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Rohit Kumar Trivedi
 College of Pharmacy, Shivalik
 Campus, Dehradun, Uttarakhand,
 India

Dr. Ankit Kumar
 College of Pharmacy, Shivalik
 Campus, Dehradun, Uttarakhand,
 India

Avadhesh Kumar
 College of Pharmacy, Shivalik
 Campus, Dehradun, Uttarakhand,
 India

Ethambutol-associated ocular toxicity: Pharmacological mechanisms and opportunities for prodrug design

Rohit Kumar Trivedi, Ankit Kumar and Avadhesh Kumar

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Abstract

Ethambutol remains an essential component of first-line antitubercular therapy despite being plagued by ocular toxicity, largely dependent on dosage and duration, most commonly ethambutol-induced optic neuropathy (AEON). For the past decade, an increasing number of clinical and experimental findings have associated damage to the retinal ganglion cells with host genetic susceptibility, oxidative stress, chelation of metal ions, and mitochondrial dysfunction. In parallel, prodrug strategies that preserve antimycobacterial potency while reducing off-target toxicity have taken on new interest following advances in the development of drugs for tuberculosis. This narrative review collates the literature related to the clinical range, pharmacological mechanisms, and translational prospects associated with ethambutol-associated ocular toxicity within the period from 2015 to 2025. Particular emphasis is placed on prodrug-based mitigation strategies.

Keywords: Prodrug, Ethambutol-associated ocular toxicity, development, off-target toxicity

1. Introduction

EMB has been in use for more than 50 years as part of a multidrug regimen to treat drug-susceptible TB, yet it has been recognised for its toxicity to the optic nerve. The balance between its helpful effect and toxicity, specifically to the optic nerve, was recognised early in its history and confirmed in modern cohorts ^[1-3]. Ocular toxicity is apparent even at therapeutic concentrations during long-term treatment, and in more susceptible populations, despite dose limitations and regular ophthalmic monitoring currently recommended ^[5, 9]. Emerging knowledge from pharmacogenetics, medicinal chemistry and mitochondrial biology offers the opportunity to revisit the mechanism of EMB toxicity and explore rational design strategies such as prodrugs to limit eye exposure without compromising the drug's antimycobacterial action ^[3, 12-16, 23].

2. Clinical Spectrum of Ethambutol-associated ocular toxicity

2.1 Epidemiology and Risk Factors

Ethambutol-induced optic neuropathy occurs in less than 1% of individuals receiving less than 15 mg/kg/day but greater than 5% of individuals receiving higher cumulative doses or for longer durations of therapy ^[2]. Cumulative dose, duration of therapy, older age, renal impairment, and pre-existing optic nerve, mitochondrial, or axonal function weakness have been associated with a statistically meaningful increased risk according to cohort and population-based studies.

2.2 Clinical Presentation

Ocular toxicity linked to ethambutol usually manifests as central or cecentral scotomas, dyschromatopsia (typically red-green), and bilateral, symmetric, painless visual loss with decreased visual acuity ^[1, 2, 8]. Early in the course of the disease, fundoscopic findings may be normal, with optic disc pallor developing later ^[8].

2.3 Reversibility and Prognosis

After stopping ethambutol, visual recovery varies. When toxicity is identified early, a significant percentage of patients experience partial or full recovery, according to a number of cohort and case-series studies ^[9].

Corresponding Author:
Avadhesh Kumar
 College of Pharmacy, Shivalik
 Campus, Dehradun, Uttarakhand,
 India

However, incomplete recovery is correlated with structural retinal ganglion cell loss detected by OCT, suggesting irreversible neuronal injury in advanced cases [8].

3. Pharmacological and Pathophysiological Mechanisms

Ethambutol-associated ocular toxicity is best understood as a multifactorial process in which primary drug-specific chemical properties interact with host cellular vulnerability, particularly within Retinal Ganglion Cells (RGCs). Contemporary evidence supports a hierarchical model in which mitochondrial dysfunction and metal chelation represent primary initiating mechanisms, while oxidative stress, calcium dysregulation, and apoptotic signalling acting as downstream amplifiers of neuronal injury [3, 6, 9, 10, 25].

3.1 Structural and Chemical Determinants of toxicity

Ethambutol has a bidentate structure with hydroxyl and amine functional groups that are close together. This gives it a strong ability to bind to divalent metal ions like copper and zinc [3]. This characteristic indirectly enhances its antimycobacterial efficacy by inhibiting arabinosyl transferases, yet simultaneously constitutes a pharmacological risk in mammalian tissues. Chelation of metal cofactors vital for mitochondrial enzymes, especially cytochrome c oxidase, has been suggested as a principal initiating factor in ethambutol-induced mitochondrial dysfunction [10, 22].

Importantly, this chelating behaviour is intrinsic to the parent compound and is not shared to the same extent by other first-line antitubercular drugs, providing a mechanistic basis for ethambutol's unique association with optic neuropathy [10, 22].

3.2 Mitochondrial dysfunction as a central mechanism

Since 2015, ethambutol-induced optic neuropathy has been linked to mitochondrial impairment, which has been the subject of numerous experimental and clinical studies [6]. In models of neurones and retinal cells, ethambutol exposure has been demonstrated to interfere with oxidative phosphorylation, decrease ATP synthesis, and increase the production of reactive oxygen species [9]. Axonal transport and neuronal survival are compromised by these bioenergetic disruptions, which are especially important in long, unmyelinated optic nerve fibres.

This mechanism is further supported by the similarities between ethambutol-induced optic neuropathy and inherited mitochondrial optic neuropathies, including Leber hereditary optic neuropathy [6, 10, 22]. Notably, even at standard doses, patients with nuclear gene variants or mitochondrial DNA mutations that impact mitochondrial dynamics are more vulnerable to ethambutol toxicity [6, 7].

3.3 Selective vulnerability of retinal ganglion cells

Retinal ganglion cells are uniquely vulnerable to mitochondrial insults due to their high energy demand, dense mitochondrial population, and long axonal projections extending from the retina to the lateral geniculate nucleus [10, 22]. Even modest impairments in mitochondrial function can therefore precipitate RGC dysfunction and death. This selective vulnerability explains why ethambutol toxicity manifests predominantly as optic neuropathy rather than diffuse neurotoxicity.

Structural imaging studies using optical coherence tomography demonstrate early thinning of the retinal nerve fibre layer and ganglion cell complex, corroborating direct RGC injury rather than secondary demyelination [8].

3.4 Metal Chelation and Enzyme Inhibition

In addition to causing general mitochondrial stress, ethambutol's ability to chelate copper and zinc might directly impede the function of metalloenzymes that are crucial for electron transport and antioxidant defence [3]. While there is no direct *in vivo* evidence from human optic nerve tissue, a combination of biochemical and clinical findings lends credence to this mechanism as a likely factor rather than a mere hypothesis [3].

3.5 Downstream Pathways

Oxidative Stress and Calcium Dysregulation. Oxidative stress and the disruption of intracellular calcium levels seem to occur as a result of mitochondrial dysfunction. Studies using models of toxic optic neuropathy have shown that an increase in reactive oxygen species and calcium entry triggers apoptotic pathways in retinal ganglion cells [9]. These processes are not thought to be the main culprits on their own, but they probably speed up neuronal degeneration after mitochondrial damage starts.

4. Diagnostic and Monitoring Approaches

Functional assessments, including visual acuity, colour vision, and perimetry, continue to be fundamental in clinical monitoring [1, 5]. Structural imaging using OCT has become a sensitive method for identifying early thinning of the retinal nerve fibre layer and ganglion cell complex, often before symptoms become apparent [8, 41]. Electrophysiological methods, such as visual evoked potentials, can detect subclinical dysfunction, though they are not widely accessible [17]. Recent research into AI-assisted screening represents emerging supplementary methods rather than established care standards [21].

5. Rationale for prodrug design to mitigate ocular toxicity

5.1 Conceptual Framework

Prodrug strategies are commonly used to enhance the pharmacokinetics, tissue selectivity, and safety profiles of existing drugs [23]. For ethambutol, the goal of prodrug design is not to increase potency but to minimize off-target toxicity, especially in ocular tissues, while maintaining or restoring antimycobacterial effectiveness at the infection site. The mechanistic insights mentioned earlier suggest that concealing ethambutol's metal-chelating functional groups could theoretically reduce mitochondrial toxicity in retinal ganglion cells without eliminating its antibacterial activity. Ester Prodrugs of Ethambutol. Experimental research has shown that esterifying ethambutol's hydroxyl groups alters its antibacterial activity and allows for controlled activation by microbial esterases [3]. These findings offer proof-of-concept that ethambutol can be chemically altered into inactive or less active derivatives that can be enzymatically reactivated. However, these studies have not yet demonstrated reduced ocular toxicity *in vivo*. Instead, they provide a biochemical and microbiological basis for developing and testing safer derivatives.

Pathogen-Activated Prodrug Strategies. Modern antituberculosis drug discovery increasingly aims for

selective activation strategies by pathogens ^[12-16]. *M. tuberculosis* expresses a wide variety of esterases and hydrolases that can activate ester or carbamate prodrugs; this strategy has already shown promise for other antituberculosis drugs ^[21]. Applying such an approach to ethambutol could theoretically restrict systemic exposure to the active parent compound while enabling its intracellular release within infected macrophage cells. Such selectivity could have the added advantage of reducing ocular exposure because retinal tissues do not express specific mycobacteria-activating enzymes.

Comparison to other mitigation strategies. Other approaches to mitigate the toxicity of ethambutol involve dose reduction, narrowing the duration of therapy, and increasing vigilance. Although these are moderately successful, no approach completely removes the risk while potentially compromising antimycobacterial efficacy in complicated cases or in drug-resistant TB ^[8]. Prodrug strategies should, therefore, be viewed as a complementary approach rather than a competitive one.

6. Translational and Clinical Implications

Reducing ethambutol-related ocular toxicity would have a strong clinical impact, particularly in regimens for multidrug-resistant TB that require extended therapy ^[8]. Prodrug strategies align with contemporary priorities of TB drug development centred around targeted delivery and toxicity reduction ^[15-16]; however, they require extensive preclinical ocular safety evaluations before clinical application.

7. Future Directions

7.1 Future work should prioritize

- Structure-toxicity relationship studies linking ethambutol chemistry to mitochondrial effects.
- *In vivo* ocular safety evaluation of ethambutol prodrugs.
- Integration of genetic risk stratification into clinical monitoring.
- Early-phase translational studies combining pharmacokinetics, ocular imaging, and functional outcomes.

8. Conclusion

Ethambutol-associated ocular toxicity remains a clinically relevant limitation of tuberculosis therapy. Evidence accumulated since 2015 supports mitochondrial dysfunction and metal chelation as central, interacting mechanisms, modulated by host genetic susceptibility. Prodrug strategies, particularly pathogen-activated ester derivatives, offer a scientifically plausible avenue for toxicity mitigation, although clinical benefit remains to be demonstrated. Continued interdisciplinary research is essential to translate these concepts into safer antitubercular therapies.

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