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Ethambutol Effect on Renal and Hepatic Tissue Changes: A Literature Review

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ABSTRACT

Background: Ethambutol is an oral chemotherapeutic drug specifically effective against the active growth of microorganisms of the genus Mycobacterium. Ethambutol is generally well-tolerated and rarely causes side effects. One of the commonly known side effects of ethambutol is optic neuritis, some others include peripheral neuropathy, numbness and tingling, hepatotoxicity, mental disorders, disorientation, hallucinations, to psychosis.
Purpose: This review aims to explain current and previous opinions about ethambutol use and its effects on kidney and liver tissue. The results of this review are expected to provide an overview of the impact of using ethambutol caused tissue damage in humans.
Methods: In this literature review, we performed a search for several keywords such as "ethambutol", "renal tissue", and "hepatic tissue" on PubMed, Science Direct, and Google Scholar databases from January 2010 to January 2022.
Results: Combination antituberculosis therapy intervention of isoniazid, rifampin, pyrazinamide, and ethambutol causes elevated liver enzymes and drug-induced liver injury. Studies reported 14 of 634 (2%) patients on ethambutol are at risk for DILI. Antituberculosis medications have also been reported to affect the kidneys because of their association with the liver as part of the excretory system. Therefore, the kidneys are exposed to the harmful effects of intermediate or waste metabolism leading to injury in these cases.
Conclusion: Ethambutol has not been shown to significantly cause damage to liver and kidney tissue, but it has been reported to have an impact on elevated liver enzymes and renal impairment supported by histological findings.

Keywords: *Ethambutol, renal tissue, hepatic tissue*

INTRODUCTION

Ethambutol is commonly known and used as a first-line and adjunctive antituberculosis drug which are usually available in loose dosage forms or in combination with other regimens, such as rifampicin, isoniazid, and pyrazinamide [1]. Research studies have also reported the use of this combination therapy regimen in the treatment of non-tuberculosis mycobacterial infections The mechanism of action of ethambutol, previously reported in mycobacterium, is to disrupt bacterial cell wall synthesis through inhibition of arabinogalactan (AG) synthesis [2]. Ethambutol is categorized as an oral chemotherapeutic drug that is specifically effective against the active growth of microorganisms of the genus

Mycobacterium. It functionally acts as a bacteriostatic agent and inhibits the synthesis of one or more metabolites, eventually impairing cell metabolism, delayed multiplication, and cell apoptosis. Currently, there's no evidence proved cross-resistance with other antimycobacterial agents. Ethambutol is reported as an effective drug against strains of mycobacterium tuberculosis, but does not seem to be active against fungi, viruses, or other bacteria 3.

Ethambutol administration orally being absorbed 75-80% from the GI tract. This drug is very well absorbed in the intestine and very rapidly, with a peak in serum concentration occurring 2 hours after dosing and is subsequently excreted in the urine. A single dose of 15 mg/kg produces about 5 g/ml plasma at 2-4 hours. The elimination half-life would be 3-4 hours. Ethambutol levels in red blood cells (RBC) are 1-2 times higher than in plasma levels. Therefore, red blood cells (RBC) can act as depots of ethambutol then release slowly into the plasma. Within 24 hours, 50% of the administered ethambutol is excreted in the original form through urine excretion, 10% as metabolites, in the form of aldehyde and carboxylic acid derivatives. Renal clearance for ethambutol administration is estimated to be around 8.6 ml/min/kg, indicating that this drug is not only secreted by glomerular filtration, but also along with tubular secretion. Ethambutol cannot cross the blood-brain barrier, but in tuberculous meningitis, therapeutic levels can be found in cerebrospinal fluid [5].

Oral administration of ethambutol is generally very well tolerated and rarely causes side effects, studies have reported that the use of doses of 15 mg/kg BW has minimal toxic effects [5]. Serious side effects that have been found due to this drug are retrobulbar neuritis which this appearance closely related to the dose given, its manifestations are blurred vision, central scotoma, to red-green color blindness. In children and patients with normal renal function, the standard daily dose of 20 mg/kg has been reported to rarely cause neuritis. In fact, in children who were uncooperative with visual function testing prior to administration or those who reported visual changes did not preclude the use of ethambutol [6]. The other adverse effects due to the administration include peripheral neuropathy, numbness and tingling, hepatotoxicity, mental disorders, disorientation, hallucinations, to psychosis [7]. This review aims to explain current and previous opinions about ethambutol use and its effects on kidney and liver tissue. The results of this review are expected to provide an overview of the impact of using ethambutol caused tissue damage in humans.

METHOD

In this review, we performed literature searching using online search engine with three databases including PubMed, Science Direct, and Google Scholar (from January 2010 to January 2022) by the keywords of "ethambutol", "renal tissue", and "hepatic tissue". We optimized the selection of the most recent articles, but also considered including older articles with strong sources of information and evidence. After the process of selecting articles through literature searching, we filtered the abstracts and then included the proper articles with full text on Mendeley®'s citation manager. Eventually, a total of 21 articles were included for review.

RESULTS AND DISCUSSION

ETHAMBUTOL

Ethambutol plays an essential role in the first-line therapy of tuberculosis patients, its role as a bacteriostatic agent against Mycobacterium tuberculosis. This drug is suspected of its function as an arabinose analogue, inhibiting the work of arabinose transferase, causing the failure of cell wall synthesis of the bacteria that causes tuberculosis. This drug is available in generic tablets of 100 and 400 mg, the recommended dose is 15 mg/kg once a day

in combination with other antituberculosis regimens, higher doses are given to patients with relapsed tuberculosis. Typically, it is given with pyrazinamide in the first two months of combination therapy for patients suspected of having rifampin- and isoniazid-sistant tuberculosis [1,8,9].

One of the most commonly known side effects is optic neuritis, this effect is closely related to the dose of administration, where more than 40% of adults experience toxicity at doses greater than 50 mg/kg compared to the standard dose of 15 mg/kg/day which only about 0 to 3%. Currently there is no official protocol to detect drug-induced ocular toxicity due to ethambutol administration, a study in Korea performed various vision tests such as color vision tests, pattern visual evoked potential results tests (pattern VEP), and retinal nerve fiber layer optical coherence tomography tests (RNFL OCT), the results show that the RNFL OCT and pattern VEP tests can detect changes in vision patterns after six months. Because its effects can decrease visual acuity, red-green color blindness, and visual field defects, attention to dose and early detection will help with reversibility[10].

In the neuronal system, optical manifestations of ethambutol-induced neuropathy have been found to be due to copper chelation of ethambutol. A study of 60 patients on treatment with ethambutol underwent monitoring of serum copper, statistical analysis confirmed significant changes in copper concentrations. Therefore, to prevent this chelating effect, copper therapy can be a potential therapy to prevent this side effect of ethambutol-induced optic neuropathy by not interfering with the bacteriostatic action of other components of ethambutol[9].

Disorders of hematological parameters such as neutropenia and thrombocytopenia have also been reported, in the gastrointestinal tract the patient may experienced nausea, vomiting, abdominal pain and other symptom of hepatotoxicity. When this drug is taken with pyrazinamide for the treatment of latent tuberculosis in patients exposed to multidrug-resistant strains, there may be an incidence of hepatotoxicity and GIT intolerance leading to discontinuation of this therapy[1]. In addition to the side effects mentioned above, studies have also reported minor side effects such as pruritus, joint pain, and headaches[10]. Until this day, there is no specific antidote has been found to reduce the toxic effects of ethambutol. Therefore it is necessary to study and pay attention more to analyze and find solutions for these effects [11].

TOXICITY OF ETHAMBUTOL ON RENAL TISSUE

Ethambutol is a commonly used tuberculosis treatment that has negative effects on hyperuricemia, liver injury, and nephrotoxicity. In the case reported, there was a patient who experienced an increase in serum creatinine to 10.66 mg/dl and blood urea nitrogen to 83 mg/dl at 7 hours after receiving ethambutol administration, another patient after receiving ethambutol therapy reported had renal insufficiency, tubular damage, diffuse interstitial fibrosis, sclerosis glomerular damage and tubular atrophy confirmed by renal biopsy [17]. In a study established by Abbara et al, five patients who received quadruple standard therapy, one of these patients who had previously received ethambutol had been replaced with moxifloxacin because of renal failure [18]. In all these cases, it was identified that after ethambutol was discontinued, renal function recovered and no long-term renal dysfunction occurred [17].

In the process within the body, about 65% to 80% of ethambutol consumed will be excreted unchanged through the urine after passing through the kidneys, this condition proceed an increase in serum ethambutol levels causing its half-life also increases (about 7 to 15 hours in patients with stage renal failure) compared to 4 hours in normal people, therefore the toxicity due to the drug either increases[19]. Administration of isoniazid, pyrazinamide, rifampicin and of course ethambutol as antituberculosis drugs causes renal impairment and dysfunction

due to involvement of these organs in the excretion of metabolites and active metabolites of these drugs. Kidney damage is measured by increasing the parameters of bilirubin, urea, uric acid, and creatinine, as well as serological measurements, such as aspartate transaminase (AST) dan alanine transaminase (AAT). The toxic effects of co-administered antituberculosis drugs also cause an increase in lipid peroxidation accompanied by a decrease in reduced glutathione, catalase enzymes, and superoxide dismutase activity in kidney and liver tissues[20]. The study reported that histopathological profile examination of the kidneys after ethambutol therapy showed glomerular and renal tubular damage [20,21].

TOXICITY OF ETHAMBUTOL ON HEPATIC TISSUE

Ethambutol is one of the anti-tuberculosis regimens that can cause hepatotoxic effects[7]. Some of the known complications of administration of combination antituberculosis regimen result in elevated liver enzymes to drug-induced liver injury (DILI). Patients with DILI and ALT elevations are more likely to have treatment interruptions and poorer treatment outcomes. In these studies, 14 of 634 (2%) patients on ethambutol are considered to be at risk for DILI, and 25 of 634 (3.9%) patients demonstrate clinically significant alanine aminotransferase (ALT) elevations [12]. Changes in levels of the exudation enzymes ALT and aspartate aminotransferase (AST) indicate changes in cell membrane function such as permeability changes or disconnection of the cell membrane. Drugs used to treat TB can cause liver damage, such as hepatotoxicity, which can be a serious problem for TB patients[13]. In other cases, it has not been possible to estimate the exact amount of serum aminotransferase frequency that was elevated due to ethambutol alone, without a combination regimen. In the last 50 years, only a few clinical cases have shown liver damage due to the use of ethambutol, while in other cases symptoms may appear 2 months after the combination therapy is given.

However, recurrence of liver injury or hepatic impairment following re-administration of ethambutol without isoniazid has been found and provides significant evidence. In another case report, it was found that liver injury occurred in the condition of DRES's syndrome, where within 2 to 6 weeks after starting antituberculosis therapy, clinical symptoms developed fever, rash, eosinophilia and effects on the liver, kidneys, and lungs. this is still unknown etiology and exact mechanism, but its suggested may be due to hypersensitivity reaction [1]. In a study by Jeong et al, 8.7% of tuberculosis patients receiving standard therapy had hepatotoxicity, smong 17 patients who had hepatotoxicity, 12 of them had antituberculosis drug-induced hepatotoxicity with a mean aspartate aminotransferase/ alanine aminotransaminase level of 249/249 IU/L, respectively[14]. Another effect caused by the anti-tuberculosis regimen, including ethambutol, is the stimulation of superoxide so that the hepatotoxic effect is triggered[15]. The study reported that histopathological profile examination of the liver in mice treated with anti-tuberculosis drugs showed prominent fat changes, disturbed lobular structure, vascular congestion, severe bleeding, and necrosis with fat vacuoles. accompanied by degenerative changes and the chromatin material shows a lumpy morphology [16].

CONCLUSION

According to this review, the occurrence of damage or injury to liver tissue due to ethambutol is not significant enough and requires further research but has proven its effect in increasing liver enzymes such as AST and ALT. Ethambutol also has a negative impact on biochemical parameters indicative of renal injury. This finding is also supported by the histopathological profile of glomerular and renal tubular damage and changes in the liver tissue.

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REFERENCE

1. Bethesda. Ethambutol. in *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* 1–16 (2020).
2. Brown-Elliott, B. A., Nash, K. A. & Wallace, R. J. Antimicrobial Susceptibility Testing, Drug Resistance Mechanisms, and Therapy of Infections with Nontuberculous Mycobacteria. 25, 545–582 (2012).
3. National Center for Biotechnology Information. Ethambutol Compound Summary. *PubChem* (2022) doi:10.5517/ccnhp3x.
4. van Crevel, R. & Hill, P. C. Tuberculosis. *Infect. Dis. (Auckl).* 271-284.e1 (2017) doi:10.1016/b978-0-7020-6285-8.00031-9.
5. Departement of Pharmacology and Therapeutic FKUI. *Pharmacology and Therapy 5th Edition (Reprint with Addendum 2012).* (Publishing Agency FKUI, 2012).
6. Chiang, S. S. & Starke, J. R. *Mycobacterium tuberculosis. Principles and Practice of Pediatric Infectious Diseases* (Elsevier Inc., 2018). doi:10.1016/B978-0-323-40181-4.00134-1.
7. Lee, N. & Nguyen, H. 'Ethambutol'. *Kucera Use Antibiot. Aclinical Rev. Antibacterial, Antifungal. Antiparasitic. Antivir. Drugs* Seventh Ed, 2346–2360 (2021).
8. Palomino, J. C. & Martin, A. Drug Resistance Mechanisms in Mycobacterium tuberculosis. 317–340 (2014) doi:10.3390/antibiotics3030317.
9. Waller, D. G. & Sampson, A. P. Chemotherapy of infections. *Med. Pharmacol. Ther.* 581–629 (2018) doi:10.1016/b978-0-7020-7167-6.00051-8.
10. N., S. & M., A. Ethambutol induced optic neuritis: a case series. *Int. J. Basic Clin. Pharmacol.* 9, 207 (2019).
11. Schaberg, T. & Lode, H. Treatment of tuberculosis. *Dtsch. Medizinische Wochenschrift* 115, 1799–1802 (2010).
12. Tweed, C. D. *et al.* Toxicity associated with tuberculosis chemotherapy in the REMoxTB study. 1–11 (2018).
13. Mirlohi, M.-S., Ekrami, A., Shirali, S., Ghobeishavi, M. & Pourmotahari, F. Hematological and liver toxicity of anti-tuberculosis drugs. *Electron. physician* 8, 3005–3010 (2016).
14. Jeong, I. *et al.* Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. *J. Korean Med. Sci.* 30, 167–172 (2015).
15. Cao, J. *et al.* Biochemical and Biophysical Research Communications First-line anti-tuberculosis drugs induced hepatotoxicity : A novel mechanism based on a urinary metabolomics platform. *Biochem. Biophys. Res. Commun.* 497, 485–491 (2018).
16. Shabbir, M., Afsar, T., Razak, S., Almajwal, A. & Khan, M. R. Phytochemical analysis and Evaluation of the hepatoprotective effect of Maytenus royleanus leaves extract against anti-tuberculosis drug-induced liver injury in mice. 9, 1–15 (2020).
17. Pablo, S., Gathe, J. & Varon, J. Ethambutol-induced nephrotoxicity: case report and review of the literature. *undefined* (2013).
18. Abbara, A. *et al.* Drug-induced liver injury from antituberculous treatment : a retrospective study from a large TB center in the UK. 1–10 (2017) doi:10.1186/s12879-017-2330-z.
19. Kanaujia, V. *et al.* Ethambutol-induced optic neuropathy in renal disorder: a clinical-electrophysiological study. *Can. J. Ophthalmol.* 54, 301–305 (2019).
20. Sahu, N., Mishra, G., Chandra, H. K., Nirala, S. K. & Bhadauria, M. Naringenin mitigates antituberculosis drugs induced hepatic and renal injury in rats. *J. Tradit. Complement. Med.* 10, 26 (2020).

21. Adaramoye, O. A. *et al*. Ameliorative effects of kolaviron, a biflavonoid fraction from Garcinia kola seed, on hepato-renal toxicity of anti-tuberculosis drugs in Wistar rats. *Tokai J. Exp. Clin. Med*. 41, 14–21 (2016).

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