Original Article

Ethambutol Induced Ocular Toxicity in Patients Receiving "Directly Observed Treatment Short-Course" Therapy

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Abstract

Objective: To determine the frequency of Ocular toxicity due to Ethambutol in Category-1 patients after receiving DOTS therapy.

Materials and Methods: Category-1 tuberculosis patients of 15-60 years (both gender) with normal ocular parameters on ophthalmological assessment at the time of initiation of DOTS therapy were included in the study. A total of 242 eyes (121 patients) were studied for any change in the Vision, Color vision, Contrast sensitivity or occurrence of any other ocular symptom while on the Ethambutol treatment. Each patient was followed up for Ethambutol compliance status at the completion of one month and again at two months of treatment, all the ophthalmological assessments for ocular toxicity were repeated for every selected patient. Category-2 patients with sputum smear-positive who have relapsed, who have treatment failure, or who are receiving treatment after treatment interruption were excluded from the study.

Results: Out of 121 patients (242 eyes), 64 (52.9%) were males and 57 (47.1%) were females. There was no sign of ocular toxicity after a month. However, after the second-month ocular toxicity was developed in 02 (1.65%) of the patients. Besides, a decrease in visual acuity, color vision abnormalities, decrease in contrast sensitivity, and optic disc abnormalities were also observed in these 02 patients.

Conclusion: There is a possibility of the occurrence of ocular toxicity when the Ethambutol is taken by tuberculosis patients. Thus, the early identification of ocular symptoms and signs is vital to avoid unnecessary delay in diagnosis and probable irreversible visual loss.

Keywords: Tuberculosis; Ethambutol; Visual Acuity; Contrast Sensitivity; Optic Disc; Color Vision.

Introduction

Tuberculosis (TB) is one of the major public health problems caused by a bacterium called Mycobacterium tuberculosis. This mainly affects the lungs and other parts of the body including the brain, optical system, kidneys, and, spine which are also prone to this infection. The first remedy against TB was the introduction of the sanatorium cure. On 24 March 1882, Robert Koch was able to isolate the tubercle bacillus.[1] In1993 World Health Organization (WHO) acknowledged TB as a global emergency. According to the recent statistics, around 10 million people were infected by TB in the year 2019 and about 1.22 million lost their precious lives to this infection.[2]

Among the 22 high TB burden countries globally, Pakistan is ranked 5th. According to the WHO report, it is estimated that 565,800 people in Pakistan developed TB in the year 2018.[2] According to an estimate 45,300 people die from TB disease in Pakistan each year.[4]

Once the statement of TB as a worldwide emergency was made by WHO, the Directly Observed Treatment Short-Course (DOTS) scheme was approved. Accordingly, Category-I TB patients are put on a combination of four drugs namely Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide for two months of therapy at the start.

Anti-Tuberculosis drugs, which are among the highly consumed drugs, because of the high rate of occurrence of this disease, may have severe adverse effects on patients (details in Table 1).

Table 1: Adverse effects of Anti-Tuberculosis Drugs

Drug	*Adverse Effect*	*Ocular Side Effects*
Isoniazid	○ Peripheral Neuropathy ○ Hepatitis ○ Skin Rash	○ Optic neuritis ○ Steven Johnson Syndrome
Rifampicin	○ Hepatitis ○ Nausea ○ Vomiting ○ TTP ○ Red discoloration of Secretions	Orange-red discoloration of tears
Pyrazinamide	○ Hepatitis ○ Hyper-uricemia	Nil
Ethambutol	Hyper-uricemia	○ Optic neuritis ○ Color vision abnormalities ○ Visual Field Defects
Streptomycin	○ Oto-toxic ○ Renal Failure	Nil

Ethambutol is a first-line anti-TB medication. It is a bacteriostatic drug that was developed in the year 1962 by Carr and Henkind.[6] However, Ethambutol does have severe adverse effects on the eyes. The most common side effect of Ethambutol is on optic nerve fibers, which can cause decreased vision, visual field defects, central scotoma, and dyschromatopsia. So, it is important to keep a check on the patients who are taking the anti-tuberculosis drug "Ethambutol". Early detection of these side effects is very important and the immediate stoppage of therapy is the only effective management that can stop further loss of vision and can even allow recovery. Keeping this in view, this study is carried out to determine the frequency of Ethambutol-induced optical toxicity in TB patients on the DOTS Category-I regimen.

Materials and Methods

A Descriptive case series study was conducted at the Department of Ophthalmology on Category-1 patients referred from the DOTS center, Rawalpindi Medical College and Allied Hospitals, Rawalpindi. The study was conducted for a period of one year. Furthermore, using the WHO sample size calculator and by non-probability consecutive technique, a sample size of 242 eyes was selected.

Inclusion criteria: Category-1 tuberculosis patients of 15-60 years (both gender) with normal ocular parameters on ophthalmological assessment (that are normal Visual acuity, Color vision, Contrast sensitivity, fundus, and optic disc) at the time of initiation of DOTS therapy were included in the study.

Exclusion criteria: However, patients with any pre-existing color vision and contrast sensitivity defects, with any ocular disease that may affect the parameters being evaluated like Diabetic Retinopathy, Hypertensive Retinopathy, Sickle Cell Retinopathy, Retinitis Pigmentosa, Retinal Detachment, Glaucoma, Optic Neuropathies, Optic Atrophy, Cataract (more than +2 nuclear cases of sclerosis), taking any medications that are known to cause optic neuropathy

e.g. Digoxin, Indomethacin, Oral Contraceptive Pills and those having Tobacco and Alcohol addiction were excluded.

Before initiation of the study, approval was sought from the Institutional Ethics Research Forum of Rawalpindi Medical University. After informed written consent from the patients, detailed history and ophthalmological examination was undertaken and those fulfilling the selection criteria were included in the study. Best-corrected visual acuity (VA), Color vision (CV), and Contrast sensitivity (CS) was checked. The pupils were dilated and the fundus was examined. Follow-up was done at one month and two months.

At baseline, before initiation of Ethambutol treatment, VA was recorded using the Snellen chart. CV was tested using Ishihara Chart under mono ocular viewing conditions in the same room under the same lighting conditions on each visit. CS was tested using Pelli Robson Contrast Sensitivity Chart at 1-meter distance monocular and binocularly. The pupils were dilated with 1% tropicamide. The fundus was examined by indirect ophthalmoscope by one researcher and then counter-checked by the other researcher. Each patient was followed up for Ethambutol compliance status at the completion of one month and again at two months, three months of treatment, all the ophthalmological assessments for ocular toxicity were repeated for every selected patient.

Results

Out of 121 patients (242 eyes), 64 (52.9%) were males while 57 (47.1%) were females, with a male to female ratio of 1:1.23, as given in Table 2.

Table 2: Gender Distribution

Gender	*Frequency*	*%age*
Male	64	52.9
Female	57	47.1

At the second month follow up, loss in visual acuity from the baseline was noted in four eyes (1.65%), and optic disc abnormalities were observed in the same two patients. Also, in these four eyes, abnormalities in CV along with the change in the CS were noted. The results for the ocular imperfections are given in Table 3 to Table 5.

Table 3: Frequency of Patients with Changes in Best corrected Visual Acuity, Color Vision, Contrast Sensitivity & Optic Disc

Change in:	*BCVA*	*CV*	*CS*	*Optic Disc*
No Defect	119	119	119	119
Defected	02	02	02	02

Table 4: Defect with respect to various Factors

Criteria	*Gender*		*Age*			*Residence*		*Monthly Income*		
	Male	**Female**	**15-29**	**30-44**	**45-60**	**Rural**	**Urban**	**< 20K**	**20-50K**	**>50K**
No Defect	63	56	64	27	28	28	91	87	29	3
Defected	1	1	1	0	1	1	1	1	0	1

Table 5: Chi-Square Test between various Factors and Defects

	Gender			*Age*			*Residence*			*Monthly Income*		
	Val	**df**	**Asy Sig**	**Val**	**df**	**Asy Sig**	**Val**	**df**	**Asy Sig**	**Val**	**df**	**Asy Sig**
P. Chi-Square	.007	1	.934	1.034	2	.596	.756	1	.384	14.045	2	.001
Likelihood Ratio	.007	1	.934	1.344	2	.511	.645	1	.422	4.935	2	.085
Valid Cases	121			121			121			121		
			App Sig			**App Sig**			**App Sig**			**App Sig**
Phi	.008		.934	.092		.596	.079		.384	.341		.001

Asy Sig: Asymptotic Significance; App Sig: Approximate Significance

The results reveal that though the frequency of the occurrence of Ethambutol-induced ocular toxicity is low but the chance of occurrence still prevails. So, the regular monitoring for ophthalmic symptoms and

signs of the patients on the Ethambutol treatment is very important.

Discussion

After WHO declared TB as an emergency for the globe, the DOTS strategy was adopted for the treatment of TB. TB Patients are divided into two categories. Category-1 is new smear-positive patients with pulmonary TB. Category-2 is sputum smear-positive patients who have relapsed, who have treatment failure, or who are receiving treatment after treatment interruption. We included only Category-1 Patients in our study.

Accordingly, for the first two months of therapy, Category-I TB patients are put on a combination of four drugs i.e. Pyrazinamide, Rifampicin, Isoniazid, and Ethambutol. Specifically, Ethambutol in the treatment of TB has been in use since the 1960s. However, consumption of Ethambutol may cause visual toxicity and this side effect was recognized soon after its introduction.[7]

Two types of optic neuritis may be there due to Ethambutol intake:

i. Axial neuritis resulting in color vision defects reduced visual acuity and central scotoma;

ii. Paraxial neuritis causes peripheral visual field deficiencies.[8]

Though the occurrence of Paraxial neuritis is rare compared to the occurrence of Axial neuritis. According to numerous studies available in the open literature, the frequency of Ethambutol-induced optic neuritis is 0.5% to more than 35%.[3] In the study carried out by Garg et al., where 126 eyes were evaluated, it was found that 9.4% of eyes had a loss of VA, 12.6% had developed color vision defects and optic disc irregularities were developed in 4.7% of eyes.[9] In another study by Raghu et al., reported the loss of VA in 10% of the eyes, color vision imperfections in 12.2% of the eyes while in 6.1% of the eyes fundus changes were reported.[10] Besides according to Mahrukh et al., who considered 198 eyes for their study, reported the reduction of VA among 10.6% of the eyes and color vision imperfections among 23.23% of the eyes was reported.[11] The occurrence of bitemporal hemianopia, is also possible from the involvement of optic chiasm which may further result in Ethambutol-induced optic neuropathy. The reports of automated perimetry examination showing the development of bitemporal hemianopia and ethambutol can be seen in the literature.[12,13]

The toxicity of Ethambutol is usually dependent on the dosage and the time period of treatment. The ocular toxicity usually arises after one month to two months from the beginning of the treatment, seven months being the average time. But toxicity even only after a few days are reported in the literature, with one such case reported by Sajjad et al. in their report they suggesting due to idiosyncratic reaction just after three days.[14] Melamud reported a patient with Bilateral optical neuropathy three months after starting Ethambutol.[15] While the data showing occurrence as late as one year is also there.[16] These reports suggest that the toxicity introduced by the intake of Ethambutol can happen after any time from the commencement of the drug.

A clear idea about the safe amount of dosage is also unknown. The overall frequency of optic neuropathy induced due to the intake of Ethambutol drug among the TB patients under the DOT scheme was about 1% is correlated to the dosage.[17] According to one of the study reports, the toxicity was still present in patients who received Ethambutol dosage of as low as 12.3 mg/mg/day.[18] However, on the high dosage of about 15 - 25 mg/kg/day of the Ethambutol drug, ocular toxicity was up to 5% - 6% when taken for at least two months.[19] Besides, at the increased dosage of 60-100mg/Kg/day optic neuropathy was developed in half of the patients.[20] Therefore, there is no safe dose for Ethambutol in the clinical practice owing to the fact that the toxicity was developed in the dosage even below the level of 15mg/Kg/day.[21]

As far as the remedial measures are concerned, the first action is to immediately cease the Ethambutol intake. The second is a referral to an ophthalmologist. Vitamin and/or trace elements may prove to be beneficial in the recovery process. However, no other specific treatment is available for ocular toxicity caused by Ethambutol other than termination of the drug intake. The timely termination of Ethambutol might stop the further progression of the vision loss and may even allow the recovery in the vision. Most patients do start showing signs of recovery after stopping the drug,[22] but the recovery might consume weeks to months.[23] Nevertheless, there are some reports where the decline in the vision has continued or failed to improve despite the termination of the Ethambutol.

However, age, renal disorders (as Ethambutol is excreted via kidneys), smoking and alcohol addiction, hypertension, diabetes mellitus have negative effects on visual recovery after Ethambutol stoppage.

Conclusion

The conclusion drawn from the observations made in this study is that even at low doses of 15mg/Kg/day Ethambutol causes ocular toxicity. However, according to the findings, age, residence (socio-economic class which is usually related to dietary intake) and gender has no significant relation with Visual Acuity, Color Vision, Contrast Sensitivity & Optic Disc. So, every patient, before the initiation of Ethambutol, should undergo an ophthalmic examination. Patients with good vision, who can report their symptoms, should be prescribed the drug. Once the Ethambutol prescription is made, the patient should be educated about the side effects of the drug along with the instruction of immediately reporting the physician on the occurrence of any visual symptom. The patients with increased risk for toxicity like diabetes, chronic renal disease, other ocular defects, patients consuming alcohol, or elderly patients, should be examined more frequently.

References

1. Barberis I, Bragazzi NL, Galluzzo L. The history of TB: from the first historical record to the isolation of Koch's bacillus. J Prev Med Hyg. 2017 Mar: 58(1): 9-12.
2. Global tuberculosis report 2020. https://www.who.int/publications/i/item/9789240013131
3. Implementing the WHO Stop TB Strategy: A Handbook for National Tuberculosis Control Programmes. Geneva: World TB in Pakistan.
4. Health Organization; 2008. 2, Treatment of tuberculosis patients. Available from: https://www.ncbi.nlm.nih.gov/books/NBK310759/
5. Carr RE, Henkind P. Occular manifeststion of Ethambutol. Arch Opthalmol. 1962; 67: 566-571.
6. Trusiewicz D. Farnsworth 100-hue test in diagnosis of Ethambutol induced damage to optic nerve. Ophthalmologica 1975; 171(6): 425-431.
7. Barron GJ, MD, Leo Tepper, MD and Gino Iovine MD, Ocular toxicity from glutametheol, AJO, Fek 1974; 77(2): 257-260.
8. 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(1):16-9.
9. Raghu V, Rajender M, Beesam K, Reddy N. A Prospective evaluation of visual function for early detection of Ethambutol toxicity. MRIMS journal of health sciences. 2016; 4(2); 89-92.
10. Mahrukh, Ashraf A, Bhat MA. Visual Field Changes in Patients Receiving Antitubercular Drug Therapy at Tertiary Care Hospital: An Analytical Observational Study. International Journal of Contemporary Medical Research. 2017; 4(2): 346-349.
11. Osaguona VB, Sharpe JA, Awaji SA, Farb RI, Sundaram AN. Optic chiasm involvement on MRI with Ethambutol-induced bitemporal hemianopia. J Neuroophthalmol 2014; 34(2): 155-8.
12. Kho RC, Al-Obailan M, Arnold AC. Bitemporal visual field defects in Ethambutolinduced optic neuropathy. J Neuroophthalmol. 2011; 31(2): 121-126.
13. Ali S, Usman U, Wasay M. Rapidly developing Optic Neuritis secondary to Ethambutol: possible mechanism of injury. Journal of Pakistan Medical Association, 2005; 55(7).
14. Melamud A, Kosmorsky GS, Lee MS. Ocular Ethambutol toxicity. Mayo Clin Proc. 2003;78(11): 1409-1411.
15. Sivakumaran P, Harrison AC, Marschner J, Martin P. Ocular toxicity from Ethambutol: A review of 4 cases and recommended precautions. NZ Med J. 1998; 111(1077): 428430.
16. Chen SC, Lin MC, Sheu SJ. Incidence and prognostic factor of Ethambutol-related optic neuropathy: 10-year experience in southern Taiwan. Kaohsiung J Med Sci. 2015; 31(7): 358-62.
17. Choi SY, Hwang JM, Optic neuropathy associated with Ethambutol toxicity in Koreans, Korean J opthalmol 1997; 11: 106-110.
18. Leibold JE. The ocular toxicity of Ethambutol and its relation to dose. Ann N Y Acad Sci 1966; 135(2): 904-9.
19. Drug-related Adverse effects of clinical importance to the ophthalmologist. American Academy of ophthalmology. 19 Oct 2014.
20. Chung H, Yoon YH, Hwang JJ, Cho KS, Koh JY, Kim JG. Ethambutol-induced toxicity is mediated by zinc and lysosomal membrane permeabilization in cultured retinal cells. Toxicol Appl Pharmacol. 2009; 235(2): 163-70.
21. 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): 447-55.
22. DeVita EG, Miao M, Sadun AA. Optic neuropathy in Ethambutol treated renal tuberculosis. J Clin Neuro Ophthalmol. 1987; 7(2): 77-86.
23. Chai SJ, Foroozan R. Decreased retinal nerve fibre layer thickness detected by optical coherence tomography in patients with Ethambutol-induced optic neuropathy. Br J Ophthalmol 2007; 91(7): 895-7.