Dealing with Adverse Drug Events in a Patient Taking Anti-tuberculosis Treatment

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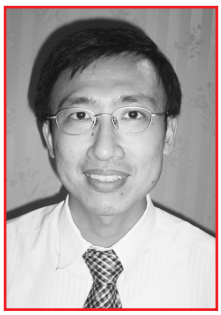

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Introduction

Despite the effectiveness of the modern six-month short course combination regimen in the treatment of tuberculosis (TB), adverse drug events are encountered at a considerable frequency, especially among the elderly and patients with various comorbidities or concomitant medications. Most of these adverse events are mild and self-limiting, but some are severe and life-threatening. Patients experiencing such effects are also more likely to default[1]. With the changing demographic and clinical profile of our patients, careful management is therefore called for.

Prevention is always the best

Proper clinical assessment is important before starting anti-TB treatment. Baseline blood and visual tests help to identify risk factors[2], and also provide a basis for comparison in case of problems. While hypersensitivity reactions and idiosyncratic toxicity are often difficult to predict, dose-related adverse events are preventable by proper prescription with due attention to underlying risk factors[3] (see Table 1). It is also essential to educate patients and their family members on common and important adverse drug events[3] (see Table 2). They should be reminded to report symptoms promptly so that appropriate actions can be taken early. Directly observed treatment facilitates early detection of adverse drug events.[3] Periodic biochemical monitoring is recommended for patients at risk of adverse drug events.[2]

A problem-oriented approach

Owing to substantial individual variations and difficulty in predicting adverse drug events, most of the following recommendations are based on expert reviews rather than controlled trials[2-5]. As untreated TB carries a high mortality as well as public health hazard, it is desirable to avoid unnecessary drug interruption or suboptimal treatment, which may lead to treatment failure and / or emergence of resistance. On the other hand, timely removal of the offending drug in presence of adverse drug events is crucial for safety. To strike a balance of these two conflicting goals, a pragmatic approach may comprise several steps: recognition, assessment of severity and risk, deciding on treatment continuation versus suspension, and sequential reintroduction of drugs.

Recognition of adverse drug events

Not all adverse events in the course of anti-TB treatment are drug-induced. For example, fungal infection and scabies may be mistaken for drug rash, thrombocytopenia due to hypersplenism for rifampicin-induced thrombocytopenia, and senile purpura for thrombocytopenic purpura. Meticulous attention to the patient's past health, the time-course of the events, careful examination and clinical acumen are necessary to identify what has actually happened.

When an adverse drug event is identified, it would be useful to review the drug history. One or more drugs may be responsible. While we may be able to ascribe relatively specific drug adverse events to certain drugs (see Table 2), it is often difficult to pinpoint the exact offending agent in the first encounter with gastrointestinal intolerance, hypersensitivity reaction or hepatitis. Adverse events may also occur as a result of interaction between rifampicin and concomitant medications[2] (see Table 3). Rifampicin is a potent inducer of cytochrome P450 (CYP), which is a complex family of metabolic enzymes. The enzyme-inducing activity of rifampicin may last for two to four weeks after its suspension. Rifabutin, a less potent enzyme inducer, is often used to substitute for rifampicin when antiretroviral therapy is co-administered[6]. However, being a partial substrate for CYP 3A, rifabutin may accumulate and predispose to uveitis in the presence of CYP 3A inhibitors.

Assessment of severity and risk

Severity of adverse events is assessed clinically and aided by blood tests as appropriate. In general, mild adverse events are either limited in distribution or associated with mild derangement in blood tests. An important reference is the patient's baseline condition (including underlying diseases). The onset and time course of treatment intolerance are also of direct

relevance. Owing to potential risks, some adverse events are always considered severe, for example, thrombocytopenic purpura, retrobulbar neuritis, and convulsion.

Continuation versus suspension of treatment

The decision to continue or suspend treatment hinges on risk assessment. In general, mild adverse events can be managed symptomatically without treatment interruption, while others require treatment suspension.[2,3] Table 4 summarises actions that may be taken for tackling some common adverse drug events.[2, 7]

If treatment is continued, the patient should be monitored carefully by clinical assessment and / or biochemical tests. While dosages may be adjusted for dose-dependent adverse effects, split doses should be avoided as they may lead to suboptimal drug levels. Suspension of treatment may be necessary in case of progressive worsening of the adverse events or failure to respond to supportive measures. If it is necessary to withhold first-line drugs, interim treatment with second-line drugs may be required when TB is severe or disease progresses after treatment suspension.[3]

Sequential reintroduction of drugs

Although it may be necessary to suspend drugs for up to four weeks in severe cases of adverse drug events, prolonged interruption of treatment may jeopardize the chance of cure or extend the overall treatment duration. Attempts should therefore be made to resume treatment as soon as adverse drug events have subsided.

As it is usually difficult to pinpoint the exact offending agent for the initial adverse events, it is often necessary to reintroduce the original drugs sequentially to identify the culprit. However, drugs that may have caused severe toxic reactions should not be reintroduced as far as possible.[3] Attempts should be made to establish an effective regimen within a reasonably short period. To avoid the emergence of drug resistance, it is essential to avoid monotherapy of any significant duration (for example, over 1 week[3]). Drugs previously not used or unlikely to cause similar effects may be added if necessary.

Drug challenge aims at identifying the culprit drug in the shortest possible time. Slightly different approaches are adopted for hypersensitivity reactions and drug-induced hepatitis because hypersensitivity reactions usually occur within two to three days of challenge while drug-induced hepatitis often takes one week or more to develop.[2]

Challenge after hypersensitivity reactions is done by reintroducing drugs one by one every two to three days in the order of increasing risk of hypersensitivity reactions, for example, rifampicin, isoniazid, pyrazinamide, and then ethambutol or streptomycin.[2] A starting dose around one-sixth of full dose is recommended (in the belief that it may cause a lesser reaction). This is followed by rapid escalation to full dose.[5] The offending drug is removed should reaction recur. Drugs are added on sequentially until an effective regimen is established.

Challenge after hepatitis is usually done in the presence of at least two other drugs (for example, streptomycin, ethambutol, and levofloxacin) to reduce the risk of acquiring drug resistance. Potential culprits are added in full dose sequentially and cumulatively in the order of increasing risk of hepatitis, for example, rifampicin, isoniazid, and pyrazinamide.[2] Liver function tests are monitored about one week after challenge. Closer monitoring may be required for major hepatotoxicity. Apart from clinical features and risk factors for hepatitis, the maximal serum alanine aminotransferase (ALT) level may serve as a useful guide to the severity of hepatotoxicity. When hepatitis occurs with ALT less than five times the upper limit of normal (ULN), challenge may be shortened by reintroducing isoniazid and rifampicin together. If ALT exceeds five times ULN, it is prudent to reintroduce potential culprits one by one weekly. When ALT exceeds ten times ULN, pyrazinamide is often omitted if both isoniazid and rifampicin can be successfully reintroduced.

Desensitisation is sometimes attempted with progressively increasing doses to overcome hypersensitivity reactions. As desensitisation may take more than one week, it is preferably done in the presence of two to three other drugs. Each increment may be around one-tenth[5] or less of full dose. If a mild reaction occurs, symptomatic treatment will be provided with antihistamine and / or topical steroid. The same dose will be maintained until the rash subsides. The procedure can be shortened by giving the concerned drug twice daily.[5] Some experts recommend giving prednisone (1-2 mg/kg body weight per day) for 3 days before desensitisation and continuing the steroids for up to 2 weeks before gradual tapering.[3] A case series reported the use of prednisone ranging from 20 mg to 80 mg daily during desensitisation.[8] Giving oral corticosteroids twice daily may control drug fever more effectively than a bigger overall dose given once daily.[9] The result of desensitization is not always predictable, and caution should be exercised against the risk of a severe reaction. The threshold for desensitisation is lowered if an optimal regimen cannot be established with alternative drugs.

Conclusions

Although there are rules of thumb for managing adverse drug events in the course of anti-TB treatment, it is difficult to standardise the management for every case.[3] Adverse drug events are preferably managed by, or in consultation with, physicians with adequate experience in the field.[3] Readers are also encouraged to refer to local guidelines for further information. [7, 10]

Table 1. Risk factors for adverse drug events complicating anti-tuberculosis treatment

Risk factor	Reasons
Ageing	Changes in drug metabolism and excretion
Malnutrition	Fatty liver reduces hepatocyte glutathione and hence neutralisation of toxic metabolites originating from drug acetylation; hypoalbuminaemia increases the unbound drug fraction.
Pregnancy	Fatty liver; hypoalbuminaemia; adverse effects on fetus (examples: aminoglycoside impairs hearing of newborns; quinolones cause growth cartilage abnormalities; ethionamide is potentially teratogenic)
Liver or kidney dysfunction	Anti-TB drugs can cause liver or kidney toxicity. Chronic hepatitis status (notably hepatitis B or C), and chronic liver diseases (notably alcoholic liver diseases), predispose to drug-induced hepatitis.
Treatment with other drugs	Cytochrome P450 has been frequently associated with the production of hepatotoxic reactive metabolites.
Disseminated or advanced TB	Probably a consequence of malnutrition or liver deterioration
Previous anti-TB treatment	Increased risk of hypersensitivity reactions; history of adverse events may recur.
Atopy	Linked to a family history of adverse anti-tuberculosis drug reactions
HIV infection	The risk of adverse reactions increases with the degree of host immunosuppression.

Table 2. Adverse reactions to anti-tuberculosis drugs

Drug	Reactions		
	Common	Uncommon	Rare
Isoniazid		Hepatitis Cutaneous hypersensitivity Peripheral neuropathy	Giddiness Convulsion Optic neuritis Mental symptoms Haemolytic anaemia Aplastic anaemia Lupoid reactions Arthralgia Gynaecomastia
Rifampicin		Hepatitis Cutaneous hypersensitivity Gastrointestinal reactions Thrombocytopenic purpura Febrile reactions "Flu syndrome"	Shortness of breath Shock Haemolytic anaemia Acute renal failure
Pyrazinamide	Anorexia Nausea Flushing	Hepatitis Vomiting Arthralgia Cutaneous reaction	Sideroblastic anaemia
Ethambutol		Retrobulbar neuritis Arthralgia	Cutaneous reaction Peripheral neuropathy
Streptomycin	Cutaneous hypersensitivity Giddiness Numbness Tinnitus	Vertigo Ataxia Deafness	Renal damage Aplastic anaemia
Thiacetazone	Gastrointestinal reactions Cutaneous hypersensitivity Vertigo Conjunctivitis	Hepatitis Erythema multiforme Exfoliative dermatitis Haemolytic anaemia	Agranulocytosis
Amikacin Kanamycin Capreomycin	Ototoxicity: hearing damage, vestibular disturbance Nephrotoxicity: deranged renal function test	Clinical renal failure	
Ofloxacin Ciprofloxacin	Gastrointestinal reactions Insomnia	Anxiety Dizziness Headache Tremor	Convulsion Tendinitis and tendon rupture
Ethionamide Prothionamide	Gastrointestinal reactions	Hepatitis Cutaneous reactions Peripheral neuropathy	Convulsion Mental symptoms Impotence Gynaecomastia
Cycloserine	Dizziness Headache Depression Memory loss	Psychosis Convulsion	Sideroblastic anaemia
Clofazimine	Nausea Giddiness Discolouration of skin (dose-related) and urine Dryness of skin	Eye irritation Diarrhoea with high doses	Taste disorder
Para-aminosalicylic acid	Gastrointestinal reactions	Hepatitis Drug fever	Hypothyroidism Haematological reactions

Table 3. Some common and important drug interactions with rifamycins and fluroquinolones

Major categories	Classified examples
Drugs with concentrations reduced by rifampicin	a. Nine subgroups with "anti-" as prefix: Anticoagulants: warfarin Anticonvulsants: phenytoin, lamotrigine Antibiotics: erythromycin, clarithromycin, doxycycline Antifungals: azoles such as itraconazole, voriconazole Antimalarials: atovaquone, mefloquine Antidepressants: nortriptyline Anti-arrhythmic agents: quinidine, tocainide, propafenone Anti-hypertensive agents: ACEI and AII-RA (e.g. enalapril, losartan) beta-blockers (e.g. propranolol, metoprolol) calcium channel blockers (e.g. nifedipine, diltiazem,verapamil) Antiretroviral agents: Protease inhibitors (e.g. indinavir, ritonavir, saquinavir) NNRTI: delavirdine, nevirapine, efavirenz b. Anxiolytics: diazepam c. Bronchodilators: theophylline d. Cardiac glycosides: digitoxin e. Hormonal agents: combined and progestogen-only pills, tamoxifen, levothyroxine f. Hypoglycaemics (sulphonylurea): tolbutamide, chlorpropamide g. Immunosuppressants: corticosteroids, cyclosporin, tacrolimus h. Lipid-lowering drugs: simvastatin, fluvastatin i. Narcotics: methadone
Drugs that increase rifabutin concentrations	Antibiotics: clarithromycin Antifungals: fluconazole Protease inhibitors: ritonavir
Drugs that reduce rifabutin concentrations	NNRTI: efavirenz
Drugs that reduce absorption of fluoroquinolones	Drugs containing divalent cations such as calcium, iron, and zinc: Antacids Vitamins Sucralfate Didanosine (chewable)

Notes. NNRTI nonnucleoside reverse transcriptase inhibitor
ACEI angiotensin converting enzyme inhibitor
AII-RA angiotensin-II receptor antagonist

Table 4. Management of common adverse drug events

Adverse events	Recommended actions
Gastrointestinal upset	1. Exclude hepatitis with blood tests. In general, symptoms are assumed to be unrelated to hepatitis if alanine aminotransferase (ALT) is less than 3 times the upper limit of normal or total bilirubin is less than 2 times the upper limit of normal. 2. Administer drugs with food. 3. If necessary, an anti-emetic may be prescribed for relief of symptoms. Avoid antacids if possible because they may reduce absorption of isoniazid and rifampicin.[3] 4. Consider daily regimens if symptoms are related to the bulk of medications in intermittent regimens. Fixed-dose combination tablets may help. 5. Avoid split doses as they may result in suboptimal drug levels. 6. Medication at bedtime may help if treatment is self-administered.
Non-petechial rash	1. Exclude other causes. 2. Mild cases: symptomatic relief with antihistamines and /or topical steroid; watch out for progression and /or mucosal involvement 3. Moderate to severe rash: suspend treatment; give anti-histamines, prescribe systemic steroids in life-threatening situations[5]; reintroduce drugs later with caution (see text).
Drug fever	1. Exclude superinfection or worsening of TB. 2. Suspend treatment. Reintroduce drugs later sequentially to identify offending agents. 3. Oral steroids may help (see text).
Hepatotoxicity	1. Identify underlying risk factors. 2. Withhold treatment if ALT exceeds 3 times the upper limit of normal or total bilirubin exceeds 2 times the upper limit of normal. 3. When hepatitis is suspected clinically, treatment may be withheld before blood test results are available. 4. Reintroduce drugs when ALT returns to normal or baseline (see text). 5. In case of treatment need, earlier reintroduction may be considered when ALT is less than 2 times the upper limit of normal. A non-hepatotoxic interim regimen (based on streptomycin, ethambutol and a fluoroquinolone) may also be employed.

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