# Adverse Reactions/Treatment Induced Side Effects

Recognition and appropriate management of adverse drug reactions is an essential part of the treatment program. Physicians and nurses responsible for the treatment of TB should be well acquainted with these reactions.

Any possible adverse event should be carefully evaluated in order to identify other potential causes or to identify the responsible drug, which is not easy with multiple-drug regimens. It is very important to avoid unnecessary cessation of a first-line drug, as the efficacy of the treatment will be less, the duration longer and the toxicity of a replacement drug possibly worse than that of the drug that was stopped.

Once a serious adverse reaction is clearly attributed to any anti-TB drug, the patient should not receive this agent again.

Table 8.12: Common Adverse Reactions with First Line Anti-Tuberculosis Drugs

| | Common adverse events | Uncommon but important adverse events | Rank for probability of hepatitis* | Rank for probability of rash |
|---|---|---|---|---|
| First-line drugs | | | | |
| INH | Rash, hepatitis, neuropathy | CNS toxicity, anemia | 2 | 3 |
| RMP | Drug interactions, rash | Hepatitis, flu-like illness, neutropenia, thrombocytopenia | 3 | 1 |
| PZA | Hepatitis, rash, arthralgia | Gout | 1 | 2 |
| EMB | Eye toxicity | Rash | 4 | 4 |
| Second-line drugs | | | | |
| Fluoroquinolones | Rash | Tendonitis, tendon rupture, QT interval prolongation | | |
| Amikacin | Nephrotoxicity, ototoxicity | | | |

CNS = central nervous system

*1 = most likely / 4 = least likely

## *INH*

INH may produce liver dysfunction ranging from asymptomatic, mild elevation of the serum transaminases to liver failure. Risk factors for hepatotoxicity include older age, daily alcohol consumption and pre-existing liver disease, particularly hepatitis C. INH may interfere with pyridoxine metabolism and cause peripheral neuropathy or other significant reactions (i.e. psychotic episodes). Rash may also occur, as may nausea and vomiting, especially with intermittent regimens administered in combination with RMP. Finally, patients may also note fatigue, drowsiness, headaches or mild hair loss.

## *RMP*

The most important adverse reactions with RMP are hypersensitivity reactions and drug interactions. Hypersensitivity reactions to RMP include skin rash, fever, abdominal pain, thrombocytopenia and a rare hypotensive reaction similar to anaphylactic shock. RMP induces hepatic microsomal enzymes and accelerates the clearance of many drugs metabolized by the liver. These include estrogens, coumadin, anticonvulsants, glucocorticoids, digoxin, antiarrhythmics, sulfonylureas, theophylline, cyclosporin, methadone and ketoconazole. Women using hormonal contraceptives should be advised to use alternative forms of birth control while receiving RMP.

RMP alone is rarely hepatotoxic, but combined with INH there is a slightly increased incidence of liver toxicity than with either drug alone. Patients receiving RMP should be informed that their saliva and urine may become orange/red in color but that this is of no significance. Those wearing soft contact lenses should be advised that the drug may lead to permanent discoloration of the lenses from pigmented tears.

## *PZA*

PZA is the most common cause of drug-induced hepatotoxicity and rash in patients taking standard initial therapy. In up to 11% of people taking PZA arthralgias will develop; these can be very painful but are easily managed with non-steroidal anti-inflammatory drugs. Almost invariably PZA will cause elevation of serum uric acid levels, but acute gout is rarely seen except in patients with pre-existing gout. Gastrointestinal upset may also occur with PZA.

## *EMB*

Visual impairment manifested by decreases in visual acuity, visual fields or colour vision is the most significant adverse effect of EMB. Risk factors include higher doses (e.g. 25mg/kg), older age and renal impairment.

Patients should be advised to report any change in vision immediately. Patients who will take EMB for longer than just the initial phase should be referred to an ophthalmologist for periodic assessment of visual acuity, colour vision and visual fields. Monthly nursing assessment of visual acuity and red-green colour discrimination is recommended. EMB-related optic neuritis is usually reversible if the drug is stopped promptly, although resolution can take several months. EMB should be used with caution in children who are too young for monitoring. Other side effects, such as rash may also occur.

## Suggested Management of Common Adverse Reactions

Appropriate management of adverse reactions is complicated. If there is uncertainty, consultation with a TB specialist is recommended.

All of the TB drugs may cause rash, although some cause rash more frequently than others. Mild itching or slight rash may be treated symptomatically without changing TB treatment. It is important to remember that failure and relapse rates are higher with alternative regimens; hence, any decision to stop the first-line drugs should never be made lightly. However, if the rash is generalized, particularly if associated with involvement of mucous membranes, wheezing, hypotension etc., then stop treatment and follow these recommendations:

- Stop all current drugs, and immediately start at least two alternative TB medications:
  - A fluoroquinolone plus an injectable or an oral second-line agent
- Review the history carefully, especially with regard to other possible causes of rash, such as food allergies or other drugs taken, including over-the-counter and herbal remedies
- When rash has resolved restart one TB drug. Give the drug judged least likely responsible but also one of the most effective TB drugs. If history is unclear (which is the norm) give INH
- Wait 2–3 days to verify if rash recurs with INH before starting the second drug – RMP
- If there is no rash after 2–3 days of RMP give EMB
- If there is no rash with EMB, assume that the rash was due to PZA. The decision to rechallenge with PZA depends on the need for PZA and the severity of the initial allergic reaction
- If the rash recurs with one agent, then discontinue that drug permanently and start all remaining drugs. Adjust the regimen according to which drug was permanently stopped

## Interactions of TB Medications with Drugs and Food

Significant interactions may occur between TB medications and other medications. The absorption of some TB drugs may be adversely affected by food. A **list of significant interactions** is available from the Heartland National TB Center, Texas.

The most important cause of interactions with other medications is RMP. Most of these drug interactions can be managed by adjusting the dosage according to measured drug concentrations (e.g. phenytoin), by monitoring the clinical effect of these drugs (e.g. international normalized ratio for warfarin) or by substituting certain drugs (e.g. antiretroviral regimens).

***Please refer to drug monograph for complete information on each drug.**

## Management of Presumed TB Drug-Induced Hepatitis

Drug-induced hepatitis can be caused by PZA, INH or RMP, in that order of probability Diagnosis may be difficult, as symptoms are nonspecific. A feeling of being unwell may be the first sign of impending hepatitis. If the serum transaminase level (aspartate aminotransferase or alanine aminotransferase) exceeds five times the upper limit of normal, signs and symptoms present or clinical jaundice develops then the following recommendations are suggested:

- Stop PZA, INH and RMP, and immediately start at least two alternative TB medications: a FQN plus an injectable, or a FQN plus an oral second-line agent
- Review the history carefully, especially with regard to other possible causes of hepatotoxicity, such as alcohol or other drugs taken, including over-the-counter and herbal remedies. Check viral serologies (hepatitis A, B and C)
- When transaminases have returned to normal restart one of the three TB drugs stopped earlier. Give RMP, as this drug is the least likely to be responsible and is the most effective TB drug
- Wait 2 weeks to verify that transaminases remain normal with RMP before starting INH. If initial hepatotoxicity was very severe (ALT >1,000U/L) it may be wiser not to rechallenge with PZA or with INH; fatalities have been reported with INH rechallenge in this situation. This depends on the need for these two drugs. Consult with a TB specialist
- If RMP and INH are restarted and transaminases remain normal, assume that the hepatitis is due to PZA. Do NOT rechallenge with PZA

If hepatitis recurs with one agent, then discontinue that drug permanently and start all remaining drugs. Adjust regimen according to which drug was permanently stopped.

# INH Drug Overdose

Table 8.13: INH Drug Overdose

| INH Drug Overdose |
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| Below is the recommended antidote for INH overdose. Consult with your on-call physician/ pediatrician **IMMEDIATELY** and initiate treatment.<br><br>Consider calling the **PADIS – Poison and Drug Information Services, Alberta and Northwest Territories contact: 1-800-332-1414.**<br><br>Management of INH overdose includes supportive care focusing on patient's cardiovascular status, protecting the airway, abolishing seizure activity and correcting metabolic acidosis.<br><br>As soon as an overdose of INH has been recognized (even in the absence of symptoms), Pyridoxine IV should be administered to prevent neurotoxic effects.<br><br>The same dose of Pyridoxine (Vitamin B6) as the dose of INH ingested should be given intravenously.<br><br>• For example, a child who has ingested 3.0g of INH should be given 3.0g of pyridoxine. If the dose is not known, Pyridoxine should be given intravenously in a dose of 5g in adults or 70mg/kg (maximum dose 5g) in children, at a rate of 1g every 2–3 minutes (CP, 2013).<br>• This dose of pyridoxine should be repeated in two hours if the response to treatment has been incomplete. A total dose of 25g may be required in the first 12 hours.<br>• A single dose of activated charcoal should be considered at a dose of 1g/kg.<br>• Diazepam IV with addition of Phenobarbital or Propofol may be used in addition to Pyridoxine to treat convulsions.<br>• Diazepam (Valium) should be given to control seizures (2mg by rectum for babies over the age of six months, or 5–10mg intravenously for older children and adults). Phenytoin (Dilantin) **should not** be given as it increases levels of INH. Please note INH also increases serum levels (Dart, 2004).<br>• Once the patient is stabilized, refer to an internal medical specialist or pediatrician for further medical treatment. |