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Antitubercular Drugs Induced Liver Injury: A Case Series & Review

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ABSTRACT

Tuberculosis (TB) is caused by tubercle bacilli, which belong to the genus Mycobacterium, namely Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum etc. Mycobacterial infections are among the most difficult of all bacterial infection to cure. Isoniazid, Rifampicin, Pyrazinamide are essential component of directly observed treatment short-course (DOTS) strategy to control TB by WHO & all the three agents is observed to cause potential hepatotoxicity. Here Causality assessment was done by using Roussel Uclaf Causality Assessment Method (RUCAM) / Council for International Organisations of Medical Sciences (CIOMS) Scale & Naranjo Algorithm. Here we have discussed four different cases of antitubercular drugs induced hepatotoxicity & also focussed on the management of the above condition.

Keywords: Tuberculosis (TB), causality assessment, anti-tubercular drugs, hepatotoxicity, Naranjo algorithm.

INTRODUCTION

Mycobacterial infections are among the most difficult of all bacterial infection to cure because of following reasons.[1] 1. Slow growth rate, 2. Development of resistance to many drugs, 3. The lipid rich mycobacterium cell wall is impermeable to many drugs, 4. A substantial proportion of mycobacterial organisms are intracellular, residing within macrophages, 5. Mycobacteria are notorious for their ability to develop resistance to any single drug (hence combination of drugs are required).[1]

Despite of these above reason the development of drug related problems such as adverse drug reactions make the treatment further more problematic which may reduce effectiveness of the therapy. Drug-induced liver injury (DILI) is common and nearly all classes of medications can cause liver disease.[1] Drug-induced liver injury (DILI) secondary to anti-tubercular treatment (ATT) is reported in 2–28% of patients.[2] The incidence of TB in India is 1.96 million cases annually, contributing to >300,000 deaths annually, including 1000 deaths every day.[3] Tuberculosis (TB) remains a huge health burden worldwide.[4]

The liver, referred to as the "metabolic factory" of the body, is central to the metabolism of virtually every foreign substance including anti-tubercular drugs.[5] Anti-tubercular drugs are one of the commonest group underlining idiosyncratic hepatotoxicity Worldwide.[6] Isoniazid, Rifampicin, Pyrazinamide are essential component of directly observed treatment short-course (DOTS) strategy to control TB by WHO & all the three agents is observed to cause potential hepatotoxicity.[7] Finding the main cause & ruling out the definite drug is essential in preventing & management of drug related problems.[8,9]

METHODOLOGY

All subject suspected as drug induced liver injury by definition were taken

in study. The causality assessment was done by Roussel Uclaf Causality Assessment Method (RUCAM) / Council for International Organisations of Medical Sciences (CIOMS) Scale &Naranjo Algorithm. Written informed consent was obtained from Patients & their representatives. The case studies were done according to declaration of Helsinki by maintaining the subject confidentiality.[10]

PATIENT 1:

A 40 years male patient was admitted in the general medicine department of tertiary Care Hospital with the complaint of abdominal pain yellowish discoloration of urine and skin. The patient is known case of Pulmonary tuberculosis & was on CAT 1 Anti-tubercular therapy (Isoniazid 300mg/day, Rifampicin 600mg/day, Pyrazinamide 1.5g/day, Ethambutal 800mg/day) from 3 months. On examination vitals were stable & systematic examination revealed (per abdomen) that abdominal tender hepatomegaly in right hypochondriac region. Other reviews of systems were normal. Laboratory investigation: Hb-9.9 g/dL (14-18g/dL), Renal Function test & electrolytes were normal. There was marked elevation in liver parameters AST (aspartate aminotransferase)-153 U/L (0-35U/L),ALT (alanine aminotransferase) -162 U/L (0-35U/L), ALP (alkaline phosphatase) -213U/L (30-120U/L), Total bilirubin was found to be 2.9mg/dl (Ref-0.1-0.8mg/dl). USG Abdomen shows hepatomegaly. The HIV-1 & HIV-2 Test & HbsAg were negative. Patient was diagnosed as ATT induced hepatitis, drug Isoniazid was withdrawn from the therapy & other anti-tubercular drugs with streptomycin was continued (Rifampicin 450mg, Ethambutol 800mg, Pyrazinamide 1.5g/day, Streptromycin-750mg). After discontinuing Isoniazid for 15days liver enzymes gradually came back to normal. Rechallenge was attempted and its data is not available.

Causality Assessment of this case was established by RousselUclaf Causality Assessment methods/ CIOMS and the Score is 11 "Highly Probable" (>8). This was confirmed by Naranjo algorithm scale with a score of 9, thus assessed as Definite ADR. This association by using various scales strengthens the Isoniazid induced hepatotoxicity for above patient.

Discussion: Isoniazid is metabolized & eliminated predominantly by liver. Main enzyme involved in the metabolic pathway is N- acetyl transferase-2 & microsomal enzymes cytochrome P4502E1 determine the risk of hepatotoxicity. N-acetyltransferase metabolize isoniazid to acetyl isoniazid that is converted to acetyl hydrazine further it is oxidised by CYP2E1 to form N-hydroxyl-acetyl hydrazine, finallydehydrates to yield acetyl diazine (toxic metabolite) or may break down to reactive acetyl oniumion, acetylradid & ketone, which could bind covalently with hepatic macro molecules leading to liver injury.

PATIENT 2:

A 68years old male patient was admitted in general medicine department of tertiary care hospital with the complaints of breathlessness since 2month abdominal pain since 2 weeks. Patient was known case of sputum positive pulmonary TB since one & half month & K/C/O COPD since 2 years & on regular medication i.e., CAT 1 Anti-tubercular therapy (Tab.Isoniazid-300mg + Rifampin-450mg + Pyrazinamide 1500mg + Ethambutol-375mg OD), Tab. Pantoprazole 40mg OD, Neb. Ipratropium bromide + Salbutamol 2puff per day. Patient is non-smoker & non-alcoholic. On examination vitals were normal systemic examination reveals: Respiratory system- shape of chest normal, chest movements equal bilateral normal vascular breathing sound positive, no added sounds, crepitations in left infrascapular area. Per abdominal tenderness present in right hypochondriac region, mild hepatomegaly. Other reviews of systems were normal. Laboratory investigation-hematology, electrolytes & RFT reports are almost normal, liver function test shows marked elevation in

liver enzymes & bilirubin levels. AST-289U/L (0-30U/L), ALT-224U/L (0-35U/L), ALP-190U/L (30-120U/L), Total bilirubin level was 3.2mg/dL (0.1-1mg/dl), prothrombin time & aPTT was also elevated. USG abdomen report reveals mild hepatomegaly. HIV, HbsAg & HCV were negative. Patient was diagnosed as sputum positive ATT therapy induced hepatitis. Initially drug isoniazid was withheld for 2 weeks there is no change in the liver parameters then physician attempted to hold both isoniazid & rifampicin after 3 weeks elevated liver parameters reduced that is AST-41.8U/L, ALT-34.2U/L & total bilirubin 0.9mg/dL. Discharge medication include Ethambutol 400mg + Pyrazinamide 750mg + Levofloxacin 750mg + Rifampicin 200mg , Isoniazid was omitted.

Causality Assessment of this case was established by Roussel Uclaf Causality Assessment methods/ CIOMS Score of 10 "Highly Probable" (>8). This was confirmed by Naranjo algorithm scale with a score of 9, thus assessed as Definite ADR.

Discussion: Rifampicin is associated with hepatocellular patter of drug induced liver injury & more often it potentiates the hepatotoxicity of other Anti-tubercular drugs. Rifampicin is a potent enzyme inducer. This activation causes elevated metabolism of isoniazid yielding toxic metabolites. Rifampicin causes hydrolysis of Isoniazid yielding hydrazine thus increases the toxicity.

PATIENT 3:

A 53 years male patient was admitted in the general medicine department of tertiary care hospital with complains of fever since one week, altered behavior since yesterday, with presence of neck stiffness. Patient was alcoholic and left 3 months back. He was a known case of Pulmonary tuberculosis and is on CAT1 Anti-tubercular therapy (Isoniazid 300mg/day, Rifampin 450mg/day, Pyrazinamide 750mg/day, Ethambutol 800mg/day) since from five months. On examination BP was low, remaining vitals are normal and reviews of systems were normal. Laboratory investigation: Hb-13.2g/dL (14-18g/dl) , Renal parameters are slightly increased and electrolytes were normal. There is marked elevation of liver parameters AST-84U/L (0-35U/L), ALT-60U/L (0-35U/L), ALP-187U/L (30-120U/L), Total Bilirubin-8.9mg/dL (0.1-1mg/dL), Direct.Bilirubin-4.5mg/dL (0-0.2mg/dL), Indirect bilirubin-4.4mg/dL (0.1-0.8mg/dL). The patient was diagnosed as ATT induced hepatitis, CAT1 drugs was dechallenge for one month during that period Inj. Streptomycin 750mg + Tab. Levofloxacin 750mg + Tab. Ethambutol 400mg were used. After a month CAT 1 anti-tubercular drugs were reintroduced.

Causality Assessment of this case was established by RousselUclaf Causality Assessment methods/ CIOMS Score of 7 "Probable" (6-8). This was supported by Naranjo algorithm scale with a score of 6, thus assessed as probable ADR. Additionally, the temporal association is strongly suggestive of Anti-tubercular drugs -induced hepatitis.

Discussion: Liver injury is the common adverse effect of first line anti-tubercular drugs alcohol consumption can increase the risk of toxicity of these drugs. Heavy alcohol use impacts retention in care and is associated with missed DOTS visits and poor medication adherence. One potential mechanism for worse TB outcomes is poor treatment adherence and loss to follow up. In comparison to patients who do not consume alcohol, those who do consume alcohol, and especially those who engage in heavy episodic drinking, have been shown to have delayed culture conversion and higher rates of treatment failure, relapse and death

PATIENT 4:

A 56 years old male patient was admitted in general medicine department of tertiary care hospital with the complaints of vomiting, abdominal pain & fever since 5 days & cough since 5 days, icterus was positive. Patient is known case of pulmonary TB on regular medication that is

CAT 1 Anti-tubercular therapy for 5months (Tab.Isoniazid-300mg + Rifampin-450mg + Pyrazinamide 1500mg + Ethambutol-375mg OD). Patient is non-smoker & non-alcoholic. On examination patient was conscious & oriented. Vitals were normal, systemic examination reveals per abdomen-tenderness positive, distended abdomen, mild hepatomegaly. Laboratory investigation - Haematology, renal function test, electrolytes were normal. Acid fast bacteria test is positive. There was marked elevation in liver enzymes & bilirubin level. AST-189U/L, ALT-98U/L, ALP-125.0U/L & total bilirubin was 2.2mg/dl. USG abdomen report shows fibrosis of liver, moderate ascites. Patient is diagnosed as liver fibrosis with PTB. After the diagnosis of fibrosis secondary to anti-tubercular drug the 3 hepatotoxic drugs i.e. Isoniazid, Rifampicin & Pyrazinamide were withheld immediately & Ethambutol is continued with 2nd line agent such as (regimen with one potentially hepatotoxic drugs) that is Ethambutol 400mg+ Rifampicin 400mg+ levofloxacin 750mg.

Causality Assessment of this case was established by RousselUclaf Causality Assessment methods/ CIOMS Score of 9 "Highly Probable" (>8). This was confirmed by Naranjo algorithm scale with a score of 9, thus assessed as Definite ADR. These associations by using various scales strengthen the Isoniazid induced hepatotoxicity for above patient.

Discussion: Patient was provided with regimens that contain one potential hepatotoxic drug as the patient was diagnosis with fibrosis which can eventually lead to cirrhosis. Other drugs such as isoniazid are highly efficacious but it is known to cause metabolic idiosyncrasy which is mainly due to bioactivation of the acetylhydrazine metabolite. And pyrazinamide is highly specific agent and active only against tuberculosis but it is extensively metabolized by liver and liver injury is caused due to metabolic intermediates.

CONCLUSION

Anti-tubercular drug induced hepatotoxicity is reversible in all most all the cases if the suspected drug is stopped.[11] Finding the main cause & ruling out the definite drug is essential in preventing & management of drug related problems. In patients with acute hepatitis antitubercular drugs such isoniazid, rifampicin & pyrazinamide must be stopped immediately till the clinical & biochemical resolution of hepatotoxicity, & at least three non hepatotoxic drugs such as ethambutol, streptomycin & any fluoroquinolones must be used.[12] After recovery anti-tubercular drugs can be safely rechallenge. In patients with cirrhosis it is recommended to start treatment with an aminoglycoside, quinolone & ethambutol, if necessary add rifampicin or isoniazid. Pyrazinamide must be avoided. In patients with unstable liver disease with hepatic decompensation & complication a regimen with no hepatotoxic agent might be required which include injectable such as streptomycin/amikacin/ kanamycin, ethambutol, fluoroquinolone & other second line oral drugs are recommended.[13]

STATEMENT OF HUMAN & ANIMAL RIGHTS:

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee & with the 1964 Helsinki declaration & its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

INFORMED CONSENT:

Written informed consent was obtained from all the four patient for anonymized patient information to be published in this article.

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Conflict Of Interest: Nil

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