

Current Overview of Anti-Tuberculosis Drugs: Metabolism and Toxicities

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Abstract

Tuberculosis, a global public health epidemic, is one of the leading causes of death by an infectious disease. According to the World Health Organization (WHO), one third of the world's population is infected with *Mycobacterium tuberculosis* (MTb), 5-10% of whom will possibly go on to develop active disease. Tuberculosis (TB) is an epidemic especially in poor countries, and each year the disease kills approximately 1.7 million people worldwide.

The Mycobacterium family has over 60 species but only a few of them can cause diseases in humans, such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycobacterium africanum* and *Mycobacterium avium*. MTb can exist in the latent state, where it resides in the human body for an extended period of time without showing any clinical symptoms. Once the host's immune system becomes weakened, whether by age or concomitant disease, the bacteria attains virulent or active form. With the increasing incidence of HIV infection, tuberculosis has reemerged as an important cause of morbidity and mortality worldwide.

Keywords Tuberculosis; Toxicity; Metabolism; Drugs

Introduction

TB is highly contagious during the active stage and the primary route of transmission is via the respiratory system. The disease can be caused by inhaling as few as 10 bacteria into the deep lung [1]. Though the pulmonary system is the prime target for MTb, it can disseminate and invade extra-pulmonary systems such as the skeletal system, gastrointestinal system, urogenital system, central nervous system and lymphatic system. Initial symptoms of TB include night sweats, fever, and weight loss, whereas advanced stage symptoms manifest as chest pain, shortness of breath, and blood in coughed up sputum.

Tuberculosis treatment consists of a multi-drug regimen with duration of 6 to 8 months. The preferred first-line drugs are isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB). When the bacterial strain becomes resistant to one or more of these drugs, second-line drugs are used. These include streptomycin, kanamycin, fluoroquinolones, ethionamide, and p-aminosalicylic acid. Generally, second-line drugs are less effective and more toxic compared to the first-line drugs. In this paper, we will be primarily discussing the metabolism and associated toxicity of first-line anti-tuberculosis drugs.

Multidrug therapy: Treatment of TB is very different from the treatment of other diseases due to the unique characteristics of MTb. There are some basic requirements for the successful treatment of TB. Firstly, the treatment must consist of a combination of antibiotics to prevent the selection of a resistant strain. Secondly, the antibiotics must be given for a minimum period of 6 months to fully eradicate the bacterial population so that there is no chance of relapse once treatment is completed. Finally, health care professionals that are involved with the patient's therapy must monitor the patient for

compliance to the drug regimen as well as any associated drug-induced toxicities.

Carnetti [2] has proposed a two phase concept of TB treatment. First is an initial bactericidal or "intensive" phase which is followed by a subsequent sterilizing or "continuation" phase. The majority of infecting bacilli are killed during the bactericidal phase thereby reducing clinical symptoms, risk of transmission and emergence of drug resistance. In the subsequent sterilization phase, the remaining slower growing populations are eliminated, thereby reducing the chance of relapse. Interestingly, some of the first-line drugs like INH are highly effective for the first bactericidal phase [3] but possess poor sterilizing activity, whereas PZA is a strong sterilizing agent with poor bactericidal activity [4]. During effective treatment, the fast growing population of bacteria is killed early and patients show negative culture within 2 months of the treatment. The remaining slow growth population accounts for relapses and is the reason for prolonged treatment. Most anti-tuberculosis drugs kill bacteria while it is dividing, which explains why more time is needed to kill the slow growth population of bacteria (Table 1).

The preferred drug regimen is as follows:

Ranking	Initial Phase	Continuation Phase
Preferred	INH, RIF, PZA, EMB daily for 2 months	INH, RIF daily for 4 months
	INH, RIF, PZA, EMB, 3 times a week for 2 months	INH, RIF, three times a week for 4 months
Optional	INH, RIF, PZA, EMB daily for 2 months	INH, EMB daily for 6 months

Ref: International standard for tuberculosis care. 2006.

Table 1: Preferred drug regimen.

Drug associated toxicity is an unfortunate outcome of this tuberculosis treatment due to the number of antibiotics used and the relatively long duration of treatment. Occasionally, the severity of adverse effects experienced by the patient forces the discontinuation of the antibiotic schedule. This in turn facilitates the emergence of drug resistant strains of MTb. Most antituberculosis drugs cause hepatotoxicity, and other side effects include rash, neurological syndrome, and visual disturbances (mainly with ethambutol).

Drug Metabolism & Toxicity

Isoniazid (INH)

INH is a bactericidal agent whose mechanism of action includes inhibiting mycolic acid synthesis in MTb. Mycolic acids, important components of the MTb cell wall, are vital for the survival of the bacteria.

INH is isonicotiny hydrazine (arylhydrazine). It is rapidly absorbed when orally dosed and attains peak plasma levels within one to two hours post administration. It is mainly metabolized in the liver, primarily through the N-acetyltransferase (NAT) enzyme system. In fact, discovery of INH as an antituberculosis drug had triggered the detail study of the NAT system.

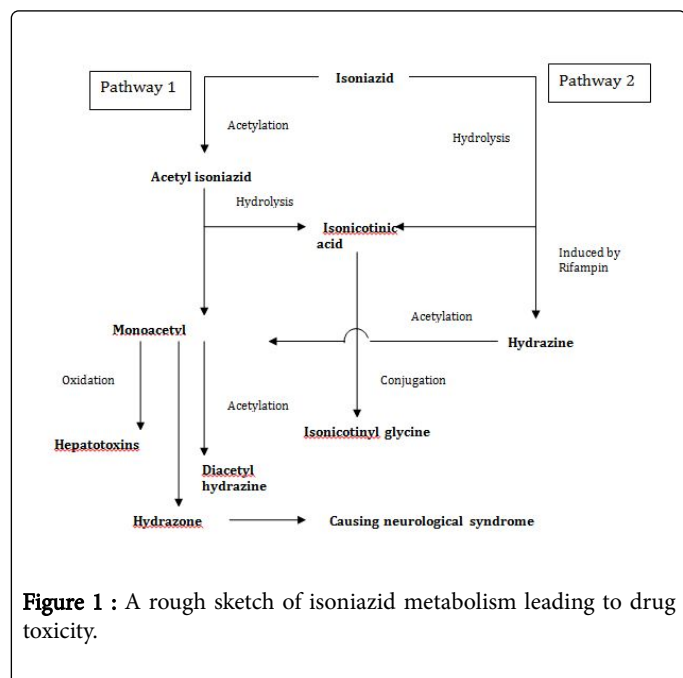
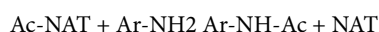


Figure 1 : A rough sketch of isoniazid metabolism leading to drug toxicity.

The NAT enzyme transfers the acetyl moiety from acetyl-CoA (AcCoA) to the nitrogen of the substrate arylamine, the process from which it derives its name. The reaction occurs over two steps: first, the acetyl group from AcCoA is transferred to NAT. Then, this acetyl-NAT complex transfers the acetyl group to a nitrogen on arylamine.

These reactions can be represented as:



This is the major metabolic pathway that produces acetylisoniazid from INH, which is subsequently hydrolyzed to form isonicotinic acid and monoacetyl hydrazine. Isonicotinic acid is conjugated by glycine

and excreted out of the body. Monoacetyl hydrazine can follow one of the three metabolic pathways leading to the formation of either diacetyl hydrazine (further acetylation), hydrazone (induces neurological syndromes) or an oxidized product. The first two metabolites are excreted out but the oxidized metabolite forms electrophilic reactive intermediates, which can covalently bind to liver proteins. This results in the formation of an antigenic macromolecule that is foreign to the immune system, which stimulates the immune system to form the respective antibody that would lead to the destruction of the metabolite-protein complex. This would result in an autoimmune reaction affecting the liver, and this is the probable mechanism for hepatotoxicity observed with INH treatment. Glutathione can to some extent detoxify the reactive metabolite, but excessive formation of the metabolite can overwhelm the antioxidant pathway and lead to liver toxicity. Studies have shown an increased risk of drug-induced hepatotoxicity in individuals lacking glutathione [5]. The oxidation of monoacetyl hydrazine is thought to be catalyzed by cytochrome P450 enzyme (probably by 2E1) because oxidation can be induced by alcohol [6].

Pathway 2, illustrated in Figure 1, is mainly active in individuals with the slow acetylator phenotype. The above depicted pathways for isoniazid metabolism can be further supported by the isolation of different metabolites from the serum and urine of individuals undergoing isoniazid treatment [7].

Among the metabolites of isoniazid, hydrazine plays the major role in hepatotoxicity and is known to cause irreversible hepatic cellular damage [8]. This can be supported by how slow acetylators have more than two-fold risk of developing INH induced hepatotoxicity [6]. This can be explained by the fact that in the slow acetylator phenotype, free INH is available for subsequent hydrolysis to hydrazine. Rifampin also induces the hydrolysis of INH into hydrazine and this partially explains the higher toxicity found with the co-administration of the two drugs.

Studies have shown that INH inhibits CYP1A2, 2A6, 2C19 and 3A4 enzymes [9]. Among the above CYPs, 1A2 participates in hydrazine detoxification [10] thereby enhancing INH's own toxicity.

Another widely recognized drug-induced toxicity of INH is neurological syndrome. This is characterized by seizure, irritability, euphoria, restlessness, insomnia and headache. One possible explanation is that INH affects pyridoxine metabolism. INH enhances the excretion of pyridoxine, and the hydrazone formed during INH metabolism competitively inhibits the enzyme responsible for conversion of pyridoxine to pyridoxal phosphate. The reduced concentration of pyridoxine and pyridoxal phosphate in turn reduces the formation of neurotransmitter GABA (gamma amino butyric acid), which leads to peripheral neuropathy [11,12].

Pyrazinamide (PZA)

PZA is an important bactericidal agent, especially for the slow growing strains of MTb. This property results in its use as an efficient and potent sterilizing agent. PZA is a prodrug - it is converted to pyrazinoic acid (POA) by the bacterial enzyme pyrazinamidase. For this reason PZA is active in acidic pH. POA inhibits fatty acid synthesis in the bacteria.

Among all the first line of antituberculosis drugs, PZA is responsible for causing dose dependent hepatotoxicity. According to an Indian study, PZA is responsible for an increased rate of antituberculosis drug-induced hepatitis compared to INH and RIF [13]. A Turkish

study reveals that reintroduction of pyrazinamide to the therapeutic regimen increases the risk of recurrent hepatotoxicity than that without it [14]. The drug is well absorbed orally and is mainly metabolized in the liver. Its metabolite products are excreted via the kidney. The enzymes involved in pyrazinamide metabolism are liver microsomal deamidase and xanthine oxidase (XO), a molybdoflavoprotein complex. Allopurinol acts as an inhibitor for the XO enzyme system.

In the liver, pyrazinamide is primarily metabolized to pyrazinoic acid (PA) by microsomal deamidase. PA is further metabolized to 5-hydroxypyrazinoic acid (5-OH-PA) by XO. This last metabolite can also be formed by first action of XO on PZA forming 5-hydroxypyrazinamide (5-OH-PZA), which is subsequently converted to 5-OH-PA by the action of deamidase. All three metabolites - PA, 5-OH-PA, 5-OH-PZA - have been isolated from rat urine [15]. In addition, some of the PA is conjugated with glycine forming pyrazinuric acid (PU).

PZA is always used in combination with other antituberculosis drugs so it is difficult to predict its exact mechanism of hepatotoxicity. According one study, pyrazinamide causes all the major side effects up to the extent of 1.48 per 100 person-months compared to 0.49 for isoniazid and 0.43 for rifampicin [16] (Figure 2).

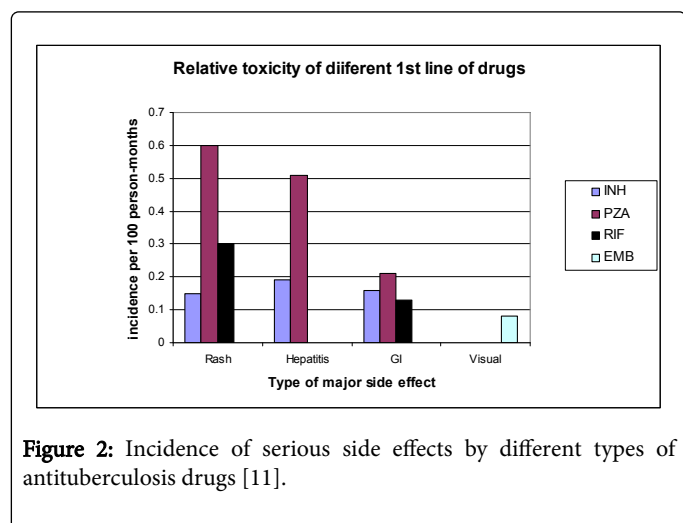


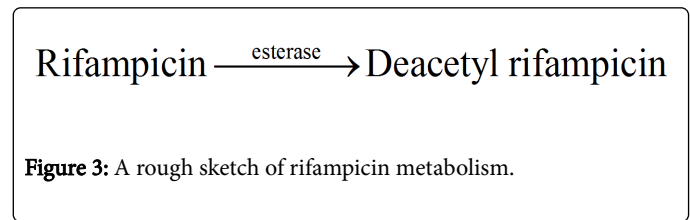
Figure 2: Incidence of serious side effects by different types of antituberculosis drugs [11].

Other vital side effects of PZA include rash, hyperuricemia and arthralgia (joint pain). PZA strongly inhibits uric acid excretion. Pyrazinoic acid, one of the major metabolites of PZA, is thought to both decrease the tubular secretion and increase the tubular reabsorption of uric acid [17]. It is this increased serum level of uric acid that causes arthralgia.

Rifampicin (RIF)

Rifampicin is an important bactericidal agent against gram-positive bacteria, which includes *Mycobacterium tuberculosis*. It acts by inhibiting bacterial protein synthesis. RIF binds with the DNA-dependent RNA polymerase enzyme of the bacteria thus preventing transcription to RNA and subsequent protein synthesis. RIF is a highly lipophilic drug and almost 90% is absorbed from the gastrointestinal tract after oral administration. It is primarily metabolized in the liver by microsomal enzymes to its deacetylated form. Deacetyl rifampicin also shows antibiotic activity, but in contrast to rifampicin, it does not

enter in the enterohepatic recirculation and is subsequently excreted out of the body. Most metabolites are excreted in feces (Figure 3).



Orally administered rifampin results in peak plasma concentrations in about 2 to 4 hours. Aminosalicylic acid can significantly reduce absorption of Rifampin, and peak concentrations may not be reached. If these two drugs must be used concurrently, they must be given separately with an interval of 8 to 12 hours between administrations.

Like other antituberculosis drugs, rifampicin is also hepatotoxic. Studies show a 5.8% incidence of severe liver toxicity when rifampicin is co-administered with pyrazinamide and 2.6% with isoniazid and 1.1% when administered alone [18]. The exact mechanism of hepatotoxicity is not well known, mainly because of the concomitant use of several drugs during tuberculosis treatment. Histopathological examinations indicate dose related hepatic necrosis, ballooning degeneration and inflammatory infiltrates [18]. Altered profile of antioxidant enzymes may also induce hepatotoxicity due to oxidative stress [18]. Most of the rifampicin hepatotoxicity occurs during simultaneous administration with isoniazid. This can be explained with consideration of Figure 1 where rifampicin induces the hydrolysis of isoniazid leading to hepatotoxic hydrazine. Other side effects include coloration of body fluids, shortness of breath, rash, arthralgia and nephrotoxicity.

Barbiturates	Metoprolol
Chloramphenicol	Methadone
Cimetidine	Phenytoin
Clarithromycin	Prednisone
Clofibrate	Propranolol
Contraceptives (oral)	Quinidine
Dapsone	Protease inhibitors
Digitoxin	Ritonavir
Digoxin	Sulfonylureas
Efavirenz	Tacrolimus
Estrogens	Theophylline
Fluconazole	Thyroxine
Itraconazole	Verapamil
Ketoconazole	Warfarin

Table 2: Examples of drugs with reduced half-lives caused by concomitant administration of rifampicin (Brody's Human Pharmacology, Chap 49.)

The primary concern with the use of rifampicin is the potential for drug-drug interactions. RIF affects the bioavailability of various drugs

thereby altering both therapeutic and toxic limits of those drugs. Rifampicin has been extensively used in clinical studies as inducer of drug metabolizing enzymes and transporters. It does so by inducing a number of enzymes in the cytochrome P450 family, which are responsible for the metabolism of majority of drugs and xenobiotics. Total human CYP production increases markedly after rifampicin administration [19]. CYP3A4 is among the enzymes that are highly induced, and it is responsible for the metabolism of more than 60% of all drugs, including contraceptive steroids, immunosuppressive agents, imidazole antimycotics and macrolide antibiotics.

CYP3A4 is a highly inducible enzyme whose induction involves a number of regulatory elements found in both distal enhancer and proximal promoter regions. Various cellular receptors play an important role in the transcriptional regulation of the enzyme. One such receptor is the Pregnane X receptor (PXR). PXR is a member of nuclear receptor family having a ligand (inducer) binding domain and a DNA binding domain. The inducers that activate PXR include rifampicin, dexamethasone, indinavir, different pesticides and many other drugs and xenobiotics. PXR not only upregulates CYP3A4 gene, but also takes part in the regulation of a number of other genes involved in drug metabolism and detoxification. These include other CYP enzymes, aldehyde dehydrogenase (ALDH), UDP-glucuronosyltransferase (UGTs), sulfotransferase, glutathione S-transferase (GSTs) and p-glycoprotein. Rifampicin has been identified as a powerful activator of PXR [20]. Various drug-drug interactions in presence of rifampicin can be explained in the context of its ability to activate PXR.

CYP enzymes are involved in the biotransformation of various endogenous as well as exogenous compounds. The process usually converts a lipophilic compound into a hydrophilic one, thereby facilitating excretion of the compound in the subsequent steps. In reality, most of the antituberculosis drugs are liposoluble. Rifampicin can induce many CYPs including CYP2A, CYP2B, CYP2C and CYP3A. However, CYP3A is the most abundant CYP enzyme in humans and is responsible for the metabolism of majority of drugs. It is also more efficiently induced by rifampicin in comparison to other CYP enzymes. In primary human hepatocytes, 20 microM rifampicin can increase CYP3A4 mRNA by 14 folds, but CYP2B6 by only 2.1 fold [21]. By inducing CYP3A, rifampicin increases its own metabolism. This autoinduction partly explains the decreased drug efficacy in some tuberculosis patients that had lead to the failure of treatment.

UGT1A (UDP- glucuronosyltransferase 1A) is an important phase 2 enzyme that transfers glucuronic acid to a number of xenobiotics (or its metabolites) and endogenous substrates resulting their elimination from the body either through renal or biliary routes, depending on molecular weight. This enzyme is also induced by rifampicin via the PXR receptor. Enzyme induction leads to increased clearance steroids, heme, environmental toxins and drugs.

In addition to the above mechanisms for drug interactions with rifampicin, there are some drug interactions that cannot be solely explained by the induction of cytochrome P450 enzymes. For instance, the interaction with digoxin, which can instead be explained by the increased level of intestinal p-glycoprotein. P-glycoprotein is a plasma membrane bound efflux transporter present in various drug eliminating organs like the liver, brain, and intestinal lumen. P-glycoprotein, a 170 KDa, 1280 amino acid long phosphorylated and glycosylated protein, is a member of ATP binding cassette (ABC) family of transport proteins encoded by multidrug resistance genes (MDR). Rifampicin also induces p-glycoprotein and its level is

increased 3.5 fold after rifampicin treatment [22]. The induction is thought to be mediated by activation of PXR by rifampicin.

MRP2 is another member of the ABC transporter family. Researchers have shown that rifampicin induced duodenal MRP2 mRNA in 14 out of 16 individuals after nine days of oral treatment with 600mg daily rifampin [23]. The same study has also found that MRP2 protein, which is expressed in the apical membrane of enterocytes, was significantly induced by the same treatment.

Complex drug interactions with rifampicin can occasionally complicate the therapy, especially when the patient has HIV infection or any other concomitant diseases. For instance, a cyclosporine dose has to be increased about 3-fold to maintain therapeutic plasma level when co administered with rifampicin [24]. Concomitant administration of rifampicin and simvastatin can lead to greatly reduced cholesterol lowering efficiency of the latter [24]. Warfarin clearance increases in presence of rifampicin and thus requires a higher dose to achieve the same therapeutic outcome. Digoxin's plasma concentration is decreased considerably during co-administration of digoxin and rifampicin, but this can be minimized during intravenous injection of digoxin [22]. Thus, rifampicin controls efficacy and toxicity of various lifesaving drugs.

Ethambutol (EMB)

Ethambutol is another important first-line of drug against tuberculosis. Ethambutol is thought to inhibit a number of metabolites essential for the survival of the bacteria. It mainly inhibits the synthesis of arabinogalactan - an important component of the mycobacterial cell wall. Almost 80% of the dose is absorbed from the gastrointestinal tract and rest is excreted unchanged via feces. The metabolism of the drug is depicted below:

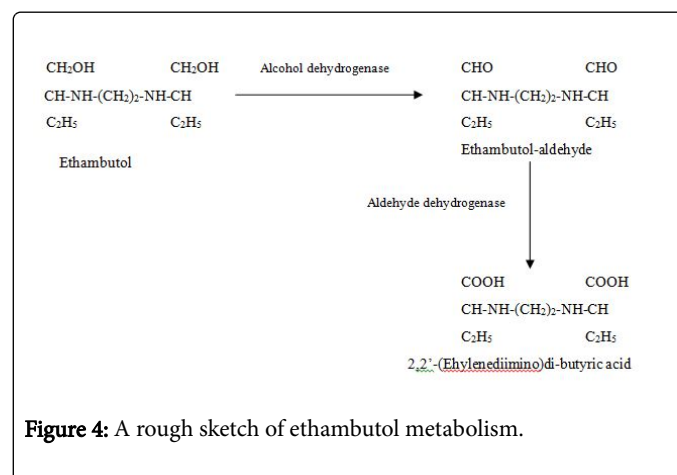


Figure 4: A rough sketch of ethambutol metabolism.

The L configuration of ethambutol is found to be the more toxic isomer [25]. Several animal studies have isolated both the metabolites from the urine. Optical toxicity is predominant with ethambutol. Optic neuritis is a rare but detrimental side effect. It manifests primarily as retrotubular neuritis with the involvement of either axial fibres or, less commonly, periaxial fibres (Figure 4). Ethambutol can chelate various cations such as zinc, and copper. Several enzymes important for maintaining normal body functions require copper and zinc as cofactors. Depleted levels of these cations during ethambutol treatment would therefore affect the normal function of various enzymes.

Zinc which influences cell metabolism through a variety of mechanisms, appears to play an integral role in maintaining normal ocular function. Zinc is present in high concentrations in ocular tissue, particularly in the retina and choroid. Zinc deficiency has been shown in a number of species to result in a variety of gross, ultrastructural and electrophysiologic ocular manifestations. Extensive studies have been carried out for understanding the role of zinc in the visual system of different species. The physiological functions for zinc have been studied predominantly in retina and retinal pigment epithelium where zinc is believed to interact with taurine and vitamin A, modify photoreceptor plasma membranes, regulate the light-rhodopsin reaction, modulate synaptic transmission and serve as an antioxidant [26].

Earlier studies have established that ethylene diamine and its substituted derivatives can form stable complexes with Zinc and many other cations [27]. Studies have shown that treatment with ethambutol in dogs and rhesus monkeys can produce the metabolite Ethambutol [(d)-2,2'-(ethylenediimino)di-1-butanol], a substituted ethylene diamine, which results in a significant decrease in ocular zinc concentrations [28]. The same study has shown that depleted copper levels are responsible for cardiac toxicity in dogs, likely due to the malfunction of cytochrome C oxidase, a copper requiring enzyme. In fact, alcohol dehydrogenase (ADH), which is also involved in ethambutol metabolism, is itself a zinc requiring enzyme. Ethambutol increases the ability of ADH to oxidize ethanol in yeast and it does so by influencing the depolymerisation of the enzyme [29].

Other side effects of ethambutol, though rare, include peripheral neuropathy, cutaneous reaction and hepatitis. Due to severe optical toxicity ethambutol is not administered in pediatric patients.

Conclusion

Hepatotoxicity is the major side effect for almost all first-line antituberculosis drugs (with exception of ethambutol). The exact mechanism of liver toxicity is difficult to predict for each individual drug as they are almost always co-administered with each other. Only exception is perhaps isoniazid that is used as monotherapy in latent tuberculosis. The incidence of hepatotoxicity varies from 2% to 28%. Liver is a common target of toxicity for the drugs administered orally. This may be due to its location, physiology and unique role in drug metabolism. The majority of hepatic blood comes from gastrointestinal viscera and spleen via the portal vein. Drugs that are taken orally also travel through this route to the liver, where they are metabolized by the abundance of various metabolizing enzymes into potentially toxic intermediates. These toxic metabolites mainly covalently bond to hepatic proteins because protein is the most abundant constituent (slightly more than 140 g/kg wet weight of liver) of liver [30]. This protein damage is irreversible in nature and is subsequently catabolized by proteosomal and lysosomal pathways. The liver can protect against damage via the glutathione S-transferase system but only if it is not overwhelmed by an excess of oxidative metabolites. The signs and symptoms of liver injury include jaundice, abdominal pain, nausea, vomiting and asthenia.

The extent of liver damage is estimated by measuring serum transaminase level. World Health Organization (WHO) defines the levels of drug-induced hepatotoxicity as follows:

Grade 1 (mild) < 2.5 times ULN (ALT 51-125 U/L)

Grade 2 (mild) 2.5 to 5 times ULN (ALT 126-250 U/L)

Grade 3 (moderate) 5-10 times ULN (ALT 251-500 U/L)

Grade 4 (severe) >10 times ULN (ALT >500 U/L)

[ALT: Alanine aminotransferase; ULN: Upper limit of normal, which is 50 U/L]

Mild to severe drug-induced hepatotoxicity has been reported as a result of the many drugs given concomitantly during tuberculosis treatment. Patient liver profile should be monitored throughout treatment at regular interval and treatment should be modified accordingly. In many poor countries, especially in sub-Saharan Africa where Tb outbreak is quite high, it is often impossible to do liver function tests. In those cases, physicians have to rely on the symptoms of drug-induced hepatitis. Medical supervision is critical during the treatment so that physicians can modify the treatment regimen depending upon the extent of liver damage. Standard guidelines for managing antituberculosis drug-induced hepatitis (ATDH) have been published by the American Thoracic Society (ATS), the British Thoracic Society (BTS), the Task Force of the European Respiratory Society, the WHO and the International Union against Tuberculosis and Lung Disease.

The incidence of liver toxicity varies with patients. This is mainly due to genetic polymorphism. Though there is 99.9% similarity in human gene expression, the remaining 0.1% interindividual variability can cause a varied response in terms of drug efficacy and toxicity. As discussed earlier, the extent of ATDH is higher in slow acetylators and the glutathione S-transferase null genotype. Genetic polymorphisms can also explain differences in incidence of ATDH among different population. The incidence of ATDH is comparatively low in the North American population than the Asian and African population.

Malnutrition, advanced age, female sex, alcoholism and pre-existing liver disease can further accelerate the drug-induced hepatitis during TB treatment. Malnutrition results in slower drug metabolism and hence higher plasma level of the drug [31]. Older patients are more prone to liver damage, which may be due to decreased activity of metabolizing enzyme cytochrome P450, reduced level of liver blood flow or changes in drug binding and distribution. Females have a greater susceptibility to ATDH as there is higher CYP3A activity in females [32] that would allow them to form higher quantities of toxic metabolites than males. During treatment, intake of alcohol is strictly prohibited because alcohol can induce drug metabolizing enzymes, thereby triggering the toxicity. Patients with pre-existing liver disease or infection like hepatitis B or C are also more prone to develop ATDH.

Tuberculosis in HIV patients is the most fatal Tuberculosis is the most common opportunistic infection that affects HIV positive patients [33] and is the leading cause of death for HIV patients [34]. These patients have higher chance of developing ATDH, possibly due to altered activities of oxidative pathways [35]. As discussed earlier, various first line drugs, mainly rifampicin, cause severe drug-drug interaction that makes the treatment challenging in case of dual infection with TB and HIV.

Extensive research is being done to design an alternative treatment regimen that would effectively eradicate the tuberculosis infection, require less time for treatment and cause minimum or no side effects.

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