PREVENTIVE MEASURES AGAINST DRUG-INDUCED OCULAR TOXICITY DURING ANTI-TUBERCULOSIS TREATMENT

(GENERAL RECOMMENDATIONS)

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Internal guidelines of
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Background

Ethambutol (EMB) 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. EMB 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. [1] It has been reported to compare favourably to isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA). [1]

The ocular side effects of EMB therapy were first described by Carr and Henkind in 1962. [2] Retrobulbar neuritis is the most important potential side effect from EMB. It is reversible in most cases and is related to the dose and duration of treatment, but may occasionally become irreversible resulting in permanent visual disability especially in the older population. It has been said that there is no so-called "safe-dosage" for EMB. [3] The reported incidence of retrobulbar neuritis when EMB is taken for more than 2 months is 18% in subjects receiving greater than 35 mg/kg/day, 5-6% with 25 mg/kg/day, and less than 1% with 15 mg/kg/day. [4,5]

Two types of retro-bulbar neuritis have been described, with involvement of either the central fibres (central toxicity) or uncommonly the peripheral fibres (peripheral toxicity) of the optic nerve. [5] Symptoms and signs of central toxicity include visual blurring, impaired visual acuity on physical examination, central scotoma and loss of perception of red-green colour. Peripheral toxicity may cause few visual symptoms but there is peripheral constriction of visual fields on physical examination. In most instances, the optic disc appears normal.

The exact mechanism by which EMB produces retro-bulbar neuritis is not known; it may be due to its ability to chelate zinc. In animal studies, EMB has been shown to deplete zinc from the optic nerves. [6] Unusual idiosyncratic hypersensitivity with irreversible blindness occurring after six days of treatment with EMB 15 mg/kg/day has also been described. [7]

Apart from EMB, INH, though to a lesser extent, has also been implicated in the development of visually related side effects. [8,9] Thus, the potential ocular toxicity of INH should not be overlooked.

Recommendations on monitoring and preventive measures for ocular toxicity during anti-TB treatment have been made by various authorities. [10-12] Opinions do differ on the dose of EMB either throughout or during the initial treatment phase, and the timing and periodicity of the use of visual tests. It would be useful to summarise the existing data on these issues and lay down some guidelines for reference of the chest clinic medical staff.

Recommendations

Basing on the available clinical information, international guidelines, and experiences from local experts, 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 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 which 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. [13]

(b) For all patients undergoing treatment with anti-TB drugs which 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 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. 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. [10] 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 (Table 1) and Ishihara chart) should be conducted before starting treatment. [10,11,14] 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. [5,8,12]

(d) With normal renal function, the recommended daily dose for EMB is 15 mg/kg/day throughout the course of anti-TB treatment. [10] 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. [12]

(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. [12,15]

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

(g) Patients developing symptoms suspicious of drug-induced ocular toxicity should be documented with vision test (e.g., using Snellen chart (Table 1) and Ishihara chart). Depending on the individual circumstances, EMB may have to be stopped and the patient referred to ophthalmologist for more detail assessment. Formal ophthalmological documentation includes fundal examination, visual acuity, visual field assessment (e.g., finger perimetry) and colour vision. If the impaired vision is due to other causes, e.g., 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 the anti-TB treatment, EMB should continue to be withheld. In such case, reassessment should be made for any change in the occurrence of risk factors, e.g., checking renal function for any recent impairment.

(h) If severe optic neuritis occurs, INH should also be stopped. In the case of less severe optic neuritis, if INH is being continued, prescription of pyridoxine at high dose (say, 50 to 100 mg daily) may be considered, particularly for those with risk factors like malnutrition, alcoholics and the elderly subjects. If the optic neuritis fails to improve within 6 weeks after stopping EMB, INH should also be stopped. [16]

Discussion and conclusions

There are a number of uncertain and difficult areas in the recommendation of preventive measures against drug-induced ocular toxicity during anti-TB treatment. The use of EMB in a patient with baseline colour vision deficiency, for example, may not be absolutely contraindicated but the standard for safety monitoring will need to be higher. Abnormal colour perception is often an earlier and more sensitive finding

of EMB toxicity than changes in visual acuity [16-18]. If the patient has baseline colour perception problem and subsequently develops some change in colour vision during treatment, one may have difficulty in distinguishing whether this is due to EMB toxicity or test variability. The clinician has to judge the pros and cons of using EMB or alternative agents in each individual circumstance and discuss with the patient for an appropriate and acceptable regimen. A high degree of awareness of this potential ocular side effect of EMB is crucial, both on the part of the health care staff as well as the patient.

Another interesting but uncertain area is the role of zinc supplement. Zinc supplement has been shown to improve diabetic neuropathy [19] and visual acuity in optic neuropathy due to alcohol and tobacco abuse. [20] It has also been reported that patients with lower plasma zinc level have a higher risk of developing EMB-induced optic neuropathy. [21] On the other hand, animal studies showed that zinc supplement may augment the pathological changes in retinal cultures with established EMB-induced vacuolar degeneration and neuronal loss. [22] In addition, correction of zinc deficiency with zinc supplementation must be done cautiously because excessive zinc can interfere with the metabolism of copper and zinc. [23] The use of zinc supplement for the malnourished patients with low zinc level prior to treatment with EMB appears sensible, but there is insufficient data to support the benefit of such strategy.

Despite the potential ocular toxicity of EMB, it is still a very useful anti-TB drug. Sometimes too much emphasis have been placed on blindness with EMB. When compared with other drugs like INH, RMP or PZA, EMB seems to have a lower chance of causing severe drug reactions leading to death. It has been estimated that the chance of occurrence of irreversible ocular toxicity in patients taking EMB is equivalent to the chance of death from drug reactions from PZA therapy. [1] With a high degree of awareness and proper precautions taken when prescribing the drug, EMB should be as safe or safer than the other standard anti-TB drugs. [1] Accumulation of local experience and the availability of more scientific data will help to further improve the above the preventive measures.

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Table 1. Tests for visual acuity

Some tests for visual acuity:

(a) Standard Snellen chart at 6 m (direct method)
(b) Snellen chart using a mirror at 3 m
(c) Near Snellen equivalent at reading distance of about 30 cm (miniature Snellen chart) (e.g., for non-ambulatory patients)

Points to note:

- All the above tests are acceptable if done at the right distance with best corrected spectacles or pin-hole (which reduces the effect of moderate degree of refractive error), and the same test is used during subsequent monitoring if required.
- When the standard Snellen chart is used and the top line cannot be read at 6 m, the test can be done closer to the chart at 2 m or 1 m. If the top line still cannot be read at 1 m, the patient may be asked to count fingers (CF), to appreciate hand movement (HM), or to perceive presence of light (LP).