

# Antituberculous Chemotherapy-General and Hepatic Toxicity Revisited

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## ARTICLE INFO

### Article history:

Received on: 27/09/2013

Revised on: 23/11/2013

Accepted on: 14/12/2013

Available online: 30/01/2014

**Key words:** Antituberculous Chemotherapy, Hepatic Toxicity, isoniazid, rifampicin and pyrazinamide

## ABSTRACT

Severe or pertinent hepatic toxicity interferes with antituberculous chemotherapy resulting in dose reductions, treatment delays or cessation of therapy. Hepatic toxicity by antituberculous agents is due to anaphylactic reactions (acetylator phenotype polymorphism) and is relative to the cumulative dose intensity. Risk of hepatic toxicity is higher in the elderly and alcoholic patients. Patients with previous hepatic diseases such as hepatitis and comorbidities i.e. HIV infections, malnutrition and renal damages are prone to an added risk of hepatic toxicity. This review consolidates the pattern of hepatic adverse effects associated with each component of the antimycobacterial regimen e.g. isoniazid, rifampicin and pyrazinamide. Higher propensities of hepatic adverse effects are associated with the first line agents, intensified by the incorporation of second line antibiotics, primarily metabolized in the liver. In conclusion the hepatic biomarkers should be monitored in the patient under a tuberculosis treatment plan as well as purposefully assessed during follow-up visits of the patients.

## INTRODUCTION

Tuberculosis (TB) is a global health problem and considered as a second leading cause of death. It is estimated that 1.4 million (99,000 among HIV negative people and 430,000 HIV associated) deaths are due to tuberculosis worldwide (Mario *et al.*, 2012). TB is a contagious disease, caused by *Mycobacterium tuberculosis* (Flynn *et al.*, 1993), which invades the lungs and also infects organs like gastro intestinal tract (GIT), skin, genitourinary tract, and brain lymphatic system (Muñoz *et al.*, 2005). Clinical signs and symptoms of TB include; loss of body mass due to anorexia, fatigue, lethargy, and fever with chills. Patients may also develop purulent cough with chest pain and bloody sputum (hemoptysis) while coughing or breathing (Flynn *et al.*, 1993).

### Transmission and Pathogenesis

The disease is transmitted by sneezing, speaking, singing and pitting mucus discharge (Flynn *et al.*, 1993). The droplets containing tubercle bacilli transmit to other persons by nasal passage (Bavin, 1949). Via inhalation, tubercle bacilli make their passage to pulmonary alveoli and their replication within

macrophages is initiated (American Thoracic Society and CDC, 2000). These replicated mycobacterium are released on destruction of the macrophages (American Thoracic Society and CDC, 2000). In live macrophages, bacilli are transported through blood or lymph to tuberculosis susceptible sites (American Thoracic Society and CDC, 2000). Macrophages are then gathered around the infected cell, forming a structure called granuloma (or fatty metamorphosis) to prevent dissemination of infection (American Thoracic Society and CDC, 2000).

Granuloma consists of central area of serous necrosis with epithelioid macrophages and lymphocytes at the margin (Hunter, 2011). Centre of granuloma undergoes calcification and converting into Ghon's complex cavities are hence formed by softening and fragmentation of necrotic mass so as large clumps are coughed out damaging the lungs (Hunter, 2011).

### How Tuberculosis Influences the Quality of life (QOL)

Quality of life is a person's perception of his/her wellbeing. According to a study conducted in 2008, TB mainly affects physical and psychological health of individuals, creating socioeconomic burdens and stress. Women have better QOL in physical and environmental domain whereas men have better economic and social health as compared to women.

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Patient's sense of security; safety, domestic environment, transport and financial security are also adversely affected due to this disease (Dhuria *et al.*, 2008).

### First line Chemotherapy of Tuberculosis

The first line agents for active tuberculous infections are isoniazid (INH), rifampin (RMF), Ethambutol and pyrazinamide (PZA), with a broad spectrum of adverse effects (American thoracic society & CDC, 2003, Combs *et al.*, 1990, Long and Ellis, 2007). Isoniazid (INH) is the mainstay in TB treatment since 1952. The structure comprises of hydrazine group and a pyridine ring (Jindani *et al.*, 2004, Kass and Shandera, 2010). It is a pro-drug, activated by tuberculosis catalase-peroxidase enzyme (Kat G) and results in production of per oxy nitrate and hydrogen peroxide (both are oxygen free radical). These radicals inhibit the mycolic acid, responsible for DNA damage and finally the death of the bacillus (Kass and Shandera, 2010, Flynn *et al.*, 1993).

### Isoniazid

INH causes severe hepatic toxicity as it is metabolized in the liver by N-acetyl transfers by acetylation, produces isonicotinic acid and acetyl INH. It is mainly (70-90%) excreted by kidney mostly in feces (Singh *et al.*, 2012). In the first phase, it is metabolized by N – acetyl transferase to acetyl isoniazid which is then hydrolysed to acetylhydrazine (Niemi *et al.*, 2003). A small portion of drug is directly hydrolyzed into isonicotinic acid and hydrazine (Baghaei *et al.*, 2010). Drugs at a dose of 10-300 mg/kg/day are used for prophylaxis of TB, such doses could rarely cause adverse effects in individuals having regular kidney and liver functions. Few uncommon adverse effects include; nausea, vomiting, and epigastric pain (initiated at chemoprophylaxis). However, symptoms can be overcome by metoclopramide, ranitidine or omeprazole after the first meal (Tai *et al.*, 2008). High levels of hepatic enzymes are usually assessed, which may be transitory and asymptomatic. Alanine aminotransferase ALT (glutamic –pyruvic transaminase) increases three folds in comparison to normal serum level and it particularly caused liver damage (American thoracic society & CDC, 2003, Jindani *et al.*, 2004, Moulding *et al.*, 1989). Arthralgia behavioral changes like headache, euphoria, insomnia, agitation, and anxiety are the other symptoms, may overcome on discontinuation of therapy (Kass and Shandera, 2010, Baghaei *et al.*, 2010). Major side effects of Isoniazid are psychosis, seizures, convulsions, coma and mental disturbances which are not common and difficult to assess. Differential diagnosis of symptoms also indicates meningitis and hepatic encephalopathy. In addition, suicidal attempts also reported in patients using INH (Campos-Franco *et al.*, 2004). Peripheral neuropathy occurs in about 20% of patients treated at dose more than 30 mg/day. Risk of polyneuritis increases in individuals having diabetes mellitus, alcoholism, advanced age nutritional deficiency, kidney failure, pregnancy and breast feeding (Combs *et al.*, 1990, Kass and Shandera, 2010, Forget and Menzies, 2006). Development of hepatitis has been dependent on the age of patients, and it is considerably rare in patients that are

under 20 years but increases up to 2% in 50-64 years old patients (Campos-Franco *et al.*, 2004). Isoniazid has better absorption in acidic medium. Carbohydrates are responsible to decrease the absorption of drug up to 57% and 30% of plasma concentration. INH is a potent inhibitor of monoamine oxidase enzyme, should not be taken with glucose or lactose fluids and foods rich in histamine and tyramine like cheese, fish, alcohol and red wine. Otherwise, interaction may produce symptoms like flushing of face, erythema, headache, palpitation and pruritus. INH increases the plasma concentration of certain drug like phenytoin, carbamazepine (Zhang and Yew, 2009). Absorption also decreases by those drugs that increasing gastric pH. It is recommended that antacids containing ranitidine and aluminum hydroxide should be taken after one hour of INH administration.

### Rifampin

Rifampin is used for the treatment of tuberculosis since 1966. It possesses bactericidal action and kills metabolically active bacilli as well as stationary bacilli (having slow metabolism) (Singh *et al.*, 2012). It inhibits RNA synthesis of bacteria, by strong binding to  $\beta$  subunit of bacterial "DNA- dependent RNA polymerase". This  $\beta$  subunit of the polymerase enzyme is necessary for the initiation and growth of RNA chain (Kass and Shandera, 2010, Yew, 2002). It is well absorbed after oral administration. It is mainly excreted by liver (85%) into bile while, 6-15% is excreted unchanged and reabsorbed by intestine (Zhang, 2005). It has ability to cross blood brain barrier, and about 10-20% of serum concentration reaches to CNS. However, concentrations may increase during meningitis (Combs *et al.*, 1990). Minor adverse reactions include; nausea, anorexia, fatigue, dyspnea, dizziness, ataxia, abdominal pain, and change of urine's color from yellow to orange. The risk of hepatitis is augmented in patients, with compromised hepatic status, treated with INH. It is a potent inducer of CYP450 system, results in increased metabolism of all those drugs metabolized by the same enzyme system (Kalars *et al.*, 1992, Combalbert *et al.*, 1989). Increased production of bilirubin (5% of patients), and development of cholestatic hepatitis (2.7% of patients) have been reported (Baciewicz *et al.*, 2008, Zhang and Yew, 2009). Immunological reactions are rare but severe in less than 0.1% of patient. Other reactions include; thrombocytopenia, leukopenia, eosinophilia, agranulocytosis, vasculitis, hemolytic anemia, acute interstitial nephritis and septic shock (Combs *et al.*, 1990, Kass and Shandera, 2010). In presence of food plasma concentrations are reduced up to 26% as well as delaying of the time (15-36%) to reach the maximum concentration (World Health Organization, 2010). It is a potent inducer of the cyp450 system and its sub families like cyp3A and cyp2C, resulting in increased the metabolism of many drugs (Slayden and Barry, 2000, Handbook of antituberculosis agents, 2008).

### Pyrazinamide (PZA)

PZA (pyrozoic acid amide) is a nicotinic acid derivative and structurally similar to INH. It has been used for the treatment of tuberculosis since 1936. It possesses potent bactericidal and

sterilizing effect and shortens the duration of treatment (Combs *et al.*, 1990, Rakotoson *et al.*, 2009). It accumulates to decrease intracellular pH, resulting in deactivation of an enzyme fatty acid synthetase 1. This enzyme is involved in fatty acid synthesis, leading to impaired biosynthesis of mycolic acid (Handbook of antituberculosis agents, 2008).

It is mainly metabolized by the liver and 70% drug is excreted in urine through glomerular filtration. The half-life is 9-10 hours, but dose adjustment is required in renal compromised patients, otherwise the half-life may be raised up to 26 hours (Combs *et al.*, 1990, Kass and Shandera, 2010). Minor side effects include vomiting, nausea and anorexia (American Thoracic Society & CDC, 2003, Kass and Shandera, 2010). If patients are non-gouty then hyper-uricemia leads towards more arthralgia. Dermatitis, exanthema subitum and pruritus are also commonly seen effects of drugs (American Thoracic Society & CDC, 2003, Tai *et al.*, 2008). Therapy should be discontinued if severe pruritus and severe exanthema occur (Combs *et al.*, 1990). It possesses a prominent hepatotoxic effect so dose should be adjusted according to the weight of the patient. The risk of liver damage decreases, if administered in a dose of 35mg/kg/day. According to new guidelines (American Thoracic Society & CDC, 2003, Long and Ellis, 2007) the recommended dose for a patient having more than 50 kg weight is 1600mg, such dose is associated with reduced hepatic adverse effects. According to WHO PZA is safe in pregnancy, breast feeding (American Thoracic Society & CDC, 2003, Brunton *et al.*, 2006) and considered as category C drug (Kass and Shandera, 2010, Yew, 2002). Hepatotoxic effect is more evident in those individuals having liver diseases (Combs *et al.*, 1990, Tai *et al.*, 2008). Metabolites of drug are eliminated by kidney, dose adjustment is critical in renal compromised patients. It is recommended that if creatinine clearance is lower than 10ml/min then dose should not be reduced to half. Food has no impact on absorption (World Health Organization, 2010). Some drugs potentiate the toxic effect of pyrazinamide-like ethionamide, rifampin, isoniazid and propencid (Combs *et al.*, 1990, Yew, 2002, American Academy of Pediatrics Committee on Drugs, 2001).

### Ethambutol

Ethambutol has been in therapeutic use against TB since 1966. The mechanism of action for bacteriostatic effect is still not fully defined. Arabinogalactan is the main component of mycobacterial cell wall and Ethambutol interferes with the biosynthesis of arabinogalactan. It prevents arabinoglycans polymerization by inhibition of the enzyme arabinosyltransferase that encodes the EmbB gene. If mutation occurs in the EmbB gene then resistance would develop against ethambutol (Combs *et al.*, 1990, Rakotoson *et al.*, 2009). It is absorbed up to 75-80% after oral administration and serum peak plasma concentration is achieved within 2-4 hours. The half-life of drug is 3-4 hours, extended in renal compromised patients (up to 10 hours). It is metabolized by liver and 50-80% drug is excreted in urine and 20% in feces (American Thoracic Society & CDC, 2003, Brunton

*et al.*, 2006, Yew, 2002). It does not cross the meninges but in meningitis the cerebral spinal fluid (CSF) level of drug reaches up to 10-50% of the drug plasma level (American Thoracic Society & CDC, 2003, Brunton *et al.*, 2006, World Health Organization, 2010). Generally drug is well tolerated and adverse effects are dose related and more common at doses of 15mg/kg. Retrobulbar neuritis usually occurs, but it is reversible, dose and time dependent. If patients received 35mg/kg/day, for more than two months, it results in development of retrobulbar neuritis (15-18% of patients). In young children ethambutol should be avoided because of red and green color blindness (Combs *et al.*, 1990, Brunton *et al.*, 2006, Yew, 2002). Peripheral neuritis occurs rarely and symptoms can be improved by administration of pyridoxine (American Thoracic Society & CDC, 2003, Brunton *et al.*, 2006, Yew, 2002). Additional effects are abdominal pain, nausea, vomiting and hepatotoxicity. Hematological symptoms include; thrombocytopenia, eosinophilia and neutropenia while neurological symptoms like headache, mental confusion and dizziness are also found. Hypersensitivity like fever, arthralgia and skin rash may also develop. It may decrease excretion of uric acid from kidney which leads toward hyperuricemic gouty arthritis (American Thoracic Society & CDC, 2003, Brunton *et al.*, 2006, Yew, 2002). According to WHO recommendations, it is safe in pregnancy, infant lactation, and considered as category B drug (World Health Organization, 2010). It does not produce any toxicity in liver failure patient and so no need to adjust the dose of drug (American Thoracic Society & CDC, 2003, Combs *et al.*, 1990). However, dose should be adjusted in patients of kidney impairment. Dose should be reduced to 15-20mg/kg thrice a week if creatinine clearance is lower than 30ml/min and if creatinine clearance is measured within 30-50 ml/min, dosing interval should be extended up to 36 hours (Combs *et al.*, 1990, Jindani *et al.*, 2004, Kass and Shandera, 2010, Tai *et al.*, 2008).

### Second & Third Line Drugs

These are used in case of XDR-TUBERCULOSIS or MDR-TUBERCULOSIS.

Six classes are included.

1. Aminoglycosides (streptomycin, amikacin, kanamycin)
2. Polypeptides (capreomycin, viomycin, enviomycin)
3. Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin)
4. Thioamides (ethionamide, prothionamide, Cycloserine)
5. Terizidone
6. Para-aminosalicylic acid
7. Oxazolidinones and its analogues (Linzolid, eprezolid) (Pandit *et al.*, 2012)

### Ethionamide (EthA)

Ethionamide is always used with other anti-tuberculosis drugs for MDR-TUBERCULOSIS when first line drugs are contraindicated. It is also effective in lepromatous leprosy. It can cause temporary asymptomatic increase in ALT, AST and acute

liver injury in 5% of patients is also reported (Tarantino *et al.*, 2009). It is a pro-drug, similar to INH, metabolized by mycobacterial enzyme EthA for activation. Upon activation, it inhibits the formation of mycobacterial cell wall by inhibiting mycobacterial fatty acid synthesis, mediated by enoyl ACP reductase (Tarantino *et al.*, 2009). It inhibits the growth of both extracellular and intracellular bacilli (Arbex *et al.*, 2010). Dose of ethionamide is 250mg twice daily, could be enhanced to 15-20 mg/kg/day, with the maximum dose up to 1g/day (Arbex *et al.*, 2010). Adverse effects are gastrointestinal (anorexia, nausea, stomatitis, diarrhea), CNS (depression, drowsiness, fatigue, hallucinations, confusion), endocrinological disturbances (gynecomastia, hypothyroidism), cardiovascular and skin conditions (decrease platelets count, pupura), swelling in feet and weight gain (Arbex *et al.*, 2010). Ethionamide can cause self-limited and asymptomatic increase in serum transaminases. It also causes fatal acute liver injury. It possess similar onset of action and clinical manifestations as that of INH. Hypersensitivity reactions are rare (Tarantino *et al.*, 2009). Metabolism takes place in liver for activation of drug and result in toxic and immunologically active intermediate and hepatitis. Transaminase elevation is observed in treatment induced hepatitis 5 times higher than normal (Tarantino *et al.*, 2009). Strict monitoring is advised in patients underlying liver diseases (Arbex *et al.*, 2010).

#### **Paraamino Salicylic Acid (PAS)/D5 Amino Salicylic Acid**

For more than a decade, PAS was thought to be first line drug, used in combination with INH and streptomycin. PAS inhibits the growth of extracellular bacilli. Liver and kidney damaged are associated with oral or parenteral administration of drug for prolonged period of time (Bavin, 1949). The proposed mechanism of drug is interruption of bacterial tetrahydrofolate formation and inhibition of iron uptake, folate and iron are essential components for bacterial growth and life (Arbex *et al.*, 2010). It causes immune induced hepatitis which generally initiated in first 3 weeks of therapy. Clinical symptoms include rashes, fever, conjunctivitis; hepatomegaly, leukocytosis, lymphadenopathy and eosinophilia. 5 to 10 % of patients come across hypersensitivity reactions which usually occurred in first 5 weeks of the therapy. PAS causes cholestatic hepatitis, elevation in transaminases, cirrhosis, liver necrosis and liver failure.

#### **Aminoglycoside**

Streptomycin is a natural derivative; kanamycin is synthetic while amikacin is semi-synthetic aminoglycosides (Arbex *et al.*, 2010). These agents are protein synthesis inhibitors, acting through binding to 30s subunit of mycobacterial ribosome in irreversible fashion (Arbex *et al.*, 2010). Resistance develops as a result of mutation in "rrs", "nad" and "rpsL" genes, encoded for S12 ribosomal RNA and S16 ribosomal protein (Arbex *et al.*, 2010). Oral absorption of aminoglycosides is poor so generally administered by intramuscular injection, and plasma peak concentrations are achieved within 30 to 90 minutes. These drugs possess low plasma protein binding and are almost excreted by

kidney through glomerular filtration (Arbex *et al.*, 2010). Ototoxicity is reported due to vestibular and cochlear damage. Vestibular damage associated with streptomycin is more common than amikacin. Nephrotoxicity (reduced urination, proteins in urine, and reduced creatinin clearance) is highly reported with amikacin as compared to streptomycin (Arbex *et al.*, 2010). Aminoglycosides are contraindicated in pregnancy and breast feeding mothers since it disturbs the intestinal flora of neonates. Amphotericin B, vancomycin, loop diuretics (furosemide and ethacrinic acid) potentiate the nephrotoxicity of aminoglycosides (Arbex *et al.*, 2010).

#### **Fluoroquinolones**

These include ofloxacin, levofloxacin, ciprofloxacin and others. These agents have been used as second line drugs for the treatment of multi drug resistance tuberculosis while moxifloxacin for extensive drug resistant tuberculosis (Yew and Leung, 2006). These agents penetrate inside intracellular mycobacteria and macrophages. DNA gyrase or topoisomerase II of *Mycobacterium tuberculosis* maintains DNA topology and essential for its life. These drugs inhibit such enzymes leading to cell death due to uncontrolled mRNA synthesis and chromosomal degradation (Arbex *et al.*, 2010).

Fluoroquinolones are actively absorbed after oral administration. Peak serum concentration is achieved within 3 hours. Levofloxacin is converted to d-ofloxacin in liver. Fluoroquinolones are excreted mainly by kidney through tubular secretion or glomerular filtration (Arbex *et al.*, 2010). Adverse effects include gastrointestinal complaints, neuro-toxicities, cardiovascular problems, musculo-skeletal disorders, and endocrinological irregularities (Arbex *et al.*, 2010).

#### **CONCLUSIONS**

Substantial risk of hepatic toxicity is associated with the first line agents employed for the treatment plan of patients with active disease. Hepatic toxicity is correlated with the elevation of serum transaminases, which should be objectively assessed during the course of treatment. The abnormal rise in enzyme levels (3-5 × of normal values) may require cessation of therapy even in the absence of symptoms. The hepatic status should also be assessed in the patients during follow-ups.

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#### How to cite this article:

Ali Akbar Sial, Aisha Jabeen, Talha bin Fayyaz, Maria Muneer, Rabia Bushra, Nusrat Bano, Mirza Tasawer Baig. Antituberculous Chemotherapy-General and Hepatic Toxicity Revisited. *J App Pharm Sci*, 2014; 4 (01): 148-152.