



Reactions to Antituberculous Drugs and Desensitization Treatment

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Abstract

Purpose of review This paper intends to review the most frequent adverse reactions to antituberculous drugs specifically those classified as hypersensitivity in nature, and how to deal with this problem in practical terms. It is known that any adverse effect can occur with any drug and antituberculous agents are not an exception.

Recent findings Some risk factors have been described including high age, malnutrition, and high alcohol consumption. We will focus on hypersensitivity reactions to isoniazid, rifampicin, pyrazinamide, and ethambutol.

Summary The paper addresses specifically the most described hypersensitivity reactions to each of these drugs. If any important reaction occurs, the drugs should be stopped until total resolution of the reaction. When other strategies fail and if the drug is necessary as one of the first-line drugs to the treatment, desensitization can be used as a method to reintroduce the drug. The authors address this issue either in theoretical terms as examples with protocols for immediate and non-immediate reactions.

Introduction

Mycobacterium tuberculosis (MT) infection remains a major cause of global mortality and morbidity and the resulting disease, tuberculosis (TB), caused an estimated 1.7 million deaths in 2009.

Although prevalent worldwide and potentially fatal if proper treatment is not instituted, tuberculosis (TB) it is curable. Moreover, it is an infectious disease and most of the 2 billion people estimated to be infected with *M. tuberculosis* having an asymptomatic infection, termed latent TB infection (LTBI) [1••, 2, 3].

Similar to other *mycobacterial* infections, treatment of TB requires simultaneous administration of multiple drugs. The treatment usually consists of rifampicin (RIF), pyrazinamide (PZA), isoniazid (INH), ethambutol (EMB), and streptomycin (SM) for six months.

Although the majority of treatment programs progress with minor side effects, adverse drug reactions (ADRs) can occur. No consensus has been reached concerning the overall incidence of the ADRs to these drugs. These adverse effects or drug interactions can make it necessary to modify or discontinue treatment. Different studies report incidences from 5.5 to 57.8%

according to different populations and ADRs definitions [4••, 5, 6••, 7•, 8, 9].

In the presence of a major ADR to an antituberculous drug, the discontinuation of that drug is advisable. Alternative agents may lead to greater toxicity, are often less effective, frequently requires longer treatment courses and as a result, the risk of treatment failure and relapses are much higher in these cases [10–13].

Of the ADR that can be induced by these drugs, some are type B, ADR reactions, and hypersensitivity reactions (DHR). These DHRs comprise all drug reactions resembling allergy. DHRs can be allergic or non-allergic with immunologically mediated DHRs being named drug allergies, a sub-type of ADR that is seen in 4–5% of the general population with cutaneous reactions in up to 5% of treated patients. These (DHR) reactions are defined as those that are objectively reproducible with signs and/or symptoms initiated by the exposure to a drug at a dose usually tolerated by non-hypersensitive patients [14••].

Major symptoms of hypersensitivity reactions, diagnosis, and management of each therapeutic drug for *M. tuberculosis* infections are discussed below.

Common first-line drugs used to treat *mycobacterial* infections: rifampicin (RIF), pyrazinamide (PZA), isoniazid (INH), ethambutol (EMB), and streptomycin (SM)

Rifampin (RIF)

Also used to treat infections with aerobic gram-negative organisms including the asymptomatic *Neisseria meningitidis* carrier state, rifampin (RIF) remains a common therapy for latent and active tuberculosis. It is rarely implicated in hypersensitivity reactions (HR) but is associated with multiple side effects.

Side effects of RIF include an influenza-like syndrome, hepatotoxicity, skin exanthems, and induction of cytochrome P450 which may cause significant drug-to-drug interactions [15]. The influenza-like syndrome is the most commonly reported ADR, with fever, chills, headaches, myalgia, and rash. Multiple published reports have also described RIF hypersensitivity reactions in both adult and pediatric patients, ranging from pruritic skin eruptions to anaphylaxis [16•].

The pruritic skin eruptions induced by this drug can be immediate (in less than 1 h after intake) or non-immediate reactions (after 1 h of intake).

Diagnosis of rifampin hypersensitivity (HR) can be difficult because most HR are not IgE-mediated. Skin testing can be helpful in determining the likelihood of an immediate IgE-mediated reaction. Skin testing should

be performed based on published protocols where the highest non-irritating drug concentration in non-allergic control subjects was 0.002 mg/mL [17]. Other authors have also reported non-irritating intradermal concentrations for evaluation HR [18•].

RIF is an important and critical component of antituberculous therapy and very often alternative drugs are not available. Therefore, in cases of hypersensitivity to RIF, and if no similar drug is available to treat the patient, desensitization to this drug is required. Recommended dosing of RIF for TB is 600 mg daily, but maintaining a desensitized state with this dose can be problematic taking the drug's short half-life of 3 h [18•, 19••].

Despite this, a variety of techniques for desensitization have been published, from rapid protocols to those of 7 or more days duration [18•, 20]. Three pediatric case reports have been published, including one by the author [21, 22, 23••]. While uncommon, allergic reactions during rapid desensitization protocols may occur [24].

For oral RIF, the 12–13th step rapid oral desensitization protocol outlined in Table 1 is effective and safe. Strict adherence to the every 12-h dosing schedule is required to safely maintain the desensitized state.

Table 1. Oral desensitization protocol to rifampin

	Volume		Concentration		
Solution A	10	mL	0.001	mg/mL	
Solution B	10	mL	0.01	mg/mL	
Solution C	30	mL	0.1	mg/mL	
Solution D	10	mL	6	mg/mL	
Solution E	15	mL	60	mg/mL	
Step #	Dose (mg)	Solution #	Volume (mL)	Time (min)	Cumulative dose (mg)
1	0.0002	A	0.2	30	0.0002
2	0.002	B	0.2	30	0.002
3	0.02	B	2	30	0.02
4	0.2	C	2	30	0.2
5	2	D	0.3	30	2.2
6	4	D	0.7	30	6.2
7	8	D	1.3	30	14.2
8	16	D	2.7	30	30.2
9	30	E	0.5	30	60.2
10	50	E	0.8	30	110.2
11	100	E	1.7	30	210.2
12	150	E	2.5	30	360.2
13	250	E	4.2	30	610.2

Full therapeutic dose administered 12 h after initiation of step 13

Pyrazinamide (PZA)

Pyrazinamide (PZA), a synthetic pyrazine analogue of nicotinamide, is one of the most effective antituberculous drugs and is generally well tolerated. Like any other drug, it may cause adverse reactions. These reactions are mainly toxic and may affect several organs: liver (cytolysis), joints (arthralgia), and gastrointestinal with nausea, vomiting, diarrhea, and abdominal pain. This drug may also induce more severe reactions like nephrotoxicity but the most severe one is hepatotoxicity until fulminant hepatitis. It is the drug most likely responsible for the occurrence of hepatitis during therapy for active TB.

Among anti-TB medications, the incidence of serious side effects defined as those requiring a documented change in therapy or hospitalization is highest with PZA. These are associated with female sex, older age, Asian origin, and HIV infection [4••, 25].

Considering HRs, cutaneous manifestations are the most common reactions although true allergic reactions are rare [26–28]. It can be associated with early onset of maculopapular rash with pruritus sometimes in association with dyspnea (possibly due to bronchospasm) and abdominal pain suggesting anaphylactic/anaphylactoid reaction. The mechanisms underlying these reactions are not known [4••, 29••].

Hypersensitivity reactions should be suspected if an immediate skin rash develops at the beginning of treatment with PZA. If the degree of skin involvement is not severe, a sequential reintroduction of the drug beginning with small doses until the full therapeutic dose should be attempted.

In a paper by Sevim Bavbek [30], an allergic reaction was proven by positive skin prick test in a patient, performed with PZA tablets at the concentration of 500 mg/ml, with negative results in ten controls, and a positive oral provocation test. Skin prick tests were performed with PZA tablet, along with a positive

Table 2. Oral desensitization protocol with PZA [30]

Time-min	Dose (mg)	Cumulative dose (mg)	Reactions
Day 1			
0	6.25	6.25	
30	12.5	18.75	
60	25	43.75	
90	50	93.75	
150	75	168.75	
210	125	239.75	
270	250	543.75	
Day 2			
0	500	500	
30	1000	1500	
Day 3			
0	750		
60	750	1500 mg	

control (histamine 0.01%) and a negative control (saline 0.9%) 1 week after the initial reaction. A positive reaction was only seen with PZA, producing a wheal of 3 mm surrounded by erythema of 5 mm after 15 min [30]. The positivity of the skin prick test suggested an IgE-mediated mechanism, although in vitro measurement of PZA-specific IgE in the circulation was not done.

In cases of vital indication of this drug and when no alternative treatment is available, drug desensitization is an option (Table 2) [30].

Isoniazid (INH)

Isoniazid (INH) is a bactericidal antibiotic against MT. It acts by the inhibition of mycolic acid biosynthesis. However, INH also disrupts DNA, lipid, carbohydrate, and NAD synthesis and/or metabolism.

The incidence of adverse reactions to INH in more than 2,000 patients has been estimated to be 5.4% [4••, 31].

Although the incidence of adverse reactions to INH is low, the most well described are hepatic, neurologic [32••, 33••], skin reactions [34, 35], and fever [36, 37].

Skin eruptions are rare, mild, and often transient usually consisting of morbilliform and maculopapular rashes, urticaria, and pruritus [38–40]. Cutaneous reactions in patients on therapy are often difficult to diagnose, as in most cases several drugs are taken simultaneously.

The liver is the most commonly affected organ [41] and up to 20% of patients experience having a mild liver injury which is usually subclinical and self-limited. A less common form of reaction to INH is hepatitis. The mechanism of liver damage is not completely understood, although it seems related to direct toxicity of the drug [41].

Table 3. Oral desensitization protocol with isoniazid [43]

Time-min	Dose (mg)	Cumulative dose (mg)	Reactions
0	0.050	0.050	
20	0.10	0.15	
40	0.25	0.40	
60	0.50	0.90	
80	1.00	1.90	
100	2.00	2.90	
120	4.10	8.00	
140	8.20	16.20	
160	16.30	32.50	
180	30.60	63.10	
200	50.30	113.40	
340	100	213.40	
480(8 h)	150.00	363.40 (total daily dose)	

Concerning the diagnosis, skin tests [42] with injectable forms for prick and intradermal tests can be useful in the rare cases of type I allergic reaction (IgE-dependent) to INH.

Skin tests were performed by S Rodrigues et al. [43] in a case of a generalized maculopapular rash, fever, and diarrhea after treatment with several antituberculous drugs. Prick test with INH was performed with an undiluted solution of 100 mg/ml and the intradermal test, with positive result, with a 1/10 concentration of the previous.

Several protocols have been published in the literature concerning desensitization to INH [21, 43–45] (Table 3).

Ethambutol (EB)

Ethambutol (EB) is a bacteriostatic antimycobacterial drug most commonly used in combination with other drugs in the treatment of tuberculosis. The mechanism of action is not completely known. There is evidence that the drug exerts its bacteriostatic activity by inhibition of arabinosyltransferase, an enzyme that polymerizes arabinose into arabinan and then arabinogalactan, a mycobacterial cell wall constituent [4••].

The dose of ethambutol is dependent upon body weight, frequency of administration, and indication. It is generally well tolerated. Side effects are usually dose-related and more common when doses exceed 15 mg/kg [46•].

The main side effect of ethambutol is ocular toxicity due to optic neuritis. Intermittent dosing may decrease the risk of ocular toxicity as confirmed by Griffith et al in a study of 229 patients treated with ethambutol for pulmonary *Mycobacterium avium* complex disease [46•].

The combination of ethambutol with pyrazinamide for the treatment of latent tuberculosis in patients exposed to multidrug-resistant strains has been associated with a high incidence of hepatotoxicity or gastrointestinal intolerance leading to discontinuation of therapy (approximately 60% of treated subjects in one report) [47].

Hypersensitivity reactions to ethambutol such as rash and drug fever have been reported in 0.5% and 0.3% of patients, respectively [48]. Others, such as dermatosis-like pigmentation [49], lichenoid eruptions [50], pulmonary infiltrates [51••], and toxic epidermal necrolysis [52] have been described.

Skin and serological tests are usually unreliable, with single reports of positive patch tests [38] and positive lymphocyte stimulation test to ethambutol. In cases of severe reactions like exfoliative dermatitis, oral provocation tests are not recommended because of the severe risks associated.

Skin prick and intradermal tests can be performed according to EAACI guidelines [52, 53••]. Immediate and late readings of intradermal tests performed with sterile solutions of 1 mg/mL and 10 mg/mL are recommended. Immediate reading can be negative with late positive intradermal readings as hypersensitivity reactions are mostly non-IgE mediated [54•].

We present a modified one-day, tolerance induction protocol based on our own experience used in several patients from the infectious department, with mild/moderate non-immediate cutaneous hypersensitivity reactions to EB (Table 4) [54•]. The protocol consisted of a two-fold increase in drug dose every 45 min until the desired total daily dose was reached.

Table 4. Rapid oral desensitization to ethambutol [54••]

Solution (mg/mL)	Time (min)	Dose (mL)	Dose (mg)	Cumulative dose (mg)
0.01	0	1	0.01	0.01
	30	2	0.02	0.03
	60	4	0.04	0.07
	90	8	0.08	0.13
0.1	120	1	0.1	0.23
	150	2	0.2	0.43
	180	4	0.4	0.83
	210	8	0.8	1.63
1	240	1	1	2.63
	270	10	10	12.63
10	300	10	100	112.63
	330	30	300	412.63

Streptomycin (SM)

Streptomycin is in the aminoglycoside class of medication and can be used to treat TB in combination with other medications. It works by blocking the ability of 30S ribosomal subunits to make proteins which results in bacterial death.

Common side effects include dizziness, vomiting, numbness of the face, fever, and rash. Fever and rashes may result from persistent use [47].

The majority of adverse drug reactions due to intramuscular injection of SM are GI problems (38.09%), followed by skin reaction (30.48%), and hepatotoxicity (14.28%) [47]. Serum sickness related to antituberculous drugs is mainly due to SM and para-aminosalicylic acid (PAS) [55].

The most concerning side effects of SM, as with other aminoglycosides, are vestibular toxicity, nephrotoxicity, and ototoxicity. Nephrotoxicity can potentially interfere with the diagnosis of kidney malfunction. Ototoxicity and nephrotoxicity are more likely to be found when therapy is continued for more than 5 days, at higher doses. In very high doses, SM can also produce a curare-like effect with a neuromuscular blockade that results in respiratory paralysis. It is not recommended in patients with myasthenia gravis [56].

In general, streptomycin has little allergenic potential and hypersensitivity reactions are rare. However, skin rashes, eosinophilia, fever, blood dyscrasias, angioedema, exfoliative dermatitis, stomatitis, and anaphylactic shock have been reported [57].

According to Mario Sánchez-Borges et al. [58], positive skin tests have been observed with SM. However, a cautious approach must be taken when evaluating anaphylactic reactions to SM, since systemic reactions have been observed after skin prick testing. The starting concentrations suggested for skin prick tests range from 0.1 to 1 mg/mL, gradually reaching the concentration of 20 mg/mL if needed. If skin prick tests are negative intradermal testing can be performed and non-irritating concentrations for intradermal testing have been established for gentamicin and tobramycin to be 4 mg/mL. There is no evidence of positive

serum IgE to aminoglycosides. Patch tests with reading at 72 and 96 h are recommended for the diagnosis of non-immediate reactions. The concentration is 1% in petrolatum for SM [58].

In patients with SM allergy, avoidance of the antibiotic is recommended. There are two old reports of desensitization to streptomycin, one describing a 3-h protocol with streptomycin beginning with 1 mg administered intravenously and the other with streptomycin given intramuscularly, 10 mg on the first day, doubled every day until it reached 800 mg. Then, 1.0 g, twice weekly [59, 60].

Recommendations

The diagnosis of a reaction to antituberculous drugs is based on the regression of symptoms with discontinuation of the drug/s and the reproducibility with reintroduction. The reintroduction of antibiotics separately is necessary to identify the culprit/s. This approach cannot be done in the presence of severe reactions like exfoliative dermatitis and hepatotoxicity. These and severe cutaneous reactions like DRESS and TEN are absolute contraindications for the challenge.

The decision to desensitize a patient with an hypersensitivity to anti-TB treatment should always be made in conjunction with the infectious diseases specialist to determine the benefit of first-line therapy over alternatives, the duration of treatment, and the goals of therapy.

Drug desensitization should not be attempted with severe skin reactions or those involving the mouth or mucous membranes (e.g., exfoliative dermatitis and Stevens-Johnson syndrome), and should always be performed and supervised by an allergy specialists training in this field.

Compliance with ethical standards

Conflict of interest

Josefina Cernadas and Eduardo Cernadas declare that they have no conflicts of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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