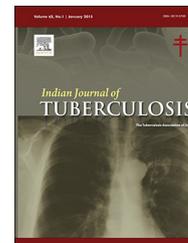


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Original Article

CYP2E1 polymorphism, acetylator profiles and drug-induced liver injury incidence of Indonesian tuberculosis patients

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ABSTRACT

Objective: A polymorphism of CYP2E1 may be directly associated with the development of INH hepatotoxicity. We conducted this study to evaluate the association between polymorphisms of CYP2E1, Isoniazid (INH) concentration and the acetylator status of INH in cases of Indonesian tuberculosis patients with drug-induced liver disease (DILI).

Methods: We conducted our study with a cohort design consisting of 55 Indonesian adult tuberculosis (TB) patients. Acetylating phenotypes were studied in using the metabolic ratio of plasma ACHZ/HZ. DILI was defined using CTCAV version 4.0. The allelic and genotypic frequency distributions of CYP2E1 rs 3813867 were studied using the polymerase chain reaction – amplification refractory mutation system (ARMS) methodology.

Results: Patients with an INH concentration of more than 7 µg/mL showed a higher risk of developing DILI when compared with patients who showed a therapeutic range of 3–6 µg/mL INH (OR: 1.3, 95% CI: 0.2–8.2). Slow acetylators had a higher incidence of DILI when compared with rapid acetylators (OR: 4.6, 95% CI: 1.3–15.9). Meanwhile, subjects with GC had a higher risk of DILI incidence (OR: 4.3, 95% CI: 0.8–24.4).

Conclusion: Our study shows that polymorphisms of CYP2E1 and slow acetylator may have role in the DILI incidence.

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1. Introduction

In 2015, the tuberculosis (TB) prevalence in the world reached 42% lower than in 1990. In 2014, of the 9.6 million of TB incidence, 58% were from South-East Asia and Western-Pacific

region. Still, India, Indonesia and China had the largest number of cases from global total number (23%, 10% and 10%, respectively). The treatment success rate for newly diagnosed TB patients reached 86% in 2013 which was still sustained since 2015.¹ Treatment success is the key outcome of TB burden reduction. Some factors may influence the

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treatment success of TB, like hospital facilities, staffing education, population covered and centralized or decentralized health care system.²

The TB treatment regimen is a four-drug combination consisting of isoniazid (INH), rifampicin (R), pyrazinamide (Z), and ethambutol (E). This anti-tuberculosis therapy can cause adverse drug events. The most commonly reported adverse drug event of anti-tuberculosis drugs is hepatotoxicity.³⁻⁵ Among these compounds, isoniazid (INH) strongly associated with anti-tuberculosis drug-induced hepatotoxicity (ATDH) or drug-induced liver injury (DILI). Previous reports showed INH induced liver injury or hepatotoxicity in approximately 5% of patients.⁴⁻⁶ Other studies showed the development of ATDH in approximately 1 to 36% of patients.^{7,8} INH is metabolized by *N*-acetyltransferase-2 (NAT-2) into acetylisoniazid. Next, the metabolite is hydrolysed to acetylhydrazine (AChZ) and hydrazine (HZ) by hepatic *N*-acetyltransferase-2 (NAT-2).⁹ These compounds are then oxidized by cytochrome P450 2E1 (CYP2E1) to form intermediate hepatotoxins.^{10,11}

There are large variations in the metabolism of the antituberculosis drug isoniazid, including polymorphisms of the NAT-2 gene. This enzyme is markedly decreased in the livers of slow acetylators (SA). The elimination of INH follows a bimodal or trimodal distribution consisting of slow (SA), intermediate (IA) and rapid acetylators (RA). There is a strong correlation between these phenotypes and NAT2 genotypes in Caucasians.¹¹⁻¹³ Previous studies have reported inconsistent results on whether slow or rapid acetylators are a risk factor for INH-induced hepatotoxicity.^{9,13-15}

The objective of this study was to determine the association between CYP2E1 polymorphisms and the development of DILI in Indonesians and determine the genotypes and phenotypes related to a change in the risk of DILI.

2. Materials and methods

2.1. Patients

This study used a cohort design. A total of 55 Indonesian adult patients with newly diagnosed TB at 20 Public Health Centres in the Provinces of Yogyakarta (10 Public Health Centres) and Lampung (10 Public Health Centres) were enrolled. The patient's recruitment was conducted from January until December 2013. The inclusion criteria included all adult patients (age >18 years) newly diagnosed as a pulmonary TB patient who were receiving category 1 TB medications and signed the informed consent for study participation. Exclusion criteria consisted of TB patients with HIV/AIDS, an AST and ALT two-fold higher than normal baseline concentrations, hepatitis or a history of hepatitis, a haemoglobin concentration <8 mg/dL, cessation of medication for more than 2 weeks, a history of kidney diseases, or refusal of blood sampling procedures and patients who refused to participate in this study.

All patients received a standard TB treatment for the first 2 months, including oral INH (300 mg), rifampicin (600 mg), pyrazinamide (20 mg/kg body weight), and ethambutol (800 mg). After 2 months of treatment, the patients were given INH and rifampicin for an additional 4 months. The total

duration of antituberculosis treatment was 6 months. Serum alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase were measured before the anti-tuberculosis therapy and then monthly until the end of treatment.

Genomic DNA was extracted from blood samples using a DNA Gene JET Genomic DNA Purification Kit (Thermo Scientific®, Nutrilab Pratama, Jakarta, Indonesia) according to the manufacturer's instructions. Analysis and Identification of SNP (-1055) C/G (Rs 3813867) was completed using an amplification refractory mutation system (ARMS) method. Two primer sets of CYP2E1 (Rs 3813867) were used: forward I "5-GTACAAAATTGCAACCTATG-3" to detect the CYP2E1 polymorphic gene (F-primer - 1), forward II "5-GTACAAAATTGCAACCTATG-3" to confirm the normal gene fragment and (F-primer - 2) reverse "5-ATCTTGTCTTTGTTGATCCC-3" (Genebank accession number P05181). The cycling conditions involved preliminary denaturation at 95 °C for 2 min, followed by 35 cycles of denaturation at 95 °C for 30 s, annealing at 55 °C for 30 s, and elongation at 72 °C for 30 s, followed by a final elongation step at 72 °C for 2 min. The PCR products of single nucleotide polymorphism (SNP) (-1055) C > G (rs3813867) were obtained for 55 subjects. The results showed a band at 230 bp. After electrophoresis using a 2% agarose gel, samples were observed under UV light and imaged. Samples with homozygote CC (cytosine-cytosine) appeared using primer set Forward 1-Reverse (F1-R), samples with homozygote GG (guanine-guanine) appeared using primer set Forward 2-Reverse (F2-R), and samples with homozygote CG (cytosine-guanine) appeared using both primer sets F1-R and F2-R.

Venous blood samples were collected 2 h after drug administration. Determination of acetylator status was made using the AChZ/HZ ratio with a cut-off point of 15.00. A slow acetylator (SA) was defined as an AChZ/HZ ratio ≤ 15.00, and a rapid acetylator (RA) was defined as an AChZ/HZ ratio >15.¹⁶ The AST and ALT levels were measured with an automatic chemical analyser. Isoniazid and its metabolites, HZ and AChZ, were measured using HPLC. Statistical significance was analyzed using correlation tests. DILI incidence was defined as an ALT and/or AST level above the upper limit normal value (ULN) listed in Common Toxicity Criteria for Adverse Events version 4.0 (CTCAE v. 4). The normal values of ALT and AST are 0-50 mg/dL and 0-33 mg/dL, respectively, for males. The normal values for ALT and AST are 0-34 mg/dL and 0-27 mg/dL, respectively, for females. Increased ALT and/or AST or an increased ALP were categorized as grade 1+, (>1.0-2.5 × ULN), grade 2+ (>2.5-5.0 × ULN), grade 3+ (>5.0-20 × ULN), or grade 4+ (>20.0 × ULN).¹⁷

This study was approved by the National Ethics Committee of the National Institute of Health Research and Development, Ministry of Health, Republic of Indonesia, and written informed consent was obtained from all participants.

2.2. Statistical methods

Statistical analysis was conducted using the SPSS® statistical package, version 16.0. The odds ratio (OR) and confidence interval (CI) were calculated using binary logistic regression analysis. This analysis evaluated the risk and association of DILI, INH and acetylator status. Allele frequencies were

calculated, and the agreement between allele frequencies and Hardy-Weinberg equilibrium was tested using a chi-square test (d.f. = 1) for each locus.

3. Results

This study recruited 55 tuberculosis patients. Table 1 shows the demographics of the patients. There were 9 patients (16.36%) genotyped as CC (c1/c1), 29 patients (52.73%) genotyped as CG (c1/c2) and 17 patients (30.90%) genotyped as GG (c2/c2). The genotype frequencies were not significantly different from those predicted by the Hardy-Weinberg equation ($P > 0.05$). According to sex and age differences, the CG genotype was predominant over CC and GG. There were also no significant differences between ALT and AST means at baseline between males and females with different genotypes ($P > 0.05$).

Table 2 shows the association between INH concentration, acetylator status and DILI incidence. Among the 55 tuberculosis patients, there were 25 patients (45%) with DILI. There was no significant difference between INH serum concentrations and DILI incidence. However, patients with INH serum concentrations more than 7 $\mu\text{g/mL}$ had a greater tendency to develop DILI when compared with subjects who had normal (3–6 $\mu\text{g/mL}$) and low (3 $\mu\text{g/mL}$) INH concentrations (OR: 1.3, 95% CI: 0.2–8.2). There was a significant association between acetylator status and DILI incidence. A total of 17 patients (30.9%) were identified as RAs, and the other 38 patients (69.09%) were SAs. SAs showed a higher risk of developing DILI when compared with RAs (OR: 4.6, 95% CI: 1.3–15.9).

Table 3 shows the distribution of INH serum concentration and acetylator status based on genotype. There were 10 patients (16.36%) genotyped as CC (c1/c1), 29 patients (52.73%) genotyped as CG (c1/c2) and 16 patients (30.90%) genotyped as GG (c2/c2). There were no significant differences in the frequencies of c1/c1, c1/c2, and c2/c2 genotypes between the patients with and without DILI. The heterozygous c1/c2 variant showed a higher DILI incidence when compared with the homozygous c2/c2 variant (OR: 4.3, 95% CI: 0.8–24.4 and OR: 2.5, 95% CI: 0.4–15.5, respectively). We did the stratified analysis according to the acetylator data to the INH serum

Table 1 – Demographics of Indonesian tuberculosis patients according to genotype.

	Genotype			P value
	CC N (%)	CG N (%)	GG N (%)	
Sex				
Male	4 (44.5)	15 (53.6)	10 (55.5)	
Female	5 (55.5)	13 (46.4)	8 (44.5)	
Total	9 (100.0)	28 (100.0)	18 (100.0)	
Age (years)				
18–35	2 (22.2)	20 (71.4)	10 (55.6)	
36–55	5 (55.5)	3 (10.7)	6 (33.3)	
>55	3 (33.3)	5 (17.9)	2 (11.1)	
Total	9 (100.0)	28 (100.0)	18 (100.0)	
	Mean \pm SD	Mean \pm SD	Mean \pm SD	
ALT (U/L) Baseline				
Male	21.8 \pm 15.98	23.2 \pm 16.81	20.8 \pm 11.72	0.07
Female	16.4 \pm 6.69	15.3 \pm 12.15	14.6 \pm 3.99	
AST (U/L) Baseline				
Male	19.5 \pm 9.03	24.4 \pm 13.54	23.4 \pm 7.19	0.35
Female	24.8 \pm 15.89	20.6 \pm 9.78	16.2 \pm 5.47	

concentration as the determinant; however, we did not find significant association ($P > 0.05$, data was not shown). Furthermore, the binary logistic regression analysis was performed; however we also did not find significant association ($P > 0.05$; data was not shown). After performing bivariate analysis, there was interesting pattern of results in this study, which are: patients who did not experience DILI had INH serum concentration between 0 and 7 ng/mL (OR; 1.8; 95% CI: 0.4–8.2). After stratified by genotyping, we found that the patients with GG genotype have more possibilities to experience DILI (OR: 0.7; 95% CI: 0.4–1.1). We conducted the stratified analysis according to acetylator status with DILI status as the determinant of INH serum concentration. We found that patients without DILI have lower serum concentration INH in slow acetylator (OR: 1.6; 95% CI: 0.3–7.6).

An INH serum concentration greater than 7 $\mu\text{g/mL}$ was found to be predominant in allgenotypes. This pattern was also found for acetylator status. A SA status is dominant in all

Table 2 – Association between INH concentration, acetylator status and DILI incidence.

Variable		With DILI N = 25	Without DILI N = 30	Total N	OR (CI 95%)	P-value
INH concentration ($\mu\text{g/mL}$)	0–3	4	4	8	Reference	
	3–6	3	4	7	0.6 (0.03–8.9)	0.63
	>7	18	22	40	1.2 (0.2–8.2)	0.83
Acetylators status	Rapid acetylators	12	5	17	Reference	
	Slow acetylators	13	25	38	4.6 (1.3–15.9)	0.02*
Genotype CYP2E1	CC(c1/c1)	2	7	9	Reference	0.09
	CG(c1/c2)	16	13	29	4.3 (0.8–24.4)	
Genotype CYP2E1	CC(c1/c1)	2	7	9	Reference	0.09
	GG(c2/c2)	7	10	17	2.4 (0.5–15.5)	

OR: odds ratio; CI: confidence interval.

* Significant difference ($P < 0.05$).

Table 3 – Distribution of INH serum concentration and acetylator status based on genotype.

Variable		CYP2E1 genotype			P-value
		c1/c1	c1/c2	c2/c2	
		N = 10 (%)	N = 29 (%)	N = 16 (%)	
INH serum concentration ($\mu\text{g/mL}$)	0–3	1 (10.0)	4 (13.8)	3 (18.8)	0.70
	>3–6	3 (30.0)	2 (6.9)	2 (12.5)	0.53
	>7	6 (60.0)	23 (79.9)	11 (68.8)	0.83
Acetylator Status	SA	8 (80.0)	19 (65.5)	11 (68.8)	0.65
	RA	2 (20.0)	10 (34.5)	5 (31.3)	0.43

genotypes. The INH serum concentration had no significant influence on DILI risk.

4. Discussion

Our study shows that the CG genotype of CYP2E1 (rs 3813867) is the most frequent in Indonesian tuberculosis patients. Moreover, according to the acetylator status, SAs had a higher incidence of hepatotoxicity when compared with RAs and SAs with the heterozygous c1/c2 variant (CG). Previous studies explained a significant association between the c1/c1 genotype and the risk of developing DILI by a higher CYP2E1 activity in patients with the c1/c1 genotype and the inhibitory effect of INH.^{18,19} Another study showed that the CYP2E1*1A/*1A polymorphism may confer a greater risk of INH-induced hepatotoxicity in a heterogeneous ethnic population; however, the patients in this study were receiving monotherapy and potential interactions were not addressed.¹⁹ A recent study from Chamoro et al. reported that the CYP2E1 c1/c2 polymorphism did not show a significance.²⁰ Our study's findings are in line with previous studies which reported that acetylator status was a risk factor for DILI in tuberculosis patients.^{9,14,15,21}

There have been several reports on the relationship between INH concentration and ATDH. A previous study showed an association between INH serum concentration and NAT2 genotype in Chinese tuberculosis patients.²² INH is hydrolysed by NAT-2 and oxidized by CYP2E1 to form a hepatotoxic substance.²³ However, our study confirmed that there is no association between these parameters. Our study reports that around 40% TB patients had higher INH serum concentrations, and 45% among them are experienced DILI. Our study is in line with previous data that showed SA status is significantly associated with DILI in the Indonesian population.²⁴ Our patients underwent a combination therapy for TB treatment, including INH, and drug–drug pharmacokinetic and pharmacodynamic interactions occurred. INH is known to have a biphasic effect on CYP2E1 activity that consists of inhibition followed by induction. Many studies have reported on drug combinations that increase the incidence of antituberculosis drug-induced hepatotoxicity up to 35%.^{25–28}

Huang et al. showed that CYP2E1 by RsaI restriction polymorphism was associated with susceptibility to INH-induced hepatotoxicity.²⁰ INH is principally metabolized by N-acetyltransferase 2 (NAT-2) and cytochrome P450 2E1 (CYP2E1). NAT-2 plays a key role in the detoxification and elimination of drugs, and it is also involved in carcinogen

metabolism.²⁹ Modifications in NAT-2 activity can result in the accumulation of precursors, such as HZ and AchZ, leading to the development of hepatotoxicity.^{30–32} CYP2E1 is predominantly expressed in the liver where it activates (via oxidation) low molecular-weight lipophilic compounds, drugs, and procarcinogens,³³ and it is involved in INH metabolism and generates hepatotoxic intermediates.^{34,35} The wild-type and mutated CYP2E1 alleles have been named c1 and c2, respectively. There are several *in vivo* studies that have associated the c1/c1 genotype with increased transcriptional activity, protein levels, and enzymatic activity.^{20,21} Therefore, patients with the CYP2E1 (c1/c1) genotype generate more hepatotoxins. Other studies have found that the c1/c1 genotype may be a risk factor for INH-induced hepatotoxicity.^{34,35} These data are in contrast with our present study that found c1/c2 may be a risk factor for INH-induced hepatotoxicity in SAs.

This study has some limitations as follows: we did not consider the complexity mechanism of antituberculosis-induced hepatotoxicity which was also interfered by roles of other genes such as NAT2 and GST.³⁶ The other mechanism of antituberculosis-induced hepatotoxicity which we did not involve in this study was due to the rifampicin-INH interaction. Rifampicin may induce INH metabolism through CYP2E1 which also induces the hepatotoxicity.^{37,38} The small sample size in our study is caused by the one criteria of the study is newly diagnosed TB patients, which only small number during the study period.

5. Conclusions

SAs were associated with an increased DILI incidence. A large-scale population study is needed to confirm the association between INH serum concentration, CYP2E1 polymorphisms, acetylator status and DILI.

Conflict of interest

The authors have none to declare.

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