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Ocular toxicity of ethambutol

乙胺丁醇引致眼睛中毒

Objective. To review the literature on ocular toxicity of ethambutol—its background, clinical presentation, toxicity characteristics, management, monitoring, and preventive measures.

Data sources. Literature search of Medline from 1962 to May 2005.

Study selection. All related literature in English using the search formula: (ethambutol OR myambutol) AND (eye* OR ophthal* OR ocular) AND (adverse OR toxic).

Data extraction. All information was collected and analysed by authors.

Data synthesis. Ethambutol hydrochloride is a commonly used first-line anti-tuberculous agent. Although rare, ocular toxicity in the form of optic neuritis (most commonly retrobulbar neuritis) has been well documented since its first use in the 1960s. Classically described as dose- and duration-related and reversible on therapy discontinuation, reversibility of optic neuritis remains controversial. International guidelines on prevention and early detection of ethambutol-induced ocular toxicity have been published. Nonetheless, opinion of the clinical effectiveness of regular vision tests to enable early detection of toxicity is divided.

Conclusions. The course of ethambutol-induced ocular toxicity is unpredictable. Measures to ensure a high level of awareness in medical staff and patients of this potential adverse effect appear to be the best current preventive method. Classified by the World Health Organization as a place with an intermediate tuberculosis burden and good health infrastructure, Hong Kong is in a good position to examine the unanswered questions about ethambutol-induced ocular toxicity.

目的：翻查文獻中關於乙胺丁醇引致眼睛中毒的資料，包括其背景、臨床表徵、毒性特質、治療、監察及預防措施。

資料來源：應用 Medline 檢索 1962 年至 2005 年 5 月的文獻。

資料選擇：以“ethambutol (或 myambutol)”、“eye* (或 ophthal* 或 ocular)”和“adverse (或 toxic)”檢索相關的英文文獻。

數據選取：由作者收集及分析所有資料。

數據綜合：鹽酸乙胺丁醇是普遍使用的第一線抗肺結核藥物。因眼睛中毒而出現視神經炎(最普遍為眼球後視神經炎)的病例雖然極為罕有，但自 1960 年代便有文獻記載。視神經炎向來被形容為與服藥量和服藥期長短有關，而且在停藥後病情是可逆轉的，但這點仍具爭議性。儘管國際社會已發出預防和及早檢查乙胺丁醇導致眼睛中毒的指引，但定期視力檢測對及早發現眼睛中毒的臨床效果，則仍意見分歧。

結論：乙胺丁醇引致的眼睛中毒，過程無法預測。現時最佳預防這種不良反應的方法，似乎是醫療人員和病人提高警惕。香港被世界衛生組織評為中等肺結核風險的地方，加上良好的醫療基建，是找尋乙胺丁醇引致眼睛中毒答案的適當地點。

Introduction

Ethambutol hydrochloride (HCL) is one of the first-line agents employed in the treatment of tuberculosis. Tuberculosis remains an important infectious disease in Hong Kong, where it is classified by the World Health Organization as a “place with intermediate burden and a good health infrastructure”.^{1,2}

Ethambutol is a commonly used drug and its associated ocular toxicity, manifesting as optic neuritis, has been described since its first use in the treatment of tuberculosis in the 1960s.^{3,4} Data regarding this potential side-effect have been published, yet much controversy remains, especially with regard to prevention

Key words:

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關鍵詞：

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眼

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of ocular toxicity. This article aimed to summarise the available literature on ethambutol-induced ocular toxicity—its background, clinical presentation, toxicity characteristics, management, monitoring, and preventive measures.

A search in Medline was performed for literature published from 1962 through May 2005, using the search formula: (ethambutol OR myambutol) AND (eye* OR ophthal* OR ocular) AND (adverse OR toxic). All relevant English-language publications were included.

Ethambutol

Optic neuritis is the most important potential side-effect of ethambutol HCL. It is nonetheless rare in patients prescribed standard doses. Retrobulbar neuritis is the most common, with involvement of either axial fibres or, less commonly, periaxial fibres. A mixed pattern is also possible.^{5,6} Other more rare side-effects include peripheral neuropathy, cutaneous reactions (rash, pruritus, urticaria, etc), thrombocytopenia, and hepatitis.^{1,7}

The exact mechanism of this ocular neurotoxic effect has not been identified. Animal studies have demonstrated ethambutol toxicity in the retinal ganglion neurons of rodents. One of the principal theories for its toxicity has been the zinc-chelating effect of ethambutol and its metabolite.⁸⁻¹⁰ Postulated biochemical pathways that mediate the toxic damage include downstream effector caspase-3 and caspase-6,⁸ and an excitotoxic pathway.¹¹

Clinical presentation

The onset of ocular symptoms is usually delayed and may occur months following commencement of therapy. Although rare, cases of toxicity occurring a few days after initiation have been reported, in one patient being prescribed a standard dose of 15 mg/kg per day, and another prescribed 25 mg/kg per day.^{12,13} No study has reported onset after withdrawal of ethambutol. The clinical course can be acute or chronic and is typically progressive.

Presenting ocular symptoms vary among affected individuals. Patients may complain of bilateral progressive painless blurring of vision or decreased colour perception. Central vision is most commonly affected, though other visual field loss has also been described.^{5,12,14} Some individuals may be asymptomatic with abnormalities detected only by vision tests.

The findings of physical examination are likewise variable. Both eyes are usually symmetrically affected, if any abnormality is detected. The 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 defects¹⁴ or peripheral field constriction have been reported. Dys-

chromatopsia (abnormal colour perception) may be the earliest sign of toxicity,¹⁵ classically documented to be red-green colour changes. In contrast to this, the report by Polak et al¹⁶ stated that blue-yellow defects were the most common and early defect in patients without any visual symptoms. Nonetheless 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 withdrawal although this has been recently challenged.

Dose-related

The reported incidence of ethambutol-related retrobulbar neuritis varies between 18% in patients receiving more than 35 mg/kg per day, 5% to 6% with 25 mg/kg per day, and less than 1% with 15 mg/kg per day of ethambutol HCL for more than 2 months.^{5,17} No 'safe dose' of ethambutol has been reported,¹⁸ with toxicity observed at doses as low as 12.3 mg/kg per day.¹⁹ In Hong Kong, the usual daily dose is 15 mg/kg for adults and children. As such, ethambutol-related ocular toxicity is not commonly seen in Hong Kong. As the major excretion pathway of ethambutol is via the kidneys, patients with poor renal function are at higher risk of ocular toxicities. Other factors that predispose subjects to toxicity include diabetes and optic neuritis related to tobacco and alcohol consumption.^{20,21}

Duration-related

The manifestation of ocular toxicity is usually delayed, and generally does not develop until at least 1.5 months after treatment.¹⁴ The mean interval between onset of therapy and toxic effects has been reported to be 3 to 5 months.^{5,18,22} Manifestations of toxicity as late as 12 months after therapy initiation have also been reported.^{23,24} It should be pointed out that these reports concerned small numbers of patients with unknown external validity.

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 a period of weeks to months), permanent visual impairment without recovery has been reported within a follow-up period ranging from 6 months to 3 years in some patients in whom there was prompt ethambutol discontinuation.^{14,18,21,22,24} No risk factor was identified for the poor visual recovery, although another study¹⁸ showed a statistically significant difference in visual recovery between groups of patients aged older than 60 years and those aged younger than 60 years. Visual improvement was reported by 20% and 80%, respectively. Even in patients who report visual improvement after therapy discontinuation, complete recovery is not always

Box 1. Recommendations by Tuberculosis and Chest Service, Department of Health, Hong Kong Special Administrative Region²⁵

- (a) Upon commencement of anti-tuberculosis (TB) treatment, patients should be assessed for feasibility and contra-indications of using ethambutol (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. Ethambutol may be contra-indicated or dosage reduction may be indicated in some situations:
 - (i) Impaired baseline vision may make visual monitoring difficult. However, in conditions such as 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. Ethambutol should be avoided in patients with significantly reduced vision
 - (ii) Patients who have difficulty in appreciating and reporting visual symptoms or changes in vision, such as young children and people with language difficulties, may also make visual monitoring difficult
 - (iii) Impaired renal function can predispose to the development of EMB-related ocular toxicity. 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 guidelines¹
- (b) For all patients undergoing treatment with anti-TB drugs that include EMB, health education should be provided to them about visual side-effects of the drug and a high level of awareness of this potential side-effect should be emphasised during treatment. Patients should be advised that, if 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 patients should be recorded in the medical notes. If 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 educational pamphlets may be beneficial
- (c) Baseline vision tests for visual acuity and red-green colour perception (eg using Snellen chart and Ishihara chart) should be conducted before starting treatment. There is controversy about the use of regular visual testing although this may be considered in certain patients with risk factors, especially when a high dose of 25 mg/kg per 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 per day throughout the course of anti-TB treatment.¹ However, the use of a higher dose of 25 mg/kg per day may be considered in certain conditions such as severe cavitary TB, drug-resistant TB, or retreatment cases. This higher dose should not be given for more than 2 months. Ideal body weight should be used in calculations for obese people
- (e) During medical consultations in the course of anti-TB treatment that includes EMB, all patients should be assessed clinically for symptoms of visual disturbance. Enquiring monthly about visual symptoms is advisable
- (f) Directly observed treatment, apart from ensuring treatment adherence, also allows health care workers to monitor patients closely for such symptoms
- (g) Patients who develop symptoms suspicious of drug-induced ocular toxicity should be documented with vision test (eg using Snellen chart and Ishihara chart). Depending on the individual circumstances, EMB may have to be stopped and the patient referred to an ophthalmologist for a more thorough assessment. Formal ophthalmological documentation includes fundal examination, visual acuity, visual field assessment (eg finger perimetry), and colour vision. If impaired vision is due to other causes, eg cataract, rather than optic neuritis, EMB may be resumed depending on the feasibility and pros and cons of using alternative drugs. If visual impairment is related to anti-TB treatment, EMB should continue to be withheld. In such cases, reassessment should be made for any change in the occurrence of risk factors, eg checking renal function for any recent impairment
- (h) If severe optic neuritis occurs, isoniazid (INH) should also be stopped. In the case of less severe optic neuritis, if INH is being continued, prescription of pyridoxine at a high dose (say, 50 to 100 mg daily) may be considered, particularly for those with risk factors such as malnutrition, alcoholic abuse, and advanced age. If optic neuritis fails to improve within 6 weeks of stopping EMB, INH should also be stopped

Box 2. Recommendations from the British Thoracic Society Guidelines in 1998—chemotherapy and management of tuberculosis in the United Kingdom²⁶

Special precautions and pretreatment screening point (1)
 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

to the observed irreversibility, as isoniazid was not also withdrawn in the affected individuals.²⁴

Management

Ethambutol must be immediately discontinued when ethambutol-induced ocular toxicity is recognised and the patient referred to an ophthalmologist for further evaluation. Therapy discontinuation is the only effective management that can halt the progression of vision loss and allow recovery of vision. It is recommended that when severe ocular toxicity occurs, both isoniazid and ethambutol should be stopped immediately and other additional anti-tuberculous agents considered. If isoniazid is not stopped immediately, it should in any event be stopped 6 weeks later if ocular toxicity is not severe and there is no improvement in vision.²⁴

Recommendations on monitoring and preventive measures

Several international guidelines have been published to

achieved.^{18,24} Progressive worsening of vision after ethambutol discontinuation has also been documented.²⁴ These series of reports are once again small-scale with unknown external validity, and only patients with severe visual deficits were recruited. Furthermore, queries were made on the possible contribution of isoniazid-induced ocular toxicity

suggest measures for prevention and early detection of ethambutol-induced ocular toxicity. In August 2002, guidelines on this issue were published by the Tuberculosis and Chest Service of the Department of Health of Hong Kong Special Administrative Region (Box 1²⁵). They were based upon available clinical information, international guidelines, and local experts' experience.²⁶⁻²⁸ There remains nevertheless no agreement on the recommendations.

The Joint Tuberculosis Committee of the British Thoracic Society²⁶ (Box 2) and the American Thoracic Society²⁷ 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 assessment of red-green colour perception prior to treatment. Hong Kong's guidelines recommend baseline vision tests for both visual acuity and red-green colour perception by the use of a Snellen chart and Ishihara chart, respectively.²⁵ These do not require ophthalmologist consultation.

It remains to be determined whether regular visual tests to achieve early detection of ocular toxicity are effective in clinical practice. Most guidelines do not recommend regular visual acuity assessment,^{26,27} because it may be normal in the early stages of toxicity. Hong Kong's guidelines suggest regular testing in patients considered at particular risk, for example, those being prescribed a high dose (25 mg/kg per day) or with prolonged treatment with ethambutol. Increasing evidence demonstrates that colour vision defects provide a comparatively better indicator and enable early detection of toxicity.^{5,15,16} Thus regular colour vision testing with an Ishihara chart may be an alternative for high-risk patients and does not require ophthalmologist referral. A descriptive study of colour vision testing in 42 patients with systemic tuberculosis who received ethambutol,²⁹ however, showed that 15 (36%) patients with high total error scores at the Farnsworth-Munsell 100 test had normal colour vision measured by Ishihara pseudo-isochromatic plates. The sensitivities of different colour vision tests have not been determined.

The standard daily dose of ethambutol recommended by the Tuberculosis and Chest Service in Hong Kong is 15 mg/kg per day.¹ Under such conditions the estimated risk of ethambutol-induced ocular toxicity falls below 1%.^{5,17} Given the low incidence of toxicity and the as-yet-unknown sensitivity of regular visual testing in early toxicity detection, the cost-effectiveness of regular vision tests (even colour vision test) in these patients is questionable.

It is unlikely that application of any guidelines will completely remove the risk of optic neuritis with ethambutol. The course of ethambutol-induced ocular toxicity is often unpredictable. Measures to ensure a high level of awareness of this potential adverse effect by medical staff and patients seem to be the best current preventative method. Medical staff should regularly ask patients about changes

in vision and, should they arise, ensure all patients understand that ethambutol should be immediately stopped and prompt medical advice sought.

Conclusions

Ethambutol is one of the safest first-line anti-tuberculous agents. Optic neuritis is a rare, yet important side-effect. The mechanism of toxicity is still under investigation although it is known to be dose- and duration-related. Although classically described as reversible, irreversibility of vision change has been reported. International guidelines on prevention and early detection of ethambutol-induced ocular toxicity have been published, but views on the use of regular vision tests for early toxicity detection are still divided. Classified by the World Health Organization as a place with intermediate tuberculosis burden and good health infrastructure, Hong Kong is ideally placed to examine the unresolved issues related to ocular toxicity and screening.

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