Therapeutic drug monitoring of rifampicin, isoniazid, and pyrazinamide in newly-diagnosed pulmonary tuberculosis outpatients in Denpasar area

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ABSTRACT

Background: Therapeutic drug monitoring (TDM) has the potency to enhance the therapeutic outcome of rifampicin, isoniazid, and pyrazinamide, the backbone of first-line anti-tuberculosis (TB) therapy. The implementation of TDM is understudied for newly-diagnosed lung TB outpatients in the Denpasar area. Aim: To determine the prevalence of low plasma concentration of three first-line anti-TB drugs (rifampicin, isoniazid, and pyrazinamide). Methods: Subjects were newly-diagnosed lung TB adult outpatients from the Denpasar area, aged >18 years old, without comorbidity (HIV or diabetes), not pregnant and not using comedications for at least two days before the test. The subjects received daily anti-TB drugs for at least ten days before the test. SGOT, SGPT, and albumin levels were tested at the time before administration of RHZE 4-FDC tablet. Subjects were tested for plasma concentration at 2 and 6 hours after ingestion of RHZE 4-FDC tablet. Plasma levels of rifampicin, isoniazid, and pyrazinamide were analyzed using HPTLC spectrophotodensitometry method. Results: 28 of 32 subjects had low plasma concentrations of rifampicin, 9 of 24 subjects had low plasma concentrations of isoniazid, 4 of 24 subjects had high plasma concentrations of isoniazid, and 14 of 31 subjects had low levels of pyrazinamide; 3 subjects had plasma concentration of three drugs within the expected range simultaneously. Conclusion: Almost all subjects had low plasma concentration of rifampicin, isoniazid, and pyrazinamide. Only a limited number of subjects had plasma concentration within the target range of the three drugs simultaneously.

Keywords: low levels, first-line antituberculosis, TDM

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INTRODUCTION

Therapeutic drug monitoring (TDM) of anti-tuberculosis (TB) drug facilitates clinicians in decision-making regarding delayed therapeutic response, adverse effects, and toxicity of anti-TB drugs. TDM provides information about individual therapeutic response through concentrations of drugs in body fluids, using blood plasma. TDM explains the incompatibility of anti-TB therapeutic response based on the drug concentration in a subject and the target concentration level. Several studies have shown the contribution of therapeutic drug monitoring to the success of anti-TB therapy.5-9 TDM becomes considerations to optimize current TB treatment,10-15 even for long-term evaluation of TB treatment through doses adjustment. TDM practice of anti-TB drugs is hoped to reach a greater population, not only to the drug-resistant and high-risk population, but also the patients receiving the first-line regimen of anti-TB drugs. The success in implementing therapeutic drug monitoring in countries with a high burden of TB is very beneficial because it will give significant contributions to the increasing success of TB treatment nationally or globally.

The practice of TDM in TB treatment in Indonesia is not common yet. However, several studies of TDM related to the suboptimal dose of rifampicin, isoniazid, and pyrazinamide, and the potency of high dose rifampicin use16 and other studies for the population in Jakarta and Bandung have been published.17-20 All of those are the means to optimize TB treatment. If the TDM of anti-TB drugs can reach a broader population, including outpatient pulmonary Tuberculosis in the Denpasar area, the information regarding dose-adequacy related to individual anti-TB drugs response may be optimized.

Denpasar municipality is an area in Bali with very high population density dan high population migration mobility. The TB case-finding in Denpasar reaches 115.94 (per 100,000 population) in 2015,21 and there is no information regarding
the therapeutic dose of RHZE four fixed-dose combinations (4-FDC) drugs. The TB outpatients were selected as study subjects as they constituted the highest proportion in the community. Another inclusion criterion is newly-diagnosed patients, as optimizing first-line therapy regimen is essential. Rifampicin, isoniazid, and pyrazinamide are the primary anti-TB drug combination, with the best effectiveness compared to other anti-TB drugs, although their adverse effects are hard to be avoided. The proper administration of rifampicin, isoniazid, and pyrazinamide without waiting for the slow therapeutic response or the toxicity, even though it results in added cost, is an effort of efficiency. The treatment cost, as well as therapeutic success in TB with sensitive mycobacteria, can be predicted earlier through therapeutic levels and response monitoring of the drugs. Therefore, TDM needs to be prepared so that in time it can be integrated into the TB management. This study is aimed to determine the proportion of subjects who receive lower or outside the range of therapeutic levels, and those who receive therapeutic levels recommended for or rifampicin, isoniazid, and pyrazinamide, both as single or combination dose using current dose regimens for newly-diagnosed lung TB outpatients in Denpasar area. Descriptions were obtained through TDM, which is assumed to be taken from the peak phase (2 h) and the time of absorption complete (6 h) in the subjects after administration of RHZE 4-FDC standard dose recommended by national TB management program.

MATERIALS AND METHODS

Study Subjects

The subjects of this study were newly-diagnosed pulmonary TB outpatients from the Puskesmas (Community Health Center) Denpasar Selatan I, Denpasar Barat I, Denpasar Barat II, Denpasar Utara I, Denpasar Timur I, Kuta I, and pulmonary outpatient clinic of Sanglah Hospital Denpasar. All locations are in the Denpasar area, except Puskesmas Kuta I. The research was conducted during the 2012-2013 period and January-October 2017 with permission from the Research Ethics Commission of the Medical Faculty of Udayana University/Sanglah Hospital Denpasar No: 08/UN.14.2/Litbang/2013 and No: 280/UN.14.2/KEP/2016. All study subjects were aged >18 years, did not suffer from other diseases (HIV, DM), and were not breastfeeding or pregnant. All subjects were given permission from the Research Ethics Commission of the Medical Faculty of Udayana University/Sanglah Hospital Denpasar No: 08/UN.14.2/Litbang/2013 and No: 280/UN.14.2/KEP/2016. All study subjects were aged >18 years, did not suffer from other diseases (HIV, DM), and were not breastfeeding or pregnant. All subjects were given information and asked to participate in the study by signing informed consent. All subjects underwent fasting at least 10 hours before sampling, and they were allowed to drink water and eat ordinary food 2 hours after taking the drug in the morning. The subjects were given standard RHZE 4-FDC for TB treatment provided by the government as part of the national tuberculosis control program. The diagnosis was made based on the results of sputum and pulmonary X-rays. The drug dosage was given according to the standard dose recommended by their physician. Data on age, body weight, dosage regimen, dose and time of taking medication, and clinical data of SGOT, SGPT, and albumin were taken before taking the medication on the day of blood sampling. Clinical laboratory testing was carried out in an ISO certified clinical laboratory.

Collection and storage of serum samples

Blood samples were taken from the cubital vein, 2 and 6 hours after taking RHZE 4-FDC tablets. The subjects were in the initial phase of treatment and had received at least 10 doses of medication. Samples were collected in a lithium heparin tube using 3 ml syringes. Samples were left for <30 minutes at 2-8°C and centrifuged at 3000 rpm for 15 minutes. The supernatant was taken and collected in an Eppendorf tube to be stored at -20°C until the process of sample analysis.

Sample analysis

The serum concentration levels of rifampicin, isoniazid, and pyrazinamide were determined using HPTLC Spectrophotodensitometry CAMAG method in Forensic and Analysis Laboratory of Udayana University using 10x10 cm Merck HPTLC RP-18 WF plate, horizontally eluted with eluent combination of ethanol : water : glacial acetic acid : diethylamine : ammonia 25% (9.5 : 0.35 : 0.5 : 0.1 : 0.15). The measurement was done at a wavelength of 274 nm.

Data analysis

Characteristics of the study subjects and dosage regimen information were described using Microsoft Excel to simply calculate descriptive statistics and create graphs of the proportion of subjects, mean values with standard deviations, or medians with a range of minimum and maximum values. Drug levels were described as the distribution of levels with the median and minimum and maximum range of values for each sampling time at $t_2$ and $t_6$ compared to the reference values.7

RESULTS

Thirty-two newly-diagnosed lung TB outpatients participated in this study. They were diagnosed by physicians based on chest X-ray and or microbiological examination. Most of the patients were
female [n = 18 (56%)]. The median age of the subjects was 33.5 years (range 19-56 years). Ten subjects were within 19-24 years old, eight subjects were within 25-34 years, and ten subjects were within 35-44 years old.

The mean body weight was 49.6 kg (range 37.5-78.5 kg), mean body mass index (BMI) was 19.7 kg/m² (range 15.03-33.71 kg/m²), mean albumin was 3.9 g/dL (range 2.7-4.6 g/dL), mean SGOT was 21.9 U/L (range 10-63 U/L), and mean SGPT was 19.7 U/L (range 6-67 U/L). The subject characteristics are summarized in Table 1.

Eighteen subjects had BMI <18.5 kg/m², three subject with albumin <3.4 g/dL, four subject with SGOT >33 U/L, and one subject with SGPT >50 U/L. All the subjects did not have co-medications in 2 days before the study. Nine subjects presented minor adverse drug effect such as nausea, vomiting, stomach pain, and or abdominal discomfort.

Dose evaluation
Determination of RHZE 4-FDC tablets dose was based on body weight and consideration of the subject condition at the time of diagnosis. If the dose for each combination drugs were taken into account, then all subjects got an average rifampicin dose of 10 mg/kg (range 7.8-12.2 mg/kg), average isoniazid dose of 5 mg/kg (range 3.9-6.1 mg/kg), and average pyrazinamide dose of 26.7 mg/kg (range 20.8-32.4 mg/kg) as presented in Table 1. One of two subjects received an inappropriate dose of RHZE 4-FDC tablet. The subject was weighed 38.5 kg, received a low dose of two tablets, but experienced side effects such as nausea, vomiting, and epigastric pain from the initial two days of therapy. From dosage calculation, it was found that the patient received low doses of rifampicin (7.8 mg/kg) and isoniazid (3.9 mg/kg).

On the other hand, the other subject received an excessive dose of three tablets for 37 kg body weight but did not experience any side effects. From dosage calculation, the patient received excessive doses of rifampicin (12.2 mg/kg), isoniazid (6.1 mg/kg), and pyrazinamide (32.4 mg/kg). Proper dosing of the tablet also proved to be inaccurate in calculating the individual dose of pyrazinamide. Subjects weighed 38 kg and 37.5 kg each received three tablets and received 31.6 mg/kg and 32 mg/kg dose of pyrazinamide respectively. In general, the proportion of subjects who received the appropriate dose of combination and individual anti-TB tablets were 94% for rifampicin, 92% for isoniazid, and 90% for pyrazinamide.

Rifampicin, isoniazid, and pyrazinamide plasma level
There were 64 plasma samples from 32 subjects; each were taken twice in t₀ and t₆. The drug plasma levels were measured simultaneously using HPTLC Spectrophotodensitometry method. Rifampicin was detected in 63 samples, isoniazid was detected in only 38 samples from 24 subjects, and pyrazinamide was detected in 61 samples from 31 subjects. Distribution of rifampicin, isoniazid, and pyrazinamide levels in t₀ and t₆ are described in Figure 2, Figure 3, and Figure 4.

The administration of standard dose RHZE 4-FDC tablet (rifampicin: 8-24 mg/L, isoniazid: 3-6 mg/L, and pyrazinamide: 20-50 mg/L) did not result in drug plasma level within the target range simultaneously in most subjects as described in Figure 1. Rifampicin showed the lowest target level in almost all subjects, followed by isoniazid and pyrazinamide. The median rifampicin target level at t₀ was 5.74 mg/L (range 1.33-11.83 mg/L) and at t₆ was 4.76 mg/L (1.96-12.29 mg/L). The median isoniazid target at t₀ was 3.68 mg/L (range 0.32-22.68 mg/L) and at t₆ was 3.62 mg/L (range 0.31-38.09 mg/L). The median pyrazinamide median target at t₀ was 21.12 mg/L (range 0.03-33.96 mg/L) and at t₆ was 16.43 mg/L (0.21-25.47 mg/L). There was a wide levels variation in both t₀ and t₆ for all three drugs after administration of RHZE 4-FDC tablets.

DISCUSSION
Monitoring of rifampicin, isoniazid, and pyrazinamide levels in newly-diagnosed lung TB outpatients in the Denpasar area aims to evaluate the current dosing regimen more accurately. The data on drug level is beneficial for clinicians in considering...

Table 1  Subject characteristics and dose information

| Characteristics                  | N  | Number (%) Female | Age (yr) [median(range)] | Weight (kg) [mean(SD)] | Body Mass Index (kg/m²) [mean(SD)] | Albumin (g/dl) [mean(SD)] | SGOT (U/L) [mean(SD)] | SGPT (U/L) [mean(SD)] | Rifampisin dose (mg/kg) [mean(SD)] | Isoniazid dose (mg/kg) [mean(SD)] | Pyrazinamid dose (mg/kg) [mean(SD)] |
|---------------------------------|----|------------------|--------------------------|------------------------|-----------------------------------|--------------------------|----------------------|------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| N                               | 32 | 18 (56%)         | 33.5 (19-56)             | 49.6 (9.7)             | 19.7 (4.3)                        | 3.9 (0.45)               | 21.9 (10.8)          | 19.7 (13.1)            | 10 (1.1)                          | 5 (0.6)                           | 26.7 (3.0)                        |

Notes: SGOT: serum glutamic oxaloacetate transaminase; SGPT: serum glutamic pyruvate transaminase; SD: standard deviation
to establishing an individual anti-TB dose regimen. Therefore, the main purpose of anti-TB treatment can be achieved, which is optimizing the therapy effect and minimizing its toxicity.\textsuperscript{3,15}

The results of anti-TB drug levels monitoring in this study are in accordance with other studies,\textsuperscript{22–24} which also showed results of suboptimal levels in most subjects after the administration of the standard RHZE 4-FDC dose. Although >90\% of subjects have received standard doses, the drug concentration levels on the subjects were very variable and mostly had suboptimal levels. The distribution of plasma rifampicin, isoniazid, and pyrazinamide levels at two sampling times as presented in Figure 2, Figure 3, and Figure 4 theoretically put the subject in suboptimal, optimal, and toxic levels. This condition is clearly shown in the description of the isoniazid levels distribution at $t_2$ and $t_6$ for each drug after administration of anti-TB combinations drugs. In both rifampicin and pyrazinamide, there were no subjects that showed plasma levels above the maximum target range or toxic levels. For rifampicin, most subjects [n=28 (87\%)] showed plasma levels below the target range of 8-24 mg/L. As for pyrazinamide, there were 14 subjects (45\%) with plasma levels below the target range. Only three subjects reached the target range of plasma levels of rifampicin, isoniazid, and pyrazinamide simultaneously. This results indicated the need for anti-TB dose adjustments.

Most subjects did not reach the target range of plasma levels of the three drugs simultaneously. This result is identified as the use of a single drug or suboptimal combination drug that is not recommended in the treatment of new tuberculosis. Theoretically, dose adjustment can be made until the target level is reached. However, dose adjustment must be made carefully as the results showed an extensive variation in plasma concentration, especially in isoniazid. The administration of standard dose results in plasma concentration above the maximum levels as in four subjects, while the administration of low dose in one subject results in plasma concentration within the target range and adverse drug effects. In such conditions, dose adjustments must be made by monitoring individual drug levels. Variations in drug levels are related to individual pharmacokinetic variations, characteristics, and disease conditions affecting the pharmacokinetics of isoniazid, rifampicin, and pyrazinamide.\textsuperscript{27–30}

Low levels of rifampicin, isoniazid, and pyrazinamide in most subjects can be associated with low body weight, malnutrition, and low immune conditions.\textsuperscript{13,28,29} The food consumed 1 hour or 2 hours after taking medication also affect the drug absorption, even though the subjects were fasting before taking medication. Rifampicin is absorbed optimally on an empty stomach.\textsuperscript{29–31} However, food consumption is needed to reduce complaints of nausea and epigastric pain.

Research conducted by Chun Lin et al. showed that ingestion of food after taking fixed-dose combinations caused a decrease in the mean peak plasma level ($C_{\text{max}}$) and a delay in reaching the maximum level ($T_{\text{max}}$) of the three anti-TB drugs.\textsuperscript{33,34,36} The delayed time to reach the maximum levels is indicated by the shift in peak levels from the estimated 2\textsuperscript{nd}-hour hour to 6\textsuperscript{th}-hour and the absorption disturbance observed from the 2\textsuperscript{nd}-hour and 6\textsuperscript{th}-hour levels which were not too different.\textsuperscript{13,15} Reduction in rifampicin levels can also be attributed to the use...
of fixed-dose combinations resulting in interaction between isoniazid and rifampicin or isoniazid and pyrazinamide simultaneously. Rifampicin is unstable in the presence of isoniazid.33,34

Adverse drug effects such as nausea and vomiting in some subjects could be associated with the use of drug combinations, given that rifampicin, isoniazid, and pyrazinamide are hepatotoxic. This condition in our subjects could appear earlier, on the 2nd day until the 2nd week of therapy. Another publication states that the drug effect could appear >1 week after the start of therapy.26,36 There was no intervention of delaying therapy, dose adjustment, or therapy replacement in our subject during the therapy period as there was no increase in the SGPT and SGOT values. Monitoring the adverse drug effects during anti-TB therapy require regular laboratory tests of SGPT, SGOT, and bilirubin. Clinical examinations, mainly related to icterus signs, may suggest a temporary delay of the therapy and even therapy replacement.26,36,39

The results of our study are quite interesting even though we used a limited number of subjects and did not represent the number of the existing newly-diagnosed lung TB patients. The use of more subjects with a more extended period of observation with cohort research will undoubtedly provide more comprehensive information related to the therapy follow-up to improve the success of anti-TB therapy. However, at least the results of this study can complement several other studies related to the use of rifampicin, isoniazid, and pyrazinamide in Indonesia, and in Denpasar particularly.17,18,35–37 This study implies that the use of standard doses in TB subjects needs to be confirmed through more extensive therapeutic drug monitoring during the treatment period, especially in subjects at risk of experiencing adverse drug effects due to low body weight. However, dose adjustment in the subjects of newly-diagnosed lung TB must be made as early as possible to get the maximum effect of the drug and minimum adverse effect of the drug through liver function monitoring. In addition to the patients’ clinical condition, the results of therapeutic drug monitoring are the benchmarks for adjusting the dose of rifampicin, isoniazid, and pyrazinamide. The optimal response to anti-TB therapy cannot be achieved only through the administration of adequate doses, but also requires information on the drug levels obtained from therapeutic drug monitoring.

In summary, suboptimal levels have been observed in most subjects. Only a small number of subjects showed isoniazid levels above the target range even though they had received a standard dose of RHZE 4-FDC tablets. Adverse drug effects could occur in subjects that reached the target level of drugs. Our findings of suboptimal levels for rifampicin, isoniazid, and pyrazinamide, and maximum levels of isoniazid, and the adverse effects of these drugs was difficult to predict but proven to exist. Suboptimal levels and levels above the maximum target have been stated to increase the risk of therapeutic failure, recurrence, and development of resistance.42,43 To get an optimal anti-TB effect, adequate drug level are needed for rifampicin, isoniazid, and pyrazinamide simultaneously. Four (16.7%) subjects showed isoniazid plasma levels

Figure 3 Isoniazid plasma in 2 hours and 6 hours after administration of RHZE 4-FDC tablet with median and range (minimum-maximum) value. Nine of the 24 subjects had lower plasma levels, but four of 24 subjects had higher plasma levels than the target range. There were only 11 of 24 subjects that had isoniazid plasma level within the target range.

Figure 4 Pyrazinamide serum level in 2 hours and 6 hours after administration of RHZE 4-FDC tablet with median and range (minimum-maximum) value. There were only 17 of 31 subjects that had serum levels within the target range, and 14 of 31 subjects had lower pyrazinamide serum level than the minimum target range.
above the maximum range of target levels. Only three people showed adequate levels of all three drugs simultaneously.

CONCLUSION

Most subjects who had received the standard dose of RHZE 4-FDC tablets did not reach the drug plasma concentration within the target range. Four subjects had isoniazid plasma level above the maximum target range. Only three subjects had drug plasma level within the target range of the three drugs simultaneously. Failure to reach the target plasma level of combination drug can increase the risk of treatment failure, recurrence, or the emergence of resistance.

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DISCLOSURE

The author reports no conflicts of interest in this work.

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