Evaluation of Liver Function in

Patients on Anti-Tuberculous Therapy

M.D. DEGREE EXAMINATION
BRANCH I - GENERAL MEDICINE

COIMBATORE MEDICAL COLLEGE
COIMBATORE

DISSERTATION SUBMITTED TO
THE TAMIL NADU DR. M.G.R
MEDICAL UNIVERSITY

SEPTEMBER 2006

CERTIFICATE

This is to certify that the dissertation titled Evaluation of liver function in patients on Anti-Tuberculous Therapy, is a bonifide work done by Dr.K.Chinnasamy. It is a regular, systematic study done under my guidance and supervision during the period of January-2005-December-2005, and submitted for the ensuing M.D Branch 1 General Medicine examination, September 2006 of the Tamil Nadu Dr. M.G.R Medical university Chennai.

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DECLARATION

I solemnly declare that the dissertation titled, Evaluation of liver function in patients on Anti-Tuberculous Therapy was done by me at Coimbatore medical college hospital Coimbatore during January 2005-December-2005 under the guidance and supervision of professor Dr. K.Umakanthan MD. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any university, board either in India or abroad.

The dissertation is submitted to the Tamilnadu DR. M.G.R Medical University towards the partial fulfillment of the requirement for the award of MD Degree (Branch1) in General Medicine.

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Acknowledgements

I thank Dr. T.P. Kalaniti M.D., Dean, Coimbatore Medical College and Hospital, Coimbatore, for permitting me to conduct this study in Coimbatore Medical college hospital.

I wish to express my deep sense of gratitude to the Professor Dr. K.Umakanthan., M.D., M II Unit chief and Professor o therapeutics Coimbatore Medical College and Hospital, Coimbatore for isinvaluable guidance and timely suggestions in doing this study.

I am grateful to Professor Dr.G. Yashodhara M.D., Head of the department, Department of Medicine, Coimbatore Medical College and Hospital, Coimbatore for her valuable help rendered during the course of the study.

I take this opportunity to thank all those who have helped me in the study especially Dr. S. Chandrasekar, Dr. Isaac Christian Moses, Dr.M.Raveendran Asst Professors of Medicine, M II Unit and Dr.Ramkumar, Asst Professor, Department of Tuberculosis and Chest Medicine, Coimbatore Medical College and Hospital, Coimbatore.

I will be failing in my duty if I don't thank all the patients who co-operated well in this study.

CONTENTS

INTRODUCTION

Tuberculosis remains a world-wide public health problem despite the fact that the causative organism was discovered more than 100 years ago and highly effective drugs and vaccine are available making tuberculosis a preventable and curable disease.[1]

India accounts for nearly one-third of the global burden of tuberculosis. Every year approximately 18 lakh persons develop tuberculosis of which about 8 lakh are new smear positive highly infectious cases and about 4.17 lakh people die of tuberculosis every year, 1 person dies every minute and about 1000 people die every day.[2]

The obstacles to success include poor patient compliance, high cost of medicines, drug resistance, insufficient duration, irregular therapy and last but not the least Drug-Induced Hepatitis(DIH).

DIH is the most unwanted adverse effect of Anti Tuberculous Treatment (ATT). Unfortunately almost all the chemotherapeutic agents used in tuberculosis cause hepatotoxicity by single or multiple mechanisms.

The absence of overt jaundice, the degree of subclinical hepatotoxicity has to be determined by monitoring the biochemical changes using the Liver Function Tests(LFT).

Reports available from studies conducted to assess the hepatotoxicity of Short Course Chemotherapy(SCC) regimens from western as well as many of the Indian studies suggests a low incidence of hepatitis. But a few of the Indian studies have shown a high incidence of hepatitis due to short course chemotherapeutic regimens.

In view of these variable reports on incidence of drug induced hepatotoxicity during SCC, a prospective study was undertaken on 108 patients with pulmonary tuberculosis receiving short course chemotherapy. In these patients LFT was monitored for a period of 6 months.

AIMS OF THE STUDY

1. To evaluate the incidence of drug induced hepatotoxicity in proved cases of pulmonary tuberculosis in patients on short term regimen of anti-tuberculous therapy in coimbatore locality.

2. To study about the predisposing factors for drug induced hepatotoxicity.

3. To study and evaluate the clinical and histopathological features of drug induced hepatotoxicity.

REVIEW OF LITERATURE

DEFINITION:

Tuberculosis is a bacterial infection caused by the acid-fast bacilli Mycobacterium tuberculosis. The principle lesions are usually in the lungs. Other organs like lymph nodes, intestines, kidney, bone, meninges are also involved through dissemination. The portal of entry of this organism is almost exclusively through the lungs (droplet infection from infected person) except in bovine tuberculosis in which the portal of entry is oral.

TB affects human beings in two forms;

1.Primary infection- in which tubercle bacilli invade the host that has no specific immunity

2. Secondary form[Re-infection or Adult tuberculosis]

- in which the bacilli produce the disease in the phase of specific immunity.

IMMUNITY :

Tuberculosis has both natural & acquired immunity.

NATURAL IMMUNITY :

Members of Caucasian and Mongolian races appear to have distinct natural resistance to tuberculosis and it is this ability to develop an immune response to infection that enables the host to survive and to recover from the primary infection.

ACQUIRED IMMUNITY :

Tuberculosis sensitive individuals are quite regularly resistant to re-infection and are able to localize the disease readily. Reactivation of infection even years after an episode of tuberculosis infection which has been successfully handled by the body is a very puzzling aspect.

Tuberculous hyper-sensitivity :

Hypersensitivity is to the protein derivative of the bacilli. Tuberculin hypersensitivity probably indicates the presence of living bacilli within the subject whether the lesion in which they lie is active or not is sometimes difficult to determine with certainity.

PATHOGENESIS

This is determined by distinctive features of the bacilli and host factors. Tubercle bacillus has three important features which distinguish it from most other pathogens and also determines the course of the disease. These are

1. Slow generation time

2. High lipid content of the bacillus

3. Lack of either exotoxin or endotoxin.

The hallmark of TB lesion is caseating necrosis with varying degrees of exudation, Langerhan giant cells, tubercle formation and fibrosis. [3]

History of tuberculosis

The contagious nature of this infectious disease was recognized by Aristotle. Hippocrates conferred the name phthysis.

Koch(1882)identified the organism and elaborated the criteria by which

one could decide upon the connection between a micro organism and the disease process (Koch's postulates)

Pharmacotherapy of tuberculosis

For a longtime, the standard duration of tuberculosis chemotherapy was 18 months. In 1972, Wallacefox and his colleagues from British medical council showed that the addition of rifampicin , pyrazinamide to regimens containing isoniazid made it possible to reduce the duration of treatment.

Advantages of short course chemotherapy are rapid bacteriological conversion ,lower failure rates, better patient compliance and reduction in the frequency of emergence of drug resistant bacilli. The only disadvantage is high cost of short term chemotherapy.

There are now a number of short course regimens of six months duration that are highly effective, of low toxicity and well tolerated. The regimens used in Directly Observed Therapy-Short course [DOTS] in Revised National Tuberculosis Control Program [RNTCP] in India are given below.(4)

TREATMENT REGIMENS

Table 1.Catagories of patients in RNTCP

Category of Treatment	Type of Patient	Regimen*
Category I	1. New Sputum Positive 2. Seriously ill – Sputum smear Negative 3. Seriously ill – Extra pulmonary**	$2(HRZE)_3+4(HR)_3$
Category II	1. Sputum smear positive Relapse*** 2. Sputum smear positive Failure.***,# 3. Sputum smear positive treatment after default	$2(HRZES)_3+1(HRZE)_3+5(HRE)_3$
Category III	1. Sputum smear negative not seriously ill 2. Extra pulmonary not seriously ill.	$2(HRZ)_3+4(HR)_3$

* -The numbers before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week. H: Isoniazid (600mg), R: Rifampicin (450mg), Z :pyrazinamide

(1500mg),E :Ethambutol(1200mg),S :Streptomycin(750mg).patients who weigh more than 60 Kg receive additional rifampicin 150mg.patients more than 50 years old receive streptomycin (500mg). Patients in categories I^{st} and II^{nd}, who have a positive sputum smear at the end of the initial intensive phase, receive an additional month of intensive phase treatment.

** -Examples of seriously ill extra pulmonary TB cases are meningitis, disseminated TB, tuberculous pericarditis, peritonitis, bilateral or extensive pleurisy, spinal TB with neurological complications and intestinal and genito urinary –TB.

*** In rare and exceptional cases, patients who are sputum smear negative or who have extra pulmonary disease can have relapse or Failure. This diagnosis should be supported by culture or histological evidence of current, active tuberculosis. In these cases, the patient should be categorized as other and given category II Treatment.

- Any patient treated with category I and category III who has a positive smear at 5, 6 or 7months of treatment should be considered as failure and started on category II treatment afresh.

CLASSIFICATION

Drugs used to treat tuberculosis have been classified into first line and second line agents [4].First line essential anti tuberculosis agents are the most effective and are a necessary component of any short-course therapeutic regimens. The three drugs in this category are rifampicin,

isoniazid and pyrazinamide. The first line supplemental agents, which are highly effective and infrequently toxic include ethambutol and streptomycin .Favorable experience in patients with tuberculosis resistant to first line essential drugs suggests that rifabutin and the fluroquinolones ciprofloxacin and levofloxacin are important additions to multidrug anti- tuberculosis regimens as first line supplemental drugs.

Second line anti tuberculous agents are clinically much less effective than first line agents and elicit severe reactions much more frequently. These drugs are rarely used in therapy. The older agents include para-aminosalicilic acid (PAS)
thiozinamide,cycloserine,amikacin

and capromycin. Newer anti-tuberculous drugs, which have not yet been placed in the above categories, include rifapentine, 8 - methoxyfluroquinolones gatifloxation and moxifloxacin.

The properties of commonly used anti-tuberculous drugs are given below [5]

SIDE EFFECTS OF COMMONLY USED ANTI TUBERCULOUS AGENTS

Table 2. SIDE EFFECTS OF COMMONLY USED ANTI TUBERCULOUS AGENTS [5,6,7]

1. Isoniazid	Common Rare-	Anorexia, nausea, vomiting, fever, skin rashes, peripheral neuropathy. Hepatitis, Vertigo, convulsions, optic neuritis and atrophy, psychiatric disturbance, haemolytic anemia, aplastic anemia, dermal reactions including pellagra, purpura and lupoid syndrome, gynaecomastia, hyperglycemia arthralgia
2.Rifampicin	Common Rare	Orange red discoloration of urine, anorexia nausea, vomiting, diarrhea, skin rashes. Flu like syndromes, Hepatitis Dyspnea, hypotension, Addisonian crisis, menstrual disturbances, muscular weakness, pseudomembranous colitis.
3. Pyrazinamide	Common Uncommon Rare	Anorexia, nausea, vomiting, fever. Hepatitis, urticaria, Skin rash, arthralgia. Sideroblastic anaemia, photosensiti zation, gout, dysuria, aggravation of peptic ulcer.
4. Ethambutol	Uncommon Rare	Optic neuritis, arthralgia Hepatitis, interstitial nephritis. Cutaneous hypersensitivity paraesthesia of extremities.
5. Streptomycin	Uncommon Rare	Vertigo, tinnitus, deafness, Cutaneous hypersensitivity Renal damage, aplasic anemia, agranulocytopenia, neuromuscular blockade in patients receiving muscle relaxants or with myasthenia gravis.

ISONIAZID

Isoniazid is still considered to be the primary drug for the chemotherapy of tuberculosis and all patients with disease caused by isoniazid sensitive strains of the tubercle bacillus should receive the drug if they can tolerate it.

Primary mechanism of action of isoniazid is to inhibit the biosynthesis of mycolic acids, important constituents of the mycobacterial wall. From 75% to 90% of dose of isoniazid is excreted in the urine within 24 hours, mosyly as metabolites. The main excretory products in human beings are the result of enzymatic acetylation(Acetyl isoniazid)and enzymatic hydrolysis(Isonicotinic acid).The rate of acetylation significantly alters the concentrations of the drug that are achieved in plasma and its half life in the circulation. Acetylator status is estimated by measuring free and total sulpha dimidine in blood and urine.

Risk factors for isoniazid hepatotoxicity include acetylator status,older age and history of severe alcohol intake.

While the Drug induced hepatotoxicity in initial studies ranged from 1 percent to 10 percent recent observations where clinically relevant hepatotoxicity was evaluated suggsted that less than 1 percent subjects receiving isoniazid for treatment of latent tuberculosis infection developed hepatotoxicity.

Jaundice occurs in 0.6% [5,8,9,10] to 1% [11,12].Increased serum enzyme levels were noted in 10 -20% of patients [5,13]. Byrd et al recommended that an elevation of s.enzymes greater than 5 times normal should be considered for discontinuation of the drug. Most hepatitis occurs within 4 to 8 weeks of therapy. Liver biopsy may show bridging necrosis and features of acute hepatitis [14].

RIFAMPICIN

Rifampicin inhibits DNA dependent RNA polymerase of mycobacteria and other micro-organisms. Rifampicin is bactericidal for both intracellular and extracellular micro-organisms. Following absorption from the gastrointestinal tract, rifampicin is eliminated rapidly in the bile; and an enterohepatic circulation ensures. Rifampicin
is distributed throughout the body and is present in effective concentrations in many organs and body fluids including the CSF.

Hepatitis from rifampicin rarely occurs in patients with normal hepatic function. Elevation of s.bilirubin and alkaline phosphatase levels are characteristic of rifampicin toxicity. Chronic liver disease, alcoholism and old age appears to increase the incidence of hepatotoxicity when rifampicin is given alone or concurrently with isoniazid.

An elevation in serum hepatic enzyme levels occurs in 5-10% of patients.[15] Clinical hepatitis occurs in 0.6 -2% of patients [8,16] though one Indian study shows 7-8% [17]Several studies have shown that the incidence Of hepatitis in regimens containing both isoniazid and rifampicin is approximately 2-4 times that of isoniazid alone [18]. Liver biopsy shows patchy cellular abnormality with marked periportal inflammation.[19]

PYRAZINAMIDE

Pyrazinamide is the synthetic pyrazine analog of nicotinamide. It exhibits bactericidal activity only at a slightly acidic PH. The target of pyrazinamide appears to be the mycobacterial fatty acid synthase I gene involved in mycolic acid biosynthesis. Pyrazinamide is well absorbed orally and is widely distributed. The drug is excreted primarily by renal glomerular filtration.

When a dose of 40 – 50mg/kg is administered orally, signs and symptoms of hepatic disease appear in about 15% of patients, with jaundice in 2% to 3% and death due to hepatic necrosis in rare instances. Regimens employed currently (15 to 30 mg/kg/day) are much safer [20,21]. In a large Indian study on hepatic toxicity with short course regimens containing rifampicin, isoniazid and pyrazinamide there was no indication that pyrazinamide contributed to the development of hepatotoxicity.[22] However, in some studies pyrazinamide was found to be significantly contributed to the development of hepatotoxicity when given along with isoniazid and rifampicin.[23,24]

ETHAMBUTOL

About 75 to 80% of an orally administered drug is absorbed within in 24 hours. Three fourths of an ingested dose of ethambutol is excreted unchanged in the urine. The drug is excreted by tubular secretion in addition to glomerular filteration . It does not produce hepatotoxicity.

BACTERIAL POPULATIONS AND ACTION OF DRUGS

Special population model, suggested by Mitchison et al [25] for explaining the early bactericidal and sterilizing properties of drugs includes :

Population A: Activity growing organisms killed mainly by INH; Other contribute to this action.

Population B : Semi-dormant organisms inhibited by a acid environment, killed mainly by pyrazinamide because it is active only at ph 5.5 or less.

Population C : Semi-dormant organisms with spurts of activity, lasting perhaps a few hours. Killed preferentially by rifampicin because its bactericidal action starts quickly. Organisms may be in neutral or acid environment.

Population D : Completely dormant bacilli, unaffected by any drug.

DRUG INDUCED HEPATOTOXICITY-MECHANISMS

Hepatic biotransformation mechanisms involving oxidative pathways, primarily by way of the cytochrome P-450 enzyme system are vital for rendering the drugs more hydrophilic. Further metabolic steps such as conjugation to a glucuronide, sulphate or glutathione result in the formation of hydrophilic metabolites that are exported into the plasma or bile and are excreted by the kidney or the gastrointestinal tract.[26,27] Drug induced liver injury is a common but often unrecognized cause of liver damage that continues to fascinate and challenge clinicians.

Several types of drug induced liver damage have been described. These include 1. Idiosyncratic damage, 2. Dose – dependent toxicity; 3. Induction of hepatic enzymes 4. Drug induced acute hepatitis and 4. Allergic reactions, among others.[28]

Idiosycratic reactions are the result of a 'multihit` process due to the succession of unlikely events and are characterized by a variable latency period from the initial time of ingestion of the drug. In the case of some drugs such as acetaminophen, hepatic damage occurs in a dose dependent fashion. Induction of hepatic enzymes by drugs enhances

hepatotoxicity. Allergic reactions

manifest with fever, lymphadenopathy, rash and severe hepatocyte injury.

CLINICAL SYNDROMES WITH DRUG HEPATOTOXICITY：

The following are the clinical syndromes observed in patients with drug induced hepatotoxicity [29]:

Abnormal liver function tests in asymptomatic patients

Acute viral hepatitis – like presentation

Acute (fulminant) hepatic failure

Subacute hepatic failure

Acute venous outflow obstruction

Cholestatic hepatitis, obstructive jaundice, chronic cholestasis

Liver disease with signs of hypersensitivity and / or disease in other organs. Auto-immune hepatitis – like injury.

Cirrhosis

Primay hepatic neoplasms.

ANTITUBERCULOUS DRUGS AND HEPATOTOXICITY：

The pathogenesis of hepatotoxicity caused by isoniazid is not well understood. Histopathological evidence resembling that of viral hepatitis showing hepatocyte necrosis, ballooning degeneration and inflammatory infiltrates suggests dose related toxicity.[30] However lack of direct correlation between serum drug levels and hepatotoxicity argues against a direct toxic effect [31].Given the delayed onset of hepatotoxicity, absence of symptoms usually associated with hypersensitivity and no hepototoxicity on re-challenge in most cases, hypersensitivity is considered unlikely.[32,33] But presence of eosinophilic infiltrates on liver biopsy and recurrence of hepatotoxicity on re-challenge with the drug suggest hypersensitivity as a possible mechanism.[33]

Altered profile of antioxident enzymes with increased lipid peroxidation indicated that isoniazid and rifampicin induced hepatotoxicity appeared to be mediated through oxidative stress.[34] Compared with isoniazid, rifampicin hepatotoxicity occurs earlier and produces a patchy cellular abnormality with marked periportal inflammation.[35] Rifampicin induced hepatitis has been postulated to

occur as a part of systemic allergic reaction and due to unconjugated hyperbilirubinemia as a result of competition with bilirubin for uptake at hepatocyte plasma membrane.[35]

The increased risk of hepatotoxicity with isoniazid and rifampicin combination has been attributed to the interaction between the metabolism of isoniazid and rifampicin. Acetyl isoniazid, the principal metabolite of isoniazid is converted to mono acetyl hydrazine. The microsomal P450 enzymes convert mono acetyl hydrazine to other compounds resulting in hepatotoxicity.[36] Rifampicin is thought to enhance this effect by enzyme induction.

The first human case of a proven hepatotoxic interaction between isoniazid and rifampicin has recently been reported by Askgaard et al.[37] A 35 year old black Somalian patient with miliary tuberculosis developed hepatotoxicity after a few days of treatment with isoniazid, rifampicin, pyrazinamide and ethambutol. On withdrawing all the drugs, the liver profile normalized and remained so after isoniazid challenge. Hepatotoxicity recurred when rifampicin was added but it was well tolerated when rifampicin was reintroduced without isoniazid.

In patients receiving a combination of isoniazid, rifampicin and pyrazinamide, two patterns of fulminant liver injury have been observed. Increased in serum transaminase activity which occurs late (usually after one month) has been attributed to pyrazinamide induced hepatotoxicity while the early increase in transaminases (usually within first 15 days) has been attributed to rifampicin and isoniazid induced hepatotoxicity.

Asymptomatic increase in AST has been observed in about 20% of patients receiving the standard four drug regimen.[38] Singh et al reported that overall mortality in patients with drug induced hepatotoxicity caused by anti tuberculous therapy was 12% while it was 75% in patients who developed acute and sub acute liver failure.[39]

DIAGNOSIS OF HEPATOTOXICITY DUE TO ATT

In a case control study from the AIIMS, New Delhi, Pande et al assessed the role of several risk factors in the development of anti-tuberculous treatment induced hepatotoxicity in patients with pulmonary tuberculosis.[40] The diagnostic criteria for anti-tuberculous treatment induced hepatotoxicity were as follows.

One more study by Sharma et al suggests almost the same.

1. Clinical features of icteric hepatitis (anorexia, nausea and jaundice)
2. Serum aspartate and alanine transaminase levels greater than 150 U/L on more than 3 occasions or greater than 250 U/L on one occasion.
3. Serum total bilirubin greater than 1.5 mg/dl and
4. Absence of serological evidence of viral hepatitis.

The authors reported that the latency period between start of anti-tuberculous treatment and development of hepatotoxicity in the cases was 4-9 days and in most cases hepatotoxicity was evident within 3 months of start of treatment

In a retrospective study of 519 patients receiving isoniazid, rifampicin and pyrazinamide from Germany hepatotoxicity was observed in 11% of patients. [41]

In another retrospective study of 456 patients receiving isoniazid, rifampicin, pyrazinamide, streptomycin or ethambutol from Argentina, signs of liver injury were found in 9.9% of patients.[42]

MANAGEMENT

Idealy treatment should be individualized according to the body weight and co-morbid illness present in the patient. Whenever feasible, baseline liver function testing must be done. When drug-induced hepatotoxicity is suspected, the patient receiving anti-tuberculosis-treatment should be systematically investigated for other causes such as viral hepatitis. Consensus guidelines for the management of patients with anti-tuberculosis treatment-induced hepatotoxicity are yet to be evolved. The Joint Tuberculosis committee of The British Thoracic Society recommendations[43] and the recent guidelines published by the American Thoracic society, Centers for Disease Control and Prevention and the Infectious Diseases Society [38] form the basis for the diagnosis and management principles listed below.

Once the diagnosis of drug induced hepatotoxicity is established, it is essential to first stop all potentially hepatotoxic drugs till complete clinical and biochemical resolution of hepatotoxicity occurs. In the interim period, at least three non-hepatotoxic drugs such as ethambutol, streptomycin and quinolones such as levofloxacin or ofloxacin or

ciprofloxacin can be used after appropriate evaluation of renal function and visual acuity.

After complete resolution of transaminases, most anti-tuberculosis drugs can be safely restarted in a phased manner. The British Thoracic Society guidelines [43] suggested that the first-line drugs can be reintroduced sequentially in the order isoniazid, rifampicin and pyrazinamide with daily monitoring of the patients' condition and liver function. Isoniazid should be introduced at 50 mg/day, gradually increasing sequentially to 300 mg/day over two to three days if it is well tolerated and continued thereafter. After a further period of two to three days, rifampicin is introduced at a dose of 75 mg/day increasing to 300 mg/day after two to three days and then increased to 450 mg (<50 kg) or 600 mg (>50 kg) as appropriate for the patient's weight after a further period of two to three days. If this is tolerated, it is then continued. Finally, pyrazinamide can be added at 250 mg/day increasing to 1000 mg after two to three days and then to 1500 mg (<50 kg) or 2000 mg (>50kg) as appropriate for the patient's body weight. If these drugs are well tolerated, they are continued and the alternative drugs introduced temporarily can be withdrawn.

According tothe American Thoracic society, Centers for Disease Control and Prevention and the Infectious Diseases Society guidelines [38] the reintroduction protocol is somewhat different. According to these guidelines, suspected anti-tuberculosis drugs can be started one at a time once the transaminase levels return to less than two times the upper normal. Rifampicin is to be restarted first. If the liver functions remain normal after one week, isoniazid can be added to the regimen. If the liver functions remain normal after one week, then pyrazinamide is added. If there is recurrence of symptoms or deterioration of liver functions, the last added drug should be stopped.

DRUG RE-INTRODUCTION

The re-introduction of anti-tuberculosis drugs has seldom been systematically studied and a great deal of controversy exists regarding sequence in which the drugs are to be reintroduced, whether the reintroduction should be done in full dosage or in gradually escalating dosages.

Usually, it is possible to safely re-introduce the same drugs that have been implicated in the causation of drug induced hepatotoxicity in a majority of the patients. Review of published literature suggests that, the recurrence rate of hepatotoxicity when antituberculosis drugs are re-introduced was less than 7 percent [39] though a recurrence rate of more

than 25 per cent has been cited in some studies.[44] In a study from New Delhi, Singh et al [40] reported that, after resolution of hepatotoxicity, reintroduction of isoniazid and rifampicin was possible in 41 of 44 patients suggesting that the recurrence rate of hepatotoxicity on reintroduction was 6.8 per cent. In the study reported by Telman et al [45] 55 of the cohort of 1036 patients (5.3%) developed hepatotoxicity.

Treatment was re-introduced in 48 patients and successfully completed in 45 patients indicating that the recurrence rate f DIH on reintroduction of antituberculosis treatment was 6.3 per cent.

In a study from Copenhagen 61 of the 752 patients with tuberculosis (8%) developed hepatotoxicity [44]. Recurrence of hepatotoxicity was observed in 16 of these 61 patients (26.2%) on reintroduction of antituberculosis treatment and they required a modified regimen. Multicentric prospective randomized studies with a large sample size are required to clarify these issues.

RISK FACTORS

Advanced age, female sex, hypoalbuminemia, high alcohol intake, acetylator phenotype, hepatitis B &C viruses, HIV, malnutrition and extensive disease were found to be the risk factors for the development of hepatotoxicity.[40,42]

ACETYLATOR STATUS :

Because acetyl isoniazid formation occurs in larger amounts in rapid rather than slow acetylators it was suggested that rapid acetylators are more prone to hepatotoxicity.[46] However the observations that both rapid and slow acetylators excreted similar proportions of mono acetyl hydrazine suggested that, in rapid acetylators, the more rapid conversion of acetyl isoniazid to mono acetyl hydrazine is compensated by its more rapid conversion to di acetyl hydrazine and its excretion contesting this theory.[47,48] Other reports have suggested that products of hydrolysis rather than acetylation are the critical toxic metabolites of isoniazid. A small portion of isoniazid is directly hydrolysed and the proportion of drug metabolised through this direct pathway is greater in slow acetylators than in rapid acetylators.[49] Studies by Sharma et al associates showed

that the hepatotoxic action of metabolites of isoniazid is due to the hydrazine formed from isoniazid.[50] Rifampicin induces the metabolism of isoniazid by isoniazid hydrolase resulting in the formation of isonicotinic acid and hydrazine.[51] It has been suggested that concomitant administration of rifampicin and isoniazid could result in increasing levels of hydrazine and this could provoke hepototoxicity especially in slow acetylators.[52] This hypothesis is supported by the finding of increased hepatotoxicity in slow acetylators. Prema Gurumurthy et al [53] states that there

is no relation especially in south Indian patients with relation to acetylator phenotype and hepatotoxicity.

ANATOMY OF LIVER

It is the largest organ of the body, weighing 1200 to 1500 gms. It is unique for its dual blood supply. Portal vein provides 60 to 70% of hepatic blood flow and the hepatic artery the reminder. Liver infarctions are rare due to dual blood supply.

functions of the liver

The functions of the liver are many and varied. Hence there is no single biochemical test which can reflect all the functions of the liver. Few functions of the liver are given below.

1.Synthetic and metabolic function.

2. Detoxifies and excretes the products of metabolism.

SYNTHETIC FUNCTION :

The hepatocytes synthesize the following

1. Plasma Proteins, except Immunoglobulin and complement.
2. Most coagulation factors, including fibrinogen, factor II (Prothrombin), V, VII, IX, X, XI, XII & XIII ,of these II, VII, IX and X are synthesized in the presence of vitamin K :
3. Lipo proteins – VLDL & HDL
4. Primary bile acids.

LIVER FUNCTION TESTS

Few liver function tests are given below :

A. Tests indicating liver cell damage.

1. Serum Aspartate Amino transferase (AST / SGOT)

2. Serum Alanine amino transferase (ALT / SGPT)

B. Tests indicating biliary tract involvement.

1. Serum alkaline phosphatase

2. Gamma glutamyl transferase

3. Serum 5’ nuceotidase.

C. Tests indicating impaired hepato cellular function.

1. Serum albumin

2. Coagulation factors.

D. Other Tests

1. Viral markers – Igm & IgG anti HAV antibody, Igm & IgG anti HEV antibody ,HBsAg, anti HbsAg antibody ,Anti HCV antibody

2. Alpha feto protein.

3. Circulating auto antibodies

4. Ultrasound abdomen – Non invasive imaging techniques like ultra sonogram is useful to find out cystic liver mass, cirrhosis and biliary calculi. Of limited use in drug induced hepatitis.

5. C.T. Scan Magnetic resonance Imaging - Architecture of the cells can be made out. Functional alterations cannot be made out.

Commonly used liver function tests

Table 3.Normal values commonly used liver function tests [54]

S.No	Tests	Normal Range	Value
1.	Bilirubin - Total - Conugated	0.3 – 1 mg/dl <0.3 mg/dl	Diagosis of Jaundice, assess severity. Gilbert's disease, hemolysis.
2.	Alkaline Phosphatase	35 – 130 IU/L	Diagnosis of Cholestasis hepatic infiltrations.
3.	Aspartate transaminase (AST / SGOT)	5 – 40 IU/L	Early diagnosis of Hepatocellular disease; Follow progress.
4.	Alanine Transaminase (ALT / SGPT)	5 –35 IU/L	ALT relatively lower than AST in alcoholism.
5.	Albumin	35 – 50 g/L	Assess Severity
6.	Prothrombin Time (PT) (after vitamin K)	12 – 16 S	Assess severity.

BILIRUBIN

Hemoglobin released by destruction of aged cells is broken down into globin and heme. The heme is further broken down into iron and bilirubin. Bilirubin attaches to serum albumin and is transported to the liver where it is taken up. In the liver bilirubin detaches from the albumin and is conjugated to glucuronide by glucuronyl transferase. The conjugated bilirubin is water soluble and can be excreted by the kidney.

The conjugated bilirubin is excreted through the bile canaliculi and reaches the intestine where it is converted to stercobilinogen and urobilinogen by the intestinal bacteria. About 70% undergoes entero-hepatic circulation. The unabsorbed stercobilinogen gives brown colour to the faeces. Circulating urobilinogen is carried to the kidney for excretion in the urine as urobilinogen.

The serum bilirubin may be increased in both cholestatic and hepatocellular disease with an associated rise in liver enzymes. In these cases the bilirubin is predominatly conjugated. As isolated rise in serum bilirubin (without enzyme elevation) may be familial or due to hemolysis. Serum bilirubin estimations are based on the Van den Bergh reaction.

Aminotransferases

Aspartate transaminase (AST; Serum Glutamic oxaloacetic transaminase or SGOT) is a mitochondrial enzyme present in large quantities in heart, liver, skeletal muscle and kidney, and the serum level increases whenever these are acutely destroyed, presumably due to release from damaged cells.

Alanine transaminase (ALT; Serum Glutamic Pyruvic transaminase or SGPT) is a cytosolic enzyme also present in liver. Although the absolute amount is less than SGOT, a greater proportion is present in liver compared with heart and skeletal muscles. A serum increase of SGPT is therefore more specific for liver damage than SGOT.

Transaminase determinations are useful in the early diagnosis of viral hepatitis. Measurement must be made early as normal values may be reached within a week of the onset. Routine screening may show unexpectedly raised aminotransferase levels. These are often due to obesity, diabetes mellitus, alcohol abuse, hepatic drug reaction or circulatory failure.

A high ratio of SGOT to SGPT (greater than two) may be useful in diagnosing alcoholic hepatitis and Cirrhosis. This is not due to hepatocyte damage but to pyridoxal 5- phosphate (vitamin B6) deficiency. The commonest causes of raised AST (SGOT) being greater than 10 times the upper limit of normal in a general hospital are hepatic hypoxia and calculous bile duct obstruction. Viral and drug hepatitis are rare.

Some workers have suggested that if the transaminase levels are less than five times the upper normal limit, the toxicity was considered mild. When the transaminase levels were increased to five to ten times the normal, the toxicity was considered to be moderate. Elevation of transaminase more than 10 times the upper normal limit suggests severe toxicity.[38]

ALKALINE PHOSPHATASE :

The level of alkaline phosphatase rises in cholestasis and to a lesser extent when liver cells are damaged. Serum hepatic alkaline phosphatase may be distinguished from bony phosphatase by fractionation into isoenzymes, but this is not routinely carried out. An isolated rise in alkaline phosphatase may be of intestinal origin.[55] A rise in Gamma – glutamyl transpeptidase confirms the likely source of alkaline

phosphatase as being hepato biliary.

ALBUMIN :

Albumin is mainly synthesized in liver. About 10 gm of albumin is synthesized by the normal liver daily, where as those with cirrhosis can only synthesize about 4gm. In liver disease, the fall in serum albumin concentration is slow, as the half life of albumin is about 22 days. A patient with decompensated cirrhosis would be expected to have a low level. Hypoalbuminemia is also found in nephrotic syndrome, malnutrition and pregnancy.

PROTHROMBIN TIME :

This is the time taken for platelet poor citrated plasma to clot after adding calcium and tissue (brain) Thromboplastin. This is an important screening test for defects of the extrinsic and common pathways of coagulation since the intrinsic pathways are bypassed by adding tissue factor and calcium. The prothrombin time before and after 10mg vitamin k given intravenously is the most satisfactory test for a coagulation defect in patients with hepato-biliary disease. Prolongation indicates not only deficiency of the prothrombin complex but also factors XI and XII.

histology of liver

Lobules consist of a central tributary of the hepatic vein and at the periphery a portal tract containing the bile duct , portal vein radicle and hepatic artery branch. Columns of liver cells and blood containing sinusoids extend between these two systems. Acini, the functional unit of liver, is centered on the portal triad. These interdigitate, mainly perpendicularly, with terminal hepatic veins of adjacent acini.

Liver biopsy

Liver biopsy is now an accepted, safe, invasive procedure in most hospitals to investigate liver disease. It samples accurately in all diffuse anatomic lesions and in majority of focal lesions.

The Menghini needle obtains a specimen by aspiration. Most commonly used puncture biopsy needle which grasps the tissue within the cannula is Vim Silverman needle. The sheathed Trucut needle is a modification of Vim Silverman needle. Other methods are guided biopsy ,biopty gun method and transjugular liver biopsy.

INDICATIONS [57]

Drug induced hepatitis, Chronic hepatitis, Cirrhosis, Liver disease in the alcoholic, Intra hepatic cholestasis, Infective conditions, Storage diseases, Post hepatic transplantations, Space occupying lesions, unexplained hepatomegaly or enzyme elevations.

CONTRA INDICATIONS

1. Abnormalities of blood coagulation and thrombocytopenia < 50,000 cells/cu.mm.
2. Hydatid cyst of liver.
3. Sepsis
4. Haemangioma.

TECHNIQUE OF PUNCTURE:

Sedation is not given routinely as it may interfere with the patient's co-operation. In supine position after adequate local anaesthesia the needle with 3 ml of sterile solution is inserted in the 8^{th} or 9^{th} intercostal space in mid-axillary line at the end of expiration with the patient breathing quietly. 2ml of solution are injected to clear the needle of any skin fragments. Aspiration is now commenced and

maintained with the patient holding his breadth in expiration, the needle is rapidly introduced perpendicularly to the skin into the liver substance and extracted. The tip of needle is now placed on sterile paper and some of the remaining saline flushed through the needle to deposit the biopsy gently into the paper. The tissue is transformed into fixative.

COMPLICATIONS :

Complications are reported in 0.06 – 0.32% patients with mortality of about 0.1%.[56] Complications range from pain in the site of puncture, mild oozing due to hemorrhage, bile peritonitis, perforation of abdominal viscera, pneumothorax and precipitation of hepatic coma.

MATERIALS AND METHODS

Patients were selected from amongst those who registered in the tuberculosis clinic of coimbatore medical college hospital, Coimbatore from January 1st 2005 to the end of June 2005 and they were followed upto December 2005.

Eligibility criteria

1. Patients above 18 yrs with adequate evidence of pulmonary tuberculosis were chosen.
2. Only sputum positive cases were selected.
3. Patients coming from within and near by nearly areas of coimbatore were selected to minimize the dropouts.

Exclusion Criteria

1. Patients who either had been on ATT previously or were on ATT at the time of the registration in the TB clinic.
2. Sputum smear negative patients.
3. Previous history of jaundice.
4. Pregnant women.

5. Those in whom baseline enzyme levels were more than upper limit of normal.

6. Patients suffering from any other diseases like diabetes, hypertension and cardiac failure.

7. Patients on chronic medication for any other diseases.

PRE TREATMENT EVALUATION :

Patients were well informed and consent was taken from the patients prior to their enrolment in the study and their compliance solicited. They were advised not to stop the prescribed medications for any reason on their own. They were asked to report immediately if any adverse symptoms were noticed such as nausea, vomiting, loss of appetite, yellowish discoloration of skin and mucous membrane. The details were recorded in a specially prepared proforma, a copy of which is annexed.

The following investigations were performed before starting chemotherapy in patients of newly discovered pulmonary tuberculosis.

1. Hb%

2. Platelet Count

3. Serum Proteins – Total

-Albumin

4. S. Bilirubin – Total

-Direct

5. Serum alkaline phosphatase (SAP)

6. SGOT

7. SGPT

8. Prothrombin time

9. Chest X-ray PA View.

TREATMENT

The patients were started on category I regimen under Revised National Tuberculosis Control Program containing isoniazid, rifampicin, Pyrazinamide, Ethambutol . The details of the dosage is given below. All drugs are given three times a week.

Initial Phase

Isoniazid, Rifampicin, Pyrazinamide & Ethambutol –For 2 months

Continuation Phase

Isoniazid, Rifampicin-For 4 months

Dosage of Drugs

Isoniazid -300 mg.

Rifampicin – 450 mg (600 mg for patients > 50 kg)

Pyrazinamide – 1.5 gm (2 gm for patients > 50 kg)

Ethambutol – 800 mg.

Liver Function Tests :

Patients liver function was assessed by measuring S. Bilirubin, SAP, SGOT, SGPT, S. Proteins and prothrombin time.

The liver function tests were done prior to drug treatment and then at 1^{st}, 2^{nd}, 4^{th}, 8^{th}, 12^{th},16^{th} , 20^{th} and 24^{th} weeks of treatment.

Procedure :

Serum bilirubin was estimated according to the method described by Varley SGOT and SGPT were estimated by the method described by Chyne. Alkaline phosphatase and serum protein were estimated according to the methods described by Wootten and Reinhold respectively.

Evaluation during therapy :

Patients were given medication on alternate days during the initial phase and for one week during continuation phase. Every effort was made to ensure the compliance of the patient. Minor symptoms were treated symptomatically. Patients with major symptoms were hospitalised. Data collected during these reviews included.

1. Drug taken
2. Any adverse symptoms with reference to liver function.
3. Liver function tests at 1^{st}, 2^{nd}, 4^{th}, 8^{th}, 16^{th}, 20^{th} and 24^{th} week of treatment.

Patients who showed the following features are considered significant. [40] Such patients were grouped separately and monitored clinically and Bio-chemically every week

1. More than a five fold (> 250 IU/L) elevation of serum enzymes (AST, ALT) or > 150 IU/L on more than 3 occasions and / or
2. S. Bilirubin > 1.5 mg and /or.
3. Clinical features of icteric hepatitis

DROP OUT FROM THE STUDY :

These patients who were irregular in their treatment were grouped separately. Among those who did not take the drugs for more than 4 weeks continuously were dropped. Among the 108 patients enrolled in the study, the follow up was given below.

1st week – 107 patients

2nd week – 107 patients

4th week – 106 patients

8th week – 104 patients

12th week – 100 patients

16th week – 98 patients

20th week – 95 patients

24th week – 95 patients

Total number of dropout was 13 patients and none of them had any adverse reactions.

ADVERSE DRUG REACTIONS :

Serum enzymes are elevated in 13 patients and in these group serum bilirubin was elevated in 5 patients. In these only 2 patients developed nausea, vomiting, anorexia, yellowish discoloration of urine and conjunctiva. Increase in serum enzymes are noted as follows**:** 4 patients on 1st week, 6 patients on 2nd week, 3 patients on 4th week. Increase in serum bilirubin are noted in 2 patients on 1st week and 2 patients on 2nd week and 1 patient in 4th week. Among the patients who developed jaundice 1 patient was on 1st week and 1 patient on 4th week.

Only clinical and laboratory monitoring was done in asymptomatic patients. In symptomatic patients all drugs were withdrawn and liver biopsy planned. Out of 2 symptomatic patients only 1 patient gave consent. After 3 doses of vitamin k, liver biopsy

was carried out. Under local anaesthesia using trucut needles liver biopsy done. Liver bits obtained were sent for histopathological examination in formalin solution and stained with H and E

stain and the results are given below.

Biopsy from 52 year male patient showed bridging necrosis and

multilobular necrosis. ATT was stopped in both symptomatic patients. LFT returned to baseline in 2 weeks. Then drugs were started as suggested by the British thoracic society guidelines. Both patients tolerated the drugs well and continued till the end of treatment period.

DROP-OUTS :

In patients on ATT, various studies showed a drop-out from 10 to

40% due to various reasons like lack of literacy, adverse drug reaction, sense of well being, social problems and rarely migration. In our study, follow-up of the defaulters showed drug adverse reactions are not the cause of dropouts. Though we selected patients in and around coimbatore and patients were well informed about the study, we had a drop out of 13 patients from the initial of 108 patients. When the patients in spite of reminder cards and calls not responding and who stops taking treatment for > 4 weeks dropped from the study.

OBSERVATIONS

1. Total patients selected for study – 108.
2. Dropout during treatment – 13
3. Total patients completed full course of Treatment 95 patients.

   Males – 49 patients ;Females – 46 patients
4. Age group – 20 – 66 years.
5. Incidence of Drug Induced Hepatotoxicity in coimbatore population who are on category I, RNTCP, 4 drug regimen is 2.1%. Male : Female ratio is approximately 1:1
6. Asymptomatic elevation of serum enzymes in 11 patients (11.6%)

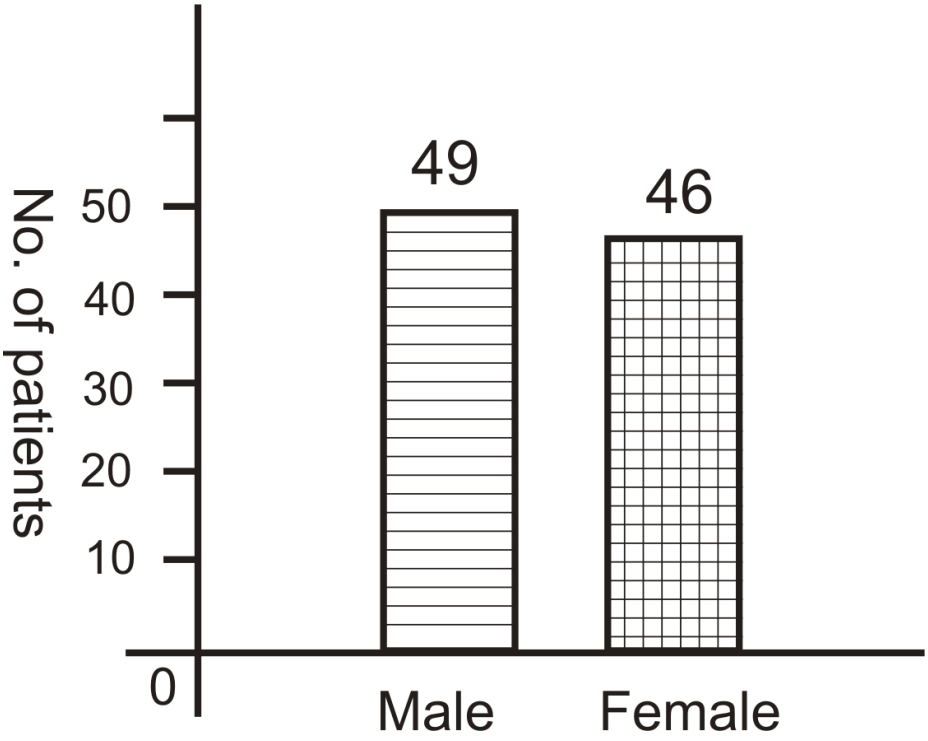
   male : female ratio =1:1.9
7. Onset of symptoms is between 1-4 weeks after starting ATT.
8. Withdrawal of the drugs produced complete recovery.
9. Hepatotoxicity confirmed by liver biopsy in 1 out of 2 patients who developed clinical hepatitis.
10. Predisposing factors : Old age, Malnutrition, chronic alcohol intake, extensive disease states like cavitary tuberculosis.

11. Re-introduction of drugs**:** Both patients who developed Drug Induced hepatotoxicity tolerated well on drug challenge and the same regimen continued.

12. Follow up drop outs : No patients developed adverse drug reactions.

SEX :

Total No. of males and females completed ATT



Asymptomatic Hepatitis

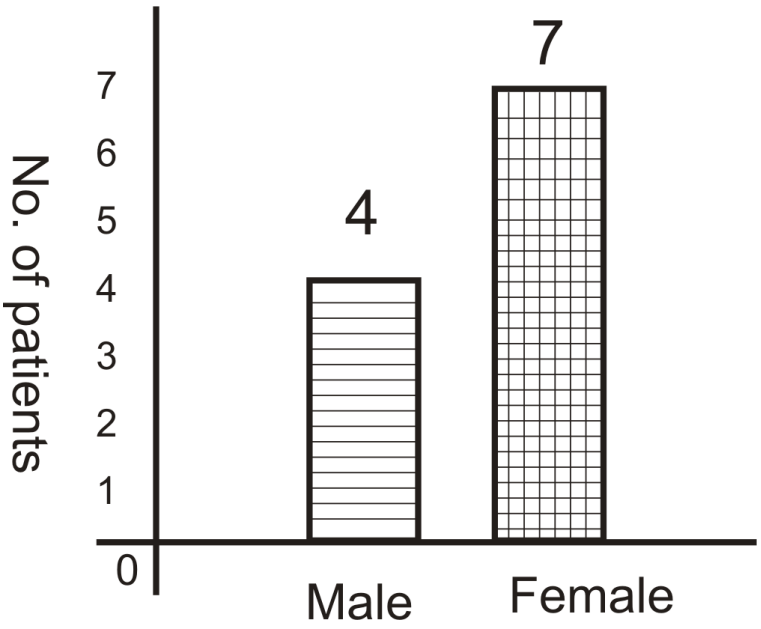


Table 4 :

AGE GROUP OF PATIENTS :

Age Group (Years)	Male	Female	Total
20 – 20	11	13	24
30 – 39	16	12	28
40 – 49	10	6	16
50 – 59	8	10	18
60 – 69	4	5	9
Total	49	46	95

AST / ALT elevation in patient's on ATT

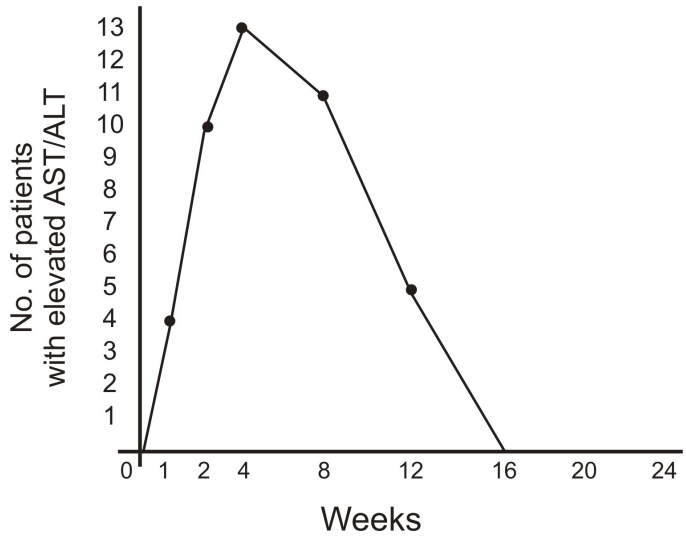
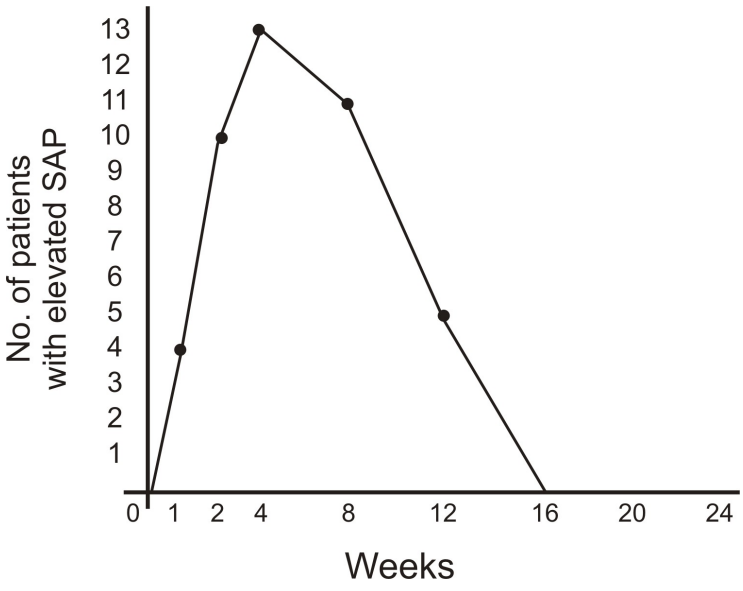


Table : 5

Elevation of Serum Enzymes & Age Group / Sex

Age Group	Clinical Hepatitis	Sub Clinical Hepatitis		Total	Percentage in total patients
		Male	Female		
20-29	-	2	-	2	8.3%
30-39	-	-	3	3	10.7%
40-49	-	1	2	3	18.8%
50-59	1(M) 52Years	1	1	3	16.7%
60-69	1(FM) 63Years	-	1	2	22.2%
TOTAL	2	4	7	13	-

SAP ELEVATION



SERUM BILIRUBIN

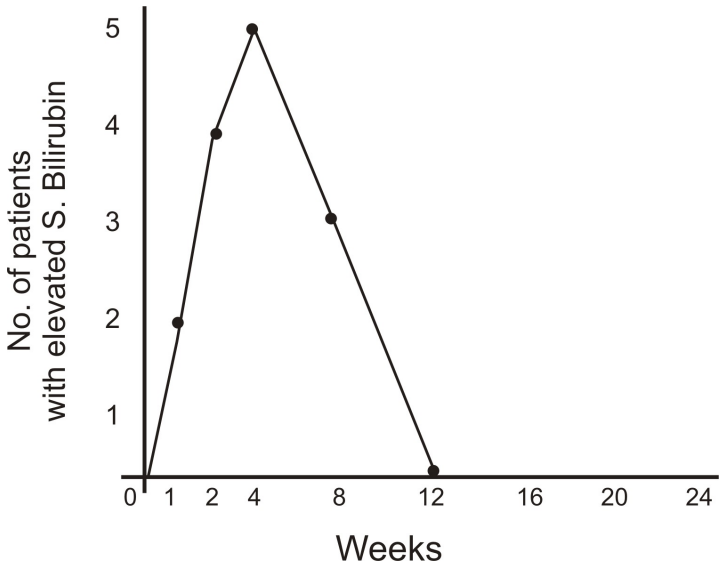


Table : 6

INITIAL ELEVATION OF SERUM ENZYMES, SERUM BILIRUBIN AND CLINICAL HEPATITIS-WEEK WISE

Weeks	No. of Patients on Study	Serum ALT	Serum AST	SAP	S. Bilirubin	Clinical Hepatitis
0	108	0	0	0	0	0
1	107	4	4	4	2	1
2	107	6	6	6	2	0
4	106	3	3	3	1	1
8	104	0	0	0	0	0
12	100	0	0	0	0	0
16	98	0	0	0	0	0
20	95	0	0	0	0	0
24	95	0	0	0	0	0
TOTAL	-	13	13	13	5	2

Table : 7

DROP OUTS

	Male	Female	Total	Percentage
Initial	57	51	108	
Dropout	8	5	13	12%
Completed the Course	49	46	95	88%

Table : 8

Disease Status and Hepatotoxicity

Lesion	No. of Patients	Clinical Hepatitis	Sub clinical Hepatitis
Cavitary Lesion	6	2	1
Non Cavitary Lesion	89	-	10

DISCUSSION

In this study of 108 patients of sputum positive pulmonary tuberculosis all are administered category I regimen of RNTCP i.e Isoniazid, Rifampicin, Pyrazinamide and Ethambutol for first 2 months followed by isoniazid and rifampicin for next 4 months. All are given in thrice weekly basis.

Total number of patients taken : 108 Patients

Drop out of Patients : 13 patients

Regularly followed till the end of treatment : 95 patients

Out of this, male patients – 49 and female patients are 46.

Male : Female ratio is approximately 1:1

AGE

The age group of the patients ranged from 20 – 67 yrs In our study, clinical hepatitis occurred in old age patients only (52 years & 63 yr) Studies from Pande et al [40] also shows that increasing age is associated with more hepatotoxicity. Subclinical hepatotoxicity were noted in the range of 26-61 yrs. No of patients had subclinical hepatotoxicity is 11.

(Male : Female ratio group) than in younger age group (8.3% in 20-29 yr age group)

SEX

Clinical hepatitis occurred in 1 male and 1 female patient. Ratio is approximately 1:1. Subclinical hepatitis occurred in 4 male and 7 female patients. Male : Female ratio is 1:1.9.

Many studies showed female patients are more prone [40,42] but in our study there is no difference in clinical hepatitis. This can be explained by our small study and only 2 patients developed clinical hepatitis. Subclinical hepatotoxicity in our study is more common in female patients and this is in accordance with many studies .[40,42]

NUTRITIONAL STATUS :

38 males and 30 females had normal nutritional status and 11 males and 16 females had mild malnutrition. (S. Albumin <3mg).Krishnaswamy says that under nutrition contributes to drug toxicity by various mechanisms.[58]

Toxicity and over dosage is much more likely to occur with even normal dosage of medicine in the presence of low serum albumin.

In our study, both patients who developed clinical hepatitis had mild malnutrition. Subclinical hepatotoxicity developed even in normal individuals.

Disease Status :

Advanced disease predisposes to hepatotoxicity. [40,42]

In our study patients who developed clinical hepatitis had cavitary lesions, subclinical hepatotoxicity occurred in patients of both cavitary and noncavitory patients.

Alcohol intake

History of Alcohol intake predisposes patients to hepatotoxicity than no history of alcohol intake. In our study one patient out of two with clinical hepatitis gives history of alcohol intake.

Viral Markers :

None of the patients found to be positive for HBsAg or anti HCV antibody in our study. Hepatitis B virus ,Hepatitis C virus patients are more prone to develop drug induced hepatotoxicity.[40,42]

COMBINATION CHEMOTHERAPY AND HEPATOTOXICITY

The incidence of hepatotoxicity due to combination chemotherapy ranges from 1% to 39%

The following is a list of incidence by some workers.

1. Parthasarathy et al [59] - TBM 16-39%
   - PT 2-8%
2. Schberg et al [41] -11%
3. Devoto et al [42] -9.9%
4. Steele et al [8] -2.6%
5. Dossing et al [44] - 8%
6. Kamat et al from Bombay [60] -18%
7. Sivaraman et al [61] - 7%

In our study it is 2.1%

The Tuberculosis Research centre, Chennai (1983) has published the first report on short course chemotherapy(SCC) on South Indian patients.[62] All patients in this study received INH and pyrazinamide and 2/3rd of them also received rifampicin. Hepatitis occurred in 17 (2.5%)

of 693 patients.In addition, 14 (2%) had transient elevation of aminotransferases detected during routine monitoring. It was noted that eight patients who developed hepatitis during first two months were from rifampicin series. Lower incidence in our study is probably due to lower duration of treatment, lower dosage used than preciously and may be because of intermittent regimen.

ASYMPTOMATIC HEPATITIS

The frequency of asymptomatic, self-limited elevations of enzymes, raises the question of whether the drugs should be stopped when an elevated level is encountered and if so, at what levels they should be stopped. Moreover, the hepatic reactions may develop with such rapidity that even weekly estimations of serum enzymes may not provide sufficient warning. Mild transient and symptom less increases in serum hepatic enzymes are usual during early weeks of treatment whatever the drug regimen and on no account should treatment be interrupted or altered because of these increases . Judgement of withhold or continue drugs should be based on clinical grounds rather than on laboratory parameters alone in a given case.

ONSET OF HEPATOTOXICITY :

Increase in Serum transaminase activity which occurs later (usually more than one month) has been attributed to Pyrazinamide while early increase in serum transaminase (usually < 15 days) has been attributed to Isoniazid & Rifampicin. Isoniazid toxicity is more common in first few weeks of therapy. In our study both clinical and sub clinical hepatitis occurred in < 4 weeks.

SYMPTOMATIC HEPATITIS :

Incidence of drug induced hepatitis in various studies were listed above. Generally asymptomatic hepatitis is more common than clinical hepatitis. Symptoms are not reliable always but Parthasarathy et al [59]states that hepatitis nearly always associated with jaundice.

In our study both patients with clinical hepatitis had jaundice and bio-chemical elevation of serum transaminases above 5 folds. Elevation of SAP was also seen in these patients though it was only 2-3 fold rise S. Bilirubin was raised in 5 patients, but > 4 mg% was seen only in symptomatic patients. After withdrawing the drug all the liver function tests returned to normal level. (In 4 weeks in 1 patient and in 2 weeks in another patient).

Withdrawal of Drugs :

Some workers says patients who developed symptomatic hepatitis does not warrant withdrawing of all the drugs.[63] But since there are a lot of reports of fulminant hepatic failure and death, withdrawal of all the drugs till the elevated serum enzyme level decline to normal level is advisable.

In our study, withdrawal of all the drugs was done in both symptomatic patients.

Drug re-introduction :

Drug re-introduction is a must, because all are very effective bactericidal drugs. There are 2 schools of thought in drug re-introduction.

We followed the guidelines prescribed by the British thoracic society. [43] None of the patients developed any reaction on drug re-introduction and the same drugs prescribed and patients were discharged with the advise to get admitted immediately if they develop any symptoms of hepatitis.

Confirmation of Hepatotoxicity due to drugs :

Both the patients who developed symptoms of hepatitis were screened for hepatitis B antigen, anti HCV antibody and found to be negative. Tests for Hepatitis A, D & E viruses could not be done due to lack of facilities.

Since the patients were only on prescribed medications ie hepatotoxic anti tuberculous drugs, it was concluded that the hepatitis is due to drug toxicity. Liver biopsy specimen correlated with clinical symptoms and bio- chemical test results. Hence drug induced hepatitis was confirmed. As Kumar states endemicity of viral hepatitis may not have chance in this study.

Dropouts :

In various studies the dropout ranges from 16 to 70%. In our study drop out was 13.6%. None of them had any adverse reactions.

Prevention of Drug induced Hepatitis :

We cannot predict which patient will develop hepatotoxicity but susceptibility is more in patients of older age group, women, malnutrition and extensive disease states.

High protein diet, abstinence from alcohol and smoking, good supportive medication with vitamins like vitamin B6, Vitamin C will reduce the incidence. Well educated patients and skilled, alert treatment supervisor can reduce hepatotoxicity, fulminant hepatitis and its complications.

CONCLUSION

1. Though drug induced hepatotoxicity occurred in 2.1% of the patients this is significant.

2. Asymptomatic rise in serum enzymes are noted in 11.6% of patients. This is reverted back to normal before the end of treatment.

3. Patients with malnutrition, old age and advanced pulmonary tuberculosis were susceptible to drug induced hepatotoxicity.

4. Patients who had clinical signs and symptoms of hepatitis showed histopathological changes in the liver. So it is justified in doing liver biopsy in patients with drug induced hepatotoxicity in the presence of clinical symptoms and signs or marked elevation of serum transaminases, since it is a simple, reliable, relatively safe procedure.

SUMMARY

In this study of 108 patients of new sputum positive patients 57 were males and 51 were females. The age group ranged from 20-67. Out of 95 patients who completed treatment 11 patients had asymptomatic rise in serum enzymes with male: female ratio of 1:1.9. Two patients had symptomatic hepatitis with male : female ratio of 1:1 in the ages of 52year and 63 year. Patients in older age group, mild malnutrition and cavitary disease only had symptomatic hepatitis.

Needle biopsy of liver conformed drug induced hepatotoxicity in 1 patient as the other did not consent for liver biopsy. Re-introduction of drugs done in the patients gradually after s. enzymes reverted back to normal levels. Both patients tolerated well on drug re-challenge. Patients closely monitored and discharged with the advice to get admit immediately if there any symptoms of hepatitis.

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PROFORMA :

Evaluation of liver functions in patients on anti tuberculous therapy.

Name : Age : Sex :

Address :

Case No :

TB O.P. No :

Diagnosis :

Regimen :

S. No.	HISTORY	Before Treatment	During Treatment(weeks)							
			1	2	4	8	12	16	20	24
1	Anorexia									
2	Nausea									
3	Vomiting									
4	Jaundice									
5	Epigastric Pain									
6	Diarrhea									
7	Clay stools									
8	Fever									
9	Bleeding Tendencies									
10	Skin Rashes									

S. No.	EXAMINATION	Before Treatment	During Treatment(weeks)							
			1	2	4	8	12	16	20	24
1	Pulse									
2	BP									
3	Temperature									
4	Resp. Rate									
5	Weight									
6	Built & nutrition									
7	Anemia									
8	Jaundice									
9	Skin Lesions									
10	Hepatomegaly									
11	Tenderness in Right Hypochondrium									
12	Fluid Thrill									
13	Shifting dullness									
14	Auscultation									
15	Miscellaneous									

S. No.	INVESTIGATIONS	Before Treatment	During Treatment(weeks)							
			1	2	4	8	12	16	20	24
1	HB%									
2	Platelet Count									
3	Prothrombin Time									
4	Urine – Bile Salt - Bile Pigments - Urobilinogen									
5	SGOT (AST)									
6	SGPT (ALT)									
7	SAP									
8	S. Bilirubin - Total - Direct									
9	S. Proteins - Total - Albumin									
10	Chest X-ray PA View *									
11	Viral Markers** - HBsAg - - Anti HCV antibody									
12	Ultrasound Abdomen#									
13	Liver Biopsy#									
14	Others									

* -Only during the initial evaluation

**-On initial evaluation and if they develop hepatitis

#- Only for symptomatic hepatitis patients.