Review Article

A Review on Management of Common ADRS of Antitubercular Drugs

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ABSTRACT

Tuberculosis is an infectious bacterial disease caused by Mycobacterium tuberculosis which spreads from person to person through air when infected people sneeze or spit. As per the Global TB report 2017 the estimated incidence of TB in India was approximately 28,00,000 accounting for about a quarter of the world's TB cases. The duration of treatment of tuberculosis for new cases will be 6 months which extend for previously treated cases. As like other drugs the antitubercular drugs also has many adverse reactions which is also a influencing factor of adherence towards the antitubercular medications. The common adverse reactions of antitubercular drugs are nausea, vomiting, hepatotoxicity, ototoxicity, peripheral neuropathy, optic neuritis, dermatological and hematological reactions. The early identification and management of these adverse reactions are necessary to improve the adherence and to avoid further complications.

Keywords: Hepatotoxicity, Optic neuritis, Peripheral neuropathy, Influenza symptoms, Hematological syndrome.

INTRODUCTION

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium tuberculosis* which spreads from person to person through air when infected people sneeze or spit. Tuberculosis is the most prevalent communicable infectious disease and remains out of control in many developing nations. These nations require medical and financial assistance from developed nations in order to control the spread of TB globally[1].TB caused about 1.3 million deaths among Human Immunodeficiency Virus (HIV) negative people in 2016, exceeding the global number of HIV and AIDS deaths[2]. As per the Global TB report 2017 the estimated incidence of TB in India was approximately 28,00,000 accounting for about a quarter of the world's TB cases[3]. Based on the anatomical site, tuberculosis can be classified as Pulmonary tuberculosis which involves the lung parenchyma or the trachea-bronchial tree and Extra pulmonary tuberculosis which involves the organs other than the lungs such as lymph nodes, pleura, intestine, joints and bones, genitourinary tract, meninges of the brain etc. Based on the history of treatment tuberculosis can be classified as new case, previously treated patients and transferred in patients[4].

World Health Organisation (WHO) recommends the 6 months regimen of first line anti-tubercular drugs for the drug susceptible TB. The first line anti-tubercular drugs are Isoniazid, Pyrazinamide, Ethambutol, Rifampicin[5]. The duration of treatment for new case of tuberculosis was 6 months and it will be extended in previously treated cases. Tuberculosis is always curable if the patients are treated with effective, uninterrupted antituberculous therapy. [6]

Just like other drugs, anti tubercular drugs used in clinical practice are not free from Adverse drug reactions (ADRs). The incidence of ADR due to anti tubercular drugs varies from 5-50%. For TB combination of four drugs are used for the prolonged period of time. It is the additional problem because the ADR of one drug may be potentiated by the companion drugs used.

All the anti tubercular drugs can cause All the anti tubercular drugs can cause ADRs that may involve almost all systems in the body including gastro intestinal tract, liver, skin, nervous system, oto vestibular apparatus and the eyes. There are common ADRs observed in DOTS therapy like Gastro intestinal disturbances, visual disturbance, rashes, peripheral neuropathy and increase in level of liver enzymes[7].These ADRs can lead to modification or stoppage of drug therapy. Sometimes it requires interruption in treatment frequently and may result in avoidable morbidity, drug-resistance, failure of treatment and reduced quality of life. The identification of ADR profile of drugs can be useful for the anticipation early detection and management of ADRs.[8] Hence in this review we discussed management for some of the common ADR associated with anti tubercular drugs.

HEPATOTOXICITY

Hepatotoxicity induced by antituberculosis drugs might result in significant morbidity and, rarely, even mortality. Such toxicity affects patient adherence to therapy and could negatively impact the treatment outcome of patients.[9] All antitubercular drugs may cause hepatotoxicity. Pyrazinamide is the most hepatotoxic and Isoniazid is the second. Combinations such as Rifampicin and Pyrazinamide may potentiate the hepatotoxic effect of each drug.[10] The severity of hepatotoxicity was classified according to the WHO Toxicity Classification Standards as follows: mild (ALT or AST <2.5 times of the ULN), moderate (ALT or AST 2.5–5 times of the ULN), severe (ALT or AST 5-

10 times of the ULN) and very severe (ALT or AST >10 times of the ULN).[11] Loss of appetite, pain or discomfort in the abdomen, yellow skin, yellow eyes and dark colour urine may indicate hepatotoxicity.[10]

1. Asymptomatic patients

If the increase in liver function test (LFT) is < 3-5x normal: continue the current regimen and monitor for symptoms of liver dysfunction. For asymptomatic patients, if the serum transaminases increases > 3-5x normal: hold Isoniazid until levels return to baseline. If the patient is receiving a two drug regimen, substitute at least one other drug (e.g.Ethambutol) until the Isoniazid is restarted. If the transaminases increase with rechallenge of Isoniazid, discontinue Isoniazid, substitute another drug (e.g. Ethambutol) and adjust the treatment duration as required.

If the serum total bilirubin increases: therapy usually does not require modification (Rifampin competes with bilirubin for elimination resulting in increased serum bilirubin initially; bilirubin levels usually return to normal with continued therapy).

2. Symptomatic patients

Hold all drugs and obtain LFTs. If LFTs are within the normal ranges, manage the symptoms. If LFTs are elevated, hold drugs until symptoms resolve and the transaminases decreases to < 2x normal.

Ethambutol and Pyrazinamide should be started if drug therapy cannot be held secondary to the patient's clinical condition (use streptomycin if pyrazinamide is suspected to be the cause of hepatotoxicity). Rechallenge the patient after resolution of signs and symptoms by adding drugs to the regimen every 4 days: Rifampin for 3 days, if patient remains asymptomatic then add Isoniazid for 3 days, if patients remains asymptomatic then add Pyrazinamide (15-20mg/kg/d) for 3 days. If signs and symptoms recur with rechallenge, discontinue the responsible drug and modify the regimen and/or duration of therapy as required.[12,13]

PERIPHERAL NEUROPATHY

Peripheral neuropathy (PN) is a condition in which the nerves are affected, compromising the relay of information from different parts of the body. It can affect sensory nerves, motor nerves, or autonomic nerves and cause a variety of symptoms and complications. Tingling, burning, numbness in hands and foot are the symptoms of peripheral neuropathy. Isoniazid has the potential to cause reversible peripheral neuropathy, which typically resolves after cessation of treatment. Ethambutol may also be the causative agent of peripheral neuropathy.

Persons presenting with signs and symptoms of neuropathy who also have TB should be assessed for other comorbid conditions that could impact the development of neuropathy. Thus all patients with PN should also undergo assessment for HIV, diabetes mellitus, hypothyroidism, malnutrition, and alcohol use.

To prevent the peripheral neuropathy, all patients with TB should be started on pyridoxine supplementation at a dose of 50mg daily. Patients who are using alcohol or other drugs should be offered treatment or counseled in harm reduction to minimize their use of substances that could contribute to PN. All comorbid conditions should be optimally managed, and, when possible, use of other medications that can cause PN should be avoided.

For the management of peripheral neuropathy systemic and topical therapies can be used. The systemic therapies tend to fall into four classes: Tricyclic antidepressants, anticonvulsants, selective serotonin reuptake inhibitors (SSRIs) and GABA-ergic compounds. The topical agents include capsaicin creams and Lidocaine/Lignocaine. For functional preservation physical therapy can be a successful way.[13-16]

OPTIC NEURITIS

Optic neuritis is one of the many causes of optic neuropathy and it involves the inflammation of the optic nerve. Ethambutol and Isoniazid are considered as the causative agents of optic neuritis. Blurred vision (decrease in the "sharpness" of objects), spots present in patient's field of vision and red/green color blindness are the clinical presentations. The neurotoxic effects of Isoniazid may be enhanced by co-morbidities like end stage renal disease requiring hemodialysis or malnutrition. If the patient has optic neuritis first the causative agent should be stopped. If the patient was prescribed with both Ethambutol and Isoniazid, Ethambutol should be stopped first. If severe neuritis occurs INH also should be stopped. In less severe optic neuritis if INH is being continued high dose of pyridoxine 50-100 mg daily is given, and if optic neuritis fails to improve within six weeks of stopping EMB, INH can be stopped. Correction of malnutrition and zinc deficiency may have a role in preventing the toxicity of EMB but there is insufficient data to support the benefit of such therapy. For adults with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody–positive, Eculizumab (a monoclonal antibody) is the first drug specifically approved by the FDA. Other pharmacologic therapies are directed at ameliorating the acute symptoms of pain and decreased vision caused by demyelinating inflammation of the nerve. Varying regimens of corticosteroids have been used for this purpose. In the acute phase a 3-day course of high-dose IV methyl prednisolone followed by a rapid oral taper of prednisone has been shown to provide a rapid recovery of symptoms. However, IV steroids do little to affect the ultimate visual acuity in patients with optic neuritis.

For patients with optic neuritis whose brain lesions on MRI indicate a high risk of developing clinically definite MS, treatment with immunomodulators (eg, interferon beta-1a, interferon beta-1b, glatiramer acetate) may be considered. IV immunoglobulin (IVIG) treatment of acute

optic neuritis has been shown to have no beneficial effect. Health education should be given to the patients regarding the visual side effects and the need to stop the drug and report immediately, if any problems arise.[13,14,17-19]

OTOTOXICITY

Ototoxicity refers to damage of inner ear structures (cochlea and vestibule) and their function (hearing and balance) following exposure to specific medications. Aminoglycosides, Capreomycin are the main causative agent of ototoxicity. Symptoms include hearing loss, tinnitus, imbalance and visual symptoms. Clinically nystagmus may be present as an early sign. Concominant use of loop diuretics particularly in the setting of renal insufficiency may exacerbate ototoxicity. The patient should be informed about the early symptoms of ototoxicity, such as tinnitus and dizziness. Audiometry of every patient on injectables should be performed monthly, starting with a baseline at the time of enrolment on treatment. If the patient is experiencing clinically significant ototoxicity, decrease the dosing frequency of the injectable to two to three times a week. Consider switching to capreomycin. Stop the injectable if symptoms worsen despite dose adjustment, and add additional anti-TB drugs to reinforce the regimen. Even when additional drugs are not available, stopping the injectable agent can be considered based on the patient's desire to maintain hearing. Ototoxicity is one of the few adverse effects that can be permanent and may necessitate discontinuation of a class of agents. If tinnitus and unsteadiness develop and these are attributable to vestibular toxicity, stop the injectable agent. Persistent vertigo and ataxia are intolerable toxicity and not reversible.[19-22]

HEMATOLOGIC SYNDROMES

Drug-induced hematologic disorders are generally rare adverse effects associated with drug therapy. The patients who had any hematological alteration due to anti-tuberculosis drugs may have had weaker natural and acquired (cell-mediated) immunologic response to tuberculosis infection, and more vulnerable bone marrow cells and hepatic cells to anti-tuberculosis drugs. The mechanisms of drug-induced hematologic disorders are the result of direct toxicity or an immune reaction.[23,24]

Leucopenia, thrombocytopenia, anemia and coagulation abnormalities can exceptionally occur with a number of anti-TB drugs. Thrombocytopenic purpura is more common with intermittent use of Rifampin. Rifampin should be stopped immediately. Shock, renal failure and thrombocytopenia should be treated aggressively and should never be reintroduced.

Linezolid can cause profound myelosuppression (suppression of white blood cells, red blood cells and platelets. In this case, stop Linezolid and manage with blood transfusion if needed. Linezolid should never be reintroduced.[14]

Arthalgia

Arthralgia is a joint pain. It is of two types,Type 1and type 2.

Type 1

Pyrazinamide, Ethambutol and Isoniazid are the causative agents. there will be mild pain and tenderness in joints of fingers, shoulders, knees, etc. it does not require discontinuation of medications. The pain can be relieved by low dose non steroidal anti inflammatory agents (Ibuprofen 400-800mg thrice a day, Paracetamol 500-1000mg twice or thrice a day). If the symptoms persist the patient can be referred for rheumatologic evaluation.

Type 2 (Gouty Arthritis)

Pyrazinamide and Ethambutol are the causative agents. The symptoms include pain, tenderness and swelling of joints which is usually severe. The serum uric acid concentration will be elevated in this. It also does not require discontinuation of TB medication. If there is acute swelling, the affected joint should be aspirated and examined for urate crystals to confirm gouty arthritis. Non steroidal anti-inflammatory agents (Indomethacin 50mg thrice a day until pain relief, then 25mg thrice a day, Ibuprofen 800mg thrice a day, Naproxen 750mg x1, then 250mg thrice a day) can be used for management. Colchicine (0.5-1.2 mg x1, then 0.5-0.6 mg q 1-2 hours until joint pain is relieved or nausea, vomiting or diarrhea occurs) can be used as an alternative to NSAIDS. The pain usually resolves after 4-8 mg cumulative dose. Recurrent episodes may occur while the patient remains on Pyrazinamide or Ethambutol. Consider using prophylactic colchicines (0.6mg one to two times daily). Continue until causative agent is discontinued. Consider referral for rheumatologic evaluation for acute gouty arthritis attacks.[13,14,25-27]

INFLUENZA SYMPTOMS

It usually occurs with the use of Rifampin and Rifabutin. The clinical presentation include fever, headache, bone pain which usually resolves within 12 hours of drug administration. It can be managed by switching from intermittent therapy to daily dosing and symptomatic therapy may be required when switching from intermittent to daily therapy to prevent the reaction with initial doses.[13,14]

DERMATOLOGIC REACTIONS

Itching and rashes with or without fever can be a clinical presentation. The causative agents include Isoniazid, Rifampin, Pyrazinamide, Ethionamide, Cycloserine, Ethambutol, Para amino salicylic acid, Streptomycin. It can be managed with discontinuation of all drugs until the reaction resolves. Identify the causative drug by rechallenging (restarting) each drug every 4 days.

Table 1: Dose for rechallenge of drugs

Drug	Dose Day 1	Dose Day 2
Isoniazid	50mg	300mg
Rifampin	75mg	300mg
Pyrazinamide	250mg	1.0gm
Ethionamide	125mg	375mg
Cycloserine	125mg	250mg
Ethambutol	100mg	500mg
Para-aminosalicylicacid (PAS)	1.0gm	5.0gm
Streptomycin	125mg	500mg

Begin the rechallenge with INH 50mg on day 1. If the original reaction was severe, begin the rechallenge with 1/10 the day 1 dose listed in Table 1 (e.g. INH 5mg). If a reaction does not occur after the day 1 dose, increase the INH to 300mg on day 2. If a reaction does not occur after the day 2 dose, continue INH 300mg q day. Continue to add drugs in the order and doses specified on Table 1 every 4 days. If the original reaction was severe, begin the rechallenge with 1/10 the day 1 dose listed in Table 1. If the day 2 dose is less than the normal recommended dose based on the patient's weight, increase to the appropriate dose on day 3. If a reaction occurs during drug rechallenge and the causative drug cannot be discontinued, drug desensitization will be necessary. 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). Consideration should be given to desensitizing patients under monitored conditions for severe reactions. [13,14,28-30]

CONCLUSION

There are many ADR due to antitubercular drugs. This review gives an idea about management of common ADRs associated with antitubercular drugs. ADR is also a factor influencing adherence to the treatment. The early identification, management of these ADR are necessary to improve the adherence and avoid unnecessary complications due to the antitubercular therapy.

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