SPANDIDOS PUBLICATIONS

Genotype and phenotype of NAT2 and the occurrence of adverse drug reactions in Mexican individuals to an isoniazid-based prophylactic chemotherapy for tuberculosis

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Received June 9, 2008; Accepted August 29, 2008

DOI: 10.3892/mmr_00000044

Abstract. Isoniazid (INH) is a drug extensively used as a prophylactic and therapeutic agent for human tuberculosis (TB). INH is metabolized by the enzymatic activity of N-acetyltransferase 2 (NAT2). Human NAT2, encoded by a highly polymorphic gene, is involved in the biotransformation of xenobiotics, including drugs and certain chemical carcinogens. Numerous studies have established the correlation between the acetylator phenotype and the NAT2 genotype in several populations; however, little is known regarding Latin-American populations and the pharmacogenetics of NAT2. Here, we report the molecular genotyping of the NAT2 gene, the acetylator phenotype, and the incidence of INH-related adverse reactions in a group of 25 Mexican individuals enrolled in a prophylactic protocol for TB. Using both the NAT2 genotyping and acetylation phenotyping approach, we found a ratio of 69.2 and 30.8% of slow and fast acetylators, respectively. Concordance of the NAT2 genotype and phenotype classification was 88% in the bimodal model. Regarding INH-related adverse reactions, only 2 individuals (8%) exhibited declared gastric intolerance. In our study group, we found an association between the NAT2 genotype and acetylator phenotype (OR=7.78, 95% CI, 0.87-87.98, Fisher's exact test, $p<0.05$), but did not find any genotype or phenotype association with the incidence of INH-related adverse reactions (Fisher's exact test, $p>0.05$).

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Abbreviations: NAT2, N-acetyltransferase 2; INH, isoniazid; AcINH, N-acetylisoniazid; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism

Key words: N-acetyltransferase 2, isoniazid, genetic polymorphism, acetylator phenotype, adverse drug reactions

Introduction

Worldwide, tuberculosis (TB) has emerged as a serious and dangerous public health issue, particularly because of the appearance of drug-resistant strains of *Mycobacterium tuberculosis* (the causative agent of TB), and due to the growing number of individuals affected by AIDS. Despite the dosage of the drug used for chemotherapy of TB, different drug-related adverse reactions have been observed, including peripheral neuritis, fever, visual damage, gastric intolerance, nettle rash and hepatic toxicity (1,2).

Isoniazid (INH), the hydrazide of isonicotinic acid, is one of the drugs frequently used as a therapeutic agent in the treatment of TB (since several strains of *M. tuberculosis* are drug-sensitive). Routinely, INH is administered in combination with other anti-TB therapeutic agents, such as rifampicine, ethambutol and pyrazinamide. Moreover, INH is regularly used as a single prophylactic agent of TB.

INH is metabolized mainly in the liver by the N-acetyltransferase 2 (NAT2) enzyme, and is converted to the inactive metabolite N-acetylisoniazid (AcINH) (3). Human NAT2 (a phase II enzyme) belongs to a family of enzymes that catalyze the acetyl transfer from acetyl-CoA to arylamines, arylhydracines and arylhydroxilamines. Biochemical studies have established that NAT2 has both the N- and O-acetylation enzymatic activities. The enzymatic activities of NAT2 are mainly involved in the detoxification mechanisms of aromatic amines, sulphonamides and aliphatic amines. These chemical structures are the core of such drugs as caffeine, isoniazid, sulphametazine, clonazepam, procainamide, dapsone and endralazine (1).

Regarding the acetylator phenotype and outcome in individuals treated with INH, the results of certain correlation studies have shown that fast acetylators metabolize the drug rapidly; hence, the dosage must be increased. On the other hand, slow acetylators have poor metabolism and are at a greater risk of developing INH-related adverse reactions (4-6). However, this observation must be interpreted carefully as certain extrinsic variables could act in favor of the development of adverse drug reactions (7-9).

The human NAT2 enzyme is encoded by a highly polymorphic gene, of which 36 alleles have been described (http://louisville.edu/medschool/pharmacology/NAT2.html). Each of these allelic variants has between 1 and 4 SNPs located within the polypeptide-encoding sequence. Recombinant DNA technology studies, using prokaryotic expression systems, have shown that the alleles NAT2*4, NAT2*12A, NAT2*12B, NAT2*12C and NAT2*13 encode enzymes with high acetylation activity, while the remaining alleles encode enzymes with low acetylation activity (10-12). Furthermore, pharmacogenetic studies carried out in different populations have suggested that the alleles NAT2*5, NAT2*6 and NAT2*7 are responsible for more than 95% of the slow acetylator phenotype (13,14).

The prevalence of a slow acetylator phenotype is highly variable among different ethnic groups (4): 50-70% in Caucasians, 35-55% in African Americans and 10-30% in Asians (15,16). African and Caucasian populations have a high frequency of the NAT2*5 allele (>28%) and a low frequency of the NAT2*7 allele (<5%), while Asian populations have a high prevalence of the NAT2*4 allele (44-79%) (13,17,18). Several genotype-phenotype association studies have found a high correlation between the genotype of human NAT2 and the acetylator phenotype; however, this is widely debated due to the discrepancies related to the methods used in obtaining each result and because of the haplotype-diplotype determinations (12,19-25,28).

Little is known about the prevalence of allelic variants of NAT2 in the Latin American population (20,25-27). Some studies have shown that the most frequent alleles are NAT2*4, NAT2*5A, NAT2*6A and NAT2*7A; however, these have been restricted to phenotypic analysis. Since knowledge regarding the pharmacogenetics of NAT2 and its clinical impact in Latin-American populations is limited, we conducted a genotype screening of NAT2 in a Mexican population, along with its acetylator phenotype association, and finally studied the occurrence of drug-related adverse reactions in individuals prophylactically treated with INH.

Materials and methods

Subjects. A prospective and observational study was carried out with healthy unrelated volunteers. Twenty-five individuals >18 years of age with a corporal weight >50 kg were included. Each individual was subjected to an INH-prophylactic protocol for TB. This study was registered in the Research Department of the General Hospital of Mexicali, Baja California, Mexico, no. 0201-HGMXL-UABC-20080404-11.

Based on the 2006 records of the Mexicali's Sanitary Jurisdiction, 69 adult individuals (>18 years of age) were included in the INH-prophylactic protocol. According to estimates using the statistical software Epi-Info v.6, a minimum population of 17 individuals was required to attain a 95% confidence and a 3-10% chance of the appearance of INH-related adverse reactions. The individuals were selected by a non-probabilistic sampling technique.

Informed consent. Each individual provided written informed consent, without receiving payment for participation. All procedures and activities were carried out following the legal dictates of the Mexican General Law of Health and the Principles of Ethics for Medical Research in Human Beings (Statement of Helsinki of the World Medical Association).

Prophylactic protocol. Before the initial drug dose, a 10-ml blood sample was obtained from each individual: 3 ml of blood was mixed with an anticoagulant (EDTA) and stored at -20˚C for further NAT2 genotype analysis, while 7 ml was used to separate and obtain serum to determine the basal biochemical parameters.

Daily, INH (300 mg) was administered orally to each volunteer for a 6-month period. All individuals were clinically evaluated on a monthly basis to ascertain their current state of health and to detect early symptoms of INH-related adverse reactions, such as peripheral neuropathy, fever, gastric intolerance, hypersensitivity reactions, nausea, vomiting, visual impairment, vertigo, ataxia, psychosis, convulsions, agranulocytosis, skin rash and hepatic toxicity.

Biochemical testing. As part of the clinical evaluation of the study group, before and during the prophylactic protocol the serum concentrations of enzymes relevant to the hepatic function were determined. These included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBL). Hepatic function was routinely monitored every two months or when an individual showed symptoms of hepatitis.

NAT2 genotyping. NAT2 genotyping was carried out by using a reported protocol that detects 4 SNPs by PCR-RFLP (29): C481T, G590A, A803G and G857A. Briefly, a 547-bp fragment of the human NAT2 gene, amplified by PCR, harbors the 4 SNPs and allows the detection of each by different patterns of endonuclease-digestion fragments (Table II).

The human genomic DNA was isolated from peripheral blood cells using the QIAamp DNA Blood Mini Kit (Qiagen), following the protocol provided by the manufacturer. The 547 bp was amplified by PCR using 100 ng of genomic DNA as a template, 20 pmoles of each synthetic oligonucleotide as primer (sense, P1: 5'-gctgggtctggaagctcctc-3'; and antisense, P2: 5'-ttgggtgatacatacacaaggg-3') and 2.5 U of Taq DNA polymerase (Qiagen) as enzyme. The thermal conditions were as follows: an initial denaturation step at 94˚C for 2 min followed by 35 cycles of denaturation at 94˚C for 1 min, annealing at 55˚C for 1 min, elongation at 72˚C for 1 min, and a final elongation step at 72˚C for 7 min.

Each SNP was detected individually and separately with different endonuclease digestion reactions. Briefly, 10-μl portions of the amplified DNA fragment (547 bp) were digested with 10 U of the following endonucleases (New England Biolabs): *Kpn*I for 16 h at 37˚C (C481T), *Taq*I for 6 h

Biochemical characteristics of isoniazid-treated ncluded in the study.

	Observed levels (mean ± SD)		Normal range
	Basal	Maximum	
ALT (U/ml)	30.3±13.7	41.2±17	13-69 U/ml
AST (U/ml)	26.8±6.3	33.9±9.4	15-45 U/ml
ALP (U/l)	75±21.5	83.5±23.1	38-126 U/l
TBL (mg/dl)	0.4±0.4	0.5±0.4	0.2-1.3 mg/dl

Table II. NAT2 allele frequencies in 25 unrelated Mexican individuals.

Alleles	Mutations				Frequency (%)
	C481T	G590A	A803G	G857A	
NAT2*4	C	G	A	G	20
NAT2*5A	T	G	A	G	2
NAT2*5B	T	G	G	G	34
NAT2*5C	C	G	G	G	6
NAT2*6A	C	A	A	G	24
NAT2*7A	C	G	A	A	14

at 65˚C (G590A), *Dde*I for 16 h at 37˚C (A803G) and *Bam*HI for 16 h at 37˚C (G857A). Restriction fragments were separated by agarose gel electrophoresis and visualized by ethidium bromide staining.

Acetylator phenotyping. The acetylator phenotype of each individual was determined using a serum sample collected 3 h after the administration of the first dose of INH. Sample preparation and HPLC analysis of INH and AcINH were performed following a previously reported method (30).

AcINH was prepared by acetylation of INH (Spectrum Chemical MFG. Corp.) with an excess of acetic anhydride (1:4) (Eastman Chemical Co.). After 1.5 h of continuous agitation at room temperature, AcINH was crystallized in a methanol-ethyl ether solution (1:4) (Mallinckrodt Baker, Inc.). The authenticity of the final product was confirmed by melting point and NMR analysis.

INH and AcINH calibration curves were plotted and human serum sample analysis was performed using an Agilent 1100 Series HPLC System (Agilent Technologies). Using a Zorbax Eclipse XDB-C18 column (4.6 mm i.d. x 250 mm, particle size 5 μm) and ammonium acetate buffer (0.05 M, pH 6.0) along with acetonitrile (99:1 v/v) as the respective stationary and mobile phase solutions, INH and AcINH were resolved at a flow rate of 1.2 ml/min. The retention time for INH and AcINH was 6.4 and 5.5 min, respectively. The concentration of each analyte in human samples was calculated using calibration curves. The acetylator phenotype was determined from the AcINH/INH metabolic ratio (MR) present in the sample.

Table III. Observed frequencies of NAT2 genotypes.

Genotype	No.	Frequency (%)
4/4	2	8
4/5C	1	4
4/6A	3	12
4/7A	2	8
5A/6A	1	4
5B/5B	6	24
5B/5C	2	8
5B/6A	1	4
5B/7A	2	8
6A/6A	3	12
6A/7A	1	4
7A/7A	1	4
Total	25	100

Statistical analysis. Allele, genotype and phenotype frequencies are reported as percentages. Fisher's exact test, odds ratios, and confidence intervals (CI) were used to compare the NAT2 genotype with the acetylator phenotype. Fisher's exact test was used to evaluate the relationship between the incidence of adverse reactions and both the NAT2 genotype and acetylator phenotype. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 12.0 Statistical Software for Windows (SPSS Inc.).

Results

Twenty-five Mexican individuals (17 females and 8 males; 31.6±11.2 years of age) were included in the INH-base prophylactic protocol of TB. Before the first dose, hepatic function was deemed normal as judged by clinical evaluation and the normal basal levels of certain biochemical parameters (Table I).

As shown in Table II, the alleles NAT2*5B, NAT2*6A and NAT2*4 were the most prevalent alleles. Hence, the most frequent genotypes were NAT2*5B/*5B, NAT2*6A/*6A and NAT2*4/*6A (Table III). Genotypically, individuals with homozygous NAT2*4/*4 or heterozygous individuals with the NAT2*4 allele were considered fast acetylators, for a total of 17 slow and 8 fast acetylators.

In order to obtain the acetylator phenotype, AcINH/INH metabolic ratios were calculated for each individual. The MR frequency displays a bimodal distribution with an antimode of 0.63, which was used as the threshold value in the acetylator phenotyping (Fig. 1). Seventeen individuals were identified as slow acetylators (MR<0.63) and 8 as fast (MR≥0.63) (Table IV).

A further comparative analysis of both approaches to obtain the acetylator metabolic status was performed. Notably, we found a genotype/phenotype concordance in 19 individuals; however, a discrepancy was found in the other 6 individuals. The possible relation between genotype and phenotype was analyzed using Fisher's exact test and odds ratio analysis. These statistical analyses indicated an association between

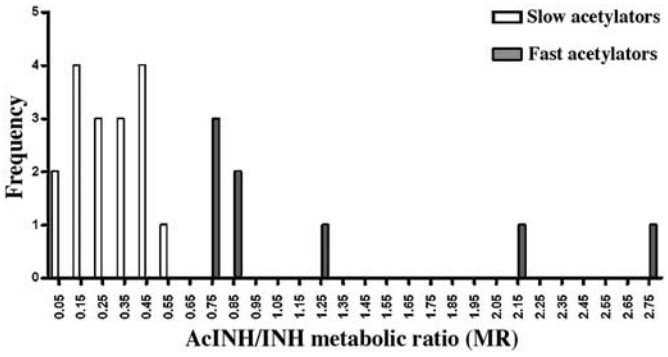

Figure 1. Frequency distribution histogram of the AcINH/INH metabolic ratio (MR).

Table IV. Distribution of the slow and fast acetylation-determining genotypes and phenotypes in both genders.

	Slow acetylators		Fast acetylators	
	Females	Males	Females	Males
Genotype	12 (48%)	5 (20%)	4 (16%)	4 (16%)
Phenotype	13 (52%)	4 (16%)	4 (16%)	4 (16%)

the NAT2 genotype and the acetylator phenotype (OR=7.78, 95% CI, 0.87-87.97, Fisher's exact test, $p<0.05$).

Regarding INH-related adverse reactions, none of the 25 individual showed any sign or symptoms of intoxication or hepatic failure; however, two suffered gastric intolerance. Both individuals were slow acetylators by phenotype (MR=0.36 and 0.55, respectively). Yet, by using the Fisher's exact test we did not find any association between the INH-related adverse reaction incidence and the NAT2 genotype ($p=0.52$) or with the acetylator phenotype ($p=0.47$).

Discussion

Here, we present a systematic preliminary study intended to correlate the genotype and phenotype of the human enzyme NAT2 with the incidence of INH-related adverse reactions in a prophylactic protocol for TB in a Mexican population.

We found that the most prevalent alleles were NAT2*5B, NAT2*6A and NAT2*4, similarly as reported for Caucasian Americans, Europeans and Omanis populations (11,13,17, 31,32,36). Importantly, the high-scored NAT2*5B allele, whose frequency is very low in Japanese and Central American Indians, was as high as the observed in Caucasian Americans and Europeans (33-42%) (23-25,33). On the other hand, we found that allele NAT2*7 which is very rare in Caucasians and relatively frequent in Eastern Asian populations, was mid-scored (31,34). In contrast, our results highly differed in comparison with those observed in Central-American populations (26,27,33).

By means of the genotyping approach, we found that the slow acetylator was the most frequent, with a high prevalence of NAT2*5B/*5B and NAT2*6A/*6A genotypes. Similar results were observed in Caucasian Americans and Omanis populations, where NAT2*5B/*5B was the most prevalent genotype (32,36). Predominance of the slow acetylator (by genotype) has been also reported in German and Hindu populations (13,35). Notably, Arab populations consist of 81.6% slow acetylators, with a predominantly NAT2*5/*5 genotype (37). These data (including our results) differ enormously from those of other populations in which the proportion of slow acetylators is low, such as Chinese, Korean, and Central American Indians (20,33,38-41).

Several populations have shown a high concordance (88-100%) between the phenotype and genotype (13,23,24,29, 36-38). In our study group, we found an association between the acetylator genotype and phenotype for NAT2, where the global rate of prediction was 88% for the acetylator phenotype from the genotype. Individual classification of slow and fast acetylator by phenotype was based on the distribution of the AcINH/INH metabolic ratio (MR) of the population. From a bimodal distribution, the antimode of 0.63 was used to classify the acetylator phenotype of our population. Finally, we did not find any serious INH-related adverse reactions, such as hepatic toxicity.

In conclusion, this study is the first NAT2 genotyping in a Mexican population, which shows that there is an association between the acetylator genotype and phenotype (OR=7.78, 95% CI, 0.87-87.97, Fisher's exact test, $p<0.05$) with a considerable prevalence of slow acetylators by phenotype as well as genotype (68%). However, no association was found between them and the incidence of adverse reactions (Fisher's exact test, $p>0.05$). This work establishes the basis for future clinical and epidemiologic research related to the acetylator polymorphism in populations from different regions in Mexico.

A clear comprehension of the existing relationship between acetylator status and the incidence of adverse effects induced by drugs against TB, particularly INH, could contribute to establishing criteria and methodologies that permit a timely identification of patients with greater susceptibility to the development of such reactions, specifically with the purpose of optimizing the dosage of these drugs.

Acknowledgements

This study was supported by a Grant of the Facultad de Medicina Mexicali de la Universidad Autónoma de Baja California (UABC). We thank Mr. Akos Nemecz for critically reading the manuscript.

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