AKT 3 Induced Hepatitis: Case Report

Cyril Sajan*, Priyanshi Rakesh Shah, Mahek Mistry

Department of Pharmacy, Sumandeep Vidyapeeth (Deemed to be University), Piparia, Waghodia, Vadodara, INDIA.

ABSTRACT

As tuberculosis is a global health problem. Non-adherence related to treatment regimen and inappropriate prescription of tuberculosis therapy may be one of the major contributing factors in public health. Hepatotoxicity is leading adverse effect of first line anti tuberculosis medication. They do not cause hepatotoxicity in all patients but there are many reported cases which showed hepatotoxicity due to antituberculosis drugs. This adverse effect occurs due to individual drug metabolize by alternative pathways. A 24-year-old female came to respiratory department with complains of dry cough and generalized weakness since one month, pedal edema for three days, breathlessness, chest pain and weight loss. She was known case of systemic lupus erythematosus with vitamin B_{12} deficiency with Hypothyroidism. She had recurrent tuberculosis in the last 15 days and for that she was put on isoniazid, rifampicin, ethambutol, pyrazinamide combination (HRZE regimen). Her laboratory reports suggest she developed hepatitis for which antituberculosis drugs were suspected. She was put on alternative regimen (streptomycin, levofloxacin, ethambutol and ethambutol). After stopping potent hepatotoxic medication, she started reliving symptoms of hepatitis. The early diagnosis of reaction and close monitoring of patient prevented the seriousness of reaction in this case.

Key words: Tuberculosis, Anti Koch Therapy, Hepatotoxicity, Isoniazid, Rifampin.

INTRODUCTION

Antituberculosis drugs are given for treatment of tuberculosis (TB).[1] Tuberculosis is caused by m. tuberculosis. tuberculosis has recently resurged as a dangerous threat to worldwide public health because of the growing prevalence of drug-resistant mycobacterium tuberculosis strains and the increasing number of patients with acquired immunodeficiency syndrome.[2] world health organization (WHO) declared tuberculosis as a public health emergency in 1993, at a time when an estimated 7–8 million new cases and 1.3- 1.6 million deaths occur every year.[1]

The currently recommended first-line treatment for tuberculosis is a regimen of isoniazid (INH: 300mg), rifampicin (600mg), pyrazinamide (25-35 mg/kg) and ethambutol (15- 25 mg/kg) for two months, followed by four months of isoniazid and rifampicin and/or ethambutol and second line agents are streptomycin, para-amino salicylic acid, cyclosporin, ethionamide, clofazimine, quinolones, macrolides/ azalides.[2] isoniazid should be taken with on empty stomach and antacids should be avoided within two hrs of isoniazid.

Major side effect of antituberculosis treatment is skin rash with or without itching, deafness, dizziness, jaundice, hepatitis, confusion, visual impairment, shock, purpura, acute renal failure and decrease urine output. Minor adverse effects include anorexia, nausea, abdominal pain, joint pains, burning, numbness or tingling sensation in the feet or hands, drowsiness, orange/red urine discoloration, flu syndrome. Isoniazid-induced peripheral neuropathy. This usually presents as numbness or a tingling or burning sensation of the feet or hands and occurs more

DOI: 10.5530/ijopp.14.4.57

Address for correspondence:
Dr. Cyril Sajan Pharm D,
Intern, Department of Pharmacy, Sumandeep Vidyapeeth (Deemed to be University), Piparia, Vadodara-391 760, Gujarat, INDIA.
Phone no: +91 7226915689
Email id: cyrilsajan97@gmail.com

www.ijopp.org

commonly in pregnant women and in people with the subsequent conditions: diabetes malnutrition, chronic liver disease, alcohol dependency, renal failure, HIV infection. These patients should receive prophylactic therapy with pyridoxine (10 mg/day) along with anti-tuberculosis drugs. If any major adverse drug reaction (ADR) of antituberculosis found, drug should be stopped.[3]

DOSAGE ADJUSTMENT OF TB MEDICATIONS IN SPECIAL POPULATION

1. Dosage adjustment of TB medications in human immunodeficiency virus (HIV) patients: In patients with CD4 cell counts <200/mm^3 (0.20 x 109/L) or <50 mm^3 (0.05 x 1069/L) reductions in mortality have been seen when antiretroviral treatment was started within two weeks of anti-TB treatment. Highly intermittent regimens (twice or once weekly) are not recommended for HIV-positive TB patients. Rifamycin-based treatments are most effective; however, agents should be selected based on susceptibility and HIV drug interactions.

2. Dosage adjustment of TB medications in renal failure: Isoniazid and rifampicin do not require dose modification in renal failure.

3. Dosage adjustment of TB medications in hepatic failure: In case liver abnormality regimen should be changed according to patients.[3]

Mechanism of Drug Induced Hepatis (DIH)

Hepatotoxicity occurs due to synergistic effect of isoniazid and rifampicin because rifampicin causes more acetylation of isoniazid by N-Acetyl Transferase in to Monoacetyl hydrazine (MAH). The microsomal cytochrome p450 enzymes convert monoacetyl hydrazine to other compounds resulting in hepatotoxicity. Reactive metabolites of MAH are toxic to tissue by free radicals.[4,5] Rifampicin enhances this effect by enzyme induction. Rifampicin causes conjugated hyperbilirubinemia and inhibit major bile salt exporter pump. Asymptomatic elevated bilirubin also can be due to from dose-dependent competition with bilirubin for clearance at the sinusoidal membrane or from impeded secretion at the canalicular level. Pyrazinamide may exhibit both dose dependent and idiosyncratic hepatotoxicity. According to one study pyrazinamide alters nicotinamide acetyl dehydrogenase levels in liver, which might result in generation of free radical species. Due to structural similarity pyrazinamide and Isoniazid may share mechanism of toxicity. Patients with previous Isoniazid induced hepatotoxicity may have more severe reaction with rifampicin and pyrazinamide. Whenever the liver disease caused due to the anti-tuberculosis drugs, all drug should be discontinued. In case of severely ill tuberculosis when stopping of tuberculosis treatment is unsafe, a non-hepatotoxic regimen consisting of fluoroquinolone, ethambutol and a streptomycin need to be started.[6,7]

CASE Description AKT3 Induced Hepatitis

A 24-year-old female came to respiratory department of tertiary care hospital with complaints of dry cough and generalized weakness since one month, pedal edema for three days. She also has complaints of breathlessness, weight loss and chest pain. She had pulmonary effusion, systemic lupus erythematosus (SLE), hypothyroidism, vitamin B_{12} deficiency anaemia. For that she was given with drugs AKT3, Tab. prednisolone (5mg), thyroxine (75mg) respectively. Patient was farmer by profession with no significant family history. And was diagnosed with known case of systemic Lupus erythematosus with Vitamin B_{12} deficiency with Hypothyroidism with recurrent tuberculosis (AKT3 Induced Hepatitis). Ultrasound Sonography test report relived where the reports were bilateral pleural effusion with mild ascites and lymphadenopathy. Other lab investigation relieved patients SGOT and SGPT level were found to be elevated which was 685 and 138 respectively. Investigation confirmed for acute hepatitis (raised urinary bilirubin levels: - Total bilirubin: -3.6, Direct bilirubin: -2.3 and indirect bilirubin - 1.3). As the temporal relationship was present between of starting of AKT 3 therapy and hepatotoxicity incidence. Due to that she was shifted to monotherapy Tab. Combutol (500mg) (1-0-0).

DISCHARGE MEDICATION

Drug (Brand Name)	Generic Name	Dose	Frequency
Tab. Moxdeep	Amoxicillin Clavulanic Acid	625 mg	1-1-1
Neb. Combimist	Ipratropium Bromide	500 mcg	1-0-0
Tab.Combutol	Ethambutol	500 mg	1-0-0
Cap.Autrin	Multivitamin	15 mcg	1-0-1

CAUSALITY ASSESSMENT

Causality and severity assessment have done with the help of five different scales and results are following:

Medication Chart

Drug (Brand Name)	Generic Name	Dose	Frequency
Tab. Moxdeep	Amoxicillin Clavulanic Acid	625 mg	1-1-1
Neb. Combimist	Ipratropium Bromide	500 mcg	1-1-1-1
MgSo4	Magnesium Sulphate	100ml NS	1-0-1
Tab. Combutol	Ethambutol	500 mg	1-0-0
Tab. Dolo	Paracetamol	650 mg	1-0-1
Tab.Mbson (Muscobon)	Multivitamin	1000mg+1000IU+7.5mg+20mg)	1-0-1
Tab. FA	Folic Acid	5 mg	OD
Tab. Thyroxine	Thyroxine	75 ug	1-0-0
Tab. Citrzin	Cetirizine	10 mg	0-01
Tab. Prednisolone	Prednisolone	40 mg	1-0-0
Inj 5m	Streptomycin	0.75gm	1-0-0
Tab. Levoflox	Levofloxacin	500 mg	1-0-0

Scale's Name	Result
Naranjo's algorithm	Probable
Hartwig and siegel	Moderate (Level 4B)
Karch and lasagna	Probable
Who probability	Probable
Shumock and thornton	Moderate (Level 4B)

DISCUSSION

Even today In India, two deaths occur every three minutes from tuberculosis major challenges to control tb in India include poor primary healthcare infrastructure in rural areas of many states Tuberculosis remains one among the foremost most threatening infectious diseases within the world and its standard treatment is alongside with complications like drug induced hepatitis which may decrease patient adherence to treatment. Moreover, the incidence due to drug induced hepatitis is higher due anti-TB drugs. This type of side effects can cause hepatoxicity which is the major complication for TB patients So, this issue is not only important for clinical practitioners to manage the patient's illness, but also the burden of this complication should be considered within the health service policy and management. There was no drug interaction reported. The effect of PZA addition to plain triple-drug regimen (INH, RIF and ETB) on DIH are incompatible.

CONCLUSION

Generally, 1st-line agents of Antituberculosis drugs are potent hepatotoxic. But proper monitoring and early detection of reaction can help in decreasing the severity of reaction. After reaction relieved medication should give according to risk- benefit ratio of medication.

Strength of the study

The present study explains about dosage adjustment of antituberculosis medication, especially when 1st line antitubercular drug causes hepatotoxicity.

ACKNOWLEDGEMENT

The authors are sincerely thankful to all the members of Department of Pharmacy, Sumandeep Vidyapeeth (Deemed to be University) (SVDU) for their support.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ADR: Adverse drug reactions; **DIH:** Drug Induced Hepatotoxicity; **EMA:** Ethambutol; **INH:** Isoniazid; **HIV:** Human immunodeficiency virus; **HRZE:** Isoniazid Rifampicin Ethambutol; **INJ:** Injection; **MAH:** Monoacetyl hydrazine; **OD:** Once daily; **PYZ:** Pyrazinamide; **RIF:** Rifampicin; **SGOT:** Serum Glutamic Oxaloacetic Transaminase; **SGPT:** Serum glutamic pyruvic transaminase Organizations; **TB:** Tuberculosis; **TAB:** Tablet; **WHO:** World Health Organization.

REFERENCES

1. Marzuki OA, Fauzi AR, Ayoub S, Kamarul Imran M. Prevalence and risk factors of anti-tuberculosis drug-induced hepatitis in Malaysia. Singapore Med J. 2008 Sep 1;49(9):688-93. PMID 18830542.
2. Jeong I, Park JS, Cho YJ, Yoon HI, Song J, Lee CT, Lee JH. Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. J Korean Med Sci. 2015;30(2):167-72. doi: 10.3346/jkms.2015.30.2.167. PMID 25653488.
3. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, Peloquin CA, Gordin FM, Nunes D, Strader DB, Bernardo J, Venkataramanan R, Sterling TR, ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006 Oct 15;174(8):935-52. doi: 10.1164/rccm.200510-1666ST, PMID 17021358.
4. Huang YS, Chern HD, Su WJ, Wu JC, Chang SC, Chiang CH, Chang FY, Lee SD. Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis. Hepatology. 2003 Apr;37(4):924-30. doi: 10.1053/jhep.2003.50144, PMID 12668988.
5. Huang YS, Chern HD, Su WJ, Wu JC, Lai SL, Yang SY, Chang FY, Lee SD. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug–induced hepatitis. Hepatology. 2002 Apr;35(4):883-9. doi: 10.1053/jhep.2002.32102, PMID 11915035.
6. Ramappa V, Aithal GP. Hepatotoxicity related to anti-tuberculosis drugs: mechanisms and management. J Clin Exp Hepatol. 2013 Mar 1;3(1):37-49. doi: 10.1016/j.jceh.2012.12.001, PMID 25755470.
7. Sharma SK, Mohan A. Antituberculosis treatment-induced Hepatotoxicity: from bench to bedside. Medicine. 2005;480.