Review Article

Ethambutol Toxicity in *HIV* Patients on Antiretroviral Therapy

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ABSTRACT

Over the years treatment of tuberculosis in persons living with *HIV* has changed. Ethambutol toxic optic neuropathy is a rare complication but consideration should be given to regular monitoring of visual function in *HIV* positive patients on antiretroviral therapy. Physicians treating patients with Ethambutol need to be wary of this and must adopt appropriate strategies for early detection and management of the potential toxicity. This review cautions against the ocular side effects of ethambutol especially among the immunocompromised patients put on directly observed short-course regimen (DOTS) for treatment of tuberculosis. The latest guidelines issued by World Health Organization (WHO) and centre for disease control (CDC) do not omit the use of Ethambutol (EMB) in patients on antiretroviral therapy (ART).

INTRODUCTION

Ethambutol is a widely used first line anti-tubercular drug and is considered least toxic. A low incidence of ocular toxicity has been reported with ethambutol use.[1] However, this review cautions against the ocular side effects of ethambutol especially among the immunocompromised patients put on directly observed short -course regimen (DOTS) for treatment of tuberculosis. *HIV* patients need to be kept under active surveillance during the course of therapy for any signs of ocular toxicity. Dose of 15-20mg/kg/day is currently recommended with a toxicity incidence of 1%.[2,3] Approximately 100 000 new cases per year of toxic optic neuropathy from ethambutol has been reported by Wang and Sudan[4] Ezer et al[5] did a systematic review estimating visual impairment in 22.5/1 000 people on Ethambutol therapy, with 2.3/1 000 having permanent visual loss.

HIV and Ethambutol

Only a few studies are present in the literature reporting *HIV* and the use of anti-retrovirals as a risk factor for the development of ethambutol toxic neuropathy. The exact mechanism of toxicity is not well understood however, it is postulated that chelating effects of ethambutol on various mitochondrial metal-containing enzymes contributes to ocular toxicity.[3,4] Ethambutol inhibits the enzyme arabinosyltransferase, which is important for synthesis of mycobacterial cell wall. It also disrupts oxidative phosphorylation and mitochondrial function interfering with iron containing complex I and copper containing complex IV leading to generation of reactive oxygen species and a cascade of events causing apoptosis.[4,5]

HIV positive patients show secondary inflammatory changes and degenerations in the optic nerve with monocyte infiltration suggesting that *HIV* affects the optic nerve immune mediated mechanisms, most notably by action of cytokines and tumour necrosis factor and may thus have vulnerable optic nerves and be more predisposed to the development of acquired optic nerve toxicity.[6,7] Optic neuritis is the most important side effect of Ethambutol. Most common side effect is retrobulbar neuritis.[1]

Viral reverse transcriptase enzyme is targeted by Nucleoside analogue reverse transcriptase inhibitors (NRTIs) in *HIV* patients. These drugs have also been noted to interfere with mitochondrial DNA (mtDNA) polymerase gamma causing mitochondrial toxicity in several tissue systems and accumulation of mtDNA mutations. Acquired mtDNA mutations may cause similar activation of transcripts of the unfolded protein. The unfolded protein response results in inhibition of protein synthesis, vesicular secretion and oligodendrogenesis resulting in neurological disease.[8]

Mustak et al[9] reported use of Stavudine and Lamivudine (NRTIs) in *HIV* positive patients with tuberculosis who were exposed to double hit effect on mitochondrial function and visual impairment. Vibhakar et al[10] reports use of Tenofovir another NRTI, a monophosphorylated nucleotide analog of adenosine, known to cause nephrotoxicity. The patient presented with deteriorating

renal function as a result of tenofovir toxicity that lead to a higher than recommended Ethambutol mg/kg dose and an acute weight loss, which further increased the risk of ocular toxicity with ethambutol.[10]

Estlin et al[11] reviewed 70 cases of optic neuritis, most cases of Ethambutol optic toxicity occur in patients with underlying kidney dysfunction due to underlying renal disease, increasing age, higher dose of EMB or prolonged duration of use, diabetes, tobacco and alcohol. Nearly two-thirds of these cases had no information about patient's renal function or of any dose-adjustment for kidney disease. One third of the cases with data showed renal dysfunction or significant risk factors for renal dysfuntion. *HIV* positive patients on antiretroviral therapy are vulnerable to the toxic effects of EMB through multiple hit effect.[11]

A study by Garg et al[12] and Kandel H et al[13] brought forth another important facet that EMB ocular toxicity can occur during intermittent DOTS therapy. The American Thoracic Society and British Thoracic Society both recommend visual screening prior to commencement of therapy but regular monitoring of visual function during therapy has not been mentioned. Several studies have shown color vision testing with Ishihara test plates to be a sensitive sign of early toxicity.[2] Most patients recover after stopping drugs, which may take weeks to months. However, there have been reports of only partial or no recovery in vision in some patient.[9,10,14-16]

CONCLUSION

Ethambutol toxic optic neuropathy is a rare complication but consideration should be given to regular monitoring of visual function in *HIV* positive patients on antiretroviral therapy. Immunocompromised patients receiving Ethambutol, in intermittent or standard dose DOTS, causes ocular toxicity, which if undetected, can result in disastrous visual defects. Physicians treating patients with EMB need to be wary of this and must adopt appropriate strategies for early detection and management of the potential toxicity.

REFERENCES

1. Koul PA. Ocular toxicity with Ethambutol therapy: timely recaution. Lung India 2015; 32(1): 1-3.
2. Chan RY, Kwok AK. Ocular toxicity of ethambutol. Hong Kong Med J 2006;2(1): 56-60.
3. Melamud A, Kosmorsky GS, Lee MS. Ocular ethambutol toxicity. Mayo Clin Proc 2003; 78(11): 1409-1411.
4. Wang MY, Sadun AA. Drug-related mitochondrial optic neuropathies. J Neuroophthalmol 2013;33(2): 172-178.
5. Ezer N, Benedetti A, Darvish-Zargar M, Menzies D. Incidence of ethambutol-related visual impairment during treatment of active tuberculosis. Int J Tuberc Lung Dis 2013;17(4): 447-455.
6. Sadun AA, Pepose JS, Madigan MC, Laycock KA, Tenhula WN, Freeman WR. AIDS-related optic neuropathy: a histological, virological and ultrastructural study. Graefes Arch Clin Exp Ophthalmol 1995;233(7): 387-398.
7. Babu K, Murthy KR, Rajagopalan N, Satish B. Vision recovery in human immunodeficiency virus-infected patients with optic neuropathy treated with highly active antiretroviral therapy: A case series. Indian J Ophthalmol 2009;57(4): 315-318.
8. Cortopassi G, Danielson S, Alemi M, Zhan SS, Tong W, Carelli V,et al. Mitochondrial disease activates transcripts of the unfolded protein response and cell cycle and inhibits vesicular secretion and oligodendrocyte-specific transcripts. Mitochondrion 2006; 6(4): 161-175.
9. Mustak H, Rogers G, Cook C. Ethambutol induced toxic optic neuropathy in HIV positive patients. Int J Ophthalmol 2013; 6 (4): 542-545.
10. Vibhakar S, Yu D, Kee R, Max B. Ethambutol Induced Optic Neuritis Associated with Tenofovir Nephrotoxicity. World Journal of AIDS 2012; 2(02):43-47.
11. K A T Estlin and A A Sadun. Risk Factors for Ethambutol Optic Toxicity. International Ophthalmology 2010; 30 (6): 63-72.
12. Garg P, Garg R, Prasad R, Misra AK. A prospective study of ocular toxicity in patients receiving ethambutol as a part of directly observed treatment strategy therapy. Lung India 2015; 32:16–19.
13. Kandel H, Adhikari P, Shrestha GS, Ruokonen EL, Shah DN. Visual function in patients on ethambutol therapy for tuberculosis. J Ocul Pharmacol Ther 2012 Apr; 28(2):174–178.
14. Chai SJ, Foroozan R. Decreased retinal nerve fibre layer thickness detected by optical coherence tomography in patients with ethambutolinduced optic neuropathy. Br J Ophthalmol 2007 Jul(7); 91:895–897.
15. Lee EJ, Kim SJ, Choung HK, Kim JH, Yu YS. Incidence and clinical-features of ethambutol-induced optic neuropathy in Korea. J Neuroophthalmol 2008 Dec; 28(4): 269-277.
16. Kumar A, Sandramouli S, Verma L, Tewari HK, Khosla PK. Ocular ethambutol toxicity: is it reversible.J Clin Neuroophthalmol 1993; 13 (1): 15-17.

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