Correlation between the Duration of Ethambutol Therapy and the Toxic Optic Neuropathy Occurene in Patients with Multidrug-Ressistance Tuberculosis

by Laily Irfana

Submission date: 27-Nov-2022 08:49PM (UTC+0700)
Submission ID: 1964060940
File name: Correlation_etambutol_and_NOT.pdf (804.57K)
Word count: 3107
Character count: 16128

Correlation between the Duration of Ethambutol Therapy and the Toxic Optic Neuropathy Occurene in Patients with Multidrug-Ressistance Tuberculosis

Muhammad Hamdan[1], Eko Wahono R.[1], Kurnia Kusumastuti[1], Laily Irfana[1]

[1]*Department of Neurology Faculty of Medicine, UniversitasAirlangga – Dr. Soetomo Teaching Hospital, Surabaya(60285), Indonesia*

Abstract

Background: Tuberculosis affects one-third of the world's population. Increasing number of tuberculosis cases also leads to the increase of anti-tuberculosis drugs use, such as ethambutol. Ethambutol is one of the most effective and rarely resistant tuberculosis drugs.

Objective: To determine the relationship between duration of ethambutol therapy with toxic optic neuropathy in tuberculosis patients

Method: This study enrolled MDR-TB patients who visited MDR-TB Unit of Dr. Soetomo General Hospital from July 2014 until the sufficient amount of sample was achieved. The patients enrolled are those who met the inclusion and exclusion criteria. Inclusion criteria consisted of MDR TB patients treated with ethambutol therapy, aged of 20-69 years old, and whose VEP examination results showed extension of P100 latency.

Results: The mean of <6 month duration was 3.24±1.348, while for the ≥6 months was 11.71±5.764. This difference was statistically significant with p = 0.043.

Conclusion: There is a correlation between duration of ethambutol therapy with toxic optic neuropathy in patients with MDR-TB.

Keywords*: ethambutol therapy, toxic optic neuropathy, multidrug-resistance, visual evoked potentials*

Introduction

Tuberculosis affects one-third of the world's population. The increasing number of tuberculosis cases leads to the more use of anti-tuberculosis drugs, such as ethambutol [1] Ethambutol is one of the most effective and rarely resistant tuberculosis drugs, and therefore is often used in the case of Multidrug-Resistance Tuberculosis (MDR-TB). However, many researches reported the occurrence of optical toxic neuropathy (TON) with clinical symptoms of decreased vision until blindness [2].

The incidence of toxic optic neuropathy associated with ethambutol varies greatly from several studies ranging from 0.5-35% of patients Visual Evoked Potentials (VEP) can be used to determine the toxic effects of ethambutol [3] Of the 14 samples, 5 were showed abnormalities in VEP, where in from the clinical findings only showed abnormal person [4]. A study reported that 42% of patients with permanent vision impairment were dependent on the initial disorder severity. As reported in most cases, toxicity occurs at doses greater than 20mg/kgBW/day. However, not too little toxicity has occurred at a standard dose of 15mg/kgBW/day. For instance is in a case reporting optic neuropathy occurrence at a dose of 12 mg/kgBW/day. The duration of drug use that causes toxic effects is averagely one to six months. However, it has been reported that the fastest duration in which

Corresponding Author :
Muhammad Hamdan
Department of Neurology Faculty of Medicine, UniversitasAirlangga – Dr. Soetomo Teaching Hospital, Surabaya(60285), Indonesia
Email: muhammadhamdan.md@gmail.com

visually impaired due to ethambutol occurs in the use duration of only three days.

Toxic optic neuropathy can provide symptoms of progressive decrease in vision, which might get worse until blindness occurs. Although the loss of vision is reversible when ethambutol is lowered or terminated, some patients experience permanent vision impairment even with standarddrug doses [5]. Some cases of progressiveness continue to run even though the drug has been stopped. Imperfect improvement was often found. Some even experienced permanent blindness [6] The mechanism of optic neuropathy due to ethambutol is thought to be caused by impaired function of the mitochondria [7]. One study found a vacuole change from the cytoplasm of ganglion cells in animals injected with ethambutol. Ethambutol is a metal chelator, which can interact with zinc, copper and iron that cause damage to the mitochondria [8] Studies conducted on animals have demonstrated the toxic effects of ethambutol on electrophysiological visual systems as well as histopathology [4].

Toxicity can be detected earlier by VEP, even before the emergence of complaints from patients. This is very useful because by detecting TON earlier, can be stopped or replacement of drugs before clinical symptoms appear. In addition, knowing the occurrence of TON and drug termination will inhibit the progression of the disease and thus permanent loss of vision can be prevented. Aim to To determine the relationship between duration of ethambutol therapy with toxic optic neuropathy in tuberculosis patients.

Method

This is an observational analytic study. The samples are MDR-TB patients who received ethambutol therapy who came in MDR-TB Unit of Dr. Soetomo General Hospital from July 2014 until the sufficient amount of samples was achieved. They all met the inclusion criteria consisted of MDR-TB patients who received ethambutol therapy, aged of 20-69 years old, VEP examination results obtained extension of P100 latency. The exclusion criteria consisted of the subjects with diabetic retinopathy, hypertensive retinopathy, renal failure, hepatic dysfunction, history of stroke, history of intracranial infection, multiple sclerosis history, cerebral neoplasm history, eye abnormalities, and those who were unwilling to participate in the study.

The sampling method of the study was conducted according to the consecutive case (sampling from consecutive admission) until the sample size was determined. The study instrument was visual evoked potentials. The duration of ethambutol therapy was the duration (within months) of patients taking ethambutol during the MDR program, calculated from the first day of drug use until the VEP examination with short duration of <6 months, and long duration of ≥6 months.

Toxic optic neuropathy is an abnormality in vision function due to optic nerve damage caused by toxic substances diagnosed from an extension of P100 latency from the normal limit of VEP examination with a 116 ms cutoff point. TON occured when the obtained P100 latency is >116 ms, and it is considered normal when the normal P100 latency is ≤116 ms. VEP is the electrical potential of the visual stimulus recorded from the scalp to assess the integrity of the afferent visual path. The examination was done by Cadwell Sierra Wave in Electromyography of Dr. Soetomo General Hospital. The results will be interpreted by a neurophysiologist consultant. All subjects included in the inclusion criteria and the family responsible for the patients were given an explanation of the purpose, usefulness and risk of the study, and were asked to be involved in the study. The identity and characteristics of the subjects signing the consent were recorded in the form. Data collection of research subjects was conducted through anamnesis, careful physical examination and neurology, selection of samples for the cases according to inclusion and exclusion criteria. The eligible samples and all necessary clinical data were recorded. VEP examination was performed in the EMG of Dr. Soetomo General Hospital. All the recording results were collected for further data tabulation and statistical analysis.

The data obtained from the data collection sheets were then analyzed. The correlation between duration of ethambutol therapy and optic neuropathy was calculated and analyzed using the appropriate statistical tests. This study will be proposed as an ethical feasibility study to the Research Ethics Committee of Dr. Soetomo Teaching Hospital Surabaya.

Result

Table 1. The difference in the proportion of duration of ethambutol therapy in each group of subjects

Characteristics	TON		p	RO (IK 95%)
	Cases N (%)	Control N (%)		
Age	43.29 ± 11.58	38.82 ± 10.06	0.239	
Gender Male Female	7 (41.2%) 10 (58.8%)	13 (76.5% 4 (23.5%)	0.03	0.215 (0.049-0.946)
Education Elementary, Junior High School Senior High School, College	7 (41.2%) 10 (58.8%)	6 (35.3%) 11 (64.7%)	0.724	0.779 (0.195 - 3.118)
Diabetes Melitus Yes No	7 (41.2%) 10 (58.8%)	6 (35.3%) 11 (64.7%)	0.724	1.283 (0.321 – 5.134)
Ethambutol dose (mg/day) ≥1200 800-1199	7 (41.2%) 10 (58.8%)	10 (58.8%) 7 (41.2%)	0.303	0.49 (0.125 – 1.921)
Ethambutol therapy history (year) ≤ 1 >1	7 (41.2%) 10 (58.8%)	6 (35.3%) 11 (64.7%)	0.271	2.275 (0.518 – 9.989)
Ethambutol therapy duration ≥6 months <6 months	12 (70.6%) 5 (29.4%)	5 (29.4%) 12 (70.6%)	0.016	5.76 (1.317-25.187)

All subjects underwent eye examination in MDR-TB and VEP units in the EMG section of Department of Neurology, Dr. Soetomo General Hospital Surabaya from July to December 2014. In this study, there were 34 subjects consisting of 17 normal subjects with normal Visual Evoked Potential (VEP) results referred to as controls and 17 subjects with VEP prolonged latency P100 results hereinafter referred to as cases. Table 1 shows the characteristics of the study subjects. In the case group there were 7 male subjects (41.2%) which were less than in control group with 13 male subjects (76.5%). There was a difference of sex proportions between each group, and this difference was statistically significant with p = 0.037. The mean of the subjects' age in the case group was 43.29 ± 11.58 years, while in the control group was 38.82 ± 10.06 years old. However, this difference was not statistically significant with p = 0.239. in the case group, However, this difference was not statistically significant with p = 0.724. Characteristics of subjects based on dose of ethambutol ≥1200 mg / day in case group there were 10 people (58.8%) more than control group that was 7 people (41.2%). However, this difference was not statistically significant with p = 0.303. Characteristics of subjects based on history of ethambutol therapy ≤1 years showed that in the case group there were 7 people (41.2%), which was more than the control group with 4 people (23.5%). However, this difference was not statistically significant with p = 0.271.

The difference in the proportion of duration of ethambutol therapy in each group of subjects can be seen in Table 1. In the case group, there were 12 subjects (70.6%) with ethambutol therapy duration of 5 months, which is more than the control group with only 5 subjects (29.4%). Meanwhile, in group <6 months duration there were 5 subjects in case group (294%), which is less than in control group with 12 people (70.6%). This difference was statistically significant with p = 0.016. Odd ratio of

5.76 (95% IK 1.317-25.187) was also obtained. Logistic regression of sex and duration indicated a significant correlation between duration of ethambutol therapy and TON with p value = 0.043 and an odds ratio of 4.93 (95% IK 1.053 - 23.082). Thus, subjects with duration of ethambutol therapy ≥6 months had 4.93 times higher risk of TON compared to subjects with ethambutl therapy duration of <6 months. This suggests that the study is clinically and statistically significant.

Discussion

The gender characteristics of a total of 34 samples 20 (58%) male and 14 (42%) female. A population-based study in Taiwan found more male with 65.8%. Similarly, in studies that linked ethambutol therapy to another TON, there were more male subjects than females 71% [9].

The mean age of the subject of the case group was 43.29 ± 11.58 years old while in the control group was 38.82 ± 10.06 years old, as seen in the older average age group. These demographic data were compared with studies that correlated the dose of ethambutol with TON obtained in the mean age of 55.4 ± 14.4 years old [5]. The study of TON incident, the obtained the mean of age range was 58.23 ± 16.68 years [10]. Characteristics of subjects based on risk factors of diabetes mellitus in case group was 7 people (41.2%) slightly more than control group 6 people (35.3%), but this difference was not statistically significant with p = 0.742.

The dose of ethambutol of ≥1200 mg/day in the case group was obtained in 10 subjects (58.8%) more than in the control group with 7 subjects (41.2%). While the dose of 800-1199 mg/day were found in case group with 7 subjects (41,2%) less than control group that was 10 subjects (58,8%), was not statistically significant. The study with 231 TON samples was 49.8% dose <800 mg, 38,1% dose 800-1199 mg, 12,1% dose ≥1200 mg/day (3). Based on the history of ethambutol therapy of ≤1 years, in case group there were 7 subjects (41.2%), which is more tha control group with 4 subjects (23.5%). However, this difference was not statistically significant with p = 0.271.

The previous studies have not reported about the history of the use of ethambutol before, possibly because the previous studies involved a sample of TB patients category 1, whereas in this study the samples are MDR-TB patients who had previously received etambutol therapy. In the case group, the number of subjects with ethambutol therapy duration of ≥6 months was 12 (70.6%), more than in control group with 5 subjects (29.4%). Meanwhile in the control group, the number of subjects with ethambutol therapy duration of <6 months is 12 (70.6%) which is more than in th case group with 5 people (29.4%). The mean of <6-month-duration was 3.24 ± 1.348, while for the ≥6-month-duration was 11.71 ± 5.764. This difference is significant statistically with p = 0.043, and clinically with odds of 4.93 (95% I 95% 955-23.082).

This study was conducted using the cut-off of >3 months. In case group, there were 143 subjects (61.9%) with 3-month duration and 88 subjects (38.1%) with ≤3-month duration, with odds ration of 1 (1.02-1.86) [11]. The case series performed by Griffith et al. found that the duration of ethambutol in the case group was 1-16 months (6.7 ± 5.8 months), with a tendency for longer duration using ethambutol with optical neuropathy [9].

Long duration of ethambutol therapy might cause TON. This can be analyzed from the following explanation: ethambutol is a metal chelator, this agent is able to strongly bind metals especially zinc required in axonal transport, and citric acid cycle. Ethambutol bonding to these metals results in calcium influx, mitochondrial dysfunction, and ultimately leads to decreased ATP, ganglion cell death, and papillomacular bundle damage. If this process lasts longer then most likely will occur more bonds causing the increased risk of TON. However, this does not occur easily. Some factors are also influential and therefore a person might develop TON while the others do not. These factors include the use of other toxic substances such as isoniazid, chloroquine, chloramphenicol, amiodarone, cyclosporine, the use of these drugs are not found in the study subjects. Isoniazid, in particular, is reported to have toxic effects as on the eyes, but the incidence is very small. When starting this MDR-TB treatment program patients are not given isoniazid therapy because MDR-TB patients are resistant to isoniazid. However, most of the patients had received isoniazid therapy previously during the DOTS program. This could have an effect but is not analyzed. In addition, systemic disorders such as kidney and liver disorders that are likely to cause drug accumulation have also been excluded. Other factors that are also influential and not examined in this study are malnutrition conditions, and zinc deficiency.

Conclusion

There is a correlation between duration of ethambutol therapy with toxic optic neuropathy in patients with MDR-TB.

Conflict of Interest: There is no concflict of interest.

Source of Funding: This study is self-funded.

Ethical Clearance: This study was approved by Ethical Commission of Health Research Faculty of Medicine University of Airlangga.

References

1. Singh S, Sushma S, Jyoti S. Validity of visual evoked response in measuring ethambutol induced optic neuritis in tuberculosis patients: evaluation using Receiver Operating Characteristic (ROC) curves. Pakistan J Physiol. 2007;3(2).
2. Yusentono S, Choi Y, Chung CY, Kwon S. Recurrence of Hip Instability After Reconstructive. 2014;1527–34.
3. Matsuda M, Ogawa T, Sitalaksmi RM, Miyashita M, Ito T, Sasaki K. Effect of mandibular position achieved using an oral appliance on genioglossus activity in healthy adults during sleep. Head Face Med [Internet]. 2019;15(1). Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85074550415&doi=10.1186%2Fs13005-019-0210-z&partnerID=40&md5=8f0e1417acc6fe8fd0be5efaeb1c81a2
4. Novita BD, Ali M, Pranoto A, Soediono EI, Mertaniasih NM. Metformin induced autophagy in diabetes mellitus – Tuberculosis co-infection patients: A case study. Indian J Tuberc [Internet]. 2019;66(1):64–9. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85046156735& doi=10.1016%2Fj.ijtb.2018.04.003& partnerID=40&md5=c 6758a2fd588e909f31 eddcde6438092
5. Chung H, Yoon YH, Hwang JJ, Cho KS, Koh JY, Kim J-G. Ethambutol-induced toxicity is mediated by zinc and lysosomal membrane permeabilization in cultured retinal cells. Toxicol Appl Pharmacol. 2009;235(2):163–70.
6. Subchi TDN, Andriani M. The effect of noni fruit (Morinda citrifolia l.) extract on interleukin 4 and interleukin 10 in wistar rats, induced b pyrazinamide, ethambutol and levofloxacin. J Public Health Africa [Internet]. 2019;10(S1):121–3. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85074423675&doi=10.4081%2Fjphia.2019.1203&partnerID=40&md5=6375c7d3f864eae64fa4a6780cc89666
7. Choi SY, Hwang J-M. Optic neuropathy associated with ethambutol in Koreans. Korean J Ophthalmol. 1997;11(2):106–10.
8. Navarro-Carrillo G, Torres-Marín J, Corbacho-Lobato JM, Carretero-Dios H. The effect of humour on nursing professionals' psychological well-being goes beyond the influence of empathy: a cross-sectional study. Scand J Caring Sci. 2019;(1).
9. Pradanie R, Nastiti AA, Jihan T. Analysis of factors related to the mother's behavior t increase breastmilk production. Indian J Public Heal Res Dev [Internet]. 2019;10(8):2642–7. Available from: https://www.scopus.com inward/record.uri?eid=2-s2.0-85073549294& doi=10.5958%2F0976-5506.2019.02267.8&partnerID=40&md5=8cc3cce0f67e2187c107e677a37cf1bf
10. Sasaki S, Yagi K, Nakamura I, Iwaki Y, Kimura M. Visually evoked cortical potentials obtained using checker patterns can detect ethambutol-induced visual toxicity in albino rats. Toxicol Appl Pharmacol. 2003;189(2):134–8.
11. Chen H-Y, Lai S-W, Muo C-H, Chen P-C, Wang I-J. Ethambutol-induced optic neuropathy: a nationwide population-based study from Taiwan. Br J Ophthalmol. 2012;96(11):1368–71.

Correlation between the Duration of Ethambutol Therapy and the Toxic Optic Neuropathy Occurene in Patients with Multidrug-Ressistance Tuberculosis

ORIGINALITY REPORT

19%	%	12%	15%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to Universitas Airlangga Student Paper	8%
2	Prabhjit Kaur, Sofia Singh, Kirandeep Kaur, Karthik Vinay Mahesh et al. "The Genetics of Ethambutol-Induced Optic Neuropathy: A Narrative Review", Neuro-Ophthalmology, 2022 Publication	3%
3	Sergio Martínez-Morato, Maria Feijoo-Cid, Paola Galbany-Estragués, Maria Isabel Fernández-Cano, Antonia Arreciado Marañón. "Emotion management and stereotypes about emotions among male nurses: a qualitative study", BMC Nursing, 2021 Publication	1%
4	Submitted to Udayana University Student Paper	1%
5	Submitted to University of Oklahoma Health Science Center	1%

Student Paper

6	Hiroshi Onodera, Shoji Sasaki, Seiji Otake, Masayuki Tomohiro, Kazumoto Shibuya, Mamoru Nomura. "General considerations in ocular toxicity risk assessment from the toxicologists' viewpoints", The Journal of Toxicological Sciences, 2015 Publication	1 %
7	Mehmet Hamamci, Temel Tombul. "Visual evoked potentials follow-up in idiopathic intracranial hypertension", Neurosciences, 2020 Publication	1 %
8	Adrian Rodriguez-Carlos, Claudia Valdez-Miramontes, Paulina Marin-Luevano, Irma González-Curiel et al. "Metformin promotes Mycobacterium tuberculosis killing and increases the production of human β-defensins in lung epithelial cells and macrophages", Microbes and Infection, 2020 Publication	1 %
9	Submitted to Liberty University Student Paper	1 %
10	Submitted to Badan PPSDM Kesehatan Kementerian Kesehatan Student Paper	1 %

11	Giuseppe Toro, Antimo Moretti, Marco Paoletta, Annalisa De Cicco, Adriano Braile, Alfredo Schiavone Panni. "Neglected femoral neck fractures in cerebral palsy: a narrative review", EFORT Open Reviews, 2020 Publication	<1 %
12	Osman toktas, Nursen Toprak, Sadi Elasan, Iskan Calli, Serhat Binici. "Treatment of Idiopathic Granulomatous Mastitis: Combined Intralesional Steroid Injection with Topical Steroid Administration vs. Systemic (Oral) Steroid", Research Square Platform LLC, 2021 Publication	<1 %
13	Felice Cardillo Piccolino, Daniela Fruttini, Chiara Eandi, Massimo Nicolò, Cesare Mariotti, Silvia Tito, Marco Lupidi. "Vigorous Physical Activity as a Risk Factor for Central Serous Chorioretinopathy", American Journal of Ophthalmology, 2022 Publication	<1 %
14	Xianchao Zhou, Xiang Shen. "MRI Semi-Quantitative Evaluation of Clinical Features of Cartilage Injury in Patients with Osteoarthritis", Concepts in Magnetic Resonance Part A, 2022 Publication	<1 %
15	Paul D. Chamberlain, Ama Sadaka, Shauna Berry, Andrew G. Lee. "Ethambutol optic	<1 %

neuropathy", Current Opinion in Ophthalmology, 2017
Publication

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	Off		