ATT-induced ADRs. The case history analysis found the "B" Type of ADRs with H, R, and Z and found to be preventable at a very early stage, and acute phases (Table 4).

ADR management

ADRs were known as diagnosed at a very early stage of ATT therapy. In general, B Type ADRs are bizarre and need hospitalization if became

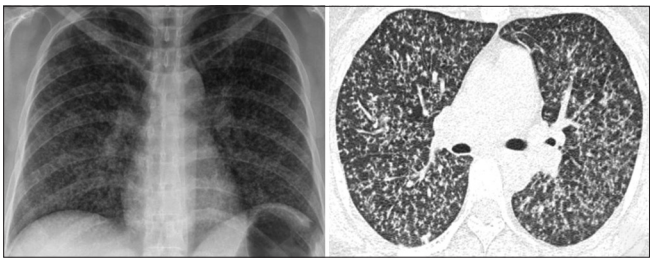

Fig. 1. Chest X-ray and high-resolution computed tomography of chest

Table 3: Discharge medication

S. No.	Drugs prescribed (Brand Name)	Generic Name	Dose	Indication
1.	Antitubercular therapy	Tab. Rifampicin	450 mg	
		Tab. Ethambutol	800 mg	OD- BBF
		Tab. Pyrazinamide	1000 mg	
2.	Tab. Benadon	Tab. Pyridoxine	20 mg	OD-HS
3.	Tab. Pentop	Tab. Pantoprazole	40 mg	OD- BBF
4.	Tab. Oflox	Tab. Ofloxacin	500 mg	OD
5.	Syp. R-Qual	Multivitamin	200ml	TDS-3 TSF
6.	Ensure protein powder, 2TSP-BD with water/milk after meals.			
7.	Hold isoniazid medications.			

Table 4: Causality assessment of suspected ADRs

ADRs	Causality		
	Naranjo's scale	WHO UMC	Karch and Lasagna scale
ATT induced hepatotoxicity	Probable	Probable	Probable
INH-induced psychosis	Probable	Probable	Probable

ADR: Adverse drug reaction, WHO: World Health Organization, UMC: Upsala monitoring center, ATT: Anti-tubercular therapy, INH: Isoniazid

Table 5: Severity, predictability, and preventability of suspected ADRs

Drug	Severity	Predictability	Preventability
Isoniazid	Moderate	Un-predictable	Probably preventable
H, R, Z	Moderate	Un-predictable	Probably preventable

ADRs: Adverse drug reactions, H: Isoniazid, R: Rifampicin, Z: Pyrazinamide

serious. Certainly, the patient's conditions were acute and preventable with the medications like tab lorazepam, haloperidol, Quetiapine and Risperidone after 8 days of treatment the ADRs vanished (Table 5).

- As a clinical Pharmacologist and Pharmacotherapist has a crucial role in early detection, management, prevention, and control of the drugs-related adverse effects.
- As a clinical pharmacologist, the possible diagnosis and prevention of ADRs are the first and priority. It helps in maintaining the QOL of patient and increase life expectancy of patients.
- The ADR detection and treatment are necessary to maintain the proper drug therapy and proper medication adherence.
- As a clinical pharmacologist should be aware of this adverse effect of INH and other ATT medications, that it may present with a broad clinical picture.
- Hepatotoxicity, gastritis, optic neuritis, thrombocytopenia, psychosis, etc. is the most important serious adverse effects of the ATT therapy.
- Patients counseling should be carried out to acknowledge the patients for complete adherence of medication moreover, in accordance with the health-care professionals, LFTs, KFTs, and other clinical investigations should be done on proper time.
- As a clinical pharmacologist, 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 proton pump inhibitor (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) should not be given with INH as it reduces the effect of INH showing Drug-Drug Interaction.

CONCLUTION

- Thus, pulmonologist and clinical pharmacologist should be aware about the drug toxicity profiles of antitubercular drugs like H, R, Z, and E.
- ATT Drug-induced adverse effects seen in most of the TB patients; Although many case reports have been published on ATT-induced hepatotoxicity, psychosis, etc., but we encountered this first case in pulmonary isolation ward.
- The patient's conditions were gradually improvised and the drug-induced psychosis and hepatotoxicity were controlled and patient was discharged with proper counseling and advised to visit everyone in months with all reports.
- Patients undergoing treatment for tuberculosis need health education in detail concerning not only adherence and the benefits of ATT but also the side effects.
- As a health-care team member clinical pharmacologists are need to be made aware of these potentially fatal adverse effects associated with antitubercular therapy through conduction of quality-based seminars, published medical literature, learning programs, conferences, and health-care awareness camps.

The study was done after getting clearance from Hospital Ethical Committee. Informed consent was obtained from all the patients.

ACKNOWLEDGMENT

I'm highly and sincerely thankful to the management and supporting staff of Collage, University, and Hospital for providing the necessary platform to pursue such conduct as a part of pharmacy practice curriculum

CONFLICTS OF INTEREST

The authors report no conflict of interest that is directly, that is, directly relevant to the content of the case report.

AUTHORS FUNDING

The research work has no funding from any funding agencies.

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