Ocular Toxicity of Ethambutol

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Introduction

Ethambutol hydrochloride is one of the first line agents employed in the treatment of tuberculosis, which remains an important infectious disease in Hong Kong, classified by the World Health Organization as "place with intermediate burden and a good health infrastructure".

Being a commonly used drug, ocular toxicity of ethambutol has been described since its first use in treatment of tuberculosis in 1960s1,2, manifesting as optic neuritis in affected individuals. Data regarding this potential side effect have been published, yet much controversy remains, especially on the issue of prevention of ocular toxicity of ethambutol.

The article aims to give a summary of literature published on ethambutol ocular toxicity - background, clinical presentation, toxicity characteristics, management, monitoring and preventive measures.

Method

We have performed a search in MEDLINE from 1962 through 2005, using the search formula: (ethambutol OR myambutol) AND ( eye* OR ophthal* OR ocular ) AND ( adverse OR toxic ). All relevant publications in English were included.

Background

Although uncommonly seen in patients on standard dosage, optic neuritis is the most important potential side effect of ethambutol hydrochloride. Retrobulbar neuritis is most common, with involvement of either axial fibres or less commonly, periaxial fibres. Mixed pattern is possible. 3,4 Other rarer side effects of ethambutol include peripheral neuropathy, cutaneous reactions (rash, pruritis, urticaria etc.), thrombocytopenia and hepatitis. 5,6

Exact mechanism of ocular neurotoxic effect of ethambutol is yet to be identified. Animal studies have demonstrated ethambutol toxicity on retinal ganglion neurons in rodents. Hypotheses for its toxicity have been made, including zinc-chelating effect of ethambutol and its metabolite 7, 8, 9, and excitotoxic pathway 10.

Clinical Presentation

The onset of ocular symptoms is usually delayed, occurring months after therapy initiation, though rare cases of toxicity occurring few days after initiation have been reported, one on standard dosage of 15mg/kg/day, another on 25mg/kg/day. 11,12 No study has reported onset after stopping ethambutol. Clinical course can be acute or chronic and typically, progressive.

Affected individuals may complain of bilateral progressive painless visual blurring. Decreased colour perception may also be experienced. Central vision is most commonly affected, though other visual field loss has also been described. Some individuals may be asymptomatic with abnormalities detected only by vision tests.

On physical examination, both eyes are usually affected symmetrically. Physical findings can be very variable. Pupils may be bilaterally sluggish to light with no relative afferent pupillary defect. Visual acuity drop varies greatly from nil or minimal reduction to no light perception. Central scotoma is the most common visual field defect, but bitemporal defects 13 or peripheral field constriction have been reported. Dyschromatopsia (abnormal colour perception) may be the earliest sign of toxicity14, classically documented to be red-green colour changes. In contrary, the report by Polak et al stated that blue-yellow defects were the most common and early defect in patients without any visual symptoms 15.

However, the subtle blue-yellow defects could only be detected using the generally unavailable desaturated panel of Lanthony and not Ishihara charts nor Farnsworth-Munsell D-15 test. Fundoscopic examination is usually normal.

Characteristics of ocular toxicity of ethambutol

Classically, the ocular toxicity is described as dose and duration related, and is largely reversible on drug discontinuation. However, the issue of reversibility is challenged by many recent studies.

Dose related

Studies gave a reported incidence of ethambutol related retrobulbar neuritis of 18% in patients receiving >35mg/kg/day, 5-6% with 25mg/kg/day and <1% with 15mg/kg/day of ethambutol HCL for more than two months. 16,17 No "safe dosage" for ethambutol was reported 7, with toxicity observed at a dose as low as 12.3 mg/kg 18. In Hong Kong, the usual daily dosage is 15mg/kg for adults and children, therefore, ethambutol ocular toxicity is not commonly seen in Hong Kong. As the major excretion pathway of ethambutol is by the kidneys, patients with poor renal function are at higher risk of ocular toxicities. Other factors predisposing subjects to ethambutol toxicity include diabetes and optic neuritis related to tobacco and alcohol. 19,20

Duration related

Manifestation of ocular toxicity is usually delayed, which
generally does not develop until after treatment for at least 1.5 months. Variable mean interval between onset of therapy and toxic effects were reported, from three to five months. Manifestations of toxicity as late as 12 months after therapy initiation were reported. However, these report series were of small scales with unknown generalisability.

Reversibility
Views on the issue of reversibility of ethambutol toxicity are divided. Although classically described as reversible on discontinuation of ethambutol (with visual acuity recovery over period of weeks to months), studies have reported permanent visual impairment without recovery in some patients with prompt ethambutol discontinuation, within a follow up period ranging from six months to three years. No risk factor was identified for the poor visual recovery, although some studies showed statistically significant difference in visual recovery between groups of over 60 years old and below 60 years old. Even in patients with visual improvement most after therapy discontinuation, complete recovery was not always achieved. Progressive worsening of vision after ethambutol discontinuation was also documented. However, these report series are again of small scale with unknown generalisability, and only patients with severe visual deficits were recruited. Furthermore, queries were made on the possible contribution of isoniazid induced ocular toxicity to the observed irreversibility, as isoniazid is not withdrawn together with ethambutol in the affected individuals.

Management
Upon recognition of ethambutol induced ocular toxicity, the drug must be immediately discontinued and patient referred to ophthalmologists for further evaluation. Therapy discontinuation is the only effective management currently, which can stop the progression of vision loss and allow recovery of vision. Some authors recommend that when severe ocular toxicity occurs, both isoniazid and ethambutol are to be stopped immediately and consider adding other anti-tuberculous agents to control tuberculosis. Isoniazid should also be stopped 6 weeks after stopping ethambutol if ocular toxicity is not severe but with no vision improvement.

Recommendations on monitoring and preventive measures
Several international guidelines have been published to suggest measures for prevention and early detection of ethambutol induced ocular toxicity. In August 2002, a guideline on this issue was published by the Tuberculosis and Chest Service of the Department of Health of Hong Kong Special Administrative Region (Table 1), based upon available clinical information, international guidelines and local experts’ experiences. However, there is no well-established agreement on the recommendations.

The Joint Tuberculosis Committee of the British Thoracic Society (Table 2) and the American Thoracic Society recommend routine visual acuity assessment prior to starting ethambutol, but no longer recommend visual acuity assessment during follow up. The American Thoracic Society also recommends performing assessment of red-green colour perception test prior to treatment. Hong Kong’s guideline recommends baseline vision test for both visual acuity and red-green colour perception by the use of Snellen chart and Ishihara chart, respectively, which do not require ophthalmologist consultation.

Another unsettled issue is the clinical effectiveness of regular visual tests to achieve early ocular toxicity detection. Most guidelines do not recommend regular visual acuity assessment, where visual acuity may be normal in the early stages. Hong Kong’s guideline suggests that regular visual acuity test may be considered in patients with risk factors, especially with high dose (25mg/kg/day) or prolonged treatment with ethambutol. However, with increasing evidence of comparatively better sensitivity of colour vision defect in early toxicity detection, regular colour vision test with Ishihara chart may be considered instead for high-risk patients, without the need of ophthalmologist referral. A descriptive study of colour vision test in 42 patients with systemic tuberculosis receiving ethambutol, however, showed that 15 of 42 patients with high total error scores at the Farnsworth-Munsell 100 test had normal colour vision measured by Ishihara pseudoisochromatic plates. The sensitivities of different colour vision tests are yet to be determined.

With the usual daily dosage of 15mg/kg/day for patients under the care of Tuberculosis and Chest Service in Hong Kong, incidence of ethambutol induced ocular toxicity is below 1%. Given the low incidence of toxicity and the yet unknown sensitivity of regular visual tests in early toxicity detection, the cost effectiveness of regular vision tests (even colour vision test) on patients on dosage of 15mg/kg/day is questionable.

It is unlikely that any guidelines will completely remove the risk of optic neuritis with ethambutol. Many a time, the course of ethambutol induced ocular toxicity is unpredictable. Measures to ensure a high level of awareness of this potential adverse effect in both medical staff and patients seems to be the best current preventive method available. Medical staff should regularly ask about vision change in patients taking ethambutol and provide education to ensure that all patients know to stop ethambutol immediately and seek prompt medical advice if visual symptoms occur.

Conclusion
Being one of the safest first-line anti-tuberculous agents, ethambutol HCl is commonly prescribed for patients with tuberculosis. Optic neuritis is a rare, yet, most important side effect of ethambutol, which the mechanism of toxicity is still under investigation. This ocular toxicity is dose and duration related. Though classically described as reversible, irreversibility of vision change was also reported in several case series. Although international guidelines on prevention and early detection of ethambutol induced ocular toxicity have been published, views on use of regular vision tests for early toxicity detection are still divided.

Classified by World Health Organization as a place with intermediate tuberculosis burden and good health infrastructure, Hong Kong is in a good position to look into the unanswered questions of ethambutol induced ocular toxicity, where studies on reversibility of ocular toxicity, sensitivity of various types of vision tests in early ocular toxicity detection, cost effectiveness of vision monitoring as compared with patient education alone can be conducted.
Table 1. Recommendations in Preventive Measures Against Drug-Induced Ocular Toxicity During Anti-tuberculous Treatment (General Recommendations) [Extracted from Annual Report (Suppl) 2002, Tuberculosis and Chest Service, Department of Health, Hong Kong]

(a) Upon commencement of anti-TB treatment, patients should be assessed for feasibility and contraindications of using EMB. In situations where there is an increased risk of ocular toxicity, the benefit of using EMB 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. EMB may be contraindicated or dosage reduction may be indicated in the some situations:

i. Impaired baseline vision may make visual monitoring difficult. However, in conditions like refractive error, which is correctable with the use of spectacles, and mild cataract that is unlikely to affect visual changes rapidly, continuous monitoring of vision can be conducted during treatment with EMB. EMB should be avoided in patients with significantly reduced vision.

ii. Patients with difficulty in appreciating and reporting visual symptoms or changes in vision, like young children, persons with language difficulties, may also make visual monitoring difficult.

iii. Impaired renal function can predispose to the development of EMB-related ocular toxicity. Hence, renal function should be checked upon commencement of anti-TB treatment. Recommendations on dosage adjustment of EMB in the case of renal impairment have been described in the recent local TB treatment guidelines.5

(b) For all patients undergoing treatment with anti-TB drugs that includes EMB, health education should be provided to them on the visual side effects of the drug and a high level of awareness of this potential side effect should be emphasised 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. The offering of such advice to the patients should be recorded in the medical notes. In case it is necessary to prescribe EMB 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.

(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. There is controversy about the use of regular visual test although this may be considered in certain patients with risk factors, especially when a high dose (25 mg/kg/day, see below) of EMB is used or the treatment is prolonged.

(d) With normal renal function, the recommended daily dose for EMB is 15 mg/kg/day throughout the course of anti-TB treatment.5 However, the use of a higher dose of 25 mg/kg/day may be considered in certain conditions like severe cavitatory TB, drug-resistant TB, or retreatment cases. This higher dose should not be given for more than two months. Ideal body weight should be used in calculations for obese people.

(e) During medical consultations in the course of anti-TB treatment including EMB, all patients should be assessed clinically for symptoms of visual disturbance. Enquiring monthly about visual symptoms is advisable for such patients.

(f) Directly observed treatment (DOT), apart from ensuring treatment adherence, also allows health care workers to monitor the patients closely for such symptoms.

Table 2. British Thoracic Society Guidelines - Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998*

| Special precautions and pretreatment screening point (I) | Because of the possible (but rare) toxic effects of ethambutol on the eye, it is recommended that visual acuity should be tested by Snellen chart before it is first prescribed. The drug should only be used in patients who have reasonable visual acuity and who are able to appreciate and report visual symptoms or changes in vision. The notes should record that the patient has been told to stop the drug immediately if such symptoms occur, and to report to the physician. The general practitioner should also be informed of this. In small children and in those with language difficulties ethambutol should be used where appropriate, with the above advice given to parents or other family members. |

References

5. Consensus statement of Tuberculosis Control Coordinating Committee of Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority of Hong Kong - Chemotherapy of Tuberculosis in Hong Kong, 2001.
10. Heng JE, Vorwerk CK, Lessell E, Zurawkowski D, Levin LA, Dreyer EB. Ethambutol toxicity is associated with anti-TB treatment. Recommendations on dosage adjustment of EMB in the case of renal impairment have been described in the recent local TB treatment guidelines.5