Interaction of Side Effects of Second Line TB Drugs Therapy in MDR-TB: Ethionamide-induced Hypothyroid and Cycloserine-induced Depression Episode

Try Nirmala Sari[1], Sumardi[2], Heni Retnowulan[2], Barmawi Hisyam[2], Bambang Sigit Riyanto[2], Eko Budiono[2], Ika Trisnawati[2]

[1] Resident of Department of Internal Medicine, FK UGM/RSUP Dr. Sardjito Yogyakarta
[2]Division of Pulmonology, Department of Internal Medicine, FK UGM/RSUP Dr. Sardjito Yogyakarta

ABSTRACT

Background: *Second line anti tuberculosis drug in MDR-TB patients is notorious for having several side effects. Ethionamide is anti tuberculosis drug that is used as a second line therapy in MDR-TB patient management. Hypothyroid is an important side effect in ethionamide administration. Cycloserine is in the fourth group of second line therapy that acts as bacteriostatics. Psychiatric side effects such as anxiety, hallucination, depression, euphoria, habit alteration, and suicide are reported in 9,7%-50% of patients in cycloserine therapy.*

Case Presentation: *A 46 year-old lady with MDR-TB started her second line anti TB drugs therapy since January 2016. Her regimen included levofloxacin, cycloserine, ethionamide, pyrazinamide, ethambutol and PAS (Para-Aminosalicylic Acid). Therapy evaluation in the first month control founded fatigueness, reduced communication, self-secluding, and behaviour alteration. Patient often felt sad, desperate, and had a lot of thought on her illness. Patient also had thoughts of suicide. Patient was then hospitalized and was diagnosed by psychiatry department with TB drugs -possibly cycloserine-induced depression episode. Then, cycloserine therapy was stopped. And at the same time, laboratory result showed an increase in TSH without hypothyroid symptoms. Levothyroxin 1x100 mcg was administered. In the third month of therapy, patient returned with a much higher TSH level, then ethionamide was stopped for 3 months. Evaluation was conducted post ethionamide cessation and found well-controlled TSH level. Ethionamide was then continued with titration doses per month.*

Conclusion: *In MDR-TB therapy, potential complication of ethionamide administration should be considered carefully. Severe neurotoxicity caused by cycloserine can be managed by delaying the drug use temporarily. It is also worth considered that hypothyroid state can exhibit depression symptoms therefore careful monitoring of the side effects of anti TB drug therapy is needed.*

Keywords: *Multi drug resistant, tuberculosis, drug-induced hypothyroid, drug-induced psychosis.*

ABSTRAK

Latar Belakang: Pengobatan TB lini kedua pada pasien TB MDR diketahui memiliki beberapa efek samping. Etionamid adalah salah satu obat dalam pengobatan TB MDR lini kedua. Hipotiroid merupakan efek samping dari pemberian etionamid. Sikloserin merupakan salah satu dari komponen pengobatan lini kedua yang bersifat bakteriostatik. Efek samping psikiatri seperti ansietas, halusinasi, depresi, euforia, perubahan kebiasaan, dan bunuh diri dilaporkan sebanyak 9,7-50% pada pasien yang menjalani pengobatan dengan sikloserin.

Presentasi kasus: Seorang perempuan berusia 46 tahun dengan diagnosis TB MDR, menjalani pengobatan TB lini kedua sejak Januari 2016. Regimen pengobatan terdiri dari levofloksasin, sikloserin, etionamid, pirazinamid, etambutol, dan PAS. Evaluasi pengobatan di bulan pertama menunjukkan adanya lelah, komunikasi yang berkurang, dan perubahan perilaku. Pasien sering merasa sedih, putus asa, dan sangat memikirkan penyakitnya. Pasien juga berpikir untuk mengakhiri hidupnya. Kemudian pasien menjalani rawat inap dan didiagnosis sebagai depresi imbas pengobatan TB, kemungkinan disebabkan sikloserin. Kemudian, pemberian sikloserin dihentikan. Dalam waktu yang bersamaan, pemeriksaan laboratorium menunjukkan adanya peningkatan TSH tanpa disertai gejala klinis hipotiroid. Dilakukan pemberian levotiroksin sebesar 1x100 mkg. Pada akhir minggu ke-3 pengobatan, kadar TSH tetap meningkat sehingga pemberian etionamid dihentikan selama 3 bulan. Evaluasi setelah penghentian pemberian etionamid menunjukkan kadar TSH terkendali. Pemberian etionamid kemudian dilanjutkan dengan dosis titrasi per bulan.

Simpulan: Pada pengobatan TB MDR, timbulnya efek samping pemberian etionamid perlu diperhatikan. Neurotoksisitas berat yang disebabkan sikloserin dapat ditangani dengan penundaan pemberian obat sementara. Hal lain yang perlu diingat adalah kondisi hipotiroid dapat memperlihatkan gejala depresi. Oleh karena itu, pemantauan terhadap efek samping obat TB diperlukan.

Kata kunci: *Multi drug resistant*, tuberkulosis, hipotiroid imbas obat, psikosis imbas obat

Correspondence:
dr. Try Nirmala Sari
Email:
try.nirmalasary@gmail.com

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BACKGROUND

Second line anti tuberculosis drugs in multiple drug resistant (MDR) tuberculosis patients is known to cause several side effects although there is minimal data on it.[1] Hypothyroid is one of the important side effects that usually manifests with unspecific symptoms therefore often missed.[1] Psychiatrics side effects such as anxiety, hallucination, depression, euphoria, behaviour alterations, and suicidal ideas are reported in 9,7%-50% patients with cycloserine therapy, especially in the first 12 weeks after cycloserine administration.[2] This case is presented to improve our awareness in the potential side effects during second line anti tuberculosis drugs for patients with MDR-TB.

CASE REPORT

A 46 year-old lady, from Yogyakarta, a Moslem, a junior high school graduate, came with chief complaint of fatigueness and reduced communication since 7 days before hospital visit. Seven days before hospital visit, patient condition worsened. Patient seemed fatigued, communication was reduced, patient often secluded herself. The patient did not feel dyspnea, fever, and cough. Patient was a Multi Drug Resistant Tuberculosis (MDR-TB) patient, diagnosed with GenExpert in 21 January 2016 as MTB detected medium, Rifampicin resistance detected. Patient received second line anti tuberculosis drug since 29 January 2016 with levofloxacin, cycloserine, ethionamide, pyrazinamide, ethambutol, and PAS regimen. At the time of visit, patient had entered the 3rd week treatment.

At the admission, patient condition and appetite dropped. The patient felt nausea, vomiting, and reduced communication. Patient was then brought to RSUP dr. Sardjito. From history taking, family reported that patient lately showed behaviour alteration. Patient felt sad and desperate, she often thought about her illness and worried about her four kids.

Physical examination revealed moderate general condition, compos mentis, nutritional status deficient (body height 155 cm, body weight 34,5 kg), and BMI 14,3 kg/m^2. Vital sign examination showed blood pressure 100/70 mmHg, measured in laying position, on right arm, with adult cuff. Heart rate was 90x/ minutes, regular, adequate fill and tension. Respiratory rate was 20x/minutes, thoracoabdominal type. Body temperature was 36.7° Celcius, measured in axilla.

Thorax examination comprising lung and heart examination revealed symmetrical left and right hemithoracal movement and similar left and right tactil fremitus. Percussion examination revealed sonor sound in both lung sides and auscultation found amphoric sound in left lung. No abnormality was found during heart examination. Abdominal examination found flat abdomen and normal peristaltic movement. Abdominal percussion found tympanic sound all over abdominal area. Palpation showed supple abdomen, liver and spleen were not palpable. No pitting edema was found in lower extremities.

Routine blood test results were as follows, hemoglobin (Hb) 11.1 g/dl, leucocyte count (WBC) 2.34x10^3/µL, thrombocyte count 275x10^3/µL, erythrocyte count (RBC) 4,10x10^6/µL, hematocrit (Hct) 32,5%, segment 67,1%, lymphocyte 22,2%, monocyte 9,0%, eosinophil 1,3%, basophil 0,4%, mean corpuscular volume (MCV) 79,3 fl, mean corpuscular hemoglobin (MCH) 27,1 pg, blood urea nitrogen (BUN) 4.6 mg/dl, creatinine 0,54 mg/dl, natrium (Na) 136 mmol/L, kalium (K) 2,47 mmol/L, chloride (Cl) 89 mmol/L, SGOT 123 U/L, SGPT 16 U/L, albumin 2,77 g/dl, total bilirubin 0,21, direct bilirubin 0,12. Thyroid function showed 5,89 (normal: 0,34 - 0,56) and free T4 1,07 (normal: 0,61 - 1,12). Based on the results above, the working diagnosis for this patient was cycloserine-induced depression episode and ethionamide-induced hypothyroid in patient with Multi-Drug-Resistant Tuberculosis (MDR-TB) on second line anti tuberculosis drug therapy.

Patient was given high calories and high protein diet with extra egg yolk, infusion premix KCl 25 meq to be given in 8 hours, injection ondansentron 8 mg/24 hrs, lansoprazole 1x30 mg, PAS 8 gr/24 hrs, ethambutol 1x800 mg, levofloxacin 500 mg/24 hrs, ethionamide 500 mg/24 hrs, pyrazinamide 750 mg/24 hrs, and levothyroxin 1x100 mcg.

Plans for patient included TSH level evaluation, administration of levotyroxin, consultation to psychiatry department, hypoalbumin and electrolyte abnormality correction, and administering of cycloserine by titration according to psychosis symptoms improvement.

Psychiatry department diagnosed patient with moderate depression episode with somatic symptoms. Supportive psychotherapy and fluoxetine 20 mg/24 hrs as antidepressant were given. During treatment, clinical condition and TSH level were evaluated. TSH

Table 1. TSH level evaluation during second line anti tuberculosis drug therapy

MONTH	29 JANUARY 2016	23 FEBRUARY 2016	01 MARCH 2016	11 MARCH 2016	20 APRIL 2016	07 J UNE 2016	14 JULY 2016	11 AUGUST 2016
TSH	1,32	5,8	**5,89**	**1,47**	**13,13**	2,54	**1,43**	2,28

level in 17th day of treatment showed improvement, the value was 1,47 (normal: 0,34 - 5,6), thus levothyroxin was reduced to 1x50 mcg. In the 24th day, patient was discharged from the hospital with anti tuberculosis drug regimen including cycloserine 500 mg/24 hrs, ethionamide 500 mg/24 hrs, pyrazinamide 750 mg/24 hrs, ethambutol 800 mg/24 hrs, and PAS 4 gr/24 hrs.

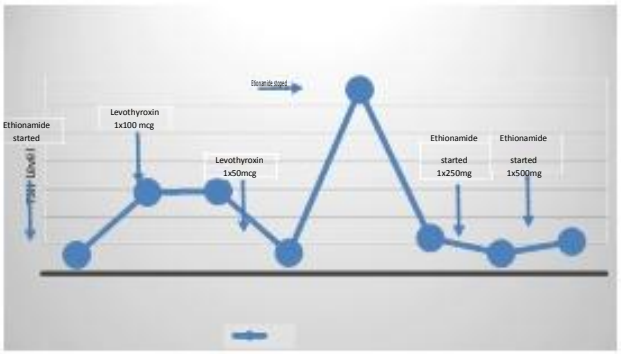

Figure 1. TSH level evaluation during second line anti tuberculosis drug therapy

DISCUSSION

Multi-drug-resistant tuberculosis (MDR-TB) is tuberculosis infection resistant to at least isoniazide (H) and rifampicin (R). This disease is the main focus of global TB control.[3] Second line anti tuberculosis drug therapy in MDR-TB patient has multiple side effects, despite minimal data related to it.[1]

During MDR-TB treatment, attention should be paid to potential complications of ethionamide administration. Hypothyroid caused by ethionamide administration is a reversible condition after the cessation of the drug. Thyroid function should be monitored carefully in patients with ethionamide therapy and ethionamide should be listed as drugs causing hypothyroid.

Ethionamide inhibits technetium accumulation and iodine formation. Ethionamide can also exhibit potential goitrogenic property in particular individuals. PAS also has inhibitory effect on thyroid glands. Synergic effects on thyroid glands can be measured with TSH level evaluation in patients receiving both of the drugs. The level may increase 10-fold from normal threshold within 6 months ethionamide-PAS therapy.[4]

The mechanism responsible for thyroid function disturbance is still unknown. However, there are mechanisms that might cause the situation; reduced conversion of T4 to T3, reduced TSH production and inhibition of thyroid hormone syntesis and iodine formation inhibition caused by ethionamide and prothionamide action.[5]

Hypothyroid may exhibit depression symptoms such as reduced concentration, slower thinking process, poor short-term memory, reduced cognitive function, and depression with paranoid. Depression is a mood disturbance marked with sad, gloomy feeling, and irritability. Patient experiences cognitive distortion like self-criticizing, guilty feeling, worthless feeling, inconfidence, pessimistic, and desperation.

Levofloxacin, terizidone, and cycloserine are second line anti tuberculosis drugs with most potent toxicity to central nervous system. Among them, cycloserine is reported to be associated with psychiatric disturbance and central nervous system abnormality such as psychotic that may manifest as suicidal tendency, compared to other second line drugs. [6]

Cycloserine (4-amino-3-isoxazolidinone) is bacteriostatic antibiotic that is effective against *Mycobacterium tuberculosis*. Cycloserine acts by inhibiting cell wall biosynthesis in the bacterium.[7]

Cycloserine has narrow therapeutic window and toxic effect on nervous system. This is because of cycloserine's ability to penetrate blood brain barrier and lower Gamma Amino Butyric Acid (GABA) production. Severe neurotoxicity caused by cycloserine can be treated by temporarily delaying the use of the drug. Cycloserine can be administered again in small dose when the patient has returned to normal condition. Cycloserine has long half-time, therefore patients need few days to few weeks to return to recover from the side effect. Replacement with other anti tuberculosis drug should be considered in patients that can not tolerate repeated cycloserine initiation.[8]

CONCLUSION

In MDR-TB treatment, potential complication from ethionamide administration should be considered

carefully. Hypothyroid caused by ethionamide use is a reversible condition after cessation of the drug administration. Severe neurotoxicity caused by cycloserine can be treated by temporarily avoiding the drug use. Cycloserine can be administered again in small dose when the patient has returned to normal condition. Replacement with other anti tuberculosis drug should be considered in patients that can not tolerate repeated cycloserine initiation. Hypothyroid may exhibit depression symptoms such as reduced concentration, slower thinking process, poor short-term memory, reduced cognitive function, and depression with paranoid.

REFERENCES

1. Ajay RM, Rohini K, Shivashankara KN, Aswini KM. Journal of Clinical and Diagnostic Research. 2015;9(8)
2. Padi A, Bratis D, Monssas A, Tselebis A. Psychiatric morbidity and other factors affecting treatment adherence In Pulmonary Tuberculosis Patients. TubercResp treat. 2013.
3. WHO. Global Tuberculosis Report 2015. 2015.
4. Drucker D, Eggo MC, Salit IE, Burrow GN. Ethionamide induced goitrous hypothyroidism. Ann Intern Med. 1984;100:837-39.
5. Isaakidis P, Varghese B, Mansoor H, Cox HS, Ladomirska J, Saranchuk P et al. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. PLoS One 7. 2012;(7)
6. Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. Int J Tuberc Lung Dis. 2013;17(10):1257-66.
7. Prsser G, de Carvallo, Luiz PS. Kinetic Mechanism and inhibition of Mycobacterium Tuberculosis d-alanine: D-alanine ligase by the antibiotic cycloserine. FEBS journal. 2011;280 (4):1150-66.
8. Coyne KM, Pozniak AL, Lamorde M, Boffito M. Pharmacology of second-line antituberculosis drugs and potential for interactions with antiretroviral agents. AIDS.2009;23:437-46.

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