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The Impacts of MDR1^{C3435T} Gene Polymorphism towards Plasma Rifampicin Levels in Javanese Pulmonary Tuberculosis

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Abstract

Rifampicin, one of the primary tuberculosis drugs, is a PGP substrate that is encoded by MDR 1 gene. The objectives of the research was to study the impacts of MDR1^{C3435T} gene polymorphism toward plasma rifampicin levels in Javanese patients with pulmonary tuberculosis. The subjects of this research are Javanese tuberculosis patients treated by fixed dosage combination (FDC) of anti-tuberculosis drugs containing rifampicin. There were 74 patients. The examination of MDR1^{C3435T} was conducted by employing restriction fragment length polymorphism (RFLP-PCR) method. Blood samplings to assays the rifampicin level were done on day 1; 4; 28; and 56. The measurement of rifampicin levels was done by high performance liquid chromatography (HPLC) method. There are significant difference on the level of plasma rifampicin between MDR1^{C3435T} CC, CT and TT with p <0,05. The polymorphism of MDR1^{C3435T} TT gene increase plasma rifampicin levels in Javanese patients with pulmonary tuberculosis.

Keywords: Polymorphism, MDR1^{C3435T}gene, rifampicin

INTRODUCTION

Therapeutic level of a drug is influenced by many factors. One factor that becomes the focus of attention is gene polymorphisms. Genetic polymorphisms may affect the pharmacokinetic profile of drugs include absorption, distribution, metabolism and elimination. These polymorphisms may cause sub therapeutic levels of drugs or upper therapeutic levels. The sub therapeutic levels of drugs can failure of the treatment. On the other hand, upper therapeutic levels will create excessive side effects. Some group tuberculosis patients were treated by isoniazid (INH) will deference responses. In individuals with rapid acetylates, blood INH levels are only about 30-40% of individuals with slow acetylates (Petri, 2006). These levels may be below therapeutic levels. Therefore, it will contribute to the failure of tuberculosis treatment.

Rifampicin is one of the main anti tuberculosis drugs (ATD). The others are Isoniazid, Ethambutol, Pyrazinamide, and Streptomycin (MOH, 2006). Rifampicin is a substrate of a PGP (P-glycoprotein) (Prakash et al., 2003). PGP is a xenobiotic pump which effluxes its substrate back into the lumen intestinal. PGP is important in the process of absorption, distribution and elimination of its substrate drug (Zang & Benet, 2001; Prakash et al., 2003). PGP is encoded by a multi-drugs resistant-1 gene (MDR-1) (Brinkmann & Eichelbaum, 2001; Prakash et al., 2003; Hwan et al., 2009; Sabahi et al., 2010). MDR-1 gene polymorphism causes a change of expression on PGP formation. One of the MDR-1 polymorphisms Gene is MDR1^{C3435T}. MDR1^{C3435T} TT is the type of MDR with low expression (2x lower than CC), while the CC type has a high expression. This leads to the expression of PGP MDR1^{C3435T} TT about 25%, CT 48% and 62% CC (Hoffmeyer et al., 2003). MDR1^{C3435T} TT causes a slight formation of PGP on the intestinal villi (Brinkmann & Eichelbaum, 2001; Hwan et al., 2009). Drug inhibition by PGP will cause drug levels in PGP substrate becomes higher. An example of this case is the treatment with verapamil, a PGP block, will increase rifampicin levels, which is the substrate of the PGP (Prakash et al., 2003). Polymorphisms changes expression of PGP that alter kinetic profile of rifampin (Pechandova et al., 2006). MDR1^{C3435T} gene is one of the common polymorphisms found in Asia. A research conducted by Li *et al*, 2006 shows the distribution of MDR1^{C3435T} in Malaysia are as follows: MDR1^{C3435T} CC genotype (25%), CT (46%) and TT (28%) (10). This research explore the impact of polymorphism of MDR1^{C3435T} toward blood rifampicin levels on Javanese tuberculosis patients

MATERIALS AND METHODS

Patients

Seventy four adult pulmonary tuberculosis with inclusion criteria: new cases of positive acid fastness bacteria; being in the intensive phase of treatment with anti-tuberculosis drugs (ATDs) fixed dose combination (FDC); Routinely consuming ATDs FDC every day; willing to participate in the research by signing a letter of approval to join the research and exclusion criteria: body mass index (BMI) > 23; 2); pregnant; suffering HIV; having hepatic malfunction (SGOT serum > 40 U / mL) and SGPT serum > 30 U / mL); Smokers and Alcoholism; consuming drugs which is inductor and inhibitors of P-glycoprotein. This study was approved by ethic committee of Faculty of medicine of Universitas Gadjah Mada with no KE/FK/32/EC.

DNA isolation

A total of 100µL of cell lysis solution was added in 300 µL of buffy coat samples were incubated 10 minutes.

On room temperature, mix solutions were centrifugated 13.000 for 1 minute. The supernatant discarded, 300 uL solutions was added on the residue. The mixture was vortexed for 10-15 seconds. The result of the mixture was added by 1,5mL of RNA solution, then was vortexed for 10-15 seconds. These mixtures were incubated on 37^0C. The resulting mixture was stored in room temperature and added by *protein presipitation solution* 100 µL, then was vortexed for 10-15 seconds and centrifugated on 13.000 for 3 min on 37^0C. Three hundred (300) µL supernatant was taken and put in 1,5 mL tube then added 300 µL isopropanol. The solution was mixed by inversion until the white treads-like strands of DNA form a visible mass, then was centrifugated on 13.000 for 1 min at 37^0C. The supernatant was discarded and the residue was added 300 uL 70% ethanol. It was mixed a few time and then centrifuged on 13.000 for 1 min on 37^0C. The ethanol was removed by inversion. The residue was added by DNA rehydration solution (100 µL for 300 µL sample volume) and incubated at 65^0C for 60 min. Periodically, the solution is mixed. The samples were store at 4^0C.

Polymerase chain reaction restriction fragment length polymorphism (RFLP-PCR) MDR1^{C3435T}

Total 12,5mL master mix and 6,5 mL dH2O, *forward*: 5'- TTG ATG GCA AAG AAA TAA AGC-3' , 2µL *reverse* 5'-CTT ACA TTA GGC AGT GAC TCG-3') and 2µL DNA (25µL total) was run by PCR. The conditions of amplification as follows: 94^0 C for 5 min, the 40cycles by 30 seconds on 94^0C, 30 seconds on 55^0C, dan 1 min on 72^0C with 5 min final extension at 72^0C. After PCR amplification, 3 µL of PCR + 5µL buffer (2x buffer) with 1 µLMboI enzyme (10U) and 1µL dH_2O (total 10 µL) was digested by 10 U MboI for 16 h at 37^0C. The digested PCR products were analyzed by electrophoresis on 1,5% agarose gel and detected by etidium bromide. The bands of DNA fragments were visualized by UV light (Li et al., 2006)

Determination of rifampicin level:

Determination of rifampicin level was used by employing high performance of chromatography system (HPLC) with reversed phase C-18 column (250nmx0, 4mm, 5µm). The mobile phase are methanol and phosphate buffered PH 7,4 (18,7 mL 0,02M KH_2PO_4 and 80,3mL 0,02M $Na_2HPO_4.2H_2O$) in the rasio 75:25. Detection eluent with UV detector on wave length 475nm, *flow rate* 1,5 mL/min. The retention time is on third minute. The chromatogram was run for 5 min. (Sabitha et al., 2009). The Validation of determination of rifampicin level with HPLC system was done several parametric: selectivity, linearity of standard, limit of detection (LOD) and limit of Quantification (LOQ) and coefficient of variation (CV).

RESULTS AND DISCUSSION

There are 74 subjects' tests who meet inclusion and exclusion criteria. The characteristics of research subject can be seen in table 1.

Table l . The characteristic demographic of research subject (n=74)

Subjects	x±SD
Sex (%)	
- Male	40(53,33)
- Female	35 (46,67)
Age (years)	42,1±16,1
Body weight (kg)	47,1±10,4
Height (cm)	160,8 ±8,3
BMI	17,47±2,6

The result of DNA isolation was performed by PCR (RFLP- PCR). The products digested of PCR-product that analyzed by electrophoresis with 1,5% agarose gel , detected by ethidium bromide can be seen on figure 1.

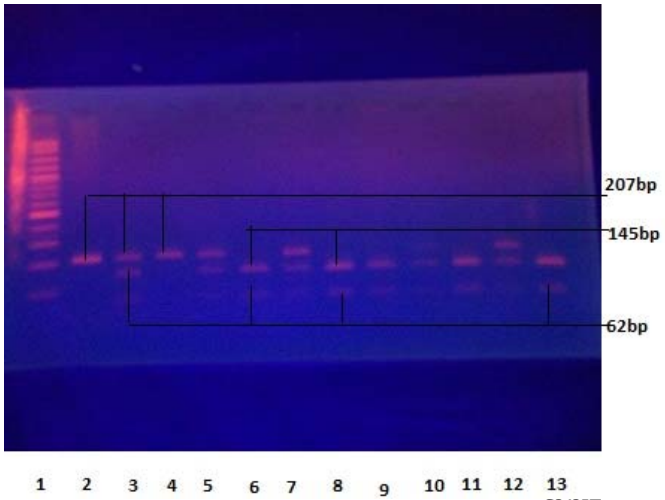

Figure 1. Electrophoresis PCR- product MDR1^{C3435T}was digested by MboI enzyme. Notes:Lane 1. Marker; lane 2. Uncut; lane 3,5,7,12MDR1^{C3435T}CT , lane 4, MDR1^{C3435T}TT, lane6, 8,9,10,11,13 MDR1^{C3435T}CT

From figure, MDR1^{C3435T}CC cut off at 145bp & 62 bp, MDR1^{C3435T}CT cut off at 207 bp, 145bp and 62bp. MDR1^{C3435T}TT not cut off. Frequency of genotype and allele MDR1^{C3435T} shown in the table 2.

Tabel 2. Frequency of genotype& allele MDR1^{C3435T} on subject test (=75)

Karakteristik	Frequency genotype n(%)	Frequency allele
MDR1^{C3435T}		
- MDR1^{C3435T} CC	27(36%)	
- MDR1^{C3435T} CT	40 (53%)	
- MDR1^{C3435T} TT	8(11%)	
- Allel C		0,63
- Allel T		0,37

From the table 2, the frequency of genotype and allele did not deviate from Hardy-Weinberg equilibrium, due to: f(C)+f(T)=1, $nC^2+2nCnT+nT^2=1$. The comparison of this study with research in others countries people can be seen on table 3.

Tabel 3.The comparison of frequency genotype and allele MDR1^{C3435T}this study with research in others countries people.

Population	Frequency	Genotype				Reff.
	C	T	CC	CT	TT	
French	0,57	0,43	0,36	0,42	0,22	(Anglicheau et al., 2003)
German	0,52	0,48	0,27	0,48	0,24	(Hoffmeyer et al., 2003)
China	0,56	0,17	0,32	0,48	0,2	(Li et al., 2006)
Japanese	0,61	0,39	0,35	0,53	0,12	(Sakaeda et al., 2001)
Saudi	0,55	0,45	0,37	0,38	0,26	(Ameyaw et al., 2001)
Spain	0,52	0,48	0,26	0,52	0,22	(Bernal et al., 2003)
German	0,52	0,48	0,27	0,48	0,24	(Hoffmeyer et al., 2003)
Malaysia	0,48	0,52	0,25	0,46	0,28	(Balram 2003)
India	0,38	0,62	0,25	0,46	0,28	(Balram 2003)
Javanese	0,64	0,36	0,38	0,52	0,10	This study

‘’’

Chromatography

Selectivity was done by compare blank with rifampicin standard. The result of the assay are: the retention time of rifampicin 3,169 minute with regression linear Y=13691,33+3351,524 and coefficient of correlation linier (R^2) is 0,993. Limit of detection (LOD) is 0,078 µg/mL. Limit of quantitation (LOQ) is 0,26 µg/mL. Coefficient of variation (CV) rifampicin standard on 10 and 20 µg/mL are 1,39% and 0,12%.

The mean of rifampicin level from subject test can be seen in table 4

Table 4. The mean of rifampicin level on day 1; 14; 28 and 56 and percent of sub therapeutic level of rifampicin

Day	Mean (µg/mL±SD)	sub therapeutic level (<4 µg/mL) (%)	Number of subject (n)
1	4.11±1.43	52,7%	74
14	3.92±1.64	50,7%	71
28	3.68±1.72	51,5%	68
56	3.59±1.82	58,2%	67

The mean of rifampicin level from subject test each MDR1^{C3435T} gene can be seen in Table 5.

Table 5.The mean of rifampicin level each MDR1^{C3435T} gene

Gene	Mean on day 1 (µg/L±SD)	Mean on day14 (µg/mL±SD)	Mean on day 28 (µg/mL±SD)	Mean on day56 (µg/mL±SD)
MDR1^{C3435T} CC	3,61±1,68	3,44±1,60	3,20±1,08	3,26±1,07
MDR1^{C3435T} CT	4,31±1,26	4,31±1,25	4,29±1,36	4,21±1,57
MDR1^{C3435T} TT	4,72±0,93	5,11±1,16	5,16±1,08	4,95±1,14

The statistic test with anova, LSD and regression linier were used to analyze difference of rifampicin level from each MDR1^{C3435T} gene.

Rifampicin level on 2 hours after taking drug can be classified into: toxic level (>20µg/mL); therapeutic level (8-20 µg/mL); low therapeutic level (4-8µg/mL); and sub-therapeutic level (<4µg/mL) (17). In this research, it is found that the average of rifampicin level on the 1st day is in low therapeutic level (4.11±1.43). The average in the 14th, 18th, and 56th day are in sub-therapeutic level (<4µg/mL). On Febrinasari research in 2010, it was revealed that the average of rifampicin level of tuberculosis patients in 2 hours after taking the drug is 4.12±0.46 4µg/mL in 56th day (Febrinasari, 2010). Other research conducted by Van Crevel *et al.* stated that about 70 % tuberculosis patients in Indonesia carried out sub-therapeutic rifampicin level (<4µg/mL), whereas toxic level was not found (Van Crevel et al., 2002). In the research, in 56th day after ATDs are given about 60 % tuberculosis patients have sub-therapeutic rifampicin level. Narita *et al.* in her research in 2001 in a hospital in Florida found that 60% patients treated by ATDs have rifampicin and isoniazid level less than the standard (Narita et al., 2001). The factors that may cause this includes the low drugs manufacturing quality (Van Crevel et al., 2002) and low dosage of rifampicin given to the patient (it is only 10mg/kg bb) (Alisjahbana, 2006). The research was done by Nijland *et al.* found C_{max} of blood rifampicin of tuberculosis patients in Indonesia was 6.74 mg/L (Nijland , 2006).

The rifampicin level in MDR1^{C3435T}TT gene group is higher than MDR1^{C3435T}CC or heterozygote MDR1^{C3435T} CT group. This happens because MDR1^{C3435T} TT causes little PGP formation in villi intestinally (Brinkmann & Eichelbaum, 2001; Hwan et al., 2009). The PGP was encoded by MDR1 gene. An individual with MDR1^{C3435T} TT has lower PGP expression than an individual with MDR1^{C3435T}CC (Larsen et al., 2007; Miladpoor et al., 2011). Rifampicin is one of PGP substrates (Greiner et al., 1999; Prakash et al., 2003; Pechandova et al. 2006; Hong et al., 2006). Thus, an individual with low PGP expression (MDR1^{C3435T}TT) will have higher plasma rifampicin level.

The relation between polymorphism of MDR1^{C3435T}gene and rifampicin level in the 1st, 14th, 28th, and 56th day is tested by analysis of variant (ANOVA). On ANOVA test, it is found that among the MDR1^{C3435T} gene variants have significant differences on the rifampicin level in the 1st, 14th, 28th, and 56 day. There are some researchers conducted to study the impact of MDR1^{C3435T}gene polymorphism toward PGP expression and kinetic profile. Hoffmeyer *et al*., in their research found that MDR1 gene polymorphism influence PGP expression and its function (Hoffmeyer et al., 2003). Other research found MDR1^{C3435T} TT causes little PGP formation in villi intestinal (Brinkmann & Eichelbaum , 2001; Hwan et al, 2009).

Researches on the influence of MDR1^{C3435T}gene variant toward pharmacokinetic and pharmacodynamics generate different results. Research by Hoffemeyer was done in 2003, concluded that PGP expression in intestinal on individual with MDR1^{C3435T}TT type two times lower than CC type. This condition cause level of digoxin in TT type higher than in CC type (Hoffmeyer et al., 2003). The $AUC_{0\text{-}4\ jam}$ (P, 0.42) and C_{max} (P.0.43) digoxin is greater in MDR1^{C3435T} TT than in MDR1^{C3435T}CC (Johne et al., 2002).

A meta-analysis shows that there is no influence of MDR1^{C3435T}polymorphism to $AUC_{0\text{-}4}$ h and $AUC_{0\text{-}24}$h digoxin, though the analysis shows C_{max} in MDR1^{C3435T} TT type is lower than in MDR1^{C3435T} CC (Balram et al., 2003). On the contrary, Von Ahsen *et al.* stated there is no different effect of cyclosporine drug on the individual with either MDR1^{C3435T} TT or CC (Von Ahsen et al., 2001).

A research was done by Hou *et al.*, 2010 showed there is no significant relation between the ratio of dosage/ concentration and side effect of tacrolimus given to patient with MDR1^{C3435T} polymorphism undertaking kidney transplant (Hou et al., 2010). In a research conducted by Buzoianu *et al*, found that plasma valproate levels on patient suffering epilepsy for CC: TT type are 59.14±17.9:76.07±26.32 µg/mL (Buzoianu et al., 2011). Meanwhile, Guo *et al*, in their research, found that there is no difference on C_{max}, T_{max}, AUC (0-48) and Cl (*clearance*) among 40 mg terlmisartan given to healthy individuals (Guo et al., 2009). The research by Strother *et al* resulted the individuals with MDR1^{C3435T} TT have volume of distribution of epotosida smaller than individuals with MDR1^{C3435T} CT and CC (Strother et al., 2008).

In the research, we find differences of rifampicin level between individuals with MDR1^{C3435T} CC and CT. This happened in the 14th;28thand 56th day. Transport of Rifampicin is influenced by PGP that encoded by MDR1. In MDR1^{C3435T} TT type, there is cytosine substitution by thymine. In fact, the substitution does not change amino acid (Ile145Ile), but in this research, there is significant influence of MDR1^{C3435T}gene toward rifampicin levels. The Statistic analyses were done by analysis of varian (ANOVA). There are significant difference on plasma rifampicin level between MDR1^{C3435T} CC (3,44±1,60 µg/mL) and MDR1^{C3435T} CT (4,31±1,25 µg/mL) (p.0,016) ; MDR1^{C3435T} CC (3,44±1,60 µg/mL) and MDR1^{C3435T} TT (5,11±1,16 µg/mL) (p. 0,006) on day 14; between MDR1^{C3435T} CC(3,20±1,08 µg/mL) and MDR1^{C3435T} CT (4,29±1,36 µg/mL) (p. 0,001); MDR1^{C3435T} CC(3,20±1,00 µg/mL) and MDR1^{C3435T} TT (5,16±1,08 µg/mL) (p. 0,006) on day 28 and on day 56 between MDR1^{C3435T} CC(3,26±1,07 µg/mL) and MDR1^{C3435T} CT (4,21±1,57 µg/mL) (p. 0,013), between MDR1^{C3435T} CC (3,26±1,07 µg/mL) and MDR1^{C3435T} TT (4,95±1,14 µg/mL) (p.0,010).

The relation between polymorphism in MDR1^{C3435T}and PGP expression is not clear. Some assumptions emerge, i.e. 1). The Cytosine or Thymine which encodes isoleusin located at wobble position (Morita et al., 2003; Huo et al., 2010); 2). Silent mutation in MDR1^{C3435T} might decrease the effectiveness of translation (Schwab et al., 2003); 3). There is a changes translation process in mRNA (Allain et al., 1996; Wang et al., 2005); 4). There is modification post transcription or it might relate to important sequence in mRNA process (Jamroziak et al., 2002). These changes affect the formation/ expression of PGP that influence blood rifampicin levels.

CONCLUSION

The polymorphism of MDR1^{C3435T} TT gene increase plasma rifampicin levels in Javanese patients with pulmonary tuberculosis.

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