

Is It Necessary to Screen Children for Ethambutol Toxicity? Recommendations for Clinical Surveillance

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Abstract

Ethambutol is an effective and well-tolerated antibiotic used to treat tuberculosis, but a serious side effect of the drug, in the form of sudden-onset optic neuropathy, was recognized soon after its release in the early 1960's. This article reviews the current world literature on ethambutol toxicity, highlights the different pharmacokinetics of the drug in young patients, and draws the conclusion that ethambutol causes fewer ocular side effects in children than in adults. Given the capricious nature of visual failure from ethambutol and its extreme rarity in children, a screening method for children seems unnecessary and impractical.

Introduction

Ethambutol has a bacteriostatic mode of action against mycobacteria, and is well tolerated by patients.^{1;2} Considerable concern has been raised over its potentially blinding toxic side effects, which is thought to be caused by the depletion of zinc from ocular structures, damaging the optic nerve, optic chiasm, and optic tracts.

Clinical Signs of Optic Neuropathy in Adults

Ocular toxicity is characterized clinically both by paracentral field defects with little effect on visual acuity, and by central field defects with marked loss of visual acuity.³ Onset of the symptoms tends to be rapid, over a period of days. Disorders of contrast sensitivity and colour perception can be sensitive indicators of early ocular toxicity.⁴ Fundoscopy typically shows few abnormal signs, but optic atrophy may develop. Investigations with electro-oculogram, electroretinogram and visual-evoked potentials all show abnormalities at an early stage of the development of the neuropathy.⁵⁻⁸

Reports of Optic Neuropathy Associated with Ethambutol

Several case reports and series have been published, almost entirely about adult patients. There appears to be wide variation in the time of onset of ocular pathology, its reversibility, its frequency, its association with drug dose, and its predilection for different sexes and ages. What is clear, though, is that the symptoms of ethambutol-associated optic neuropathy always develop rapidly over a matter of days. These facts hold important implications for any planned paediatric visual screening programme.

TIME OF ONSET

Severe visual impairment due to ethambutol has been reported after just three days of treatment, whilst the longest reported interval is over 12 months. The mean interval is in the region of 4 – 5 months.^{7;9-19}

REVERSIBILITY

Some papers report restoration of visual function following withdrawal of the drug,^{7;9;18;20;21} while other more recent papers report cases of severe and irreversible visual impairment.^{12;13;22;23} It is not possible to distinguish accurately between those patients who will have reversible visual loss and those that will not.

FREQUENCY AMONGST ADULT PATIENTS TAKING ETHAMBUTOL

There are no satisfactory reports of the frequency of optic nerve toxicity among paediatric patients. However, the frequency of optic neuropathy is less than 2% amongst adult patients taking ethambutol at the currently agreed standard dosage of 15mg/kg/day.^{9;24-26} But there appears to be no “safe dose” of ethambutol in adults.^{10;16;23;27;28}

HIGH RISK PATIENTS

Patients with **chronic renal failure** and **renal tuberculosis** have been amongst those reported to develop ocular side effects at modest doses of ethambutol. Furthermore, patients with **mycobacterial meningitis** appear to be at greater risk of ocular toxicity, presumably due to break-down of the blood-brain barrier. It can be difficult to distinguish drug-induced optic neuropathy from that caused by the infection itself.^{29;30;19}

Minimization of the ocular side effects of ethambutol requires that the patient has a solid understanding of the risks and can adequately report any visual symptoms if they occur. **Patients with poor understanding and communication** (e.g. very young children, non-English-speaking patients, and patients with learning difficulties) are therefore at a greater risk of visual loss.¹⁴

Case reports in children

It is becoming increasingly apparent that ethambutol has very few ocular side effects in children.³¹ Out of the published literature spanning 40 years, there were 2 children who developed subjective and transient visual symptoms after 4 months,³² one child with blurred disc margins⁷, and one further non-confirmed case with incomplete clinical details.³³ Not one of the members of this Paediatric

Subcommittee of the Professional Standards Committee has encountered a single case of ethambutol-associated ocular toxicity in children.

Pharmacokinetics of ethambutol in adults and children

In children, ethambutol does not reach the same plasma concentrations as in adults, presumably due to sequestration in a larger extravascular volume.^{34;35} In fact, we may actually be *underdosing* our paediatric patients for fear of ocular toxicity and ignorance of the different pharmacokinetic profile of ethambutol in children.³¹

Existing guidelines in children and adults

Because of the capricious nature of ethambutol toxicity, some physicians feel that the drug should be banned altogether,^{10;11;15;36} while many recommend monthly visual acuity testing as the safest way to detect toxicity.^{3;37;38} Other authors variously recommend repeated tests of colour vision, contrast sensitivity, visual fields, and electrodiagnostic testing as the most sensitive tools to detect ocular toxicity.^{5;6;13;23;28;39-43} Many of these recommendations are impractical due to lack of equipment or resources, especially in young children.

One extensive review of the literature concludes that the visual *symptoms* of ethambutol toxicity are more sensitive than objective clinical ophthalmological *signs*, and recommends that only a baseline test of vision be performed on all patients.¹⁹ The British Thoracic Society states that regular screening is not necessary after a mandatory baseline test, but that ethambutol should be used with discretion in very young children and patients with language difficulties.⁴⁴

New recommendations for visual screening of children taking ethambutol

Currently, many hospital eye departments in the UK are screening children for ethambutol toxicity. A screening programme is defined as "*the systematic application of a test or inquiry, to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action, amongst persons who have not sought medical attention on account of symptoms of that disorder.*"⁴⁵

It requires a slowly-evolving disorder (eg, carcinoma of the breast), a cost-effective

investigation (eg, mammography), and a disorder which can be effectively treated at the stage at which it is detected.

In the case of ethambutol toxicity in children, the at-risk individuals are easily identified. But the frequency of toxicity is so low as to be almost non-existent, and when it occurs it does so in a matter of days. The investigations required (frequent visual acuity estimation, colour vision testing, perimetry and electrodiagnostic tests) are potentially time-consuming and inaccurate in young children. Furthermore, withdrawal of the drug is not always effective. In fact, we may end up merely recording the *prevalence* of a rare and often irreversible disorder, in a process more accurately defined as surveillance. We therefore recommend that screening for ocular side effects of ethambutol in children under 16 years of age is not performed.

Conclusion

Ethambutol ocular toxicity is extremely rare in children. It is theoretically more likely to occur in children taking high or prolonged doses, patients with renal disease, and in children with mycobacterial meningitis. When it occurs, it occurs rapidly, and assessing vision in children is challenging and potentially inaccurate. The intervention required upon detection of ocular toxicity, withdrawal of the drug, is not always effective in reversing visual failure. It is therefore impractical to attempt to prevent ocular toxicity in children by means of a screening programme.

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On review of the literature published since our paper was first posted in 2004^{46,47} there is no new evidence to alter our opinion that screening for ocular side effects of ethambutol cannot be justified. However, when ethambutol is prescribed the family and carers should be made aware of the possibility of this rare side effect and children with vision symptoms or cerebral tuberculosis should be referred for an ophthalmic opinion. There is some evidence that those with a family history of Leber's hereditary optic neuropathy or dominant optic atrophy may have a higher risk of optic neuropathy associated with ethambutol use^{48,49}.

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