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Abstract

Anti-tuberculosis (TB) drugs can cause adverse drug reactions, particularly the older second-line drugs. Early intervention and adequate management of adverse drug reactions are important to prevent complications. Laboratory testing at baseline and during treatment, in addition to clinical monitoring, is protocolized to improve patient and treatment management. This chapter provides an overview of the most frequent and severe adverse effects caused by the first- and second-line drugs used for the treatment of tuberculosis. An approach on how to manage the adverse drugs effects is briefly described.

Keywords

Anti-TB drug · Adverse drug reaction · Hepatotoxicity · Peripheral neuropathy · QTc prolongation · Management · Pharmacovigilance

13.1 Introduction

Drug susceptible tuberculosis (TB) is treated with a combination of four drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) and at least five drugs in case of rifampicin-resistant (RR-TB) or multidrug resistant TB (MDR-TB) for a period of 6–20 months [1, 2]. Like any other drugs, anti-TB drugs can cause adverse drug reactions, particularly the older second-line drugs. It is estimated that approximately two-thirds of patients experience at least one adverse drug reaction (ADR) during treatment. Adverse drug reactions range from mild, transient gastrointestinal intolerance to life-threatening acute hepatic failure. Not surprisingly, adverse drug reactions are one of the most common reasons for treatment interruption by the treating physician or patient themselves. Implications of adverse drug reactions are substantial and include increased risk of treatment failure or irreversible damage such as hearing loss. Early intervention and adequate management of adverse drug reactions are important to prevent complications. Laboratory testing at baseline and during treatment, in addition to clinical monitoring are protocolized to improve patient and treatment management [1, 2]. With the increased number of new and repurposed drugs, the World Health Organization (WHO) has recommended active pharmacovigilance to increase the detection, assessment, understanding, and prevention of adverse drug reactions [3].

13.2 Aim

The aim of this chapter is to provide an overview of the most frequent and severe adverse effects caused by the first- and second-line drugs used for the treatment of tuberculosis. An approach on how to manage the adverse drugs effects is briefly described.

13.3 Adverse Effects

13.3.1 Isoniazid

Drug-induced hepatotoxicity is a serious adverse effect of isoniazid. Incidence of isoniazid-related hepatotoxicity in the combination TB drug regimen ranges from 1.6 to 2.7%. Slow acetylator status due to genetic polymorphisms in *N*-acetyltransferase 2 (NAT-2) has been proposed to be a risk factor. Abnormalities in liver enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase (ALP) should prompt a clinical assessment for drug-induced hepatotoxicity. Isoniazid, and concomitant hepatotoxic drugs, should be withheld when ALT level is ≥3 times the upper limit of normal (ULN) in the presence of hepatitis symptoms, or ≥5 × ULN in the absence of symptoms. Symptoms may include nausea, vomiting, abdominal pain, jaundice, and fatigue. Rechallenge could be considered when ALT <2 × ULN [4].

Peripheral neuropathy can occur with isoniazid treatment (2%) and may be prevented by prophylactic pyridoxine (vitamin B6) in patients treated with isoniazid-containing regimen.

13.3.2 Rifampicin

Rifampicin-induced hepatotoxicity occurs in about 2.7% of the patients when given concomitantly with isoniazid. Cholestatic hepatitis may be observed with hyperbilirubinemia and increases in ALP disproportionately to ALT. The same clinical and biochemical criteria for drug cessation apply for rifampicin, like all other first-line drugs.

Rechallenge can be considered in a sequential manner once ALT is <2 × ULN. Due to the least likelihood for hepatotoxicity, rifampicin is usually the first drug to be started with or without ethambutol, followed by isoniazid a week later. The sequence of reintroducing the first-line drugs remains to be optimized [5].

13.3.3 Pyrazinamide

Hepatotoxicity induced by pyrazinamide, reported in up to 5% of patients, can be severe and fatal. The onset is generally within 9 weeks of treatment initiation. The drug should be ceased upon development of clinical and biochemical hepatic abnormalities. Prothrombin time (PT) or international normalized ratio (INR) should also be monitored if hepatotoxicity is observed.

In mild to moderate hepatotoxicity, pyrazinamide can be restarted a week after isoniazid, if no symptoms or increases in ALT are observed. If hepatotoxicity is prolonged or severe (ALT >10 × ULN), but rifampicin and isoniazid can

be tolerated after re-introduction, pyrazinamide should not be added due to high likelihood of being the drug causing hepatotoxicity. If pyrazinamide cannot be used, the total treatment duration should be extended to 9 months for drug susceptible TB [4].

13.3.4 Ethambutol

Optic neuropathy, including optic neuritis and retrobulbar neuritis, is the most serious, dose-dependent adverse effect of ethambutol. It presents with symptoms of reduced visual acuity, color blindness, or visual defects. Although usually reversible up to several months upon cessation of ethambutol, permanent visual deficits may occur. Incidence of any visual impairment has been reported in about 2% of patients and permanent visual impairment in 0.2% of patients at doses up to 25 mg/kg/day with treatment duration of 2–9 months [6]. Regular monitoring for visual acuity and color vision is recommended at baseline, and at monthly intervals.

13.3.5 Levofloxacin/Moxifloxacin

Although fluoroquinolones are usually well tolerated, serious adverse effect includes prolongation of the QTc interval (QT interval, corrected for heart rate) with increased risk in elderly, females, and patients with pre-existing bradycardia. Fatal arrhythmias can occur when QTc is >500 ms (normal QTc is <440 ms), including Torsades de Pointes, a type of ventricular tachycardia increasing risk of sudden cardiac death. The risk of QTc interval prolongation and related arrhythmia seems to be lower for levofloxacin (5.1%) compared to moxifloxacin (8.3%) although not conclusive, and for this reason, levofloxacin may be preferred in MDR-regimens in high-risk patients [7, 8].

Management for QTc interval greater than 500 ms includes cessation or dose reduction of QTc interval prolonging medications (whenever clinically appropriate), and correction of hemoglobin, and potassium, calcium and magnesium imbalances.

13.3.6 Bedaquiline

QTc interval prolongation is a major adverse effect of bedaquiline, and the risk is increased when combined with other QTc-prolonging drugs such as fluoroquinolones, clofazimine, and delamanid. Mean QTc prolongation of about 10–15 ms has been reported, and QTc prolongation >500 ms occurs in about 3% of patients. Discontinuation of bedaquiline due to prolonged QTc is infrequent, occurring in 0.9% of patients [9].

Liver function test abnormalities are common in regimens that include bedaquiline. Drug discontinuation should be considered if aminotransferases are >5 × ULN or >3 × ULN with symptoms such as jaundice.

13.3.7 Linezolid

Linezolid is associated with treatment-interrupting adverse effects including anemia (38.1%), peripheral neuropathy (47.1%), and optic neuritis (13.2%) [10]. Peripheral neuropathy and optic neuritis are managed by treatment interruption. Anemia and less common thrombocytopenia (11.8%) can be reversed by dose reduction. The risk of adverse effects is significantly greater with linezolid daily dose exceeding 600 mg.

13.3.8 Clofazimine

The main side effect of clofazimine is a red-black discoloration of the skin observed in 75–100% of patients. It is reversible but could take several months to years until normalized. Discoloration of body secretions including urine, feces, sweat, and sputum can also occur. Gastrointestinal intolerance is reported in 40–50% of patients. Symptoms can vary, such as abdominal and epigastric pain, diarrhea, nausea, and vomiting. Adding a proton pump inhibitor and/or an antiemetic drug can relieve these symptoms. Furthermore, QTc prolongation (>60 ms from baseline) has also been reported during clofazimine use in a small study (6.7%) and case reports [11].

13.3.9 Cycloserine/Terizidone

Cycloserine and its structural analogue terizidone are poorly tolerated in most patients across diverse ethnicities. On average, about 9.1% of patients treated with cycloserine experience treatment discontinuation due to adverse effects, with some studies reporting up to 20–30% of patients with treatment cessation. Psychiatric adverse effects including psychosis, depression, and suicidal ideations are most commonly observed in 5.7% of patients, and central nervous system related adverse effects such as seizure and peripheral neuropathy are reported in 1.1% of patients [12]. Frequency of adverse effects is reported to be similar between cycloserine and terizidone, although data is very limited.

These adverse effects are generally dose-related, and reversible upon cessation of the drug. The exception to this is severe peripheral neuropathy, which may not fully resolve. High-dose pyridoxine (not exceeding 75 mg daily) may have a protective effect and is usually co-prescribed.

13.3.10 Meropenem/Imipenem

Meropenem and imipenem are generally well tolerated. Most common adverse effects are mild and include diarrhea (2.5%), skin rash (1.4%), and nausea/vomiting (1.2%). Prolonged intravenous use can be associated with injection site inflammation in 1.1% of patients. In pediatric patients, adverse effects were more frequently observed with meropenem compared with imipenem/cilastatin.

13.3.11 Delamanid

Prolongation of QTc interval is a recognized adverse effect of delamanid, reported in about 9.9–13.1% of patients at a dose of 100 or 200 mg twice daily [13]. The main metabolite DM-6705 contributes to QTc prolongation, despite its lack of antimycobacterial activity. Hypoalbuminemia is correlated with increased risk of QTc prolongation, as albumin is involved in the regulation of DM-6705. Delamanid is contraindicated in patients with albumin <2.8 g/dL and in patients with baseline QTc > 500 ms. Replacing moxifloxacin with levofloxacin may be considered to reduce QTc prolongation in delamanid-based regimens also containing bedaquiline or clofazimine. If delamanid is to be used concomitantly with bedaquiline, baseline QTc should not exceed 450 ms due to the increased risk of cardiotoxicity, although more prospective data are required for the long-term safety of their combination [14].

13.3.12 Prothionamide/Ethionamide

A common adverse drug reaction of ethionamide and prothionamide is gastrointestinal intolerance (25.6–33.5%), including nausea, vomiting, diarrhea, and abdominal discomfort, especially at daily doses greater than 750 mg. There is a suggestion that ethionamide is slightly better tolerated than prothionamide. The gastrointestinal intolerance may be severe enough to interfere with absorption of concomitant anti-TB drugs. Dividing the dose (250 mg three times daily) or pre-medication with an antiemetic such as ondansetron (4–8 mg) may provide a benefit. Endocrine effect such as hypothyroidism occurs in 20% of patients and requires thyroid hormone supplementation during treatment.

13.3.13 Amikacin/Streptomycin

Amikacin and streptomycin are associated with ototoxicity, which is potentially severe and irreversible. Risk increases with cumulative dose, duration, and age. Hearing loss occurs in up to 39% of patients and vestibular toxicity in 14% of patients. Nephrotoxicity occurs in 5–15% of patients and is usually reversible, although it has led to chronic kidney failure. Risk increases with older age, dehydration, and previous exposure to the drug. Electrolyte disturbances may also be observed due to renal tubular excretion of potassium, calcium, and magnesium.

13.3.14 *p*-Aminosalicylic Acid

Gastrointestinal intolerance due to *p*-aminosalicylic acid (PAS) includes symptoms of nausea, vomiting, bloating, abdominal pain, and diarrhea. Severe symptoms occur in about 4% of patients, requiring treatment interruption. Improvement with diarrhea often occurs after several weeks, and nausea and vomiting can sometimes

Box 13.1. Management of Adverse Effects of First-Line Anti-TB Drugs

Isoniazid, rifampicin, pyrazinamide-induced hepatotoxicity
• Isoniazid, rifampicin, and pyrazinamide should be ceased when ALT ≥3 x ULN with symptoms or ALT ≥5 x ULN without symptoms
• Rechallenge can be considered in a sequential manner, once ALT <2 x ULN and with continued monitoring
• Current recommendation is to restart in the order of rifampicin (± ethambutol), isoniazid, pyrazinamide, at weekly intervals [5]
• If symptoms or ALT increase are observed, the last added drug is withheld, and a monitoring cycle of withhold and re-evaluation is recommended
Ethambutol-induced optic neuritis
• Visual acuity test (Snellen test) at baseline and color discrimination test at baseline and at monthly intervals is recommended during ethambutol use
• Prompt and permanent cessation of the drug is required if visual abnormalities are detected

Box 13.2. Management of Adverse Effects of Second-Line Anti-TB Drugs

QTc prolongation due to quinolones, clofazimine, bedaquiline, and delamanid
• Baseline QTc should not exceed 450 ms when a combination of these drugs is started
• Weekly ECG is recommended
• When QTc is >500 ms, these drugs should be ceased
• Moxifloxacin can be replaced by levofloxacin to reduce the risk
Linezolid induced polyneuropathy and optic neuritis
• Prompt cessation of linezolid is required if complaints related to PNP are reported
• If an electromyography shows no linezolid induced polyneuropathy, and if possible, linezolid can be restarted at a lower dose
• Prompt and permanent cessation of linezolid is required if visual abnormalities are detected
Psychiatric adverse effects due to cycloserine or terizidone
• Prompt and permanent cessation of cycloserine/terizidone is required when symptoms of psychosis, depression, and suicidal ideations are observed

be managed with antiemetic drugs. Concurrent PAS and ethionamide are poorly tolerated. Hypothyroidism may occur in up to 40% of patients but thyroid function generally returns to normal upon drug cessation.

13.4 Main Conclusions and Recommendations

Adverse drug reactions are common during drug susceptible as well as drug resistant TB treatment. Baseline assessment of risk factors and monitoring during treatment (see Chap. 18) are important to prevent adverse drug reactions and treatment interruption.

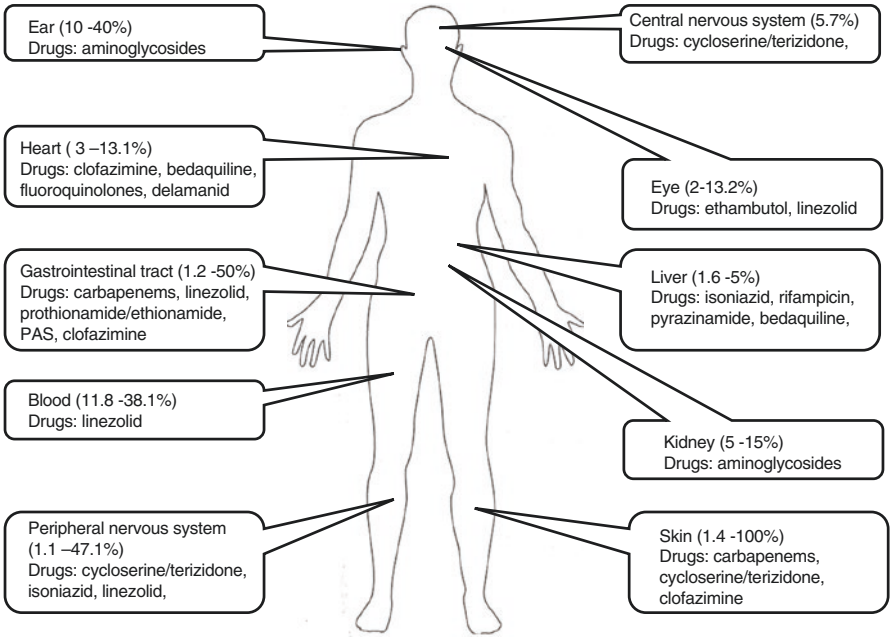

Fig. 13.1 Overview of adverse drug effect by organ/system

As many drugs have overlapping toxicity profiles (see Fig. 13.1) which may aggravate the severity of the adverse drug reaction, prompt response is required when toxicity is observed. Recommendations on severe and frequently occurring adverse drug reactions are summarized below.

- Hepatotoxicity.
- Alcohol and concomittant use of other hepatotoxic drugs should be avoided to minimize the risk of elevated AST/ALT/bilirubin. When drug-induced hepatotoxicity is encountered, other causes such as viral hepatitis, biliary disease, or alcohol-induced liver disease should be ruled out and potential causative drugs should be stopped.
- Peripheral neuropathy.
- Patients with alcohol dependence, diabetes, and human immunodeficiency virus (HIV) have an increased risk for peripheral neuropathy. Prophylactic pyridoxine (vitamin B6) to prevent peripheral neuropathy in addition to early detection and supplementation of pyridoxine may lead to improvement or resolution of symptoms and occassionally allow drug to be continued.
- QTc prolongation.
- In addition to baseline QTc assessement, combined use of anti-TB drugs known to cause QTc prolongation such as bedaquiline, clofazimine, delamanid, or fluoroquinolones requires regular and more frequent electrocardiogram (ECG) monitoring (e.g., at 2, 4, 8, 12, and 24 weeks), especially if on bedaquiline+delamanid or >3 QTc-prolonging drugs [15]. Patients should also be asked to report any symptoms

of palpitations or episodes of syncope. Any prolongation of QT interval (QTc >500 ms) should prompt a thorough investigation including correcting for electrolytes imbalances (potassium, magnesium) or severe anemia, and suspension of some QTc-prolonging medications (consider non-TB drugs first, then short-acting TB drugs).

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