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Review Article

Ocular side effects of antitubercular drugs- A focus on prevention, early detection and management

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Abstract
Given the increasing prevalence of tuberculosis, antitubercular drugs frequently used are also associated with ocular toxicity. Ethambutol is the most commonly implicated drug. It is generally well tolerated, but known to cause optic neuritis, more specifically retro bulbar neuritis causing blurred vision, decreased visual acuity, central scotomas, and loss of red-green color vision. The exact mechanism of toxicity is not understood. Though optic neuritis due to ethmabutol is generally considered to be reversible upon prompt discontinuation of the drug, there are reports of reversible toxicity, particularly in the elderly population. Isoniazid can rarely cause retro bulbar neuritis. Dose relationship is usually not seen. Streptomycin is known to cause pseudo tumorcerebri. Thiacetazone can produce severe cutaneous reactions including Steven Johnson Syndrome affecting the skin and mucosa including conjunctiva. Educating the patients for early detection of the ocular manifestations and regular follow-ups are very essential.

Keywords: Anti- tubercular drugs, Ethambutol, Ocular side effects

"Who would believe that so a small space could contain the images of the entire universe? Oh! Mighty process" exclaimed *Leonardo da Vinci* regarding the eye. Our impressions about the external world are stored mainly in the form of visual images. So, a good eye sight is a prerequisite required for leading a normal life. Tuberculosis is one of the major diseases of public health importance in the world. It accounts for 2.5% of the global burden of disease.[1] Global estimate in 1997 indicated that 8 million people developed active tuberculosis every year with 2 million deaths.[2] The incidence has increased 2-4 folds in 1990 in countries with high prevalence of Human Immunodeficiency Virus (HIV) infection.[3] The treatment of drug resistant tuberculosis is lengthy, costly, difficult to both patients and staff and often unsuccessful.[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. So it is important for the physician to avoid the potentially toxic drugs and to choose from the alternatives, or use them very judiciously, to prevent his tuberculosis patient from losing his beautiful eyes. Among the antitubercular drugs (ATDs), ethambutol (EMB), isoniazid (INH), streptomycin, kanamycin, thiacetazone, amikacin and rifampicin are known to cause ocular toxicity. In this review article we are trying to highlight the potential toxicity of the ATD and detailing the measures to prevent the catastrophe of losing sight. Though there are many systemic adverse effects of ATD, in this article, the authors make an attempt to provide an outline of ocular toxicity due to ATDs.

Ethambutol (EMB): Ethambutol is a first-line drug for treating all forms of tuberculosis. It is included in initial treatment regimens primarily to prevent emergence of rifampicin resistance when primary resistance to INH may be present. It is a bacteriostatic drug, which is useful in both the intensive and continuation phase of treatment of tuberculosis. In the wake of worsening of the tuberculosis situation due to HIV co-infection there has been a need for an alternative drug like EMB to thiacetazone and streptomycin.[31] Thiacetazone is associated with high risk of severe, sometimes fatal skin reactions in HIV infected individuals.[5] Streptomycin, though a useful drug, should not be used in areas of high prevalence of HIV infection if adequate sterilization of syringes and needles cannot be ensured. [4] Ethambutol is generally well tolerated, but ocular toxicity is a well known adverse effect. The ocular toxicity is optic neuritis, more specifically retrobulbar neuritis causing blurred vision, decreased visual acuity, central scotomas, and loss of red-green color vision.

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Carr and Henkind in 1962 first described the ocular side effect of EMB.[6] Optic nerve can be involved at the optic disc, orbital optic nerve [retrobulbar portion] or at optic chiasma. Optic neuritis due to EMB may be central or uncommonly peripheral.[7] Patient usually presents with variable amount of visual blurring, and on examination decreased acuity is associated with dyschromatopsia. Peripheral type may cause few symptoms but field examination shows peripheral constriction. In a prospective descriptive study of color vision in 42 tubercular patients receiving EMB, *Kaimbo WA et al* [8] found color vision defects in 36% of patients. Red-green, blue-yellow or combined defects and anarchic axis were observed. *Srivastava AK et al* found recording of Visual Evoke Response (VER) to be an extremely useful objective test for sub clinical optic nerve damage in EMB induced optic neuritis.[9]

The exact mechanism of toxicity is not understood. Animal studies have shown EMB to deplete zinc from optic nerve.[10] *Heng JE et al* suggested the toxicity to be mediated through an excitotoxic pathway, so that the ganglion cells are rendered sensitive to the normally tolerated levels of extra cellular glutamate.[11] 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.[7,12] Renal failure prolongs the half-life of ethambutol and increases the risk of ethambutol-induced optic neuritis.[13]

Optic neuritis due to EMB 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. [14] A study from India in 47 children, including 27 children aged less than 5 years treated with a dose of 20 mg/kg/day for 12 months found no effect on visual evoked potential during or 3-6 months after stopping treatment.[15] A study from Mexico followed 36 children, 21 being infants, for four years and found no evidence of optic toxicity.[16] *Choi SY et al* reported ocular ethambutol toxicity at a dose as low as 12.3 mg/kg and for the early detection of this, a color vision test is important.[17] *Sajjad Ali et al* reported a case of EMB induced optic neuritis after 3 days of exposure to the drug whose visual acuity improved to 20/20 in left eye and to 20/40 in right on withdrawal of the drug suggesting it to be a idiosyncratic reaction.[18]

Following chronic ethambutol therapy, optic neuropathy is not always reversible, particularly in the elderly population. *Tsai and Lee* collected ten consecutive patients with severe visual defects due to ethambutol toxicity, and these patients had received presumably safe ethambutol dosages. Although ethambutol was stopped immediately in all cases, only five patients (50%) experienced visual improvement after a period of 12 months to 3 years follow-up. The other five patients (50%) had permanent visual impairment without recovery. There was no predisposing or risk factors to contribute to poor visual outcome. In the group over 60 years old, only 20% (1/5) experienced visual improvement; in the group less than 60 years old, 80% (4/5) had some visual recovery, the difference between these two age groups being statistically significant. The authors mention that they need more patient collections to answer whether the older patients with ethambutol optic neuropathy have poor prognoses. Ethambutol optic neuropathy, in the follow-up study was not always reversible, especially in the older population. It may cause permanent visual disability. There is no so-called "safe-dosage". The authors suggested reconsideration regarding the use of ethambutol as one of the first-line antitubercular drugs, especially in older patients.[19] In another study consisting of four cases of optic neuritis, symptoms developed after 2.5, 7.5, 8, and 12 months after therapy. Three cases had reversible neuritis with one patient developing permanent severe visual impairment. [20]

Based on the existing literature and with purpose of getting high cure rates and preventing the emergence of drug resistant tuberculosis following measures are considered for the use of EMB in tuberculosis. [21,22]

1. If an alternative drug becomes available it is better to avoid EMB in the treatment of tuberculosis as toxicity occurs at the lowest recommended dosage levels despite close medical and ophthalmic follow up and can cause severe vision loss that sometimes may not be recovered after stopping the drug.
2. If there is no alternative, before commencing treatment patients should be assessed for visual acuity, color vision and field of vision. EMB dosage reduction should be done or it should be contraindicated in patients with low baseline visual acuity that cannot be corrected with glasses, in patients unable to report their symptoms like children, persons with language difficulties and in persons with impaired renal function.
3. 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.

4. With normal renal function the dose of ethambutol is 15 mg/kg/day. If a dose of 25mg is needed it should not be given for more than 2 months.
5. 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.
6. At Directly Observed Treatment Short course (DOTS) sitting, health care workers are advised to monitor closely the visual symptoms of the patients and refer the patient appropriately.
7. 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 is stopped.
8. 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.

The management of EMB induced optic neuritis involves immediate discontinuation of EMB.High dose systemic prednisolone can be tried to bring down the inflammation around the optic nerves. High dose vitamins may be useful for neuroprotection, but to what extent it influences the final visual outcome is uncertain.

Isoniazid (INH): It is a hydrazide of isonicotinic acid first synthesized in 1942.[4] It can rarely cause retro bulbar neuritis. Dose relationship is usually not seen. *Jimenez-Lucho VE* reported a patient with optic neuropathy while on treatment with both EMB and INH and optic neuropathy resolved only when both the drugs were discontinued suggesting an additive effect.[23] Definite documentation of isoniazid- induced ocular toxicity is lacking in recent literature; however, it is suggested that ophthalmologic examination, including baseline visual evoked potentials, be performed in patients receiving isoniazid and ethambutol.[24]

Streptomycin: It was isolated in 1943 by *Walksman* from soil organisms.[4] It is bactericidal. Toxicity increases with impaired renal function. It can produce pseudotumor cerebri and myasthenic neuromuscular blockade. It should not be given in a patient with myasthenia gravis. 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.

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

Rifampicin: It is a semi-synthetic compound first synthesized in 1965. [4] It can produce conjunctivitis and orange staining of contact lenses.[25] These discolorations may be bothersome to the patient but do not require medical attention.

Thiacetazone: Thiacetazone can produce severe cutaneous reactions including Steven Johnson Syndrome affecting the skin and mucosa including conjunctiva. As mentioned earlier HIV positive patients are at major risk for cutaneous reactions. Conjunctival involvement may result in extensive scarring of the conjunctiva producing severe dry eye.

Advice to the patients: Patients on rifampicin should be warned that the drug causes orange red discoloration of all body fluids including tears which doesn't need any modification of treatment. Patients on soft contact lenses should be advised not to use contact lenses as long as rifampicin is taken as it causes permanent discoloration of soft contact lenses.

Patients on EMB should be explained the ocular toxicity of the drug and the need to stop the drug at the earliest signs of toxicity to prevent significant visual loss. Optic neuritis is often manifest by disturbances of color vision. Changes in color vision along the protan or deuteran axis are among the first changes seen in ethambutol toxicity. The color discrimination changes may be subclinical in many cases.[26] They should be asked to find any problem in appreciating different colors compared to their relatives and to check the status of their distance and near visual acuity regularly covering each eye separately. They can be given an Amsler chart to monitor for any scotomas (non seeing areas) in central fields. Patients are advised for an immediate detailed ophthalmic check up if any symptoms develop and tri-monthly routine detailed eye check up even if there are no symptoms. Patients with compromised renal function may require more frequent follow ups. Adequate dietary intake to prevent protein energy malnutrition and zinc deficiency may help in preventing severe optic neuritis. 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.

Conclusion

In conclusion, though it is very important to cure tuberculosis patients, to address the global problem of HIV associated increased prevalence of tuberculosis and to prevent the development of drug resistant tuberculosis, it is equally important to preserve the sight of the tuberculosis patients. There is a need to have periodic assessments of visual status of the patient during follow ups and DOTS sittings. It is advisable to avoid EMB if possible, especially in the elderly patients and if absolutely required use it very judiciously according to the guidelines suggested. One should be extra careful in presence of renal insufficiency. One should also not lose sight of the fact that INH also can cause retro bulbar neuritis and have index of suspicion and respond appropriately.

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