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NAT2 and *CYP2E1* polymorphisms and susceptibility to first-line anti-tuberculosis drug-induced hepatitis

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SUMMARY

BACKGROUND: Most cases with anti-tuberculosis drug-induced hepatotoxicity (ATDH) have been attributed to isoniazid.

OBJECTIVE: To evaluate whether the polymorphisms of the cytochrome P450 2EI (*CYP2E1*) and N-acetyltransferase 2 (*NAT2*) gene are associated with ATDH.

DESIGN: A total of 140 tuberculosis (TB) patients without liver diseases before treatment who received anti-tuberculosis treatment were followed prospectively. Their *CYP2E1* and *NAT2* genotypes were determined using the TaqMan polymerase chain reaction assay.

RESULTS: Forty-five (32.1%) patients were diagnosed with ATDH. No significant differences were reported in age and sex between patients with and without ATDH. Slow acetylators defined by *NAT2* genotypes had a higher risk of hepatotoxicity than rapid acetylators (51.2% vs. 25.2%, $P = 0.0026$). Odds ratio (OR) analysis showed that slow acetylator status (OR 3.15, 95%CI 1.47–6.48) was the only independent risk factor for ATDH. Pyrazinamide co-administration induced hepatitis was also associated with *NAT2* acetylator status. *CYP2E1* c1/c1 homozygotes are prone to developing more severe hepatotoxicity than other c1/c2 and c2/c2 genotypes.

CONCLUSION: The slow acetylator status of *NAT2* is a significant susceptibility risk factor for ATDH. *CYP2E1* is associated with the severity of ATDH.

KEY WORDS: *NAT2*; *CYP2E1*; anti-tuberculosis drug-induced hepatitis; ATDH

MAJOR ADVERSE reactions to anti-tuberculosis drugs can cause significant morbidity and compromise treatment regimens for tuberculosis (TB).[1] Regimens containing isoniazid (INH), rifampicin (RMP), ethambutol (EMB) and pyrazinamide (PZA) are traditionally used as first-line treatment for TB. However, acute or chronic hepatitis frequently develops in patients receiving these drugs.[2–5] PZA, INH and RMP cause drug-induced hepatitis,[6] and PZA-induced hepatotoxicity is substantially higher than other drugs.[1]

Anti-tuberculosis drug-induced hepatotoxicity (ATDH) is commonly defined as a treatment-emergent increase in serum alanine aminotransferase (ALT) greater than three or five times the upper limit of normal (ULN), with or without symptoms of hepatitis.[7] INH, RMP and PZA are potentially hepatotoxic drugs.[8] Metabolism is crucial in ATDH and toxic metabolites play a central role.[7]

N-acetyltransferase 2 (*NAT2*) is mainly responsible for INH metabolism and exhibits a hereditarily determined polymorphism.[7] The individual *NAT2* phenotypes can be classified as rapid, intermediate or slow acetylators according to their acetylation activity.[8] In the liver, INH is first metabolised into acetylisoniazid via N-acetyltransferase,[9] followed by hydrolysis to acetylhydrazine. Acetylhydrazine is then oxidised into hepatotoxic intermediaries by cytochrome P450 2E1 (*CYP2E1*).[10] It has been suggested that the *NAT2* genotype slow acetylators have a higher incidence of ATDH than rapid and intermediate acetylators, and study results are consistent in Taiwanese,[11] Japanese[12] and Korean[13] TB patients. However, study results on the association of the *CYP2E1* genotype and ATDH are inconsistent in Taiwanese[14] and Korean[13] TB patients. In one meta-analysis, *NAT2* and *CYP2E1* genotypes showed genetic association to anti-tuberculosis drug-induced liver injury.[15]

NAT2 variants *5, *6, *7 and the *CYP2E1* c1/c2 allele have been investigated for their association with ATDH in previous studies on Asian populations.[11–14] In this study, the contribution of *NAT2* and *CYP2E1* polymorphisms to first-line ATDH were validated in TB patients at a TB centre in Taoyuan General Hospital. Furthermore, the association of *NAT2* acetylator status and hepatotoxicity induced by PZA co-administration with INH, RMP and EMB were evaluated.

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MATERIALS AND METHODS

Subjects

A total of 140 patients treated for active TB at the General Taoyuan Hospital, Taoyuan, Taiwan, between 2007 and 2008 were surveyed consecutively. Inclusion criteria were as follows: adult patients newly diagnosed with active TB, having evident lesions of TB by simple X-ray, computed tomography, positive results of sputum smears and cultures for detection of mycobacteria. Patients with any of the following conditions were excluded from the study: 1) positive serum hepatitis B virus surface antigen, antibody to hepatitis C virus; 2) alcoholic liver disease or habitual alcohol drinking; 3) any other hepatic or systemic diseases that may cause liver dysfunction; 4) abnormal serum ALT, aspartate aminotransferase (AST) or bilirubin levels before anti-tuberculosis treatment.

Except for those patients who had developed severe ATDH, all patients received oral INH 300 mg, RMP 600 mg (or 450 mg if body weight was < 50 kg), PZA 200 mg/kg body weight and EMB 800 mg daily for the first 2 months. PZA was then discontinued, while INH, RMP and EMB were continued for another 4 months. ATDH was designated as an increase in serum ALT level of $>2 \times$ ULN after anti-tuberculosis treatment, according to the criteria of drug-induced liver injuries developed by the international consensus meeting organised by the Council for International Organizations of Medical Sciences (CIOMS).[16] Thirty-seven of 45 patients with ATDH were re-challenged, beginning with INH 50 mg, 100 mg, 150 mg and 300 mg (the full dose of INH), and then started with RMP 150 mg, 300 mg, 450 mg (the full dose for patients with bodyweight < 50 kg) or 600 mg (the full dose for patients with bodyweight > 50 kg). If AST, ALT and total bilirubin levels were normal in the re-challenge process, INH, RMP and EMB combination treatment was continued for 9 months.[17] PZA co-administration induced hepatitis was diagnosed based on negative INH and RMP re-challenge tests. EMB is not considered to be incriminated in ATDH.[1]

Written informed consent was obtained from each patient enrolled in this study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Taoyuan General Hospital.

DNA preparation

Genomic DNA was extracted from oral swabs collected from 140 TB patients using a QIAamp DNA Mini Kit (QIAGEN, Valencia, CA, USA) according to the manufacturer's instructions. The extracted genomic DNA was analysed using agarose gel electrophoresis and quantitatively determined by spectrophotometry and stored at -80°C until use.

SNP genotyping

*NAT*5*, **6*, **7* and *CYP2E1* c1/c2 polymorphisms were selected to perform genotyping. The representative single nucleotide polymorphisms (SNPs) of *NAT*5*, **6*, **7* and *CYP2E1* c1/c2 are respectively rs1801280, rs1799930, rs1799931 and rs3813867. All SNP genotyping was performed using the TaqMan® SNP genotyping assays (Applied Biosystems Inc [ABI], Foster City, CA, USA). The primers and probes of selected SNPs were from an ABI assay on demand (AOD) kit. Reactions were carried out according to the manufacturer's protocol (Taqman SNP Genotyping Assays, protocol, part number 4332856 Rev C). Probe fluorescence signal detection was performed using the ABI Prism 7900 real-time polymerase chain reaction system.

Statistical analysis

All association analyses between ATDH and polymorphisms were tested by the χ^2 test. Odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated from contingency tables. Other statistical analyses, including *t*-tests and the Mann-Whitney *U* test, were performed using SPSS 11.0 software (SPSS Inc, Chicago, IL, USA).

RESULTS

Characterisation of patients

Forty-five patients were diagnosed with ATDH. There was no statistical difference in sex and age between patients with and those without hepatotoxicity (Table 1). Eight patients had an ALT of 2–3× ULN during treatment, and anti-tuberculosis drugs were continuously and uneventfully administered throughout. Thirty-seven patients had ALT of >3× ULN, and thus treatment was discontinued temporarily. After the liver biochemical tests had normalised, INH and RMP were re-challenged, gradually increasing the doses; for the 33 patients susceptible to PZA-induced (or co-administration) hepatotoxicity, this was performed safely; the other four patients were susceptible to RMP-induced hepatotoxicity.

NAT2 *variant(s) associated with drug-induced hepatotoxicity*

Four SNPs in the *NAT2* and *CYP2E1* genes were genotyped by TaqMan SNP genotyping assays on the enrolled subjects. *NAT2*7* (rs1799931) showed different genotype frequencies between TB patients with and those without ATDH (Table 2). *CYP2E1* c1/c2 (rs3813867) did not show an association with ATDH.

NAT2 *slow acetylators associated with drug-induced hepatotoxicity*

According to the *NAT2* genotypes, 24 rapid acetylators and 21 slow acetylators were defined in TB patients with ATDH, and 75 rapid acetylators and 20 slow acetylators in TB patients without ATDH (Table 3). As Table 3 shows, the slow acetylators were at higher risk of developing ATDH than rapid acetylators. The OR of slow acetylators compared to rapid acetylators was 3.28 (95%CI 1.53–7.06).

Table 1 Characteristics of patients with or without drug-induced hepatitis

	With hepatitis (n = 45) mean ± SD (range)	Without hepatitis (n = 95) mean ± SD (range)	P value
Sex, female/male	18/27	32/63	0.47
Age, years	58.4 ± 18.5 (26–89)	54.9 ± 20.3 (20–90)	0.33
Baseline values*			
AST, U/ml	22.9 ± 7.5	20.9 ± 7.1	0.13
ALT, U/ml	16.5 ± 6.7	15.5 ± 7.1	0.43
Total bilirubin, mg/dl	0.7 ± 0.2	0.7 ± 0.2	1
Duration of anti-tuberculosis treatment			
Peak AST, U/ml	189.1 ± 200.5 (48–1259)	25.8 ± 10.9 (10.9–59)	<0.0001
Peak ALT, U/ml	198.1 ± 231.0 (38–1392)	17.5 ± 8.2 (5–46)	<0.0001
Peak total bilirubin, mg/dl	2.2 ± 2.3 (0.4–10.1)	0.7 ± 0.3 (0.3–1.4)	<0.0001

*Normal intervals: AST 0–40 U/ml, ALT 0–40 U/ml, total bilirubin 0.3–1.2 mg/dl.
SD = standard deviation; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 2 NAT2 and CYP2E1 genotype frequencies in patients with and without drug-induced hepatitis

Polymorphism	SNP ID	Allele	With hepatitis	Without hepatitis	P value
		1/2*	11/12/22†	11/12/22†	
NAT2*5	rs1801280	C/T	0/5/40	3/8/84	0.44
NAT2*6	rs1799930	A/G	7/14/24	8/29/58	0.41
NAT2*7	rs1799931	A/G	8/9/28	1/25/68	0.0008
CYP2E1 c1/c2	rs3813867	G/C	26/18/1	55/38/2	1.00

*1 = allele 1; 2 = allele 2.
†11 = homozygous of allele 1; 12 = heterozygous; 22 = homozygous of allele 2.
NAT2 = N-acetyltransferase 2; CYP2E1 = cytochrome P450 2EI; SNP = single nucleotide polymorphism.

Table 3 NAT2 rapid acetylator and slow acetylator genotypes and susceptibility of drug-induced hepatitis

	With hepatitis (n = 45) n (%)	Without hepatitis (n = 95) n (%)	OR (95%CI)
Rapid acetylators	24 (24.2)	75 (75.8)	1 (reference)
NAT2*4/*4	9	29	
NAT2*4/*5	3	8	
NAT2*4/*6	9	21	
NAT2*4/*7	3	17	
Slow acetylators	21 (51.2)	20 (48.8)	3.28 (1.53–7.06)*
NAT2*5/*5	0	3	
NAT2*5/*6	1	0	
NAT2*5/*7	1	0	
NAT2*6/*6	6	8	
NAT2*6/*7	5	8	
NAT2*7/*7	8	1	

*P = 0.0019.
NAT2 = N-acetyltransferase 2; OR = odds ratio; CI = confidence interval.

Table 4 *NAT2* acetylator status and susceptibility of PZA-induced hepatitis

	With hepatitis (n = 33) n (%)	Without hepatitis (n = 95) n (%)	OR (95%CI)
Rapid acetylator	16 (17.6)	75 (82.4)	1 (reference)
Slow acetylator	17 (45.9)	20 (54.1)	3.98 (1.72–9.25)*

*P = 0.0009.
PZA = pyrazinamide; OR = odds ratio; CI = confidence interval.

NAT2 *slow acetylators associated with PZA-induced hepatotoxicity*

Thirty-three TB patients with ATDH were susceptible to PZA co-administration with INH, RMP and EMB. The slow acetylators were at a higher risk of developing ATDH than rapid acetylators (Table 4). The OR of slow acetylators compared to rapid acetylators was 3.28 (95%CI 1.53–7.06). The slow acetylators were at a higher risk of developing hepatotoxicity induced by PZA co-administration with INH, RMP and EMB than rapid acetylators. The OR of slow acetylators compared to rapid acetylators was 3.98 (95%CI 1.72–9.25).

CYP2E1 c1/c2 *polymorphism and severity of drug-induced hepatotoxicity*

Among the 45 patients with ATDH, *CYP2E1* c1/c1 homozygous patients had a higher mean serum AST level, but not ALT level, than patients with the c1/c2 and c2/c2 genotypes (Table 5). Furthermore, *CYP2E1* c1/c1 homozygous patients were more likely to have >3× ULN of serum AST levels than did patients with the c1/c2 and c2/c2 genotypes during the first 2 months of anti-tuberculosis treatment, or to develop severe ATDH (Table 5).

DISCUSSION

Our study shows that *NAT2* acetylator status can be regarded as an important risk factor for developing ATDH in the Taiwanese population. Previous reports in the Taiwanese population have shown that *NAT2* slow acetylators are susceptible to INH-induced hepatitis.[11] Our results indicate that slow acetylators develop ATDH more frequently in current anti-tuberculosis first-line (INH+RMP+PZA+EMB) treatment, and where PZA is administered at the same time as INH, RMP and EMB. *CYP2E1* c1/c2 polymorphism did not show a significant association with ATDH in this study.

Table 5 Characteristics of patients with drug-induced hepatitis, stratified by *CYP2E1* genotype

	c1/c1 (n = 26) mean ± SD (range)	c1/c2+c2/c2 (n = 19) mean ± SD (range)	P value
Peak AST, U/ml	220.88 ± 236.61 (58–1259)	147.37 ± 134.64 (48–495)	0.019
Peak ALT, U/ml	218.58 ± 264.63 (48–1392)	170.00 ± 178.12 (38–710)	0.12
Peak total bilirubin, mg/dl	2.209 ± 2.499 (0.4–10.1)	2.231 ± 1.900 (0.5–7.1)	0.46
AST >3× ULN, n (%)	19 (73)	6 (31)	0.003
ALT >3× ULN, n (%)	16 (61)	9 (47)	0.41
Age, years	57.2 ± 18.5 (28–89)	60.1 ± 18.8 (26–89)	0.62

AST = aspartate aminotransferase; SD = standard deviation; ALT = alanine aminotransferase; ULN = upper limit of the normal value.

Patients in this study were taking drugs concomitantly with INH. Co-administration of drugs may result in quantitative and qualitative alteration of the drug metabolism, and it is very difficult to exclude the presence of confounding factors in assessing ATDH. Rat studies have shown that INH and hydrazine induce CYP2E1 activity.[17–19] INH has an inhibiting effect on CYP1A2, 2A6, 2C19 and 3A4 activity.[20,21] RMP is a potent inducer of the hepatic CYP450 system in the liver and intestine, thus increasing metabolism of many other compounds.[22,23] RMP is also known to reduce NAT2 activity.[24,25] PZA has been shown to inhibit the activity of several CYP450 isoenzymes in a rat study,[26] but had no inhibitory effect on CYP450 isoenzymes in a human liver microsomes study.[27] As a combination of these drugs is known to increase the incidence of ATDH by up to 35%,[26–29] it is obvious that drug-drug interactions do occur. Our data, especially on PZA co-administration, are consistent with the above observation and indicate that some interactions are still unknown. The *CYP2E1* c1/c1 genotype is associated with a high CYP2E1 activity and is involved in ATDH.[14,30,31] Although the previous results of an association study[14] were not revealed in our study, the *CYP2E1* c1/c1 genotype in this study was more likely to develop severe hepatic injury than other genotypes.

CONCLUSIONS

As birthplace in Asia is a risk factor for developing ATDH,[1] the determination of *NAT2* and *CYP2E1* genotypes for anti-tuberculosis treatment should be clinically useful for the prediction and prevention of ATDH in Asian TB patients.

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RÉSUMÉ

CADRE : La plupart des cas d'hépatotoxicité due aux médicaments antituberculeux (ATDH) ont été attribués à l'isoniazide.

OBJECTIF : Evaluer dans quelle mesure le polymorphisme des gènes cytochrome P450 2EI (*CYP2E1*) et *NAT2* est en association avec l'ATDH.

SCHÉMA : On a suivi de manière prospective au total 140 patients tuberculeux sans pathologie hépatique avant traitement et qui ont bénéficié d'une chimiothérapie antituberculeuse. On a déterminé leurs génotypes *CYP2E1* et *NAT2* au moyen d'une réaction de polymérase en chaîne avec la technique TaqMan.

RÉSULTATS : On a diagnostiqué une ATDH chez 45 patients (32,1%). On n'a démontré aucune différence significative en matière d'âge ou de sexe entre les patients souffrant ou non d'hépatite induite par les médicaments. Les acétyleurs lents définis par leurs génotypes *NAT2* ont un risque plus élevé d'hépatotoxicité que les acétyleurs rapides (51,2% vs. 25,2% ; $P = 0,0026$). L'analyse des odds ratio a montré que le statut d'acétyleur lent est le seul facteur indépendant de risque d'ATDH (OR 3,15 ; IC95% 1,47–6,48). L'hépatite induite par la co-administration de PZA est également en association avec le statut d'acétyleur *NAT2*. De plus, les homozygotes *CYP2E1* c1/c1 ont une plus grande tendance à développer une hépatotoxicité plus grave que les autres génotypes c1/c2 et c2/c2.

CONCLUSION : Le statut d'acétyleur lent de *NAT2* représente un facteur de risque significatif de sensibilité en matière d'ATDH. Le *CYP2E1* est en association avec la gravité de l'ATDH.

RESUMEN

MARCA DE REFERENCIA: La mayoría de los casos con hepatotoxicidad inducida por los medicamentos antituberculosos (ATDH) se ha atribuido a la isoniazida.

OBJETIVO: Evaluar los polimorfismos de los genes citocromo P450 2E (*CYP2E1*) y N-acetiltransferasa 2 (*NAT2*) que se asocian con este tipo de hepatotoxicidad.

MÉTODOS: Se llevó a cabo un seguimiento prospectivo de 140 pacientes tuberculosos sin enfermedad hepática previa al tratamiento antituberculoso. Se determinaron los genotipos *CYP2E1* y *NAT2* mediante la prueba de reacción en cadena de la polimerasa (TaqMan).

RESULTADOS: Se diagnosticó hepatotoxicidad debida al tratamiento antituberculoso en 45 pacientes (32,1%). No se observaron diferencias significativas con respecto a la edad ni el sexo entre los pacientes que presentaron hepatitis inducida y quienes no la padecieron. Los acetiladores lentos, definidos por los genotipos *NAT2*, presentaron un mayor riesgo de hepatotoxicidad que los acetiladores rápidos (51,2% contra 25,2%; $P = 0,0026$). El análisis del cociente de posibilidades (OR) reveló que la condición de acetilador lento era el único factor de riesgo independiente de presentar hepatotoxicidad (OR 3,15; IC95% 1,47–6,48). La hepatitis inducida por la administración simultánea de pirazinamida también se asoció con el fenotipo de acetilación definido por el gen *NAT2*. Además, se observó predisposición a una hepatotoxicidad más grave en los homocigotos c1/c1 para el gen *CYP2E1* que en los portadores de genotipos c1/c2 y c2/c2.

CONCLUSIÓN: La condición de acetilador lento, determinada por el gen *NAT2*, constituye un importante factor de susceptibilidad de padecer hepatotoxicidad medicamentosa. El genotipo *CYP2E1* se asocia con la gravedad de la ATDH.