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Gene dose effect of *NAT2* variants on the pharmacokinetics of isoniazid and acetylisoniazid in healthy Chinese subjects

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Abstract

Background: The aim of this study was to elucidate the gene dose effect of *NAT2* and the effect on the pharmacokinetics of isoniazid (INH) and its metabolites acetylisoniazid (AcINH) in Chinese subjects.

Methods: A total of 24 healthy Chinese subjects, consisting of eight homozygous wild types (wt/wt), eight heterozygous mutants (m/wt) and eight homozygous mutants (m/m) for NAT2, were enrolled in the study. The blood samples (0–14 h) of the subjects were taken after oral administration of a single dose (300 mg) of INH. Concentrations of INH and AcINH in plasma were measured by a reversed-phase HPLC method.

Results: The ratio of AcINH and INH ($R_{A/I}$) 3 h post-dose of wt/wt, m/wt and m/m groups were 3.22±1.34, 1.35±0.20 and 0.22±0.06, respectively ($p<0.01$). The area under concentration-time curve (AUC) values of three groups were 10.35±2.12, 16.34±3.05, 42.24±8.51 mg/h/L for INH and 42.19±8.80, 38.05±5.32, 19.78±3.72 mg/h/L for AcINH, respectively ($p<0.01$). There was a good linear relationship between pharmacokinetic parameters and the number of active *NAT2* genes.

Conclusions: The results suggest that there is a conspicuous gene dose effect in the pharmacokinetics of INH and AcINH. This finding may be valuable in the personalized therapy of tuberculosis with INH.

Keywords: acetyl isoniazid (AcINH); gene dose effect; isoniazid (INH); N-acetyltransferase 2 (NAT2); pharmacokinetics.

Introduction

Pulmonary tuberculosis remains one of the most serious public health problems in both developing and developed countries (1, 2). Isoniazid (INH) is the principal component of all antituberculosis regimens for use in patients with drug-sensitive organisms. A substantial part of INH absorbed is metabolized to N-acetylisoniazid (AcINH) in liver. N-acetyltranferase2 (NAT2), an important phase II enzyme, catalyzes this reaction. AcINH can be hydrolyzed to acetylhydrazine and can further be converted to diacetylhydrazine under the catalysis of NAT2. Although these metabolites have no antituberculosis activity, they are thought to have an association with adverse effects, such as peripheral neuritis and hepatic toxicity (3–5).

NAT2 activity displays a polymorphism. People with high NAT2 activity are named extensive metabolizers (EMs), and those with defective activity are named poor metabolizers (PMs). The polymorphism of NAT2 activity has a great impact on the pharmacokinetics and efficiency of INH. Horai et al. (6) found that $t_{1/2}$ of INH in PMs and EMs was two and 1.39±0.06 h, respectively. A more recent study found that $t_{1/2}$ of INH in homozygous EMs, heterozygous EMs and homozygous slow were 1.06±0.19, 1.35±0.19 and 2.73±0.49 h, respectively (7). Kubota et al. (8) studied pharmacokinetics in homozygous and heterozygous EMs. They found that plasma concentrations of the heterozygous EM group were within the therapeutic range. They propose that the proper daily dose for RA-type patients is 1.5 times higher than that currently recommended (8). It is well established that PMs of NAT2 are more likely to develop polyneuropathy and hepatotoxicity during INH therapy (9, 10). Hiratsuka et al. (11) studied 102 Japanese patients treated with INH and found that six of them developed various adverse effects, five of these six patients were PMs. Expression of various genotypes of the *NAT2* gene is the cause of PM (12, 13). Various combinations of single nucleotide polymorphisms (SNPs) are identified as *NAT2* alleles or haplotypes. Currently, over 27 *NAT2* alleles were found. According to the international nomenclature committee (http://N-acetyltransferasenomenclature.louisville.edu), *NAT2*4* is considered as the 'wild-type' allele. Variant *NAT2* alleles possessing combinations of SNPs are segregated into clusters possessing a signature SNP either alone or in combination with others. Mutant allele **5*, **6*, **7* can explain over 98% PMs in Caucasians and Orientals (14, 15). In our previous study of a population of 215 Chinese people, we found allele frequencies of *NAT2 *5*, **6*, **7* were 3.3%, 24.6% and 10.0%, respectively. There were 85, 96 and 34 homozygous wild type (wt/wt), heterozygous mutant (m/wt) and homozygous mutant (m/m) subjects, respectively (16). Smith et al. (17) found that the metabolic ratio (ratio of plasma concentration of AcINH and INH at 3 h, $R_{A/I}$) in wt/wt, m/wt genotype was 28.5- and 9.5-fold higher than m/m genotypes, which corresponded to a trimodal distribution without overlapping. The *NAT2* gene of the wt/wt, m/wt and m/m group contained

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2, 1 and 0 active *NAT2* genes, respectively. Metabolic activity of NAT2 correlated well with the number of active genes. This phenomenon is called gene dose effect. However, there is no similar study done in Chinese subjects.

The aim of this study was to investigate the genetic polymorphism of *NAT2* and gene dose effect of *NAT2* on the pharmacokinetics of INH and AcINH in healthy Chinese subjects.

Materials and methods

Subjects

A total of 24 healthy male subjects enrolled in this study were all students in Nanjin University. All subjects were Han nationality (age=24.4±2.1 years, weight=64.6±5.8 kg, height=172.7±4.1 cm). The creatinine clearance (CL_{cr}), plasma urea nitrogen concentration was 82.5±11.3 μmol/L and 5.2±1.1 mmol/L, respectively. The study was approved by the Ethics Committee of Jinling Hospital. Written informed consent was obtained from all subjects. The volunteers were all recruited from our previous study of a Chinese population consisting of 215 subjects who have had genotyping of *NAT2* by allele-specific amplification (16). There were five different NAT2 genotypes in 24 subjects, including **4/*4* (n=8), **4/*6* (n=5), **4/*7* (n=3), **5/*7* (n=1) and **6/*6* (n=7). They were divided into three groups according to the genotypes. Eight subjects with **4/*4* genotype were wt/wt genotype. Eight subjects with **4/*6* and **4/*7* were m/wt genotype. Eight subjects with **5/*7* and **6/*6* genotypes were classified as m/m genotype. All subjects were non-smokers. Subjects were excluded for any history of abnormal hepatic or renal functions, alcohol abuse, drug allergy and intoxication. No medication was ingested within the last 7 days.

Study protocol

All volunteers received 300 mg INH tablets (Qianjin Pharmaceutical Company, Hunan, China) orally after an overnight fast. An intravenous catheter (B. Braun, Melsungen, Germany; 1.1 mm×33 mm) was inserted into the vein in either arm of each subject, and 3-mL blood samples were drawn into sterile anticoagulated tubes at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 14 h after administration. As INH is only stable in plasma samples stored at –70°C, plasma was separated from blood cell and stored within 1 h.

Drug analysis

A reversed phase HPLC method was used to determine the plasma concentration of INH and AcINH simultaneously (18). Briefly, 10% perchloric acid was added to plasma to precipitate protein. After centrifugation at 11,620 *g* for 10 min, supernatant was eluted with 2 mM sodium heptanesulfonate-acetonitrile (98:2) on a Lichrospher C18 column (250 mm×4.6 mm, 7 μm) and detected under λ 266 nm. The linear concentration range for INH and AcINH were 0.12–15.89 mg/L and 0.13–17.08 mg/L, respectively (r>0.99). Within-day and between-day relative standard deviation (RSD) was 2.2%–5.0%, 2.5%–3.8% for INH and 2.4%–8.1%, 3.0%–5.6% for AcINH, respectively.

Data analysis

Non-compartmental pharmacokinetic parameters of INH and AcINH were simulated with a Winnonlin 5.01 computer program (Pharsight Corp., Mountain View, CA, USA). Area under concentration-time curve (AUC) was estimated by means of trapezoidal method and extrapolation of the area to infinite time. Data obtained from our study were expressed as mean values±SD. The pharmacokinetic parameters of INH and AcINH among different *NAT2* genotypes were compared with one-way analysis of variance. When the null hypothesis was rejected, the differences between the two groups were compared with the least significant difference test (7, 19). Multiregression analysis was used to compare the influence of various factors on pharmacokinetic parameters of INH and AcINH. Values of 0, 1 and 2 was used to represent m/m, m/wt and wt/wt of *NAT2*.

Results

Gene dose effect of metabolic ratio

The $R_{A/I}$ 3 h post-dose was used as the index of the metabolic activity of *NAT2*. Subjects with $R_{A/I}$ 3 h lower than 0.7 were classified as PMs (20). The $R_{A/I}$ 3 h of wt/wt, m/wt and m/m groups were 3.22±1.34, 1.35±0.20 and 0.22±0.06, respectively. All subjects with m/m genotypes had $R_{A/I}$ lower than 0.36, and all of them can be classified as PMs. $R_{A/I}$ 3 h in wt/wt and m/wt groups was 14.6- and 6.1-fold higher than the m/m group. A significant difference was found among different genotypes ($p<0.001$) (Figure 1, Table 1). $R_{A/I}$ 3 h correlated well with the number of **4* alleles ($r=0.8520$, $p<0.05$). Metabolic ratio of INH showed a conspicuous gene dose effect.

Gene dose effect of pharmacokinetics parameter

There were remarkable differences of concentration-time curve of INH and AcINH among wt/wt, m/wt and m/m groups (Figure 2, Table 1). Multiregression analysis was used to relate the pharmacokinetic parameters of INH and AcINH to the underlying factors that may influence the metabolic ratio (MR), including age, weight, height, CL_{cr}, plasma urea nitrogen concentration and *NAT2* genotypes. The $t_{1/2}$, C_{max}, AUC and CL of INH had good correlation with the number of **4* alleles ($r=0.9479$ for $t_{1/2}$, $r=0.6506$ for C_{max}, $r=0.8821$ for AUC and $r=0.9027$ for CL, $p<0.05$). There was also a good relationship found for AcINH ($r=0.6983$ for $t_{1/2}$, $r=0.8920$ for C_{max},

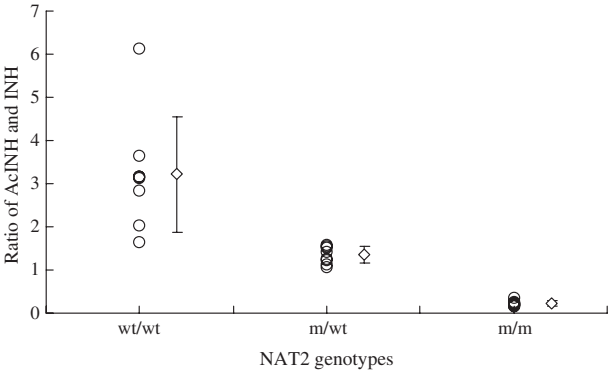

Figure 1 Ratio of AcINH and INH ($R_{A/I}$) 3 h post-drug administration of different *NAT2* genotypes.

Table 1 Pharmacokinetic parameters of INH and AcINH in different *NAT2* genotypes.

	wt/wt	m/wt	m/m	Total
INH				
$t_{1/2}$, h	1.15±0.18	1.76±0.17[a]	3.23±0.28[a,c]	2.05±0.91
C_{max}, mg/L	4.93±1.85	5.72±1.95	8.28±2.40[a,d]	6.31±2.47
AUC, mg/h/L	10.35±2.12	16.34±3.05[b]	42.24±8.51[a,c]	22.23±14.03
CL, L/h	30.05±6.02	19.17±5.04	7.79±1.62[a,c]	19.00±10.28
AcINH				
$t_{1/2}$, h	3.84±0.46	3.59±0.40	6.04±1.20[a,c]	4.57±1.35
C_{max}, mg/L	5.59±1.38	3.99±0.50[b]	1.38±0.24[a,c]	3.65±1.95
AUC, mg/h/L	42.19±8.80	38.05±5.32	19.78±3.72[a,c]	33.13±11.86
CL, L/h	7.40±1.54	8.03±1.20[b]	16.07±2.58[a,c]	10.50±4.41
$R_{A/I}$	3.22±1.34	1.35±0.20[a]	0.22±0.06[a,d]	1.60±1.47

[a]p<0.001, [b]p<0.05: compared with wt/wt genotype, [c]p<0.001, [d]p<0.05: compared with m/wt genotype.

r=0.8089 for AUC and r=0.8199 for CL, p<0.05). However, other factors, such as age have little effect (p>0.05). This suggests that genotypes of *NAT2* play an important role in the interindividual differences of INH disposition. There is a gene dose effect in the pharmacokinetic parameters of INH and AcINH.

Discussion

There is substantial variability with the efficiency and adverse effect of INH, and a 'one-size fits all' dosing strategy is an inflexible approach to individualize the drug dose in the therapy of tuberculosis (21, 22). Previous studies demonstrated the influence of pharmacokinetic parameters of antibacterials on the antimicrobial efficiency. There are similar studies on INH. Donald et al. (23) reported that ratio of INH C_{max} to the minimal inhibition concentration (MIC) could be used to predict the early bactericidal activity of infections with *Mycobacterium tuberculosis*. Jayaram et al. (24) found that the cumulative antibacterial effect of INH related well to AUC and C_{max}. Different INH pharmacokinetic parameters can be used as a therapeutic index of INH. It can be inferred that the interindividual differences of INH pharmacokinetics may lead to variation of INH efficiency (25).

Studies have suggested that polymorphisms of NAT2 activity cause interindividual differences in INH pharmacokinetics (5, 6, 20). However, most of these studies classified the subjects as EMs and PMs according to the phenotyping. Some other studies pointed out that activity of NAT2 showed a trimodal distribution (17). Using genotypes as the index of NAT2 metabolic activity is advisable. Kita et al. (26) studied the urinary excretion of INH in healthy volunteers and in tuberculosis patients, and found that the urinary recovery of INH was lower in subjects with a higher number of active *NAT2* alleles. In another study, Kinzig-Schippers et al. (27) reported that genotype of *NAT2* accounted for 88% of variability in apparent isoniazid clearance. Individual isoniazid clearance could be predicted as clearance=10+9×(number of *NAT2*4* alleles). Donald et al. (25) evaluated the pharmacokinetics of INH associated with optimal early bactericidal activity (EBA) in 66 tuberculosis patients. The therapeutic index was defined as 90% of the maximum EBA [EBA(90)]. They suggested EBA(90) was reached at an AUC of 10.52 μg/mL/h and 2 h serum concentrations of 2.19 μg/mL. They found that most of wt/wt patients achieved a therapeutic target associated with EBA(90) at a 6-mg/kg dose, as did all m/m patients receiving 3 mg/kg of INH. The dose reduction below 6 mg/kg body weight will tend to disadvantage a significant proportion of EM patients (25). As there are significant differences in the *NAT2* allele frequency between various populations, the conclusion of previous studies should be verified in Chinese people. Our study is the first similar study in a Chinese population. The $R_{A/I}$ at 3 h (an index of *NAT2* polymorphism)

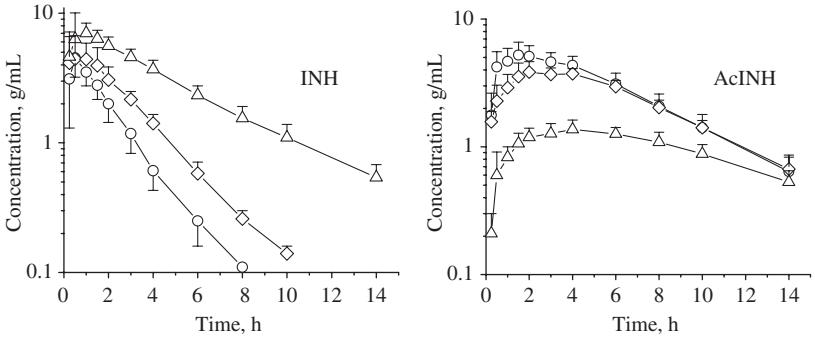

Figure 2 Concentration-time curves of INH and AcINH in different *NAT2* genotypes.

correlated well with the number of active *NAT2* genes (r=0.8520, p<0.05) (Figure 2), which suggests that *NAT2* activity showed a gene dose effect. The same results were obtained in pharmacokinetic parameters of INH. The $t_{1/2}$, C_{max} and AUC of INH in wt/wt, m/wt and m/m genotypes were 1:1.5:2.8 (p<0.01), 1:1.2:1.7 (p<0.01) and 1:1.6:4.1 (p<0.01), respectively (Table 1). Remarkable differences existed among various genotypes. INH exposure is increased gradually in m/m, m/wt and wt/wt groups. There are gene dose effects in $t_{1/2}$, C_{max}, AUC and CL of INH (Figure 3). C_{max} of INH showed a relatively poor correlation with *NAT2* genotypes. This may be caused by interindividual differences in the absorption of INH. As C_{max} and AUC of INH are crucial in drug efficiency, it can be inferred that patients with more active *NAT2* genes may need higher doses of INH.

Some studies suggest an association between AcINH and side effects. AcINH can be hydrolyzed to acetylhydrazine. The latter can be either converted to relatively untoxic metabolite diacetylhydrazine by NAT2 or metabolized to a reactive acylating intermediate metabolite through CYP2E1, which can covalently bind to liver protein and cause toxichepatitis (28–30). The apparent $t_{1/2}$ of AcINH was two times longer

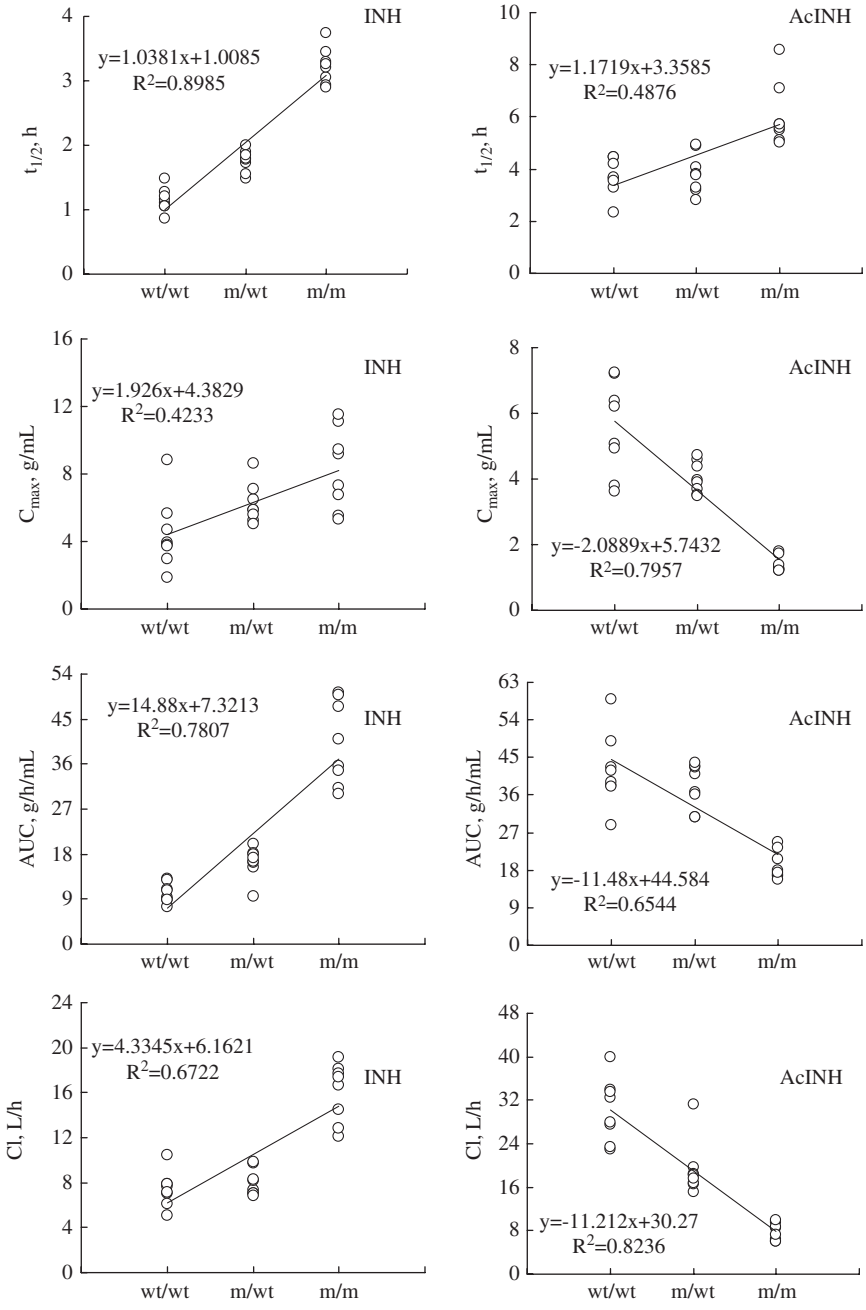

Figure 3 Correlation of pharmacokinetic parameters of INH and AcINH and various *NAT2* genotypes.

than INH (4.57±1.35 vs. 2.05±0.91 h). The $t_{1/2}$ of acetylhydrazine was even longer, especially in PM subjects ($t_{1/2}$=20 h) (3). It can be deduced that repeated doses of INH may cause the accumulation of AcINH and acetylhydrazine in PM subjects, and an adverse reaction may occur. AcINH exposure may play an important role in the occurrence of adverse reactions. Understanding the AcINH pharmacokinetics of various *NAT2* genotypes may help alleviate the risk of fatal hepatotoxicity. This is the first study on the influence of *NAT2* genotypes on the disposition of AcINH. We found a gene dose effect in the pharmacokinetic parameters of AcINH, especially in C_{max} and AUC. Further research is needed to elucidate the relationship between gene dose effect of AcINH and side effects.

In this study, we found that there was a conspicuous gene dose effect in the pharmacokinetics of INH and AcINH. Gene dose effect can explain the interindividual differences of disposition of INH and AcINH in the Chinese population, and furthermore differences in efficiency and side effects may be understood. It should be noted that all subjects in this study were healthy and were of similar age and weight. Further studies are needed on other populations, such as tuberculosis patients, patients with renal deficiency or hepatic diseases. On the basis of carefully designed prospective clinical trials, personalized dosage regimens can be designed according to the gene dose effect of *NAT2*, which can increase efficiency and diminish side effects.

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