Adverse Drug Events With Anti Tuberculosis Therapy:

What Every GP Should Know

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ABSTRACT: The success of tuberculosis treatment rests on multidrug antituberculosis therapy at least for six months. During the prolonged course of therapy, patients and providers may confront many adverse drug events (ADE). While minor ADE are common, some are rare and potentially life threatening. Hence it becomes obligatory for the providers to anticipate ADE during therapy, and take necessary measures when ADE occur. The common adverse events are mild elevation of liver enzymes, skin rash, gastrointestinal intolerance, neuropathy and arthralgia and can be managed symptomatically without discontinuation of the offending drugs. Serious adverse events are severe hepatitis, Steven Johnson syndrome, immune thrombocytopenia, agranulocytosis, hemolysis, renal failure, optic neuritis and ototoxicity. These warrant immediate stoppage of drugs and in some cases contraindicate re-challenge. Single most important factor to prevent adverse patient outcomes in terms of severe/chronic disease or fatality is prompt recognition of ADE, discontinuation of the probable drug/s with appropriate evaluation and management. Patients must be educated about symptoms of adverse events and asked to report them promptly. Prevention of monotherapy during the management of ADE is critical to prevent emergence of drug resistant TB.

Key words: tuberculosis; treatment; adverse drug events; drug reactions; monitoring.

According to the Standards of TB Care in India,[1] pulmonary tuberculosis patients are to be treated with Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) and Ethambutol (EMB) as the first line therapy given as intensive phase for first two months followed by INH, RIF and EMB in the continuation phase for next four months. The course of treatment can be complicated by occurrence of adverse events necessitating treatment interruptions and modified regimens. Lack of adherence to drugs and treatment interruptions are the driving factors for emergence of drug resistance during the treatment.

Adverse drug events (ADE) during anti-tuberculosis therapy (ATT) contribute to 7% of all drug related adverse events and 30% of fulminant hepatitis. This review is limited to the common adverse drug events on first line ATT which are extensively used by general practitioners. Patients requiring second line drugs are best managed by pulmonary or infectious diseases physicians. So, adverse events during second-line therapy are not discussed in this review. The most common ADE while on ATT, namely drug induced hepatitis, skin rash, gastrointestinal and neurological events, will be discussed in detail. **Table 1** provides an overview of the common ADEs during ATT.

DRUG INDUCED LIVER INJURY

Drug induced liver injury is the most severe of the ADE. Occurrence of ATT induced hepatitis is estimated to be 5-33%, depending on the definitions used to diagnose hepatitis.[2] Most widely used definition of drug induced hepatitis is serum aminotransferase level >5 times the upper limit of normal [ULN] without symptoms or >3 times the ULN with symptoms of hepatotoxicity like nausea, vomiting, or pain abdomen.[2,3] ATT may be associated with asymptomatic elevation of transaminases in about 20% of patients. It may also result in acute hepatitis, even subacute to fulminant hepatitis, which may be fatal.

The frequency of hepatitis associated with rifampicin is 0.6-2.7%, while that with Isoniazid is 0.6%.[4] Among the first line ATT drugs, PZA is the most hepatotoxic, with 15% of patients experiencing hepatic adverse events when higher dose of PZA is used.[5] The risk of hepatitis is more with combination of INH with RIF or PZA.

TYPES OF HEPATOTOXICITY AND CLINICAL FEATURES

- **Hepatic adaptation.** Transient asymptomatic elevation of alanine aminotransferase (ALT) may be seen as a physiological response to drug exposure because of Cytochrome P450 enzyme induction.
- **Drug induced acute hepatitis.** It is associated with hepatocyte necrosis and elevation of hepatic transaminases with or without jaundice. Patients may be asymptomatic or may present with nausea, vomiting, abdominal pain and jaundice. Occasionally they may report constitutional symptoms including fe-

ver. INH and Rifampicin can produce hepatotoxicity by this mechanism.

- **Granulomatous hepatitis.** e.g. Pyrazinamide can produce this and it is a hypersensitivity reaction to the inciting drug with granuloma formation. Patients may present with fever, lethargy, body ache, rash, lymphadenopathy and hepatosplenomegaly. Biochemical examination will reveal elevation of serum transaminases along with alkaline phosphatase.
- **Cholestasis.** Usually associated with asymptomatic elevation of alkaline phosphatase along with bilirubin because of failure of bilirubin transport. e.g. seen with rifampicin.

TABLE 1. COMMON ADVERSE EVENTS WITH FIRST LINE ATT DRUGS

Drug	Common adverse events
Isoniazid (INH)	Asymptomatic transient elevation of transaminases (20%), hepatitis, peripheral neuropathy, fever, skin rash, seizures, psychosis
Rifampicin (RIF)	Reddish orange color of urine and tears, Pruritus, GI intolerance, Isolated hyperbilirubinemia, hepatitis, pancytopenia, flu like syndrome, acute kidney injury
Pyrazinamide (PZA)	Nausea, vomiting, hepatitis, arthralgia, hyperuricemia, skin rash
Ethambutol (EMB)	Optic neuritis (1-5%), peripheral neuropathy, skin rash
Streptomycin (SM)	Ototoxicity, nephrotoxicity, skin rash

RISK FACTORS FOR HEPATOTOXICITY:

- Age >35 years
- Children
- Female gender
- Recent child birth (<3 months post-partum)
- Alcohol abuse
- Abnormal baseline liver enzymes
- Slow acetylator status- associated with INH associated hepatotoxicity
- Malnutrition/hypoalbuminemia

RECOGNITION OF DRUG INDUCED HEPATITIS

It is important for doctors to suspect drug induced liver injury when patients on ATT present with nausea, vomiting, right hypochondriac pain, and jaundice. Temporal pattern of disease evolution after exposure to drugs is important to diagnose drug induced adverse events. Liver function tests must be requested on suspecting liver injury. Drug induced hepatitis is diagnosed when serum aminotransferase level >5 times the ULN without symptoms or >3 times the ULN with symptoms. Bilirubin may or may not be elevated. Early detection of drug induced liver disease is critical to prevent severe or chronic liver disease. Patients should be advised to report any untoward symptoms, like nausea, malaise, lethargy, right hypochondriac pain or new onset fever.

MANAGEMENT OF PATIENTS WITH DRUG INDUCED HEPATOTOXICITY

Once hepatotoxicity is suspected, all hepatotoxic drugs must be stopped and promptly investigated as mentioned above. Failure to discontinue a drug that is causing liver injury leads to poor outcome such as acute liver failure or chronic hepatitis. The specific risk factors for drug induced hepatotoxicity have to be carefully elicited. In all patients with liver abnormality, history of hazardous intake of alcohol, other hepatotoxic drug ingestion must be enquired about and viral hepatitis must be ruled out. No hepatoprotective agent has been effective in ameliorating drug induced liver damage. Non hepatotoxic ATT drugs which could be used are streptomycin, ethambutol and levofloxacin or moxifloxacin.

Patient should be observed for progress and the liver function tests [LFT] should be monitored once in 3 days. Usually symptoms and laboratory abnormalities promptly improve within days or weeks once the inciting drugs are stopped. When the ALT returns to less than 2 times the ULN, gradually drugs are reintroduced sequentially with rifampicin, INH and PZA in that order with a gap of 3-7 days between each drug and monitoring of LFT.[2] If symptoms recur or ALT increases, the last drug added should be stopped. In those patients who had experienced severe or prolonged hepatotoxicity, reintroduction of PZA may be avoided and the duration of ATT may be extended to 9 months.

GASTROINTESTINAL ADVERSE EVENTS

GI adverse events are usually minor. They include nausea, vomiting and abdominal discomfort, which may be self-limiting. This may be due to mild gastritis and can be managed by the addition of proton pump inhibitors, anti-emetics, administering drugs after meals or by giving drugs at an interval. Discontinuation of ATT is usually not required. However, in all such patients with the above mentioned symptoms, LFT must be requested to rule out early liver toxicity.

DERMATOLOGICAL ADVERSE EVENTS

Skin related ADE can occur with all anti TB drugs and is one of the commonest side effects in up to 6% of patients on ATT.[6] It can be in varying forms like maculopapular rash, erythema multiforme syndrome, acneiform eruptions, urticarial, lichenoid eruptions, and the more severe exfoliative dermatitis and Steven Johnson Syndrome. Exfoliative dermatitis also called erythroderma, a form of cutaneous hypersensitivity occurs after 6-8 weeks of therapy. The propensity of the drugs to cause erythroderma is PZA >SM >EMB >RIF >INH with rates for PZA being 2.4%.[6] Steven Johnson syndrome is a life threatening muco- cutaneous syndrome and it has been described with RIF, INH, PZA and thiacetazone.[7]

In patients with itching/ minimal rash, ATT can be continued along with symptomatic treatment with antihistamines. If visible maculopapular rash, all the drugs have to be stopped and antihis-

CLINICAL HIGHLIGHTS

- The course of treatment of TB can be complicated by drug induced adverse events and GP's knowledge about their occurrences and competency to diagnose them are critical for the successful outcome.
- Minor adverse reactions to TB medications include nausea, gastric intolerance, neuropathy, itching and joint pains that can be managed symptomatically and do not warrant stoppage of medications.
- Major adverse reactions include hepatitis, severe skin reactions, optic neuropathy thrombocytopenia, hemolysis, and renal failure. Symptoms and signs suggesting a major reaction should be treated by stoppage of drugs, and close monitoring.
- Drug induced liver injury is the most common serious adverse event which may present as nausea, vomiting, jaundice, right hypochondriac pain and requires stoppage of all hepatotoxic drugs with monitoring of liver functions and subsequent reintroduction of drugs sequentially.
- Patients with pre-existing liver disease, viral hepatitis, chronic alcohol consumption, pregnant women, or postpartum period, HIV infection and on concomitant hepatotoxic medications are particularly at high risk of ATT induced hepatitis and these risk factors must be carefully sought prior to the initiation of ATT and are to be monitored with LFT every 2-4 weekly on therapy.
- On reintroduction of ATT, it is important to avoid mono therapy to prevent emergence of drug resistant TB. Non hepatotoxic drugs like streptomycin, ethambutol and moxifloxacin can be given, when hepatotoxic drugs need to be stopped.
- Life threatening complications like immune thrombocytopenia, immune hemolytic anemia, Steven Johnson syndrome, and organ threatening complications such as ototoxicity, nephrotoxicity, and ocular toxicity are absolute contraindications to rechallenge with the suspected drug.
- All patients need to be counselled on how to identify ADEs, before initiation of ATT.

tamines have to be prescribed. Reintroduction of the ATT is to be done with INH followed by RIF, EMB and PZA with careful monitoring.

NEUROLOGICAL ADVERSE EVENTS

CNS adverse events include seizures, psychosis, ototoxicity, and optic neuritis.[8] The drug most commonly implicated in psychosis is INH followed by cycloserine. Seizures are a side effect of INH, fluoroquinolones, and cycloserine. Ototoxicity and neuromuscular blockade are adverse events of aminoglycosides, while ethambutol is known to cause optic neuritis. Ototoxicity and optic neuritis are dose dependent.

It is important to ask patients about tinnitus, imbalance, vertigo or decreased hearing while the patients are on aminoglycosides. As children may not be able to complain about decreased vision, or impairment of color perception (which is a classical symptoms of optic neuritis), ethambutol is best avoided in children. Peripheral neuropathy, manifested by tingling and numbness in hands and feet is a side effect of INH (seen in up to 2% of patients), less commonly ethambutol and ethionamide.

The risk factors for peripheral neuropathy are malnutrition, HIV infection, diabetes mellitus, alcohol abuse and concomitant drugs having neuropathy potential such as Stavudine. It is best to prevent peripheral neuropathy by pyridoxine supplementation (40mg daily) to all patients with the neuropathy risk factors receiving INH. The involved drugs have to be stopped promptly on the first suspicion of seizures, psychosis, ototoxicity or visual toxicity and never administered again.

MUSCULOSKELETAL ADVERSE EVENTS

Mild arthralgia may be associated with PZA, and is associated with elevated uric acid. It can be managed symptomatically with NSAIDS.

RENAL ADVERSE EVENTS

Acute kidney injury (acute renal failure) with normal urine output can occur with aminoglycosides. Rarely, rifampicin can give rise to interstitial nephritis.

DRUG INDUCED HAEMATOLOGICAL ADVERSE EVENTS

Immune mediated cytopenia of all three cell lines, including agranulocytosis have been described with ATT. Thrombocytopenia is an uncommon but potentially life-threatening complication and is characterized by rapid destruction of platelets in susceptible patients due to immune mechanisms. Patients usually present with purpuric rashes all over the body. Although this has been reported classically with RIF; PZA, EMB and INH are also implicated in various case reports.[9] The diagnosis is by resolution of symptoms and improvement of platelet count on stopping the drugs. Treatment is by discontinuation of the drugs, transfusion of platelets if platelet count is <20,000/μL. Patient has to be managed with 3 new anti tuberculosis drugs including one parenteral agent.

Rifampicin is also implicated with life threatening drug induced hemolytic anemia due to immune mechanisms.[10] It can manifest with severe anemia requiring blood transfusion and jaundice due to indirect hyperbilirubinemia. Re-challenge with the offending drug is contraindicated both in drug induced thrombocytopenia and hemolysis as minute

quantity of the drug can trigger a very severe reaction.

MONITORING OF PATIENTS FOR ADE ON ATT

All patients should undergo baseline testing of serum bilirubin, transaminases, alkaline phosphatase, creatinine, and complete blood count. In those with risk factors for hepatotoxicity, every 2-4 weekly monitoring of liver function tests is recommended. In those without risk factors, routine LFT monitoring is not required unless symptomatic. During each visit, patients should be asked about symptoms of possible ADE relevant to the regimen they are receiving. ■

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Questions

1 **Which of the following drugs has the highest potential to produce exfoliative dermatitis?**

a) Isoniazid

b) Rifampicin

c) Pyrazinamide

d) Ethambutol

2 **Which of the following adverse events is a contraindication to rechallenge of the possibly implicated drug during treatment with ATT?**

a) Hepatotoxicity

b) Drug rash

c) Drug induced thrombocytopenia

d) Vomiting

3 **Which of the following ATT drugs has no hepatotoxicity potential?**

a) Rifampicin

b) Pyrazinamide

c) Isoniazid

d) Ethambutol

4 **Which of the following is a risk factor for ATT induced hepatitis?**

a) Female gender

b) Advancing age

c) Malnutrition

d) All of the above

5 **Which of the following is false regarding adverse reactions to TB drugs?**

a) Jaundice is a common adverse effect and is always due to liver adaptation which is self-limiting.

b) Drug induced neuropathy can be prevented by routine supplementation with pyridoxine

c) Joint pains are an adverse reaction to pyrazinamide and usually respond well to non-steroidal anti-inflammatory drugs

d) Females and those with pre-existing liver disease are more susceptible to drug induced hepatitis

Answers

1. **The correct answer is (c).** The propensity of the drugs to cause erythroderma (exfoliative dermatitis) are PZA >SM >EMB >RIF >INH with rates for PZA being 2.4 %. All the drugs have to be stopped and reintroduction of the ATT is to be done with INH followed by RIF, EMB and PZA with careful monitoring. To prevent monotherapy, 2 new drugs which were not used previously should be added while introducing individual drugs.

2. **The correct answer is (c).** Drug induced thrombocytopenia is because of immune mediated mechanisms because of production of autoantibodies or drug dependent antibodies resulting in rapid destruction of platelets. It is a life threatening complication and is an absolute contraindication to rechallenge as even minute quantities of the drug can trigger immune mediated destruction of platelets leading to severe hemorrhage.

3. **The correct answer is (d).** The propensity to produce hepatotoxicity is with PZA> INH> RIF. Ethambutol, streptomycin and moxifloxacin do not have hepatotoxic potential and they can be administered safely in patients with hepatotoxicity while discontinuing those drugs with hepatotoxic potential and to accompany the individual drugs on rechallenge to prevent monotherapy .

4. **The correct answer is (d).** Advancing age, female gender, chronic alcohol consumption, pre existing liver diseases, hepatitis B, C and HIV coinfection, malnutrition are some of the important risk factors for drug induced hepatotoxicity. They have to be carefully sought prior to the initiation of ATT and their presence warrant close monitoring of liver function tests every 2-4 weeks on therapy.

5. **The correct answer is (a).** Jaundice is a sign of hepatitis and warrants stoppage of all TB medications, and investigations for drug-induced hepatitis. However, it can also occur rarely due to drug induced hemolysis which is a life threatening complication. Liver function tests and complete blood counts are to be requested to differentiate drug induced hepatitis and hemolytic jaundice. Drug induced hepatitis is diagnosed when serum aminotransferase level >5 times the upper limit of normal [ULN] without symptoms or >3 times the ULN with symptoms