

Ocular toxicity of Anti-Tubercular drugs

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Abstract

Tuberculosis is the most common cause of infectious disease-related mortality worldwide caused by Mycobacterium tuberculosis. Ethambutol (EMB) and isoniazid (INH) are synthetic first-line agents of the anti-tubercular treatment (ATT) against Mycobacterium tuberculosis. Ethambutol, though well tolerated, is known to cause optic neuritis, more specifically retro bulbar neuritis causing decreased visual acuity, central scotomas, and loss of red-green color vision. Isoniazid can rarely cause retro bulbar optic neuritis. Streptomycin is known to cause pseudotumor cerebri. Thioacetazone can produce severe hypersensitivity cutaneous reactions including Steven Johnson Syndrome affecting the skin and mucosa including conjunctiva. Optic neuropathy has been reported as a side effect of long-term use of linezolid. This is particularly seen in cases of drug resistant tuberculosis where treatment with linezolid may continue for about 18-24 months. Educating the patients for early detection of the ocular manifestations and regular follow-ups are very essential. The purpose of this review is to update the clinicians on the ocular side effects of anti tubercular drugs and the type of eyecare to be provided to the patients treated with these medications.

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Introduction

Tuberculosis is an airborne communicable disease of public health importance in many countries across the world. It is caused by Mycobacterium tuberculosis that can affect many organs including the eye. More than 1.7 billion people are estimated to be infected with M.tuberculosis.^{1,2} According to WHO in 2018, 10 million individuals became ill with TB and 1.5 million died. There is an increase in the incidence of tuberculosis due to human immunodeficiency virus infection and multidrug resistance.³

Ethambutol is one of the first line anti TB medications. The other drugs in the treatment regimen include isoniazid, rifampicin and pyrazinamide. The treatment of drug resistant tuberculosis is lengthy and costly which poses difficulty to both patients and staff.⁴ Given the increasing prevalence of tuberculosis, antitubercular drugs are one of the frequently used drugs and some of them are very toxic to the eye. Among the antitubercular drugs (ATDs), ethambutol (ETB), isoniazid (INH), streptomycin, linezolid, kanamycin, thiacetazone, amikacin and rifampicin, rifabutin and clofazimine are known to cause ocular toxicity. The purpose of this article is to give an update of the published literature on ATT induced ocular toxicity and detailing the measures to prevent the catastrophe of losing sight.

Ethambutol (Etb)

Ethambutol is one of the important first line drugs in the treatment of tuberculosis (TB). It is also commonly employed in the treatment of non-tuberculous mycobacterial infection. ETB may occasionally cause ocular toxicity but evidence suggests that it is as safe as or safer than the other standard anti-TB drugs provided proper precautions are taken when prescribing the drug.⁵

The ocular toxicity is optic neuritis, more specifically retrobulbar neuritis causing decreased visual acuity, central scotomas, and loss of red-green color vision. Symptoms usually appear between four and twelve months after the onset of ethambutol, but rarely, they may also occur within a few days of initiation of therapy.⁶ Patients usually report bilateral progressive painless blurring of vision and colour vision abnormality. However, some patients may be asymptomatic with disorders only detected by ocular examination.^{7,8,9} Central scotoma is the most reported visual field defect but bitemporal defects or peripheral field constriction can also occur. Colour vision abnormality (dyschromatopsia) may be one of the first detectable signs of ocular toxicity owing to ethambutol.^{10,11,12} Blue-yellow (tritan) defects are the most common and they occur earlier while red-green (protan) defects occur later on in the course of the toxicity.

Toxicity is said to be dose related, with the incidence being 18% in a dose of 35 mg/kg/day, 5-6% with 25 mg/kg/day and less than 1% at 15 mg/kg/day when taken for more than two months.^{13,14} Renal failure prolongs the half-life of ethambutol and increases the risk of ethambutol induced optic neuritis.¹⁵

Optic neuritis due to ETB is generally considered to be reversible when the drug is discontinued promptly. Gorbach states that vision returns virtually to normal after the drug is withdrawn.¹⁶ Following chronic ethambutol therapy, optic neuropathy is not always reversible, particularly in the elderly population. Permanent visual impairment has been reported within a follow-up period ranging from 6 months to 3 years in some patients in whom there was prompt ethambutol therapy discontinuation.

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. During medical consultation and follow up, routinely assess visual status. In case of any minute Suspicion, refer the patient for a detailed ophthalmic examination including visual acuity, color vision, visual fields and recording of visually evoked responses.

In case it is necessary to prescribe ETB to young children or patients with language difficulties, appropriate advice should similarly be given to parents or other family members. The use of written instructions or education pamphlets would be beneficial. Baseline and periodic eye examinations should be conducted; the prescribing information for ethambutol recommends monthly examinations for patients taking >15 mg/kg/day.¹⁷

Isoniazid

Isoniazid is frequently prescribed concurrently with ethambutol. Isoniazid therapy has also been associated with optic neuropathy^{18,19} but differentiating ethambutol-related toxicity from isoniazid-related toxicity could be challenging. However, in general, toxicity from isoniazid is less frequent, less severe and is always reversible.²⁰ Dose relationship is usually not seen.

Streptomycin

It is bactericidal drug used for the treatment of drug resistant tuberculosis. Toxicity increases with impaired renal function. It can produce pseudotumor cerebri and myasthenic neuromuscular blockade. It can potentiate the neuromuscular blocking agents used during anesthesia. All adverse effects are reversible on discontinuation of the drug. Use of sterile syringes and needles are important to prevent spread of HIV and hepatitis B infection. Patients on streptomycin or other aminoglycosides should be asked to report for an eye check up if they develop symptoms like headache and vomiting suggestive of raised intracranial pressure.

Kanamycin and Amikacin are also known to produce effects similar to streptomycin.

Rifampicin

It is a semi-synthetic compound first synthesized in 1965. The drug causes orange red discoloration of all body fluids including tears which doesn't need any modification of treatment. It can produce conjunctivitis and orange staining of contact lenses.²¹ These discolorations may be bothersome to the patient but do not require medical attention.

Thioacetazone

Thioacetazone can produce severe cutaneous reactions including Steven Johnson Syndrome affecting the skin and mucosa including conjunctiva. HIV positive patients are at major risk for cutaneous reactions. Conjunctival involvement may result in extensive scarring of the conjunctiva producing severe dry eye. However, this drug is no longer used in the management of tuberculosis.

Clofazimine

Clofazimine has shown activity against MDR TB. It can

cause red-brown discoloration of conjunctiva, cornea and lacrimal fluid (tears).²² Vision is usually not affected. 38-57% of patients may develop conjunctival discoloration which is dose related.²³ Resolution usually occurs when clofazimine is discontinued. Patients should be counseled that discoloration may occur. The benefits of clofazimine should be weighed against cosmetic changes that may occur.

Rifabutin

Rifabutin is used to treat Mycobacterium Avium Complex (MAC) disease in patients with HIV/AIDS on antiretrovirals who cannot tolerate rifampicin. Rifampicin decreases the therapeutic levels of non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine) and protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir).²⁴ Thus rifampicin is not given in patients with HIV. Rifabutin associated uveitis is well documented in patients with HIV infections and AIDS. Patient presents with eye pain and blurred vision.

In clinical trials with HIV infected patients, uveitis occurred with increased rifabutin serum levels (doses > 300mg/d with concomitant use of clarithromycin or fluconazole).²⁵ Uveitis is usually mild to moderate in severity. Management includes the use of topical steroids and cycloplegics and mydriatics. Discontinuance of rifabutin is not required unless the uveitis recurs or is refractory to treatment.

Linezolid

Linezolid is recommended by the World Health Organization (WHO) to treat drug-resistant tuberculosis and is a group A medicine in the management of drug resistant TB. It is usually well tolerated but has certain serious adverse effects demanding withdrawal of the drug eg. myelosuppression, peripheral and optic neuropathy, lactic acidosis, and serotonin syndrome.²⁶

The safety of linezolid treatment has been established for use only up to 28 days.²⁷ There are several case reports of linezolid-induced optic or peripheral neuropathy in patients treated for a time period beyond 28 days.²⁸ Only two cases of toxic optic neuropathy have been reported following short-term linezolid treatment of 16 days.²⁹ Fundus picture can be varied, showing temporal pallor, disc edema, or essentially normal. After discontinuation of the drug, complete visual recovery has been reported in all cases except one.

Role Of Awareness Among Physicians

The role of awareness amongst the physicians treating patients of Tuberculosis cannot be undermined. Timely detection, diagnosis and management of ocular effects of ATT averts the serious manifestations and loss of eyesight. Stopping the drugs at an early stage is beneficial, as these effects are reversible once the drugs are stopped.

The following measures are recommended for the prevention of drug-induced ocular toxicity during anti-TB treatment.

(a) Upon commencement of anti-TB treatment, patients should be assessed for feasibility and

contraindications of various Antitubercular drugs especially with respect to their ocular toxicity. In situations where there is an increased risk of ocular toxicity, the benefit of using such drugs should be carefully balanced against its risk. The availability, efficacy and toxic profile of alternate drugs should be taken into account in the choice of an effective treatment regimen.

(b) For all patients undergoing treatment with anti-TB drugs, health education should be provided to them on the possible visual side effects of the various Antitubercular drugs and a high level of awareness of this potential side effect should be emphasized during treatment. The patients should be advised that, in case visual symptoms arise, the drug should

be stopped immediately and they should report promptly to the health care staff.

(c) Baseline vision tests for visual acuity and red-green colour perception (e.g., using Snellen chart and Ishihara chart) should be conducted before starting treatment.

(d) During medical consultations in the course of anti-TB treatment, a strict vigil to be maintained regarding their side effects including ocular toxicity. All patients should be assessed clinically for symptoms of visual disturbance. Enquiring monthly about visual symptoms is advisable. In case of any visual symptoms patient should report without any delay.

Table 1 : Summary of ocular toxicity of Anti-Tubercular drugs

DRUGS	OCULAR DISEASE	SYMPTOMS	DIAGNOSIS	MANAGEMENT
ETHAMBUTOL	Retrobulbar optic neuropathy	Decreased visual acuity, field defects, decreased color vision	Color vision assessment, contrast sensitivity, perimetry. Fundus examination may be normal. Subclinical cases by VEP and OCT.	Discontinue the drug promptly. Toxicity is usually reversible
ISONIAZID	Retrobulbar optic neuropathy(rarely)	Decreased visual acuity, field defects, decreased color vision	Color vision assessment, contrast sensitivity, perimetry. Fundus examination may be normal. Subclinical cases by VEP and OCT.	Discontinue the drug promptly. Toxicity is usually reversible.
STREPTOMYCIN	Pseudotumor cerebri Enhances Neuromuscular blockade. in Myasthenia gravis	Headache associated with projectile vomiting	Fundus examination may reveal papilloedema	Discontinue the drug. Streptomycin is contraindicated in patients of Myasthenia gravis.
THIOACETAZONE	Severe cutaneous reactions including Steven Johnson Syndrome	Conjunctival scarring may occur Dry eye		Discontinue the drug. Antihistaminics are advised.
RIFAMPICIN		Orange red discoloration of tears. Orange staining of contact lenses.		No need to discontinue the drug. Patient counselling should be done.
RIFABUTIN	Uveitis	Decreased visual acuity and ocular pain. Mild to moderate uveitis	Slit lamp examination may reveal cells, flare in anterior chamber, sometimes associated with hypopyon. Vitritis may be present.	Topical steroids and cycloplegics. No need to discontinue the drug.
CLOFAZIMINE		Red brown discoloration of conjunctiva, cornea and tears.		No need to discontinue the drug. Patient counselling should be done.
LINEZOLID	Optic neuropathy	Decreased visual acuity, field defects, decreased color vision	Color vision assessment, contrast sensitivity, perimetry, fundus examination may show temporal pallor, disc edema, or essentially normal.	Discontinue the drug promptly. Toxicity is usually reversible.

Conclusion

Antitubercular medications can cause ocular adverse effects, and the potential risks should be discussed with patients prior to initiating therapy. There is a need to have periodic assessments of visual status of the patient during follow ups and DOTS sittings. Prompt ophthalmic evaluation is paramount, and that, along with discontinuation of the offending drug when possible, constitutes the basis of treatment of drug-induced optic neuropathy.

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