

Potential side effects of medicine on patients with tuberculosis fixed-dose combination in dr. Pirngadi Hospital, Medan

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Abstract. Tuberculosis (TB) caused by the bacterium *Mycobacterium tuberculosis* (Mtb), is curable disease which by only using a few new antibiotics. TB treatment has several stages, namely intensive and advanced stages. Compliance in taking *Obat Anti Tuberkulosis* (OAT) is an important factor to the success of TB treatment but the side effects of drugs make patients simply stopping treatment and it creates failure the TB treatment process. Improved adherence can do by using a fixed-dose combination OAT. In the intensive phase, the patient will get a fixed-dose combination containing a mixture of four antibiotics. The purpose of this study is to evaluate the potential side effects that occur during fixed-dose combination OAT treatment at an intensive stage and see the level of compliance of patients taking TB drugs. Observational sampling in TB patients was taking OAT at an acute stage by looking at side effects that arise during treatment and then analyzed using SPSS version 23 and Naranjo algorithm. The results showed the most common potential side effects for fixed-dose combination OAT in the intensive stage were itching, headache and nausea with a percentage of 72% each, joint pain 45%, stomach pain 36.4%, lack of appetite and rashes 27.3% each and reddish color in the urine 18.2%. The results of the analysis using Naranjo algorithm obtained results eight, which means the side effects might cause due to the use of the drug. The results of patient compliance achieved a 100% compliance rate.

Keywords: fixed-dose combination, anti-tuberculosis drugs, potency, side effect

INTRODUCTION

Tuberculosis caused by *Mycobacterium tuberculosis*. Where these bacteria are acid-resistant and most often attack the lungs even though other organs can attacked as well as bones, brain, kidneys, or lymph nodes [1,2]. Transmission of TB bacteria in two ways, namely directly or indirectly, into the respiratory tract [3]. Indonesia is one of the countries that have the most TB cases in the world, namely 10% of the pulmonary TB cases that occur in the world. According to WHO, the success rate of TB treatment is 85%, but

Indonesia has not reached that percentage. The success rate of TB treatment in Indonesia is only 81.3%, or below the target of WHO [4]. The potential cause of increased side effects can occur due to consuming drugs regularly, drugs in more than one amount or polypharmacy, or treatment for an extended period, one of which is Tuberculosis.

Tuberculosis is a disease that must treat with large amounts of antibiotics. TB treatment that commonly used today is a fixed-dose combination that aims to increase TB compliance because patients only consume one type of drug that contains several antibiotics. The occurrence of side effects can be a significant factor in the severance of TB treatment because OAT does have a variety of side effects [5]. The patient's level of adherence to undergoing treatment indicates the success rate of TB treatment. Side effects that arise,

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lack awareness in patients, and the use of drugs in the long term is the cause of non-compliance with treatment. Because one of them is the side effects that cause medication noncompliance, the monitoring of side effects becomes very necessary. All TB patients who are currently undergoing treatment should inform of the potential side effects that may arise due to the use of TB drugs. Because many of the TB patients who drop out of treatment due to not resistant to side effects from OAT. Providing education about the side effects of OAT becomes very important so that patients remain obedient in consuming OAT even though after consumption, various side effects can occur, and TB patients do not stop treatment if there are events these side effects occur. According to the Indonesian Ministry of Health (2018), side effects from consuming OAT can occur either mild or severe. Potential side effects that may occur include nausea, vomiting, decreased appetite, hearing loss, visual disturbances, headaches, itching, joint pain, and redness in the urine ⁴. The study was conducted on 11 TB patients using intensive stage OAT, who met the inclusion criteria at Dr. Pirngadi Medan. Potential side effects that occur most in men at 54.5%, the most age suffer from TB that is 18, 24, and 31 years, respectively 18.2%. Most side effects that occurred in the first month were two side effects of 54.5%, and in the second month, the most were three side effects of 45.5%. Patient compliance in using OAT is 100%.

METHODOLOGY

This research used MESO sheets, Naranjo Algorithm sheets, and questionnaires to use compliance drug sheets.

The study was a descriptive study that used a prospective observational method in sampling. Inclusion criteria included patients diagnosed with TB and received a fixed-dose combination OAT. The use of OAT in patients is monitored for two months and seen side effects that arise during the use of fixed-dose combination OAT from September to October 2018. Patients who sampled are patients who are willing to fill out informed consent and compliance questionnaires. The description of patient characteristics includes several criteria, namely, age, age, occupation, and life habits. Data analysis uses SPSS version 23.

Data analysis of the side effects of anti-tuberculosis drugs (ATDs) combined with a fixed-dose and level of compliance was descriptively using SPSS version 23.

RESULTS AND DISCUSSION

Patient characteristics from the medical records of patients were included in the inclusion criteria, as shown in Table 1.

Table 1. Characteristic of Tuberculosis Patient

Characteristic patient	Amount (n)	Percentage (%)
Gender		
Male	6	54.5%
Female	5	45.5%
Age		
18 – 25	4	36.4%
26 – 35	3	27.3%
36 – 45	2	18.2%
46 – 55	1	9.1%
56 – 65	1	9.1%
Occupation		
Work	6	54.5%
Not work	5	45.5%
Living habits		
Smoke	6	54.5%
not smoke	5	45.5%
Alcohol consumption	3	27.3%
No alcohol consumption	8	73.7%

Table 1 shows the characteristics of TB's patient which most male patients descriptively suffering from tuberculosis (54.5%) with activities as workers (54.5%). The highest age of patients suffering from TB is 18, 24, and 31 years (18.2%), with the habit of consuming cigarettes (54.5%), but most do not drink alcohol (73.7%). The incidence of TB suffering in both women and men is the same, but the increase in TB occurrence in men with age due to work and social environment makes it easier to exposed to TB germs where this study is following the review of Shamiya et al. (2015) which statesmen are more susceptible to TB.

Smoking is a factor that speeds up a person's exposure to TB because toxic substances produced from burning cigarettes will produce free radicals that can reduce the body's defense system, especially the lung organs, where these organs are organs that are favored by TB germs [6]. TB will be nine times more likely to attack the respiratory tract in people who consume cigarettes. The incidence of latent TB will be two times greater when exposed to cigarette acid [7]. Nurjanah (2015) states the same thing that the most critical risk factor for contracting TB at a productive age is the habit of consuming cigarettes. TB often infects patients during a fertile period because they interact more frequently with unfavorable surroundings

[8]. TB incidence rates can increase in both active smokers and passive smokers because exposure to cigarette smoke can weaken the respiratory system, especially the lung organs. A person often has TB but does not realize it is called latent TB. Latent TB is TB that is already present in a person's body but does not yet cause symptoms, but if the person's immune system decreases, it can develop into active TB [9]. TB can infect a person unnoticed due to primary infection in childhood, which not handled correctly [2,10].

Table 2. Comparison between the drug side effects of TB patient's who use Anti-Tuberculosis Drugs (ATDs) for one month and two month.

Drug side effect	Observation			
	One month		Two month	
	N	%	N	%
Itchy				
Yes	2	18,2%	8	72.7%
No	9	81,8%	3	27.3%
Headache				
Yes	6	54,5%	8	72.7%
No	5	45,5%	3	27.3%
Joint pain				
Yes	1	9,1%	5	45.5%
No	10	90,9%	6	54.5%
Reduced appetite				
Yes	-	-	3	27.3%
No	11	100,0%	8	72.7%
Nausea				
Yes	5	45,5%	8	72.7%
No	6	54,5%	3	27.3%
Blurred vision				
Yes	-	-	-	-
No	11	100,0%	11	100.0%
Stomach ache				
Yes	1	9,1%	4	36.4%
No	10	90,9%	7	63.6%
Rash				
Yes	-	-	3	27.3%
No	11	100,0%	8	72.7%
Reddish urine				
Yes	-	-	2	18.2%
No	11	100,0%	9	81.8%

Table 2 Results of interviews with TB patients every month for two months in TB patients taking fixed-dose OAT obtained data in the first month that most often appeared were complaints of headaches (54.5%) and nausea (45.5%). In the second month, the effects of charges on patients were itching (72.7%), headache (72.7%), nausea (72.7%). Fixed-dose ATDs consists of a combination of several TB

drugs consisting of Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol in one tablet preparation to increase TB patient compliance in taking medicine [11,12]. Fixed-dose combination OAT aims to simplify prescription medication, simplify drug management to prevent the occurrence of resistance due to the use of ATDs in a single form or monotherapy [13]. Other side effects that appeared in the first month were two side effects of 54.5%, while in the second month, most patients suffered three side effects of 45.5%. Side effects in the first month are itching, joint pain, and abdominal pain, while in the second month, besides those mentioned, there are more side effects of rashes and redness in the urine. Research conducted by Diana Sari (2014), from interviews with patients using ATDs, the frequency of occurrence of side effects in the initial month of use is nausea and dizziness. The use of ATDs for the second month only appeared complaints of nausea, dizziness, pain, and itching [14]. Potential side effects can appear even though the drug has used following the dosage and instructions for use. Possible side effects on the use of ATDs greatly influenced by dosage, time of administration, age, nutritional status, and a history of diseases such as impaired liver function, impaired kidney function, or the presence of HIV [15]. The most common potential side effects for Isoniazid use are nausea, vomiting, and headaches. If there is nausea due to the use of Isoniazid, it can overcome by administering omeprazole or metoclopramide.

Rifampicin can cause urine to be red and should consume on an empty stomach because of its increased bioavailability an empty stomach. Other side effects due to Rifampicin are nausea and vomiting and dizziness. Pyrazinamide also often causes nausea and vomiting, wherein Pirazinamide is a nicotinic acid derivative whose structure is similar to isoniazid. Ethambutol is bacteriostatic with side effects that often arise in the form of nausea, vomiting, headaches, and vision problems [11]. Ethambutol is an antibiotic used in ATDs, which is bacteriostatic. Adverse reactions depend on each individual where not all individuals experience side effects due to the use of ATDs [11,16]. In the method of fixed-dose combination OAT, if side effects occur, it will be challenging to determine which side effects due to drugs because the fixed-dose combination OAT, especially at the intensive stage, uses four types of medications at once in one tablet. If severe side effects occur, such as decreased vision or blindness, the use of fixed-

dose ATDs can be stopped and replaced with compact ATDs therapy [17].

Table 3. The assessment of causality Naranjo Algorithm on research subjects using anti-tuberculosis drugs (ATDs)

No	Drug side effect	Amount of patients	Score	Suspected drug
1	Itchy	8	8	Isoniazid Ethambutol Rifampicin Pyrazinamide
2	Headache	8	8	Ethambutol
3	Nausea	8	8	Rifampicin Isoniazid Ethambutol Pyrazinamide
4	Joint pain	5	8	Pyrazinamide
5	Stomach ache	4	8	Rifampicin Isoniazid Ethambutol
6	Rash	3	8	Pyrazinamide Rifampicin
7	Reduced appetite	3	8	Isoniazid Pyrazinamide Ethambutol Rifampicin
8	Reddish urine	2	8	Rifampicin
9	Blurred vision	-	-	Ethambutol Isoniazid

Assessment of potential side effects often uses the Naranjo Algorithm scale, especially commonly used in Indonesia (Table 3). This algorithm measures side effects through a questionnaire. Researchers conducted interviews with patients, and after the results obtained, researchers will do the sum of each question point, and the results adjusted to the available score. Causality analysis is an evaluation of the causal relationship between the occurrence of side effects that occur with the use of drugs by the patient. Causality analysis uses Naranjo logarithms to individually evaluate patients with the treatment to be given [18]. The causality category based on WHO consists of several groups based on existing scores. Score 0 (doubtful), which means there are no side effects. A score of 1-4 (possible) means that the clinical condition that appears may be a side effect. A score of 5-8 (Probable) means that the possibility of an unwanted state is a side effect of a suspected drug, and a rating greater than or equal to 9 (definite) means that specific side effects will occur [1]. The result of the sum of the scores in the Naranjo logarithms in this study is a score of 8. The value is probable, which means it is likely a side effect of a suspected drug [19]. All side effects such as itching, headache, nausea, joint pain, abdominal

pain, rashes, lack of appetite, redness in the urine have a score of 8. Undesirable conditions such as itching, nausea, lack of desire that arise may be a side effect of RHZE. Side effects from ethambutol may cause headaches, joint pain may be due to pyrazinamide side effects, rashes are possible side effects of pyrazinamide and rifampicin, and reddish urine are possible side effects from rifampicin.

The number of patients who experienced nausea, headaches, and data was 72.7%, respectively, which experienced joint pain by 45.6%, abdominal pain 36.4%, rashes, and lack of appetite 27.3% each and redness in urine by 18.2%.

Table 4. TB's patient compliance data

Level of compliance	Percentage (%)
Obey	100%
Not obey	-

Patients in this study were all compliant (100%) taking fixed-dose OAT even though side effects appeared during use (Table 4). The level of adherence to consume drugs becomes very important in handling TB. Fixed-dose combination OAT is a polypharmacy drug. Polypharmacy consists of several medications so that drug interactions are possible [20]. Compliance plays a significant role in the success of therapy. In TB, long-term drug consumption can reduce the level of adherence. Drug side effects are also a common cause of patients stopping treatment. If the use of OAT is irregular and does not correspond to the specified time; as a result, there is resistance to the bacteria that causes tuberculosis to the OAT consumed. When resistance occurs, the treatment will be more extended, and the number of tuberculosis-killing antibiotics will be more numerous, and the side effects caused greater [21,22].

CONCLUSION

The study was only carried out in one outpatient setting, and the results cannot be generalized to all patients in all hospitals in North Sumatra. Based on the results of the dominant side effects that arise, namely, itching, headaches, and nausea that is the highest percentage (72.7%). Based on the results obtained from the level of adherence, the patient underwent intensive treatment very well and assessed the causality of the Naranjo algorithm regarding drug side effects obtained by a score of 8, which means that side effects might be caused by using ATDs.

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