Case Report

A Rare Case of Tremor Induces by Cycloserine in Drug-Resistant Tuberculosis Patient

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Abstract

Background: Tuberculosis is a contagious disease that generated by *Mycobacterium tuberculosis.* Drug-Resistant tuberculosis (DR-TB) is inculpated the use of the second-line anti-tubercular treatment which is associated with many drug side effects or so called, Adverse Drug Reactions (ADR). Cycloserine (Cs) is an important drug against drug resistant tuberculosis (DR-TB). Cycloserine has been used in tuberculosis therapy since the late 1950s. Identical with most drug, Cycloserine can cause many Adverse Drug Reactions (ADR).

Case Illustration: A 23-year-old woman diagnosed with drug-resistant tuberculosis is undergoing long-term treatment. The patient received treatment for DR-TB with the Bdq-Lfx-Cfz-Cs-E regimen. After the patient underwent the 10th month of advanced phase treatment, the patient complained of shaking in both hands (tremors). The tremor is felt to be more severe in the right hand and the patient cannot grip objects tightly.

Discussion: Cycloserine (Cs) play an important role in second-line drug management of DR-TB. Cs-Induced psychosis and other neurological side-effects can be detrimental towards patients yet they are rarely reports in DR-TB cases. Cs is correlated with severe psychiatric cases and Central Nervous System related ADRs. Cs-associated ADR is most likely because of production of gamma-aminobutyric acid as a result of inhibition of glutamic decarboxylase. Study Shown that among 132 patients who reported side effects in the cycloserine group, 2 (1.4%) experienced major side effects, namely tremors. Side effects possibly or probably related to Cs appeared after a median of 71 days (range 10–331 days) of Cs treatment.

Conclusion: the drug side effects such as tremors are very rare in drug-resistant tuberculosis patients. In this case, the patient's complaint of tremors could be caused by cycloserine as an anti-tuberculosis drug.

Keywords: Drug-Resistant Tuberculosis, Cycloserine, Tremor, Adverse Drug Reaction

Introduction

Drug-resistant tuberculosis (DR-TB) remains a major health problem in Indonesia. Tuberculosis is an contagious disease caused by bacteria infection Mycobacterium tuberculosis.[1] This disease affects the lung parenchyma (pulmonary TB), this bacteria

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also can infect other organs (extra pulmonary TB). Tuberculosis (TB) is one of the highest death threats around the world.

Drug-resistant tuberculosis (DR-TB) is a threat to control among the health workers, is the enemy among the world. Statistically in 2019, estimated that 3.3% of active tuberculosis patient and 17.7% of reinfection patients is a drug-resistant patients. In Indonesia alone, the estimated DR-TB is 2,4% of tuberculosis patients and 13% of reinfection TB with total incidence of 24.000 cases or 8.8/100.000 populace. Study shown in 2019, around 11.500 Rifampicin-resistant TB (RR-TB) patients was found, around 48% of patients started second-line TB management with 45% success rate.[2]

The drug-resistant tuberculosis (DR-TB), for example multidrug-resistant tuberculosis (MDR-TB) is involves in second-line anti-tubercular treatment (ATT). This treatment is associated with multiple Adverse Drug Reactions (ADR). Cycloserine (Cs) (D-4-amino-3-isoxazolidine) is a very important second-line drug used in the management of MDR-TB.

Cs-Induced psychosis and other neurological side-effects can be detrimental towards patients yet they are rarely reports in DR-TB cases. Cycloserine, a cyclic analog to D-alanine, that targetalanine racemase and D-alanine ligase, thus blocking the formation of the bacterialcell wall.[3] Cycloserine has been used in TB therapy since the late 1950s.

Case Illustration

A 23-year-old woman complained of a cough with phlegm for one month, fever at night, weight loss of around 3 kg (from 48 kg to 45 kg), and decreased appetite. The patient went to the Community Health Center and underwent a rapid molecular test (Gene Xpert) examination with results of Rifampicin Resistance. The patient doesn't have any precursory history with TB treatment and doesn't have any trace with other tuberculosis patient. The patient went to Muhammadiyah Ahmad Dahlan Kediri Hospital on August 1, 2022. The patient underwent a baseline examination before starting treatment. On physical examination, rhonki in the upper ⅔ of the right hemithorax. The patient's weight is 45 kg with a height of 156 cm, and the patient's body mass index is 18.49 (underweight). The results of the chest X-ray examination showed infiltration at the apex pulmo dextra with minimal lesion. On the 2nd line LPA (Line Probe Assay) examination, Mtb was Not Detected. Still, on the DST (Drug Sensitivity Test) examination, the results were Sensitive on H DT, Lfx, Mfx DT, Amk, Bdq, Lzd, Cfz, Z. The patient decided to start treatment on August 9, 2022 with a short-term regimen (Bdq-Lfx-Cfz-E-H-Eto-Z).

After undergoing treatment for 25 days, the patient often complained of nausea, vomiting, and haematemesis. Based on the patient's complaint, the treatment was stopped because she was intolerant to Ethionamide. The patient restarted treatment with a long-term regimen (Bdq-Lfx-Cfz-Cs-E) on September 6, 2022.

After the patient underwent the 10th month of advanced phase treatment with the Lfx-Cfz-Cs-E regimen, the patient complained of shaking in both hands (tremors). Tremors are felt to be more severe in the right hand, tremors occur in the hands during activity and at rest. Patients complain of being unable to grip objects tightly, which interferes with daily activities. The patient was consulted by a Neurology Specialist and received Trihexyphenidyl 2x1 mg and Mecobalamin 500 mcg 1x1 for one month. The evaluation showed that the tremors reduced after one month and the patient was able to carry out activities well. However, in the 15th month of treatment, the patient complained of tremors in both hands returned with a lighter intensity. The Cycloserine was stopped for two months accompanied by the administration of mecobalamin 500 mcg 1x1 without Trihexyphenidyl. As a result of discontinuing cycloserine, the patient's tremor complaints were reduced very significantly.

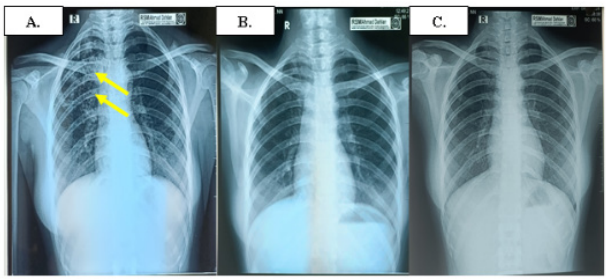

Figure 1.

A. Chest X-ray before anti-tuberculosis therapy, showing infiltrates in the upper middle field of the pulmodextra (showing pulmonary TB)

B. Fibro-infiltrates improvement, after 6 months with anti-tuberculosis therapy,

C. Completed therapy of anti-tuberculosis for 18 months.

Figure 2: Tremors in the patient's hands

Discussion

Treatment of drug-resistant TB uses second-line therapy, one of the drug used in the treatment of drug-resistant tuberculosis is cycloserine which has neurological side effects when used. a cyclic analog to D-alanine, target alanine racemase and D-alanine ligase, thus blocking the formation of the bacterialcell wall.[3] Cycloserine has been used in TB therapy since the late 1950s[4–6] Cycloserine is used as second-line therapy for group B drug-resistant TB at a with dose of 10-15mg/kg. Studies shown, Cycloserine can cause psychiatric side effectsand neurotoxicity.[6]

Cs-Induced psychosis and other neurological side-effects can be detrimental towards patients yet they are rarely reports in DR-TB cases. Cs is correlated with severe psychiatric cases and Central Nervous System related ADRs. Cs-associated ADR is most likely because of production of gamma-aminobutyric acidas a result of inhibition of glutamic decarboxylase.[7] A study conducted by Li Y, et al (2019) reported that 2 of 132 patients who reported side effects in the cycloserine group (1.4%) experienced serious side effects, namely tremors.[4] In a retrospective study conducted by Pratibha S,etal. (2020), 3 out of 89 patients who used cycloserine could cause neurotoxic side effects which were known from neuroimaging changes in the form of restriction in the caudate nucleus which resulted in motor symptoms.[6,8] A study also shows that Cs itself can cause neurological side effects due to its ability to penetrate the brain barrier and work as an NDMA agonist which causes motion sickness, sleepiness, depression, vertigo, confusion, dysarthria, paresthesia, hyperirritability, seizures, tremors and psychosis.[9]

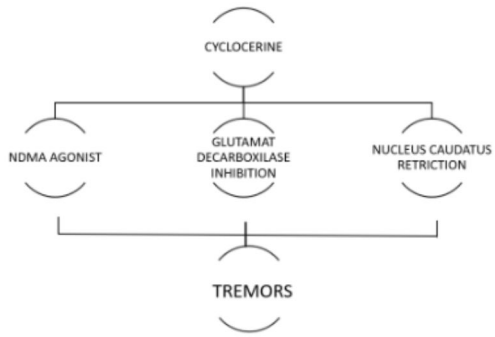

Figure 3: Mechanism of Cycloserine Induction of Tremors

In this patient, the neurological side effect that occurred was tremors, which were experienced in the 10th month of advanced phase treatment. As stated by Li Y, et al (2019) in the retrospective study on 144 patients shows that the effects of Cs is possible. It appears after a median 71 days (range 10–331 days) ofCs treatment.[4]

When complaints of tremors occurred, the patient was consulted by a Neurology Specialist and received Trihexyphenidyl 2x1mg therapy and Mecobalamin 500 mcg 1x1 for one month. The patient has undergone

a thyroid function test and is not taking any other medications that could cause tremors. This was done to rule out other potential causes of the tremors aside from cycloserine. Evaluation of this therapy showed that tremors were reduced and the patient was able to carry out activities well. This is by Meijer et. al (2019) that Trihexyphenidyl is given to stop drug-induced tremor symptoms with a minimum recommended dose of 1 mg per day until the patient can control the tremors symptoms they are suffering from.[10]

According to research conducted by Li Y, et. al (2019), patients who experienced side effects from cycloserine were stopped from treatment for 6 months to minimize side effects. In a case series conducted by Yadav et al, (2019), patients who experienced neurological side effects and psychosis were temporarily discontinued with cycloserine to overcome the side effects that occurred. This is consistent with the patient that complaints of tremors reappeared in the 15th month of treatment, then Cycloserine was stopped for 2 months (accompanied by the administration of mecobalamin 500 mcg 1x1 without giving Trihexyphenidyl).[4,7] As a result of stopping cycloserine, the patient's complaints of tremors were reduced very significantly.

The side effect of tremor associated with cycloserine has been listed by the brand/ manufacturer. However, this information is not included in the technical guidelines for managing multidrug-resistant tuberculosis (MDR-TB) in Indonesia. Tremors in MDR-TB patients are rare and have not been reported in Indonesia, and patients have been informed about this side effect. Therefore, this case finding has been reported to the TB program managers and local health authorities to be considered for inclusion in the next update of the MDR-TB technical guidelines.

Conclusions and Recommendations

Drug-resistant tuberculosis (DR-TB) is leaded by theaversion of Mycobacterium tuberculosis (Mtb) bacteria mutation in chromosome. DR-TB requires complex management with treatment consisting of various anti-tuberculosis drugs. Interactions with drug use have various side effects and each patient has different complaints.[11] This patient reported side effects in the form of tremors that appeared in the 10th month of treatment and recurred in the 15th month of treatment. Drug side effects such as tremors are very rare in drug-resistant tuberculosis patients. In this case, the patient's complaint of tremors was caused by cycloserine as an anti-tuberculosis drug because after stopping cycloserine, the patient's complaints of tremors reduced very significantly. Even though when the tremor complaints first appeared, cycloserine had not been stopped and only Trihexyphenidyl and Mecobalamin were given so the tremor recurred in the 15th month of treatment. If side effects such as tremors occur in DR-TB patients, what can be done is to immediately stop cycloserine permanently. All patients with multidrug-resistant tuberculosis (MDR-TB) undergo a comprehensive examination every 6 months for 2 years after treatment.

Limitation

There was no objective and measurable examination of the tremor symptoms experienced by the patient. The patient did not undergo a head CT scan and MRI to rule out the possibility of other brain lesions.

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