World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Case Study

Anti-tubercular drugs induced hepatotoxicity in patient with miliary tuberculosis: A case study

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Received: 18-01-2018 / Revised Accepted: 26-02-2018 / Published: 11-03-2018

ABSTRACT

Miliary tuberculosis is also called pulmonary TB because of the innumerable tiny spots that form in the lungs is the size of millet, the small round seeds in bird food. Miliary tuberculosis may affect one organ or several organs or occur throughout the body. [1] Treatment includes first line and second line anti tubercular drugs in which most of the drug have the potency to produce hepatotoxicity. A female patient of age 62yrs with the history of military tuberculosis was admitted because of abdominal distension and loss of appetite. And she was diagnosed as chronic liver disease induced by ATT.

Keywords: military, hepatotoxicity, pulmonary, tuberculosis

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How to Cite this Article: Vishnu Das. Anti-tubercular drugs induced hepatotoxicity in patient with miliary tuberculosis: A case study. World J Pharm Sci 2018; 6(3): 119-122.

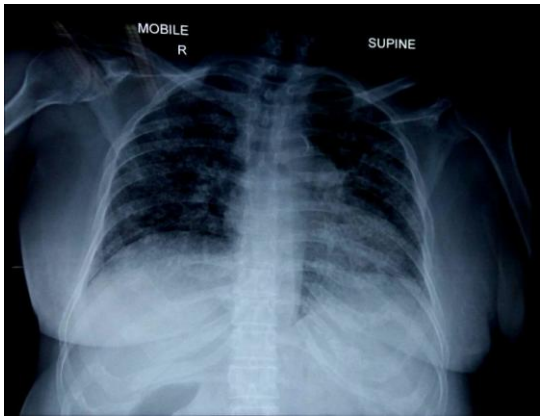
BACKGROUND

Tuberculosis (TB) is a leading cause of preventable morbidity and mortality worldwide. The disease primarily involves the lungs, and at times distant blood-borne spread results in the development of extra pulmonary TB (EPTB). Miliary TB is a pathological name describing millet seed-sized (1–2 mm) granulomas in various organs affected by tubercle bacilli. It results from massive lymphohematogenous dissemination from a *Mycobacterium tuberculosis*-laden focus.[1] According to the WHO guidelines, Miliary TB is classified as pulmonary TB because there are lesions in the lungs..[2]

TB is usually treated with multiple drugs to prevent emergence of MDR strains. There is a high incidence of hepatotoxicity ranging from 2% to 28%. The use of multiple drugs that makes the determination of the exact drug responsible for hepatotoxicity becomes difficult. An asymptomatic, self-limited increase in aminotransferase levels was observed in most patients treated with isoniazid. Approximately 0.5% of all patients treated with isoniazid monotherapy for latent TB developed clinically important increases in aminotransferase levels in a large study.[2] The percentage was higher in combination therapy. Isoniazid-induced hepatotoxicity is seen mainly as hepatocellular steatosis and necrosis, and it has been suggested that toxic drug metabolites may bind covalently to cell macromolecules. Hepatotoxicity associated with rifampicin is usually idiosyncratic. Rifampicin may occasionally cause dose-dependent interference with bilirubin uptake due to competition with bilirubin for clearance at the sinusoidal membrane, resulting in mild, asymptomatic unconjugated hyperbilirubinemia or jaundice without hepatocellular damage. Occasionally, rifampicin can cause hepatocellular injury and can potentiate hepatotoxicity of other antitubercular drugs. Hepatotoxicity is a major toxic effect of pyrazinamide. Previously reported studies have shown high rates of hepatotoxicity with high doses of pyrazinamide. Doses used currently (< 35 mg/kg per day) are considered much safer.[3]

Adverse drug reactions (ADRs) are a major cause of morbidity, hospital admission, and even death. Hence it is essential to recognise ADRs and to establish a causal relationship between the drug and the adverse event. The Naranjo algorithm, Naranjo Scale, or Naranjo Nomogram is a questionnaire designed by Naranjo *et al.* for determining the likelihood of whether an ADR (adverse drug reaction) is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible or doubtful. Values obtained from this algorithm are sometimes used in peer reviews to verify the validity of author's conclusions regarding adverse drug reactions.[4]

The idea of creating a standardized assessment for the relationship-likelihood of case reports of suspected ADRs was in the hope that this would, in a structured way, lead to a reliable reproducible measurement of causality. The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO–UMC), and the Naranjo Probability Scale are the generally accepted and most widely used methods for causality assessment in clinical practice as they offer a simple methodology. [4]



CASE PRESENTATION

A 62 year old female lady now admitted with the complaints of gradually progressing and pitting pedal edema for 20days. Along with this she was also suffering from abdominal distension for 15 days and persistent loss of appetite for 2 months. On physical examination it was found that she had no history of gastrointestinal bleeding or altered sensorium.

While asking to the patient it was found that she has a past history of fever for past 2 months and was diagnosed as military tuberculosis and started on ATT. And she also is suffering from DM and HTN for 7 years and Hypothyroidism for 2 years. After taking four doses of ATT, she was admitted in the hospital with the complaints of fever, vomiting and loose stools. For detailed evaluation laboratory parameters of the patient was assessed. Hematological values such as patient hemoglobin level of 11.7g/dl, total count of 4590cell/cumm and platelet count of 1.84lakhcell/cumm were found to be normal. While her Liver Function Test showed abnormal which includes Total bilirubin 3.8g/dl,

Protein 5.9g/dl, Albumin 2g/dl, liver enzymes including SGOT 107IU/L, SGPT 125IU/L, ALP 325IU/L and C-reactive protein 55. Renal package shows serum urea 36mg/dl and creatinine 1.23mg/dl. Even though the electrolytes such as Serum sodium and potassium were low and is 132mEq and 2.5mEq respectively.

Ascetic fliud/peritoneal fluid was analyzed and it shows a protein level of 0.34g/dl (transudate) and albumin level of 0.13g/dl (low albumin gradient). In addition glucose was also high of 126mg/dl. Ascetic fluid gross examination shows the appearance is pale yellow and slightly turbid. Its microscopy reveals total RBC count of 400 and few RBC was seen. WBC shows 20cell/microlitre. Radiological studies include ultrasound was done and found that a gross ascitis with 16.7cm and dopler studies reveals no signs of deep venous thrombosis.

Because of the elevated liver enzymes due to anti tubercular therapy, all the drugs are stopped and then monitor the liver enzymes regularly. Along to this patient was getting hepatic supplements such as T. Usodeoxycholic acid 300mg BD, T. S-adenosyl methionine 200mg BD T. Acetylcysteine 600mg BD and T. silymarin 70mg BD. It takes 2 week to for the liver enzymes to reach normal level. After that ATT was started and gave T. Rifampicin 150mg od as initial drug. But after the administration of drug, LFT started raising which leads to further stop of the drug. Further T. Isoniazid 300mg started on regular analysis of liver enzyme level but it also produce much greater raise in liver values. Thereafter T. Pyrazinamide 800mg was also given eventhough it also resulted the same. To confirm the adverse effect that occurs due to this drugs, we used Naranjo Adverse Drug Reaction Probability Scale which got a score of 10 and WHO-UMC causality assessment system shows ADR was certain due to the drug.
She was advised with T. Ethambutol 800 mg PO 1-0-0, T.Benadon 40mg PO 1-0-0, T.Bronac 600mg PO 1-0-1, T.Pantocid D 80mg PO 1-0-1, T. Glevo 750mg PO 1-0-0, T.Metrogyl 400mg PO 1-1-1, Syp. Potchlor 15ml PO 1-1-1-1, T. S-Adenosyl Methionine 200mg 1-0-1

DISCUSSION

Tuberculosis is a contagious infection caused by the airborne bacteria *Mycobacterium tuberculosis*. Tuberculosis usually affects the lungs in one or a few locations. Miliary tuberculosis is so named because of the innumerable tiny spots that form in the lungs are the size of millet, the small round seeds in bird food. Miliary tuberculosis may affect one organ or several organs or occur throughout the body. It often affects the lungs, liver, and bone marrow but may affect any organ, including the tissues that cover the brain and spinal cord (meninges) and the membrane around the heart (pericardium).[3]

The currently recommended first-line treatment for TB is a regimen of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) for 2 months, followed by 4 months of INH and RMP and/or EMB. Hepatotoxicity is one of the most frequent and serious adverse effects of anti-TB medications and may reduce treatment effectiveness by compromising treatment regimens. Among the first-line quadruple therapy drugs (INH, RMP, PZA, and EMB), INH, RMP, and PZA are metabolized mainly by the liver, and therefore, are potentially hepatotoxic. The incidence of anti-TB drug-induced hepatotoxicity (DIH) during standard multidrug TB treatment has been reported to be between 2% and 28%.[2]

Treatment regimens should ideally contain one of either isoniazid or rifampicin because they are the most potent antitubercular drugs. Currently, rifampicin is generally the preferred single hepatotoxic agent due to its potentially lower hepatotoxicity, although this has not been proven in an RCT. Some authors do not favor the use of pyrazinamide, but at currently used doses, pyrazinamide has not been shown to be more hepatotoxic as compared to isoniazid or rifampicin. Pyrazinamide is generally substituted with a fluoroquinolone or an aminoglycoside as per the clinician preference. It is prudent to use only two hepatotoxic drugs in treating compensated cirrhosis until a randomized controlled trial (RCT) proves the safety of low-dose pyrazinamide-containing combinations of three potentially hepatotoxic drugs.

Drug induced liver injury usually occurs in the first 2 months of treatment. The signs and symptoms of liver injury include but are not limited to jaundice, abdominal pain, nausea, vomiting and asthenia. Anti-tubercular treatment drug hepatotoxicity (ATDH) is usually reversible on withdrawal of the offending drug. Monitoring liver function tests more frequently at the start of therapy is a reasonable way to identify these patients. No recommendation for monitoring interval duration exists but once weekly liver function test for the initial 2 mo followed by once monthly should be reasonable. It should be supplemented by liver function tests in between if clinically warranted.
An asymptomatic, self-limited increase in aminotransferase levels was observed in most patients treated with isoniazid. Approximately 0.5% of all patients treated with isoniazid

monotherapy for latent TB developed clinically important increases in aminotransferase levels in a large study. The percentage was higher in combination therapy. Isoniazid-induced hepatotoxicity is seen mainly as hepatocellular steatosis and necrosis, and it has been suggested that toxic drug metabolites may bind covalently to cell macromolecules.

Hepatotoxicity associated with rifampicin is usually idiosyncratic. Rifampicin may occasionally cause dose-dependent interference with bilirubin uptake due to competition with bilirubin for clearance at the sinusoidal membrane, resulting in mild, asymptomatic unconjugated hyperbilirubinemia or jaundice without hepatocellular damage. Occasionally, rifampicin can cause hepatocellular injury and can potentiate hepatotoxicity of other antitubercular drugs. Hepatotoxicity is a major toxic effect of pyrazinamide. Previously reported studies have shown high rates of hepatotoxicity with high doses of pyrazinamide. Doses used currently (< 35 mg/kg per day) are considered much safer. In patients with advanced liver disease with complications of cirrhosis and signs of liver failure, it may not be possible to use even a single hepatotoxic drug. The presence of hepatorenal syndrome or other renal dysfunction further complicates the situation, limiting the use of aminoglycosides.

The Adverse Drug Reaction (ADR) Probability Scale was developed in 1991 by Naranjo and co-workers from the University of Toronto and is often referred to as the Naranjo Scale. This scale was developed to help standardize assessment of causality for all adverse drug reactions and was not designed specifically for drug induced liver injury. The scale was also designed for use in controlled trials and registration studies of new medications, rather than in routine clinical practice. Nevertheless, it is simple to apply and widely used. Many publications on drug induced liver injury mention results of applying the ADR Probability Scale.

The WHO-UMC system has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Since pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse reactions, other criteria such as previous knowledge and statistical chance play a less prominent role in the system. It is recognised that the semantics of the definitions are critical and that individual judgements may therefore differ. There are other algorithms that are either very complex or too specific for general use. This method gives guidance to the general arguments which should be used to select one category over another.

CONCLUSION

Military tuberculosis is one is the widespread dissemination of Mycobacterium tuberculosis. Female patient with age 62 years taking antitubercular drugs found to have elevated liver enzymes due to the hepatotoxicity drugs. To point out this we used Narango scale and WHO- UMC causality assessment scale which produce a positive result confirms that the elevated liver enzymes due to first line drugs such as Isoniazid, Rifampicin and Pyrazinamide. These drugs are stopped from the treatment and given with ethambutol and levofloxacin. Even though the regimen include aminoglycosides, but it is not indicated because of its hepatotoxicity.

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