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Measurement of Self-Reported Fixed-Dose Combination Antituberculosis Drugs Therapy Regimen

Yuni Priyandani[1,2], Abdul Rahem[2], M.Djunaedi[2], Umi Athiyah[2], M.B.Qomaruddin[3], Kuntoro[4]

[1]Doctoral Student, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia, [2]Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia. [3]Department of Health Promotion and Health Behavior, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia. [4]Department of Biostatistic, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia

Abstract

Objective: The World Health Organization encourages the use of fixed-dose combinations (FDC) of rifampicin, isoniazid, pyrazinamide and ethambutol for the treatment of TB. This study was aimed to determine the rate of medication adherence of the patient with indicators including right dose, right frequency, right interval, right time to take the medication, and right duration of drug therapy.

Method: This cross-sectional study applied self-reported questionnaire as the research instrument that was administered to a total of 249 TB patients at primary health care centers in Surabaya, Indonesia. This questionnaire uses the Guttman scale consisting of statements about patient behavior in taking FDC drugs. Completing this questionnaire was accompanied by the researcher after the patient received an explanation before approval and filled out informed consent. Data collection was carried out for 3 months from July to September 2018. The data analysis using Statistical Product and Service Solutions (SPSS) version 18 for Windows.

Results: Based on research data, there were 103 (41,37%) patients of total 249 TB patients who met the adherence of the FDC antituberculosis drugs therapy regimen with five indicators including right dose, right frequency, right interval, right time to take the medication, and right duration of drug therapy.

Conclusion: Medication of the FDC antituberculosis drug is not only taken by mouth but must be taken according to the indicator of therapeutic regimen including right dose according to the number of caplets, right frequency as the amounts of TB medicine caplets every time, right interval at the same time every time, right time to take the medication in 2 hours before meal or 4 hours after meal on an empty stomach, and right duration of drug therapy as scheduled.

Keywords: *therapeutic regimen, patient 's adherence, tuberculosis patient, primary health care center*

Introduction

Tuberculosis (TB) is still one public health problem in the world. Globally, in 2017 there were 10 million people suffering from TB with 5.8 million of the patients were male, 3.2 million female, and 1 million children. There are many cases of TB in all countries with 90% of TB cases suffered by adults over the age of 15 years and 9% of TB cases suffered by people with HIV. In Indonesia, TB cases rank third in the world. The biggest TB cases in the world are in India 27%, China 9%, Indonesia 8%, Philippines 6%, Pakistan 5%, Nigeria 4%, Bangladesh 4%, and South Africa 3%. These eight countries, and 22 other countries, are included in 30 countries with a high burden of TB, comprising 87% of TB cases in the world. A total of 6% of TB cases in the world also occur in Europe 3% and America 3%.[1] Of the

Corresponding author:
Yuni Priyandani,
Doctoral Student, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia; Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia.
Email: yuni.priyandani-12@fkm.unair.ac.id.; yuni-p@ff.unair.ac.id.; Kuntoro,

total TB cases in 2017 in all provinces in Indonesia, it turns out that East Java Province is ranked second with 48,323 total TB cases after West Java Province with 78,698 TB cases.[2] Surabaya ranked first in East Java with 5,428 TB cases in 2016.[3,4] Therefore, this study was conducted in the city of Surabaya.

Effectiveness of tuberculosis (TB) medication depends mainly on two factors, namely the efficacy of the medication and the rate of medication adherence of the patient.[5] The World Health Organization encourages the use of fixed-dose combinations (FDC) of rifampicin, isoniazid, pyrazinamide and ethambutol for the treatment of TB. The main advantages of such FDCs are the simplification of procurement and prescribing practices and the protection they afford against the potential selection of rifampicin-resistant strains of *Mycobacterium tuberculosis*.[6] The government's role in controlling TB disease is indicated by the provision of fixed-dose combination (FDC) antituberculosis drugs at each primary health center in Indonesia. The primary health care center is the first level health service for the people in Indonesia.[7,8]

TB treatment is given in long term therapies, in two stages, ie 2 months intensive stage and the next 4 months advanced stage. Tuberculosis is a chronic disease with the key treatment is adherence to medication. The following definition of chronic diseases: ''*Diseases which have one or more of the following characteristics: they are permanent, leave residual disability, are caused by nonreversible pathological alteration, require special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation or care*''.[9] Drug therapy in chronic diseases requires a long time so medication compliance is very important. ''Drugs don't work if people don't take them''. This observation made by former Surgeon General C.Everett Koop in his keynote address at a symposium on *Improving Medication Compliance* provides a clear statement of one of the consequences of non-compliance.[10] The probability of occurrence of non-compliance of patients during TB treatment is huge. Non-compliance can be caused by a long period of therapy, polypharmacy in patients with TB, expensive cost of therapies, and adverse drugs reaction (ADR).[7,8] The risk factors of non-compliance may result from the factors of the disease, the therapeutic regimen, and the interaction with health care providers. Medication must be taken according to the therapeutic regimen. The factor of therapeutic regimen includes the multiple types of drugs (polypharmacy), drug frequency which is difficult to comply, too long duration of therapy, adverse drug reaction, the patient feeling as have been cured, medical expenses, the method of drug use, and the drug taste. [10]

Compliance includes two different aspects: dose-taking and dose-timing reflected by taking compliance and timing compliance. The two different aspects were defined in this study as follows. Taking compliance is the proportion of days in which the prescribed dose regimen was taken as prescribed or as the proportion of tablets taken. Timing compliance is the proportion of prescribed doses taken within ± 25% of the prescribed interval. Compliance was also calculated by counting the number of pills left in the container and the number of days of delay in getting a refill medication (refill compliance). If the patient was too early for his or her refill the tablets to be consumed were reduced. The therapeutic regimen includes right dose, right frequency, right interval, right time to take the medication, and right duration of drug therapy.[5]

Most health care providers use the term "compliance" instead of "adherence," although these concepts are quite different. Compliance has been defined as the extent to which a person's behavior coincides with medical advice. Adherence has been defined as the active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result.[9,11] This research then uses the term adherence. This study was aimed to determine the adherence of the FDC antituberculosis drugs therapy regimen with indicators including right dose, right frequency, right interval, right time to take the medication, and right duration of drug therapy.

Material and Method

The Ethical Approval for this research was published by the Health Research Ethics Commission, Faculty of Public Health, Universitas Airlangga. Furthermore, research permit were submitted to Surabaya City Health Service. Data collection is carried out for 3 months from July to September 2018. The study population was patients with tuberculosis who received FDC antituberculosis drugs at 63 primary health care centers in Surabaya in July to September 2018. The samples were 249 TB patients who received FDC antituberculosis

drugs at 63 primary health care centers in Surabaya in July to September 2018. The inclusion criteria were TB patient's at least 13 years old (not children), willing to become respondents, communicates well, or are still getting FDC antituberculosis drugs.

Data source of this research was primary data, ie the data collected by the researchers based on the results of the study. This cross-sectional study applied self-reported questionnaire as the research instrument that was administered to a total of 249 TB patients who received FDC antituberculosis drugs at 63 primary health care centers in Surabaya, Indonesia. This questionnaire uses the Guttman scale consisting of statements about patient behavior in taking FDC drugs with five indicators including right dose, right frequency, right interval, right time to take the medication, and right duration of drug therapy. Completing this questionnaire was accompanied by the researcher after the patient received an explanation before approval and filled out informed consent.

Each indicator is described in a favorable statements and unfavorable statement. Favorable statements is the respondent's answer that indicate patient's behavior to support the adherent idea, while the unfavorable statement is not supporting the statement idea. The method of statement measuring of adherence medication indicators questionnaire that each correct answer from favorable statements is worth 1 (yes) and the wrong answer is 0 (no). Each correct answer from unfavorable statements is worth 1 (no) and the wrong answer is 0 (yes). The total value with this data ratio scale is the value of adherence medication indicators from the TB patients. Adherence to therapeutic regimen in TB patients is indicated by a total score of 10 of self-reported questionnaire. Non-adherence is indicated if the total score is less than 10. Each indicator with favorable statements and unfavorable statements has a minimum value of 0 and a maximum value of 2. Data analysis of the study was carried out using Statistical Product and Service Solutions (SPSS) version 18 for Windows.

Findings

In 63 primary health care centers in Surabaya, Indonesia, there were 173 (69.48%) patients of total 249 TB patients in productive age of <20-50 years. The data are in line with those in the literature that about 75% of the productive age group suffer from tuberculosis. Productive age group is people who belong to economically productive workforce.[5,6] Mapping in 249 TB patients in this study showed that 125 (50.20%) patients who received 4-FDC antituberculosis drugs and 124 (49.80%) patients who received 2-FDC antituberculosis drugs.

Table 1. Demographic data of TB patients respondents at primary health care centers

Characteristics of TB patients respondents	**n (%)** *N=249*
Sex Female Male	 110 (44.18%) 139 (55.82%)
Age Productive age (< 20 – 50 years) Non-productive age (>50 years)	 173 (69.48%) 76 (30.53%)
Education No formal education Not finishing elementary Elementary school Junior high school Senior high school Higher education	 8 (3.21%) 7 (2.81%) 51(20.48%) 47 (18.88%) 119 (47.79%) 17 (6.83%)

Cont... **Table 1. Demographic data of TB patients respondents at primary health care centers**

Occupation Unemployed Students Household mothers Government employees Private workers Entrepreneurs	 40 (16.06%) 21 (8.43%) 52 (20.88%) 3 (1.20%) 64 (25.70%) 69 (27.7%)
TB Drug Stages Intensive Stage (4-FDC antituberculosis drugs) Advanced Stage (2-FDC antituberculosis drugs)	 125 (50.20%) 124 (49.80%)

Table 2. Measurement of indicators of FDC antituberculosis drugs therapy regimen in TB patients respondents

Indicators of FDC antituberculosis drugs therapy regimen	Achievement Score (N=249)				Number of TB patients with a total score of 10	Percentage
	Min.	Max.	Mean	SD		
Right Dose	0	2	1,90	0,33	103	41,37%
Right Frequency	0	2	1,79	0,49		
Right Interval	0	2	1,74	0,62		
Right Time to Take The Medication	0	2	1,28	0,85		
Right Duration of Drug Therapy	0	2	1,92	0,32		
Total Score		10				

Adherence to therapeutic regimen in TB patients is indicated by a total score of 10 of self-reported questionnaire. Non-adherence is indicated if the total score is less than 10. Based on research data, there were 103 (41,37%) patients of total 249 TB patients who met the adherence of the FDC antituberculosis drugs therapy regimen with five indicators including right dose, right frequency, right interval, right time to take the medication, and right duration of drug therapy.

Discussion

Mean of indicator of right time to take the medication in 249 TB patients respondents showed the smallest value (1.28 ± 0.85) between five indicators. This means that many TB patients are not taking the FDC antituberculosis drugs caplets in 2 hours before meal or 4 hours after meal on an empty stomach. When taken on an empty stomach, peak rifampicin serum concentrations are achieved within about 2 hours, but if it is ingested with food, absorption is delayed and incomplete.[6,12] Rifampicin is easily absorbed from the gastrointestinal tract. Food consumption, on the other hand, inhibits absorption from the gastrointestinal tract, and the drug is more quickly eliminated. When rifampicin is taken with a meal, peak blood concentration falls by 36%. Antacids do not affect absorption. The decrease in rifampin absorption with food is sometimes enough to noticeably affect urine color, which can be used as a marker for whether or not a dose of the drug has been effectively absorbed.[6,12]

Conclusion

There were 103 (41,37%) patients of total 249 TB patients who met the adherence of the FDC antituberculosis drugs therapy regimen with five indicators. Medication of the FDC antituberculosis drug is not only taken by mouth but must be taken according to the indicator of therapeutic regimen including right dose according to the number of caplets, right frequency as the amounts of TB medicine caplets every time, right interval at the same time every time, right time to take the medication in 2 hours before meal or 4 hours after

meal on an empty stomach, and right duration of drug therapy as scheduled.

Conflict of Interest: Nil

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References

1. Ministry of Health (MoH) RI. Tuberculosis. Jakarta : Kementerian Kesehatan RI.2018 ISSN : 2442-7659.
2. World Health Organization. Global tuberculosis report 2018.Geneva.World Health Organization.2018
3. MoH RI. Indonesian health profile 2017. Jakarta.2019
4. East Java Department of Health. Health Profile. Surabaya.2017.
5. Paes AH, Bakker A, Soe-Agnie CJ. Measurement of Patient Compliance, *Pharmacy World & Science. 2008*. Vol. 20 No.20, p.73-77.
6. Rana F et al.Rifampicin An Overview, International Journal Of Research In Pharmacy And Chemistry, IJRPC 2013, 3(1), ISSN: 2231-2781
7. MoH RI. National Tuberculosis Prevention and control programs.2013.Jakarta
8. MoH RI. *Tuberkulosis, Temukan dan Obati sampai Sembuh*, Infodatin Pusat Data dan Informasi Kesehatan Kementerian Kesehatan RI, Jakarta.2010
9. World Health Organization. *Adherence to Long-Term Therapies*, *Evidence for Action*, World Health Organization.2013 p.123-131.
10. Hussar DA. Patient Compliance, *Remington: The Science and Practice of Pharmacy*, 21st Edition, 2005 p. 1782-1792.
11. Delamater, AM, Improving patient adherence, Clinical Diabetes.2006.24 (2): 71-72, 75-77.
12. Jian Xu, et al. Oral Bioavailability of Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide in a 4-Drug Fixed-Dose Combination Compared With the Separate Formulations in Healthy Chinese Male Volunteers, Clinical Therapeutics.2013.Volume 35, Number 2.