Antituberculotic Chemotherapy-General and Hepatic Toxicity Revisited

Ali Akbar Sial, Aisha Jabeen, Talha bin Fayyaz, Maria Muneer, Rabia Bushra*, Nusrat Bano, Mirza Tasawer Baig
Faculty of pharmacy, Ziauddin University, Karachi, Pakistan.

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ABSTRACT
Severe or pertinent hepatic toxicity interferes with antituberculotic chemotherapy resulting in dose reductions, treatment delays or cessation of therapy. Hepatic toxicity by antituberculotic agents is due to anaphylactic reactions (acetylaor 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 antimyobacterial regimen e.g. isoniazid, rifampicin and pyrazinamaide. 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 (hemoptyisis) 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 epitheloid macrophages and lymphocytes at the margin (Hunter, 2011). Centre of granuloma undergoes calcification and converting into Ghon’s complex cavities are hence form 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.
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 polynuereitis 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.

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) and structurally similar to INH. It has been used for the treatment of tuberculosis since 1936. It possesses potent bactericidal and 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.

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 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.

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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 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 pruritis are also common effects of drugs (American Thoracic Society & CDC, 2003, Tai et al., 2008). Therapy should be discontinued if severe pruritis and severe exanthema occur (Combs et al., 1990). It possesses 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 guideline (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 individual 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 main component of mycobacterial cell wall and Ethambutol interferes with the biosynthesis of arabinogalactan. It prevents arabinylglycos polymerization by inhibition of enzyme arabinosyltranferase that encoded EmbB gene. If mutation occur in EmbB gene then resistance would developed 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 decreases 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, enviomyacin)
3. Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin,)
4. Thioamides (ethionamide, prothionamide, Cycloserine)
5. Terizidone
6. Para aminosalicylic acid
7. Oxazolidiones and its analogues (Linzolide, eprazole)
(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 damage 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 oflaxacin, levofloxacin, ciprofloxacan 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-oflaxacin 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, cardio vascular 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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