

Tuberculosis in Special Situations: Liver disease, Renal Impairment, Pregnancy and Epilepsy

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Drug Induced Liver Injury

Three of the first-line antituberculosis drugs, INH, RIF, and PZA, can cause drug-induced liver injury (AST level three or more times the upper limit of normal in the presence of symptoms, or five or more times the upper limit of normal in the absence of symptoms)

AST < 5 times N : Mild

AST 5 to 10 times N: Moderate

AST > 10 times N: Severe

AST= Aspartate transaminase (SGOT)

Drug-Induced Hepatitis

Serum AST > 3 times ULN in presence of symptoms

Serum AST > 5 times ULN in absence of symptoms

If hepatitis occurs RHZ stopped

- Check for Hep B and C
- Change to SE Fluoroquinolones
- Start again when serum AST less than 2 times normal (AST= SGOT)

Drug-Induced Toxicity

- **Hepatitis : Isoniazid , Pyrazinamide**
- **Cholestasis: Rifampicin**

- **Latency period: Period between ingestion of drug and onset of symptoms**
- **Short (hr to days) : Acetaminophen**
- **Intermediate(1 to 8 weeks) : Phenytoin**
- **Long(1 to 12 months): Isoniazid**

Nathwani Drug hepatotoxicity 2006

Clinical Hepatitis in Persons Taking Isoniazid and Rifampicin*

Drug	No of studies	Patients	Clinical hepatitis%
• INH	6	38,257	0.6
• INH plus other drugs but not RIF	10	2,053	1.6
• RIF plus other drugs but not INH	5	1,264	1.1
• INH plus RIF	19	6,155	2.7

Definition of abbreviations: INH = Isoniazid; RIF = Rifampicin.

* *Source: Steele MA, Burk RF, Des Prez RM. Toxic hepatitis with isoniazid and rifampicin: a meta-analysis. Chest 1991;99:465–471. Reprinted with permission*

Anti-Tb Hepatotoxicity

Clinical hepatitis: 0.6% with INH alone
1.1% with Rif but not INH
1.6% with INH but not Rif
2.7% with Rif and INH

Increase with age/underlying liver
disease/alcohol/postpartum in Hispanic women¹

Steele et al Chest 1991;99 465-71

¹*Franks et al Public Health Rep 1989; 104 151-55*

British Study

Clinical hepatitis : 0.3% with INH (6m)

1.4% with Rifampicin(6m)

1.25% with PZA (2m)

Hepatitis rate per patient PZA 3 times >Rif

Hepatitis rate per patient PZA 5 times > INH

Ormerod 1994

Ormerod 1996

TB drugs in liver disease

- **Problems in Hep B/C and cirrhosis**
- **Avoid PZA in these situations**

Child's classification

- **Class A: 2REH/7RH**
- **Class B or C: RE Fluo+ Cycloserine ± injectable (12 to 18 months)**
- **Class B or C : SM + Etham + Fluo+ any 2nd line (18 to 24 months)**

Nathwani 2006

Liver Disease

If serum AST > 3 times normal several treatment options:

- REZ for 6 months (HK Chest service/BMRC)**
- 2REH/7RH (total 9 months)**
- RE for 12 months (with Fluoroqui 2months)**
- Frequent liver function tests**

Fatal Hepatitis

- 0.023% but probably lower ¹ ²

¹Snider DE, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. *Am Rev Respir Dis* 1992;145:494–497.

²Salpeter S. Fatal isoniazid-induced hepatitis: its risk during chemoprophylaxis. *West J Med* 1993;159:560–564.

Summary

- 20% of patients with 4 drug regimes have asymptomatic increase in AST
- Stop if AST > 5 times without symptoms
- Stop if AST > 3 times with symptoms

Relative risk of developing drug-induced hepatotoxicity in tuberculosis patients with *hepatitis C virus or HIV infection* was *5- and 4-fold*, respectively, compared with a 14-fold relative risk in patients with both hepatitis C virus and HIV infections(*Ungo et al 1998*)

This finding was not confirmed in a study from Baltimore, in which rates of transaminase elevation were *not greater* in patients with HIV and hepatitis C virus who were given INH (*Sadaphal 2001*)

Renal TB

- Medical therapy for 6 months
- Surgery to relieve obstruction (stenting and nephrostomy)

Renal Impairment

- Haemodialysis: Give drugs after dialysis to prevent removal of drugs eg PZA and cycloserine
- PD: little information on drug clearance

Decreasing the dose of selected antituberculosis drugs may not be the best method of treating tuberculosis because, although toxicity may be avoided, the peak serum concentrations may be too low.

Therefore, instead of decreasing the dose of the antituberculosis agent, increasing the dosing interval is recommended (*Peloquin 1991*)

Drugs in renal failure

RIF and INH are metabolized by the liver, so conventional dosing may be used in the setting of renal insufficiency. RIF is not cleared by hemodialysis because of its high molecular weight, wide distribution into tissues, high degree of protein binding, and rapid hepatic metabolism (Malone 1999) Therefore, supplemental dosing is not necessary for INH, RIF

PZA is also metabolized by the liver but its metabolites (pyrazinoic acid and 5-hydroxy-pyrazinoic acid) may accumulate in patients with renal insufficiency (Malone 1999/Ellard 1969)

EMB is about 80% cleared by the kidneys and may accumulate in patients with renal insufficiency (Strauss 1970)

Creatinine Clearance <30ml/min or on Haemodialysis

- **Rifampicin and INH: No change**
- **PZA : 25 to 35 mg/kg 3 times/week**
- **Ethambutol : 15 to 25 mg/kg 3 times/week**
- **Levofloxacin 750 to 1000mg 3 times/week**
- **Cycloserine 250 mg daily or 500mg
3 times /week**
- **Ethionamide and PAS no change**
- **Aminoglycoside : 12 to 15mg/kg
2-3times/week**

EXPERT CONSENSUS ON MANAGEMENT OF COMMON AILMENTS IN INDIAN SCENARIO, API CONSENSUS GUIDELINES 2005:

Management of Pulmonary Tuberculosis, Extra-Pulmonary Tuberculosis and Tuberculosis in Special Situations

K Vijayan¹, S K Jindal², K Jagganath³, Camilla Rodrigues⁴, S B Gupta⁵ and J M Joshi⁶

Renal failure: Dosages may have to be adjusted according to the creatinine clearance especially for streptomycin, ethambutol and isoniazid. Creatinine clearance should be estimated for adjustment of some of the antituberculosis drugs.

Creatinine clearance= $\frac{(140 - \text{Age}) \times \text{Weight}}{72 \times \text{serum creatinine}}$

This formula gives a rough estimate of the glomerular filtration rate. According to the creatinine clearance *either the dosage interval is changed or the dose is reduced* as a percentage of the normal daily dose

In post renal transplant patients: Rifampicin-containing regimens are avoided as rifampicin causes increased clearance of cyclosporin.

Aminoglycosides

- Doses of streptomycin, kanamycin, amikacin, and capreomycin must be adjusted in patients with renal failure because the kidneys excrete essentially all of these drugs.
- Approximately 40% of the dose is removed with hemodialysis when these drugs are given just before hemodialysis (Matzke 1984) Far less drug is likely to be removed once the drugs have had time to distribute throughout the body, and some accumulation occurs.

Aminoglycosides

- The dosing interval should be increased.
- Dose should not be reduced because the drugs exhibit concentration dependent bactericidal action (Peloquin 1997) and smaller doses may reduce drug efficacy.

Other Drugs

- Ethionamide not cleared by the kidneys, and not removed with hemodialysis, so *no dose adjustment* is necessary (Malone 1999)
- PAS is modestly cleared by hemodialysis (6.3%) but its metabolite, acetyl-PAS, is substantially removed by hemodialysis; twice daily dosing (4 g) should be adequate if the granule formulation is used (Jacobus Pharmaceuticals) (Malone 1999)

Other Drugs

- Cycloserine is excreted primarily by the kidney, and is cleared by hemodialysis (56%).
 - Increase in the dosing interval is necessary
 - After hemodialysis to avoid underdosing (Malone 1999)

- The fluoroquinolones undergo some degree of renal clearance that varies from drug to drug.

eg. levofloxacin undergoes greater renal clearance than moxifloxacin (Fish 1997)

Guidelines developed for pyogenic bacterial infections may not be applicable to the treatment of tuberculosis in patients with end-stage renal disease.

Renal Failure (Other Factors)

- DM with gastroparesis may affect the absorption of the antituberculosis drugs
- Medications interact with these drugs.
- Careful clinical and pharmacologic assessment
- Serum drug concentration measurements may be used to get optimum dose of the drugs
(Peloquin 1997)

No data for peritoneal dialysis.

Pregnancy and Breast Feeding

REH cross placenta but no teratogenic effects
(Briggs 1998)

PZA : recommended by WHO1997/IUATLD1996

Streptomycin: congenital deafness

No indication for termination if pregnant

Breast feeding encouraged (Snider 1984)

Pregnancy and Breast Feeding

- 40 pregnancies with SM.... 17% babies had 8th nerve damage (mild to severe)
Briggs 1998/Varpela 1969
- Kanamycin, Amikacin and Capreomycin similar
- PAS no teratogenic effects
- Fluoroquinolones : arthropathies in young animals
(Briggs 1998)

TB in Pregnancy

- 5 to 10% have extrapulmonary disease
- Congenital TB is rare ..perhaps in woman with Tb endometritis or miliary Tb¹

Congenital TB:

- TB in newborn, Primary complex in newborn's liver, if none then must have lesions in first few days of life²
- Symptoms: respiratory distress, fever, liver/spleen enlargement, poor feeding, lethargy, and LN ²
- More common is neonatal TB

TB in Pregnancy

- Hepatitis more common in pregnant patients with INH

Drugs Not to be Used in Pregnancy

- Ethionamide: crosses placenta and teratogenic in lab animals
- Streptomycin: foetal hearing loss^{1 2 3}
- Amikacin/Kanamycin/Capreomycin: risk of foetal nephrotoxicity and congenital hearing loss¹
- Fluoroquinolones: Teratogenic effects ⁴

US pharmacopoeia 1999 ¹ *Conway 1965* ² *Robinson 1964* ³
Peloquin 1991/Lipsky1999 ⁴

TB and Epilepsy

Isoniazid is a relatively potent inhibitor of several cytochrome P450 isozymes (CYP2C9, CYP2C19, and CYP2E1) (Self 1999) but has minimal effect on CYP3A (20). Inhibitory activity of isoniazid on anticonvulsants, phenytoin (Kutt 1970/Miller 1979) and carbamazepine (Block 1982/Valsalan 1982)

Isoniazid also increases concentrations of diazepam

Rifampicin has the opposite effect on the serum concentrations of many of these drugs thus reducing effect of phenytoin (Kay 1985) and diazepam (Ochs HR 1981)

Isoniazid may increase toxicity of other drugs—valproate (Jonville 1991)

Isoniazid and Seizures

- 10 to 15% of people are genetically slow acetylators of INH
- Seizures in INH overdose Sullivan in 41 cases of overdose ..found 53.6% had seizuresPyridoxine is antidote

*Goldstein and Harden Managing epilepsy and co-existing disorders
2002*

Table 3. TB Drugs in Special Situations

<i>Drug</i>	<i>Pregnancy</i>	<i>CNS TB Disease</i>	<i>Renal Insufficiency</i>
Isoniazid	Safe	Good penetration	Normal clearance
Rifampin	Safe	Fair penetration Penetrates inflamed meninges (10% - 20%)	Normal clearance
Pyrazinamide	Avoid	Good penetration	Clearance reduced Decrease dose or prolong interval
Ethambutol	Safe	Penetrates inflamed meninges only (4% - 64%)	Clearance reduced Decrease dose or prolong interval
Streptomycin	Avoid	Penetrates inflamed meninges only	Clearance reduced Decrease dose or prolong interval
Capreomycin	Avoid	Penetrates inflamed meninges only	Clearance reduced Decrease dose or prolong interval
Kanamycin	Avoid	Penetrates inflamed meninges only	Clearance reduced Decrease dose or prolong interval
Ethionamide	Do not use	Good penetration	Normal clearance
Para-amino salicylic acid	Safe	Penetrates inflamed meninges only (10% - 50%)	Incomplete data on clearance
Cycloserine	Avoid	Good penetration	Clearance reduced Decrease dose or prolong interval
Ciprofloxacin	Do not use	Fair penetration (5% - 10%) Penetrates inflamed meninges (50% - 90%)	Clearance reduced Decrease dose or prolong interval
Ofloxacin	Do not use	Fair penetration (5% - 10%) Penetrates inflamed meninges (50% - 90%)	Clearance reduced Decrease dose or prolong interval
Amikacin	Avoid	Penetrates inflamed meninges only	Clearance reduced Decrease dose or prolong interval
Clofazimine	Avoid	Penetration unknown	Clearance probably normal

Safe = The drug has not been demonstrated to have teratogenic effects.

Avoid = Data on the drug's safety are limited, or the drug is associated with mild malformations (as in the aminoglycosides).

Do not use = Studies show an association between the drug and premature labor, congenital malformations, or teratogenicity.

Case study

- 29 Siamese man
- Moderate PTB with TB cervical LN and abdominal LN (portal nodes) on ultrasound
- RV positive
- REH low dose
- ALP 800.4....620.....518.....380.....214
- ALT 45.....33.5.....normal range
- On day 55 treatment

Case Study

- 48 yr old Chinese lady with cough, fever LOA, LOW
- Had left 'ureteric stone' with hydronephrosis
- SHRZ ..developed rashes...changed to REHZ....but creatinine increasing
62...215....329..475...withheld treatment 21 days but rising trend 563....symptoms of TB worsened ...so re-treatment with RHZ and improved