

# Update on ocular toxicity of ethambutol



## Authors:

Priscilla Makunyane<sup>1</sup>  
Solani Mathebula<sup>2</sup>

## Affiliations:

<sup>1</sup>Department of  
Ophthalmology, University of  
Pretoria, South Africa

<sup>2</sup>Department of Optometry,  
University of Limpopo,  
South Africa

## Corresponding author:

Priscilla Makunyane,  
prisilla.makunyane@up.ac.za

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The purpose of this review is to update clinicians on available literature on the ocular toxicity of ethambutol and the type of eye care to be provided to patients treated with these medications. Ethambutol is a commonly used first-line anti-tuberculosis drug. Since its first use in the 1960s, ocular toxicity is described as related to dose and duration, and it is reversible on therapy discontinuation. However, the reversibility of the toxic optic neuropathy remains controversial. The mechanism of ocular toxicity owing to ethambutol is still under investigation. Other than discontinuing the drug, no specific treatment is available for the optic neuropathy caused by ethambutol. Doctors prescribing ethambutol should be aware of the ocular toxicity, and the drug should be used with proper patient education and ophthalmic monitoring.

## Introduction

Tuberculosis (TB) has been present since 460 BC, as the most widespread disease of the time, and it was fatal. The causative organism of TB is *Mycobacterium tuberculosis* which is a slow-growing bacterium that divides every 16–20 hours.<sup>1</sup> Today, TB is still the most common infectious disease, and a major public health problem, infecting millions of people worldwide, including South Africa. It is estimated by the World Health Organization (WHO) that a third of the world's population is infected by *M. tuberculosis*. As per WHO estimates, South Africa, with 80% of the infected population having active TB, is one of the countries with the highest burden of TB after India and China.

Ethambutol is one of the first-line anti-TB medications. The other medications or drugs in the treatment regimen include isoniazid, rifampicin and pyrazinamide. Ethambutol is a bacteriostatic drug,<sup>1</sup> developed in the early 1960s. Even today, it is considered a first-line therapy against *M. tuberculosis*. It has synergistic actions when combined with other agents to create a combined antimycobacterial effect which is key in treating multi-drug-resistant TB for a minimum period of 6 months. Since then, mild-to-severe toxic neuropathy and amblyopia owing to ethambutol have been reported.<sup>2,3,4,5,6,7,8,9</sup>

The purpose of this paper is to give an update of published literature on ethambutol-induced ocular toxicity. Ophthalmologists should be aware of the ocular features and management strategies so that they can control the toxicity effectively.

## Method

We performed a literature search for publications from 1950 to January 2016, using the search 'toxic or adverse effects of ethambutol in the eye or the ocular'. All relevant English language publications were included.

## Toxicity of ethambutol

The most commonly reported side-effect of ethambutol is optic neuritis; however, it is uncommon in patients prescribed standard doses.<sup>1,2,3,4,5,6,7,8,9,10,11,12</sup> Retrobulbar neuritis is the most common, with involvement of either the axial fibres or less commonly the peripheral axial (periaxial) fibres. A mixed pattern occasionally occurs.<sup>5,6,7,8,9</sup> Ethambutol toxicity has been identified as being related to dose and duration. The daily dosage of ethambutol in patients who have not previously received this medication is usually 15 mg/kg of body weight, given as a single dose for adults and children.<sup>7,8,10,11,12</sup> The daily dosage in patients who have received previous anti-TB therapy is 25 mg/kg of body weight, which is usually decreased after 60 days to 15 mg/kg/day.<sup>7,8,10,11,12</sup>

The literature describes a dose-related incidence of ethambutol-related ocular side-effects, with 50% of patients taking 60 mg/kg/day – 100 mg/kg/day and 1% with dosage less than 15 mg/kg/day.<sup>11</sup> No safe dose of ethambutol has been reported. Since the kidney is the major

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excretion pathway of ethambutol, patients with poor renal function are at a higher risk of ocular toxicities. Even prolonged duration of ethambutol, a higher dose, hypertension, diabetes, alcohol consumption and tobacco smoking can predispose patients to toxicity.<sup>12</sup> Patients with risk factors should be prescribed the drug only after careful thought is given to the pros and cons of the therapy.

### Mechanism of ocular neurotoxic effect of ethambutol

The exact pathophysiology and pathobiology of ethambutol optic neuropathy has not yet been identified. Authors have postulated that mitochondrial disturbance, the zinc-chelating effect and its metabolite are the possible underlying mechanisms.

Ethambutol disrupts oxidative phosphorylation and mitochondrial function by interfering with iron-containing complex I and copper-containing complex IV. The resultant effect is the generation of reactive oxygen species and a cascade of events, resulting in tissue injury and cellular apoptosis. Another theory is the zinc-chelating effect of ethambutol and its metabolite (ethylenediamine dihydrochloride) in the retinal ganglion.<sup>13,14,15,16,17,18,19</sup> Ethambutol is a metal chelator and its anti-mycobacterial properties are related to the inhibition of arabinosyltransferase, which is an important enzyme for mycobacterial cell-wall synthesis.

The metabolite of ethambutol is a strong chelator of copper, which is required as a cofactor for cytochrome *c* oxidase, a key enzyme in the electron transport chain and cellular oxidative metabolism within the inner layers of the mitochondria. It is possible that ethambutol decreases the levels of copper available for cytochrome *c* oxidase, the required energy for axonal transport around the optic nerve. Heng et al.<sup>13</sup> have shown that ethambutol causes a decrease in cytosolic calcium, an increase in mitochondrial calcium and an increase in mitochondrial membrane potential. The insufficiency of mitochondria in the optic nerve fibres may underlie the impairment of axonal transport in the optic nerve and lead to optic neuropathy. The postulated biochemical pathways that mediate the ocular toxic damage include downstream effector caspase-3 and caspase-6 and an excitotoxic pathway.<sup>13,15</sup>

### Clinical presentation

The onset of ocular symptoms is usually delayed and may occur months after the commencement of the therapy. However, rare cases of idiosyncratic reaction presenting days after the commencement of a standard dose have been reported.<sup>8,20</sup> Symptoms of toxicity do not generally occur until 2 months after the commencement of the therapy.<sup>8</sup> Signs and symptoms of ethambutol-induced optic neuropathy can be subclinical in the early stage. Presenting ocular symptoms may vary among affected individuals.<sup>21,22,23,24,25,26,27,28,29,30</sup> Patients usually report bilateral progressive painless blurring of vision and colour vision abnormality. However, some

patients may be asymptomatic with disorders only detected by ocular examination.<sup>6,7,8</sup>

The results of clinical examination are likely to vary. Both eyes are usually equally affected but can be asymmetric if any disorder is detected.<sup>11</sup> The loss of visual acuity usually starts with a blur at the point of fixation (a relative scotoma) and is followed by a progressive, bilateral and painless decline. The visual acuity reduction varies from no reduction to no light perception (NLP) in rare cases. Slit lamp examination generally reveals mild punctate epithelial erosion on both corneas and brown irides and melanosis on conjunctivas of both eyes. The pupils are usually sluggish to light but there is no relative afferent defect because the optic neuropathy is always bilateral and symmetric.<sup>21,22,23,24,25,26,27,28,29,30</sup> In the early stages, most patients have normal-appearing optic discs but oedema, haemorrhages and hyperaemia may occur in some acute cases. Thereafter, papillomacular bundle loss and optic atrophy may develop as temporal pallor of the optic disc. Some authors have proposed the use of electrophysiological tests to screen for ethambutol toxicity. These include pattern electroretinography (PERG) and visual-evoked potentials (VEP). These tests can be useful in early or subclinical optic neuropathy.<sup>31,32,33,34</sup> VEP usually reveals normal or near-normal latency with significantly reduced amplitude of P100. However, some authors believe demyelinating disease may become visible in MRI in some cases. PERG can be useful in patients with abnormal VEP to identify a macular lesion while multifocal electroretinogram (ERG) may be used to exclude retinal diseases. Also, optical coherence tomography (OCT) has been proposed as a tool to detect subclinical optic neuropathy. Zoumalan et al.<sup>35</sup> observed significant retinal nerve fibre layer (RNFL) thickness loss while a study by Kim and Park<sup>23</sup> revealed an increase in average RNFL thickness. Contrast sensitivity measurements may be useful in detecting subclinical ethambutol toxic neuropathy. Contrast sensitivity should be assessed using the Pelli-Robson chart since the Arden plates are affected by the ambient lighting conditions.<sup>36,37</sup>

The incidence of visual field defects vary among studies. In general, visual field defects tend to appear with the use of higher dosages of the drug. Central scotoma is the most reported visual field defect but bitemporal defects or peripheral field constriction can also occur. Colour vision abnormality (dyschromatopsia) may be one of the first detectable signs of ocular toxicity owing to ethambutol.<sup>21,22,23,24,25,26,27,28,29,30</sup> Blue-yellow (tritan) defects are the most common and they occur earlier while red-green (protan) defects occur later on in the course of the toxicity. Ishihara plates are commonly used to screen colour vision defects in patients. However, Ishihara plates are mainly designed to detect protan colour vision defect only. Blue-yellow defects can only be detected using the generally unavailable desaturated panel of Lanthony and not Ishihara charts or the Farnsworth D-15 (simplification of Farnsworth-Munsell 100) hue test. The fundus examination is usually normal.

## Reversibility

The toxicity of ethambutol is considered reversible on discontinuation of the therapy; however, views are divided.<sup>21,22,23,24,25,26,27,28,29,30</sup> Even though described as reversible on discontinuation of ethambutol, there are also reports of permanent visual impairment without recovery. Permanent visual impairment has been reported within a follow-up period ranging from 6 months to 3 years in some patients in whom there was prompt ethambutol therapy discontinuation.<sup>6,23</sup> Even in patients who show visual improvement after therapy discontinuation, complete recovery was not always achieved. Cases of progressive worsening of vision after ethambutol have been reported.<sup>29</sup> However, these case reports were of small scale.

Isoniazid is frequently prescribed concurrently with ethambutol. Isoniazid therapy has also been associated with optic neuropathy,<sup>38,39</sup> but differentiating ethambutol-related toxicity from isoniazid-related toxicity could be challenging. However, in general, toxicity from isoniazid is less frequent, less severe and is always reversible.<sup>13,31,32</sup>

## Management

Once ethambutol-induced ocular toxicity is recognised, the drug should be immediately stopped and the patient referred to an ophthalmologist for further evaluation. Presently, therapy discontinuation is the only effective management strategy that can stop the progression of vision loss and allow recovery of vision. Clinicians should consider OCT and contrast sensitivity testing as these tests could detect subclinical optic neuropathy not detected with baseline examination.

## Recommendations

Clinicians should obtain baseline examination which should include visual acuity testing, anterior segment examination, pupillary testing, colour vision and contrast sensitivity testing, fundus and optic nerve examination and OCT testing. Health education should be provided to patients on visual side-effects. Patients should be advised that if any visual symptoms occur, they should see an ophthalmologist. Treatment includes discontinuation of the drug. Check-up should be done monthly for patients taking more than 15 mg/kg/day. The prognosis depends on the dosage and duration of being on the ethambutol drug.

## Conclusion

The patient, the prescribing doctor and the ophthalmologist or optometrist should work closely together to make ethambutol a safe drug. TB is a public health problem and it would be difficult to eradicate the disease, and the use of ethambutol is most likely to continue. All newly diagnosed TB patients should have an ophthalmological examination before commencing treatment with ethambutol. The doctor prescribing ethambutol should be aware of its potential for ocular toxicity, and all patients treated with this drug

should be educated on its potential side-effects (loss of visual acuity, contrast sensitivity, colour vision and visual fields). When the side-effects are noticed, ethambutol should be immediately discontinued. When ocular toxicity is severe, both ethambutol and isoniazid should be immediately stopped. However, it is crucial to consult the prescribing doctor and other managing doctors before discontinuing any medication to prevent harm to the patient's overall health.

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### Competing interests

The authors declare that they have no financial interest or personal relationships which might have inappropriately influenced them in writing this article.

### Authors' contributions

The authors, P.M. and S.M., were equally responsible and contributed equally to the preparation and the writing of this article.

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