Drugs reviews

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1. Drugs and damage to the liver

This short review was inspired by an article in "*Hospital Medicine*" [1]. The availability of plasma liver function tests (LFTs) to monitor hepatotoxicity (liver [hepatic] damage) is uncommon in many resource-poor countries. Even so we must be aware of and not ignore the risk of hepatic damage from many commonly used drugs. It is important to realise that drugs are the commonest cause of liver failure.

The likelihood (susceptibility) of an individual suffering the hepatotoxic effects of any chemical depends on many factors:

- In **children salicylates** and **valproic acid** more commonly cause microvesicular steatosis[1].
- **Older people** are more at risk from **isoniazid**.
- **Females** are more at risk of adverse drug reactions in the liver than males.
- **Nutrition** influences the chance of hepatotoxicity.
- **Alcohol abuse**: e.g. small amounts of **paracetamol** may cause liver damage.
- **Pregnancy**.
- **Underlying liver disease**: toxicity may not necessarily be more common but if a toxic effect does occur it is likely to be more serious because of the reduced liver reserve.
- **Genetic** differences in enzymes (e.g. cytochrome p450) and immunity.

There are two main mechanisms in the generation of a toxic effect; these may work separately or together:

- An immune response (in which there may be a rash, fever and eosinophilia which should be fairly easily detected on a blood film) and/or
- Interference with cellular biochemistry.

A number of biochemical and clinical patterns of drug-induced hepatotoxicity may occur as shown in Table 1.

Table 1. Patterns of drug/chemical hepatotoxicity

Type	Features	Enzymes
Acute hepatocellular damage (commonest)	Hepatitis, necrosis, steatosis	ALT = 2 x ULN or Ratio ALT : ALP > 5
Acute cholestatic[2] damage	Pruritus (itching), jaundice, pain, rash, fever	ALP > 2 x ULN or Ratio ALT : ALP < 5
Mixed		Ratio ALT : ALP = 2 - 5

[ALT: alanine transaminase; ALP: alkaline phosphatase; ULN: upper limit of normal.]

How do we conclude that a drug (or chemical) may be the cause of an hepatic problem?

- Firstly ***consider*** the possibility - i.e. be very suspicious and remember the eight bullet points listed above.
- If the patient has been on the drug for over 3 months the chance of toxicity is less likely.
- Has the clinical/biochemical situation improved since the drug was withdrawn?
- If the drug has been given more than once (not a wise thing to do!!) has the patient experienced the same toxic problem?

The problem with many patients is that they are taking several drugs often including herbal traditional remedies.

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1 'Microvesicular steatosis of the liver' refers to a type of liver fat accumulation. It was originally described in association with conditions which share a limited number of similar features: acute fatty liver of pregnancy, Reye's syndrome, sodium valproate toxicity, high-dose tetracycline toxicity and certain congenital defects of urea cycle enzymes. Recently the disease has been described in many conditions: alcoholism, toxicity of several medications, delta hepatitis in South America and Central Africa, sudden childhood death, congenital defects of fatty acid beta oxidation and cholesterol ester storage disease. Our understanding of the pathogenesis of microvesicular steatosis is limited. In some cases it may be linked to a mitochondrial abnormality.

2 Conditions giving rise to **cholestasis** (i.e cholestatic situations) fall into two main categories. Those where there:

- is a mechanical blockage in the duct system - obstructive or extrahepatic cholestasis.
- are disturbances in bile formation - hepatocellular or intrahepatic cholestasis.

Drugs that may cause hepatic problems

- **Sulphonylureas** (e.g. glibenclamide, chlorpropamide) may cause an hepatitis with a cholestatic or granulomatous[3] pattern associated with hypersensitivity features of rash, fever, arthralgia and eosinophilia. In severe cases erythema multiforme and exfoliative dermatitis may occur. These reactions usually appear within the first eight weeks of treatment.
- **Chlorpromazine and prochlorperazine** commonly cause cholestasis.
- **Phenytoin and carbamazepine** may lead to the 'reactive metabolite syndrome'. This occurs up to eight weeks after taking the drug. The features are fever, rash, lymphadenopathy and often Stevens-Johnsons syndrome. There is frequently hepatocellular damage.
- **Erythromycin** may lead to pruritus (itching), jaundice and a blood eosinophilia reflecting cholestatic toxicity.
- **Anti-tuberculous drugs** cause LFT disturbance in 20% of patients but do not usually lead to clinical problems as the abnormalities resolve even as treatment is continued. Nevertheless hepatic toxicity can be serious and life-threatening. So beware!

Rifampicin + isoniazid
↓
Induction of p450 enzymes
↓
Enhanced production of toxic metabolites from isoniazid
↓
Serious hepatotoxicity in 1% (hepatocellular pattern)

Similarly **pyrazinamide** causes hepatotoxicity. This is dose-related so **reduce the dose for small patients.**

Advice for the treatment of tuberculosis
Measure LFTs before treatment and if abnormal repeat every two to four weeks. If enzyme levels rise to more than five times the upper limit of normal withhold treatment until there is a return to baseline figures.

- **Anti-retroviral drugs (ARVs):** many raise the liver enzymes (e.g. **ritonavir, saquinavir**) and some cause a severe hepatitis (e.g. **nevirapine**) which may be fatal, or hepatic steatosis (e.g. **stavudine**). As the availability of ARVs increases there will be a need to widen the facilities for LFTs.

Herbal medicines

Herbal and other 'traditional' remedies are used widely in Africa. However little has been published about their use or adverse effects.

Reference

1. Rashid M, Goldin R and Wright M. Drugs and the liver. *Hospital Medicine* ***65*** *(8): 456 – 461. 2004*

2. Side-effects of drugs used to treat tuberculosis

The review above stated that "**Anti-tuberculous drugs** cause Liver Function Test (LFT) disturbance in 20% of patients but uncommonly lead to clinical problems as the abnormalities resolve even as treatment is continued". However in a small number of patients severe hepatotoxicity may result. The more drugs that are prescribed to a patient **at the same time** the more likely there is to be an adverse reaction. The treatment of tuberculosis usually involves the use of four drugs in the initial phase. This review summarises the potential complications that rifampicin, isoniazid, pyrazinamide and ethambutol may cause. Thiacetazone is mentioned although it is much less commonly used.

3 A **granuloma is** a roughly spherical mass of immune cells that forms when the immune system attempts to wall off substances that it perceives as foreign but is unable to eliminate. Such substances include infectious organisms such as bacteria and fungi as well as other materials such as keratin and suture fragments. A granuloma is a special type of inflammation that can occur in a wide variety of diseases. The adjective **granulomatous** means *characterized by granulomas* (from "Wikipedia").

Potential complications

Rifampicin

- Gastro-intestinal symptoms are common with many drugs and often these will clear if the patient is able to tolerate them: **anorexia, nausea, vomiting and diarrhoea.**
- **Urine, saliva and other body fluids may be coloured orange-red**: this can be very alarming to patients so they should be warned and reassured.
- The **hepatic microsomal enzymes are induced** and these increase the rate of metabolism of certain medications such as oral contraceptives and antidiabetic drugs (sulphonylureas [e.g. glibenclamide, chlorpropamide] and biguanides [e.g. metformin]), steroids and dapsone. The effectiveness of these drugs is likely to be reduced.

Side-effects are uncommon but include:

- **Skin reactions**: rash, urticaria, flushing. Fortunately many of these reactions are self-limiting and gradually clear; the patient only needs symptomatic relief and reassurance until this happens.
- **Myalgia** (muscle aches and weakness).
- **Hepatitis**: see advice for patients under isoniazid.
- **Fever.**
- **Thrombocytopaenia** (reduced platelet numbers so predisposing the patient to bleeding) **and rarely haemolytic anaemia, leucopaenia** (low white blood cell count predisposing the patient to infection) and **eosinophilia**.

Isoniazid

- Gastro-intestinal symptoms: **nausea, vomiting.**

Most serious side-effects are uncommon (except **peripheral neuropathy**). There are two groups of patients: **slow and fast acetylators.** The fast acetylators metabolise isoniazid more rapidly than the slow acetylators. Therefore the slow acetylators are more likely to experience adverse reactions.

- **Peripheral neuropathy** is more common in patients with **diabetes mellitus, alcoholism, chronic renal failure, malnutrition and infection with the HIV**. Pyridoxine 10 mg daily should be given to these at-risk patients as a prophylaxis.
- **Hypersensitivity reactions**, which may occur together: **fever, purpura, erythema multiforme.**
- **Hepatitis** (more common in the over 35-year-olds): patients should be advised to report any nausea, vomiting, malaise and jaundice especially if in combination.
- **Gynaecomastia.**
- **Hyperglycaemia.**

Pyrazinamide

- Gastro-intestinal symptoms: **anorexia, nausea, vomiting and aggravation of the symptoms of peptic ulcer.**
- **Hepatitis** (see above): this may range from symptomless changes in LFTs to the **rare** occurrence of liver necrosis.
- **Rashes** including light sensitivity and urticaria.
- **Arthralgia.**
- **Gout:** pyrazinamide breaks down to pyrazinoic acid, which inhibits the excretion of uric acid by the kidney tubules.
- **Sideroblastic anaemia.**

Ethambutol

- **Ocular toxicity (retrobulbar neuritis)** which tends to be dose-related (i.e. the higher the dose the greater the chance of this problem)**.** Avoid this drug in patients with impaired renal function otherwise serum levels will rise and increase the risk of this eye side-effect. **Warn patients to report any changes in their vision.**
- **Red/green colour blindness.**
- **Peripheral neuropathy.**
- **Rashes** including urticaria and pruritus.
- **Hepatitis** (see above).
- **Thrombocytopaenia.**

Thiacetazone

- Gastro-intestinal symptoms: **anorexia, nausea, vomiting.**

- **Skin hypersensitivity** including erythema multiforme and exfoliative dermatitis. *"Skin rash has been reported as a common problem among HIV-positive people receiving thiacetazone. In a retrospective survey, 24/79 (30.4%) Zambian HIV-positive adults who were treated with a thiacetazone-containing antituberculous regimen were found to have developed a skin rash that required a change of treatment. A cohort study of Zambian children aged between 1 month and 15 years also reported a high rate of adverse effects among HIV-positive children treated with thiacetazone (19/88 [22%]). Twelve children (14%) developed a severe mucocutaneous reaction (Stevens-Johnson syndrome) and 11 (13%) of these children died"* [1].
- **Vertigo.**
- **Conjunctivitis.**
- **Hepatitis.**
- **Haemolytic anaemia and agranulocytosis** (strictly means the absence of polymorphonuclear granulocytes).

HIV-infected patients: a special note

These patients are more likely to experience side-effects from anti-tuberculosis chemotherapy (see thiacetazone above). The particular adverse reactions are:

- Cutaneous.
- Hypersensitivity reactions.
- Blood complications.
- Hepatic toxicity.
- **Rifampicin** may cause anaphylaxis.
- **Rifampicin** and **isoniazid** reduce the beneficial effects of ketoconazole and fluconazole.
- The absorption of **rifampicin** by the gastro-intestinal tract may be reduced by ketoconazole.

Editor's note: If any of our readers come across an unusual reaction to a drug (perhaps in association with other diseases) please send a case report to this journal. Such experiences can then be widely shared amongst colleagues.

Reference

1. Antituberculous treatment containing thiacetazone: http://bestpractice.bmj.com/best-practice/evidence/intervention/0920/0/sr-0920-i3.html

Do you think many medicines are prescribed, dispensed or sold inappropriately in South Sudan?

If so you may be interested to read about the **Rational use of medicines** in:

- WHO Fact Sheet 338 of May 2010 at http://www.who.int/mediacentre/factsheets/fs338/en) and
- The Lancet, Volume 375, Issue 9731, Page 2052, 12 June 2010.