Antituberculosis Drug Induced Hepatitis: A Case- Report

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ABSTRACT

Isoniazid, Rifampin and Pyrazinamide are first line antituberculosis medication. Among them isoniazid and pyrazinamide inhibit mycolic acid synthesis and rifampicin inhibit RNA polymerase. They are potent hepatotoxic. These drugs metabolize in liver by CYP450 enzyme. The drug toxicity is differing in different individuals because in some individuals drug metabolize by different pathway. Apart from hepatotoxicity, there are some reported cases of antituberculosis drug induced cutaneous reaction and gastrointestinal disturbances. A 31-year-old female patient came to respiratory department with complain of breathlessness, chest pain, abdominal pain, weight loss and loss of appetite. She was diagnosed with tuberculosis two months. For that she was put on HRZE regimen. Her laboratory data showed she had hepatitis. After stopping potent hepatotoxic medication her laboratory data started to normalize and symptoms relived. For tuberculosis she was shifted to alternative regimen. To prevent adverse drug reaction close monitoring of patient and therapy is required.

Keywords: Adverse drug reaction, Liver metabolism, Antituberculosis drugs, Hepatotoxic drugs, Liver injury, Cutaneous reaction.

INTRODUCTION

Tuberculosis is one of the huge global health burdens.[1] 1st-line antituberculosis medications include: Isoniazid (INH), Rifampicin (RIF), Ethambutol (EMB) and Pyrazinamide (PZA). 2nd line antituberculosis medications include: Streptomycin, P-Amino Salicylic acid (PASA), Cycloserin, Ethionamide, Clofazimine, Quinolones, Macrolides/ Azalides.[2]

Nonadherence to treatment regimen and inappropriate prescription of tuberculosis therapy can be major factor for resistant to antituberculosis drugs.[3] As in the tuberculosis treatment regimen, large number of tablets are used, fixed dose combination tablets were introduced.[4] For Tuberculosis therapy, WHO model list of essential lists include, two drug combinations [INH+RIF / INH+EMB], 3 drug combinations [INH+RIF+EMB / INH+RIF+PZA] and 4 drug combinations [INH+RIF+EMB+PZA]. According to RNTCP (which is now called as National Tuberculosis Elimination program) recommendations, standard treatment of tuberculosis is Directly Observed Therapy (DOT).[5-6] Currently recommended 1st line regimen for tuberculosis is INH, RIF, EMB, PZA for two months followed by INH and RIF for four month. Among these agents INH, RIF and PZA are potent hepatotoxic.[7] Apart from antituberculosis drugs which can cause hepatotoxicity are allopurinol, acetaminophen, amiodarone, carbamazepine, azathioprine, methotrexate, macrolide, NSAID, phenytoin, sodium valproate, etc.[3]

Hepatic Drug Metabolism of Tuberculosis Drugs

The Ingested drugs are carried out directly into the liver splanchnic circulation and drug pass through 'first pass metabolism'

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in the liver. Metabolic enzymes convert drugs in to their metabolites through phase 1 pathways (which is carried out principally by the CYP450), Phase two pathways (to form compounds that are readily excreted from the body) and Phase three pathways (cellular transporter proteins facilitate excretion of these compounds into bile or the systemic circulation). The differences in toxicities are due to in some individual some drugs metabolized through alternative pathway.[8-9]

Drug Induced Hepatotoxicity

The incidence rate of antituberculosis induced Hepatotoxicity (DIH) is 2-28%.[10] Drug induced liver injury (DILI) could be an immunologically mediated response or a result of direct toxicity of the primary compound which affects hepatocytes, biliary epithelial cells, and/or liver vasculature. The exact mechanism of DIH is poorly known. DILI may be dose dependent. Injurious free radicals cause hepatocyte necrosis in zones farthest from the hepatic arterioles, where metabolism is greatest and antioxidant detoxifying capacity is that the least.[10] Distribution of hepatocyte necrosis is usually occurred throughout hepatic lobules instead of being zone wise, as is usually found out in predictable DILI. The immunogenic drug or its metabolites could also be free or covalently sure to hepatic proteins, in forming haptens or neoantigens in hypersensitivity reactions. Antibody-dependent cytotoxic T-cell and infrequently eosinophilic hypersensitivity responses could also be evoked. Released TNF- alfa, IL-12 and IFN-gama promote apoptosis of hepatocytes (hepatocellular programmed cell death) which is opposed by IL-4, IL-13, IL-10 and monocyte chemotactic protein-1. According to one study, dose independent DIH is due to Unpredictable or idiosyncratic reactions which comprise most types of DILI.[3]

Management of Drug Induced Hepatitis

If the liver disease caused due to the anti-tuberculosis drugs, all drugs should be stopped. But in case of severely ill tuberculosis when stopping of tuberculosis treatment is unsafe, a non-hepatotoxic regimen should be started which consist of streptomycin, ethambutol and a fluoroquinolone. Once the LFT normalize and all clinical symptoms of hepatitis resolve, only then antituberculosis drug can be reintroduce one at time basis. On the reintroduction if hepatotoxicity seen, the lastly drug added should be stopped. In the case of persistent hepatotoxicity even after stopping lastly added drug (signs and symptoms do not resolve and hepatotoxicity become severe), the non- hepatotoxic regimen should be continued for total 18- 24 months.

- If DIH is known to be due to RIF, then it is suggested that two months therapy of isoniazid, ethambutol and streptomycin f/b ten months of ethambutol and isoniazid can be considered.
- If DIH is known to be due to PZA and it is necessary to stop PZA before completing intensive phase, then the isoniazid and rifampicin therapy would be extended to 9 months.
- If INH and RIF can't be followed, the non-hepatotoxic regimen should be continued for a total of 18–24 months (consisting of streptomycin, ethambutol and fluoroquinolone).
- In the intensive phase of tuberculosis during treatment with INH, RIF, PZA and EMB if the presence of hepatitis with jaundice seen: Once hepatitis has resolved, restart the same drugs except replace PZA with streptomycin to complete the two-month course of initial therapy, followed by RIF and INH for the 6-month continuation phase.
- In the case of, hepatitis with jaundice during the continuation phase: Once hepatitis resolved, restart INH and RIF to complete the 4-month continuation phase of therapy.[10]

CASE

31-year-old female patient came to respiratory department of tertiary care hospital on 26/8/2019. She has chula-exposure for past 25 years. On admission, she had complaint of breathlessness for four days, chest pain for 15 days, loss of appetite for two-month, weight loss 2-3-kilogram, generalized weakness. According to her chest X- ray and sputum analysis, she was diagnosed with Pulmonary Tuberculosis 2 months back and started with HRZE regimen of Directly Observed Therapy, as per RNTCP guideline.

Before three days of her admission, she had complaint of loss of appetite, abdominal pain, and weight loss. As she had hepatotoxicity, her hepatotoxic antituberculosis medications were stopped and she was shifted from HRZE regimen to non-hepatotoxic antitubercular medications (Levofloxacin, Ethambutol and Amikacin) as she won't be able to admit in hospital at that time (on 23/8/2019). After 3 days she was admitted to hospital (on 26/8/2019) and was given with Streptomycin, Levofloxacin and Ethambutol regimen.

During hospital stay her vitals – BP, Pulse rate and respiratory rates were in a normal range. Her laboratory investigation with given treatment were described in the Table 1.

After the laboratory data and symptomatic relief showed improvement in condition, on 10th day of patient's admission she was discharged with certain medication given in Table 2.

Causality Assessment

Causality and severity assessment had done with the help of six different scales and results are following:

Table 1: Laboratory investigation and treatment given to the patient before hospitalization and during hospital stay.

Day	Abnormal laboratory investigation	Treatment given
Before admission (23/8/2019)	Hb = 10.9 gm% TC = 8630 cells/cumm PLT = 2lacs/cumm Creatinine = 0.4mg% SGOT = 2105 IU/L SGPT = 912 IU/L ALP = 62 Bilirubin = 3 mg%	Tab. Levofloxacine (500mg) 1-0-0 Tab. Ethambutol (800mg) 1-0-0 Tab. Amikacin (0.5g) 1-1-1
Day 1 (26/8/2019)	Hb = 10.3 gm% TC = 7200 cells/ cumm PLT = 2 lacs/cumm Creatinine = 0.6 mg% SGOT = 820 IU/L SGPT = 110 IU/L Bilirubin = 4 mg%	Tab. Ceftriaxone (1g) 8hrly Tab. Levofloxacin (day-4) (500mg) 1-0-0 Tab. Ethambutol (day-36) (800mg) 1-0-0 Neb. with combimist 1-1-1-1 Tab. Spironolactone/ Furosemide (20/50) 1-0-0 Inj. Pantoprazole (40mg) 12hrly IVF. DNS with MVI (500ml @40cc/hr)
Day 2 (27/8/2019)	SGOT = 199 IU/L SGPT = 511 IU/L Bilirubin = 2 mg%	Continuous same treatment Add- Tab. Streptomycin (day 1) (0.5g) 1-0-0 Inj. Cefodroxil (1.5g) 8hrly Stop- Tab. Ceftriaxone (1g) 8hrly
Day 3 (28/8/2019)	-------	Continuous same treatment Add- Syp. liv 52 2tsp TDS
Day 4 (29/8/2019)	Potassium – 3.2mmol/l	Continuous same treatment Add- Syp. Potassium Chloride (15ml) 1-1-1 Stop- Tab. Streptomycin (day 2) (0.5g) 1-0-0
Day 5 (30/8/2019)	----------	Continuous same treatment Add- Inj. Hydrocort STAT 100mg Stop- IVF. DNS with MVI (500ml @40cc/hr)
Day 6 (31/8/2019)	----------	Continuous same treatment Stop- Syp. Potassioum Chloride (15ml) 1-1-1
Day 7 and 8 (1/9/2019 – 2/9/2019)	----------	Continuous same treatment
Day 9 (3/9/2019)	SGOT = 35 IU/L SGPT = 26 IU/l	Continuous same treatment
Day 10 (4/9/2019)	----------	Continuous same treatment Add- Syp. digine 2TSP BD

Table 2: Discharge medications.

Brand Name	Generic Name	Dose	Frequency	Rout of Administration
Tab. Levoflox	Levofloxacin	500mg	1-0-0	PO
Tab. Combutol	Ethambutol	800mg	1-0-0	PO
Neb. Combimist	Ipratropium Bromide+ Levosalbutamol	500 mcg/ 1.25 mg	1-1-1-1	PO
Neb. Asthalin	Salbutamol	5 mg	1-1-1	PO
Tab. Lesilactone	Spironolactone+ Furosemide	20/50 mg	1-1-1	PO
Syp. Potklor	Potassium Chloride	15ml	1-1-1	PO

Scale's Name	Result
WHO	Probable
Naranjo	Probable
Shumock and Thronton	Probably Preventable
Karch and Lasagna	Possible
Hartwigs and Siegel	Moderate (level 4(b))

CONCLUSION

Though antituberculosis medication has many adverse drug reactions, hepatotoxicity is most common and serious one. If it is left untreated, then it can lead to death as well. Early diagnosis and treatment and monitoring can decrease morbidity and mortality due to antituberculosis drugs. Serum drug concentration needs to be monitor to prevent adverse reaction.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ADR: Adverse Drug Reactions; **BD:** Two tomes daily; **BP:** Blood pressure; **DIH:** Drug induced hepatotoxicity; **DILI:** Drug induced liver injury; **DOT:** Direct observe therapy; **EMB:** Ethambutol; **FDC:** Fixed drug combination; **HRZE:** Isoniazid, Rifampin, Ethambutol, Pyrazinamide; **IL:** interleukin; **INH:** Isoniazid; **LFT:** Liver function test; **mg:** Milligram; **PASA:** P- amino salicylic acid; **Inj.:** Injection; **PO:** Per oral; **PZA:** Pyrazinamide; **RIF:** Rifampicin; **RNTCP:** Revised national tuberculosis programme; **SGOT:** Serum glutamic oxaloacetic transaminase; **SGPT:** Serum glutamic pyruvic transaminase; **Stat:** Statum (immediately); **Syp.:** syrup; **Tab.:** Tablet; **TB:** Tuberculosis; **TDS:** Three Times Daily; **TNF:** Tumour Necrosis Factor.

Strength of the study

Present study explains about mechanism by which fixed dose combination induces hepatotoxicity.

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