The effect of *CYP1A2* gene polymorphism on the metabolism of theophylline

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Abstract. This aim of the study was to investigate the effect of CYP1A2 gene polymorphism on the metabolism of theophylline in minority and Han nationality. A total of 50 cases of Han (Han group) and 50 minority nationalities (ethnic groups) treated with theophylline were selected for the study. The genotype and allele frequencies of the two groups of *CYP1A2* gene, G-3113A and G-3860A, were compared to determine the rate of theophylline clearance. The results showed that there was no significant difference in the concentration of the homeostasis and the rate of the theophylline removal rate (P>0.05). There was no significant difference in the genotype and allele frequencies of the *CYP1A2* gene, G-3113A and G-3860A apolymorphic site. This study employed a logarithm to determine theophylline clearance in order to correlate it with the normal distribution. The results showed that the theophylline clearance of the two groups of *CYP1A2* G-3113A gene loci A allele carriers (AA+GA genotype) was significantly lower than that of the G allele carriers (GG genotype), and a significant difference between the groups was identified (P<0.05). There was no significant difference in the theophylline clearance rates in the two groups for the *CYP1A2* gene, G-3860A apolymorphic site (P>0.05). Compared to the GG genotype of the *CYP1A2* gene, the G-3113A site AA and GA genotype patients had a low clearance rate in the theophylline, whereas there was no correlation between teh genotypes of the *CYP1A2* gene, G-3860A and the rate of theophylline clearance.

Introduction

Cytochrome P450 (cytochrome P450, CYP450), which is commonly found in organisms, is also known as monooxygenase or mixed functional enzymes, which belong to a group of functional and structurally related superfamily genes encoding heme enzymes. Since the carbon monoxide complex and the reduced cytochrome P450 have the same absorption peak at 450 nm, it is known as CYP450 (1,2).

CYP450 plays a key role in the metabolism of exogenous and endogenous substances. Of more than 300 identified P450 isozymes, 2E1 (CYP1A2, CYP2E1) and P4501A2 in chemical carcinogenesis play a critical role, and are classified as 'toxic' isoenzyme (3-5). The content of CYP1A2 in the liver is relatively high, carcinogens such as amino acids, aflatoxin, toxins and aromatic compounds are metabolized by CYP1A2 and eventually produce carcinogenic substances. It has been observed that many drugs are metabolized by CYP1A2 (6-8). Thus, there are some drugs involved in the metabolic process and the role of individual differences in the key factors, that is, the activity of CYP1A2 *in vivo* differences between individuals.

The aim of the present study was to investigate the genotype frequencies of G-3113A and G-3860A loci and the correlation between allele frequencies and theophylline metabolism in *CYP1A2* gene of 50 cases of Han and 50 minority nationalities.

Materials and methods

Subjects and groups. A total of 50 cases of Han (Han group) and 50 cases of minorities (ethnic groups) were enrolled in the hospital between November 2015 and May 2016.

Inclusion criteria. Criteria for inclusion were: Patients with bronchial asthma or chronic obstructive pulmonary emphysema; aged, 20-60 years, with a weight of 40-70 kg. Patients who actively cooperate with the study and signed informed consent were included in the study. The study was approved by the Ethics Committee of Guizhou Provincial People's Hospital.

Exclusion criteria. Patients with severe liver and kidney disease, patients with short-term use of theophylline on the metabolism, with severe mental illness, pregnant or lactating women, or patients who refused to cooperate with the researchers were excluded.

Research methods
Clinical specimen collection. Blood samples were collected via the elbow vein as the blank blood sample. Patitents were treated with aminophylline solution i.v.gtt 250 mg q.d. x10 days, after which the blood samples were collected and

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preserved under fasting conditions. Blood samples were placed in EDTA anticoagulant, centrifuged for 10 min at 1,610 x g, and blood cells and plasma were separated and stored at -80℃ in a refrigerator for subsequent use.

Determination of theophylline and 1,3-dimethylxanthine using chromatography mobile phase acetonitrile. The chromatographic conditions were mobile phase acetonitrile: formic acid solution (0.3%) at a ratio of 5:95; the AgilentZORBAXSB-C18 column (150x4.6 mm, 5 μm) was used at a column temperature of 30℃, the column flow speed was 1 ml/min and the detection wavelength was 280 nm with an injection volume of 20 μl. Preparation of the standard solution was: 49.90 mg theophylline and 49.73 mg acetaminophen were accurately weighed, and the stock solution was prepared with double-distilled water (mass concentration of 500 μg/ml). In addition, 100.00 mg 1,3-two urate was accurately weighed with sodium hydroxide solution (0.25%) to store the stock (mass concentration of 1 mg/ml), and the stock solution was stored at 4℃ at a dilution of ?. Blank serum was produced from our hospital outpatient examination center, and the subject serum was obtained from our hospital center laboratory. For serum sample handling, 480 μl of serum sample was taken and 20 μl of internal standard acetaminophen (mass concentration of 100 μg /ml) was added. Following agitation and mixing, 1.5 ml acetonitrile was added, and the samples were vortexed and mix for 2 min. The samples were then centrifuged for 10 min at 1,605 x g, and 1.5 ml supernatant was removed, vacuum-concentrated and air dried. The residue was then placed in 200 μl formic acid solution (0.3%) solution. At the speed of 1,605 x g, the resulting solution went through the microporous membrane (pore size, 0.22 μm) filter, after which the filtrate 20 μl injection, and HPLC analysis was performed.

Detection method of CYP1A2 gene polymorphism. The *CYP1A2* gene was screened by tag and SNP using HapMap and Haploview software (Broad Institute, Cambridge, MA, USA) G-3113A and G-3860A single nucleotide polymorphisms were selected according to the minimum allele frequency >10%, the linkage disequilibrium parameter was D=1 and r2 >0.8. The G-3113A and G-3860A polymorphisms of the *CYP1A2* gene were typed by genotyping.

Statistical analysis. The basic clinical information of sex and age of the two groups were counted by questionnaire. The genotypes of the different polymorphic loci were determined and the corresponding allele frequencies were calculated. The subjects in the two groups were medium. Whether or not the gene frequency satisfied the population representation was tested by Hardy-Weinberg equilibrium. The data in the present study were all analyzed by SPSS 20.0 (IBM Corp., Armonk, NY, USA) statistical analysis software. The data were expressed as mean ± standard deviation (SD). The variance homogeneity test was performed by one-way ANOVA. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of characteristic data between two groups. According to the results of the survey, there were no significant differences ($P>0.05$) between the Han nationality and the ethnic patients with regard to sex, age, weight, smoking status and disease. Thus, the data were comparable (Table I).

Comparison of steady-state serum theophylline concentration and theophylline clearance rate between the two groups. The steady-state serum theophylline concentration used for Han subjects was 3.52±0.46 mg/l, while that for the minority group were 3.48±0.48 mg/l. The difference between the two groups was not statistically significant ($P>0.05$). The theophylline clearance rate for the Han subjects was 0.058±0.010, while that for the minority group was 0.059±0.009. The difference between the two groups was not statistically significant ($P>0.05$) (Table II).

Comparison of genotype distribution of G-3113A locus of CYP1A2 gene between the two groups. The frequencies of *CYP1A2*, GA and GG genotypes were 82, 16 and 2% in the G-3113A loci of Han subjects, respectively. The frequency of A alleles was 90% and the frequency of G alleles was 10%. For the minority groups of subjects with *CYP1A2* G-3113A gene AA, GA and GG genotype frequencies were 80, 18 and 2%, respectively. The A allele frequency was 89% and G allele frequency was 11% for the two groups. The genotype and allele frequencies were not significantly different ($P>0.05$) (Table III).

Comparison of genotype distribution of the CYP1A2 gene G-3860A locus between the two groups. The frequencies of AA, GA and GG genotypes of the *CYP1A2* gene in Han subjects were 46, 44 and 10%, respectively. The frequency of A allele was 68% and that of G allele was 32% for G-3860A. By contrast, the minority groups of subjects *CYP1A2* G-3860A gene AA, GA and GG genotype frequencies were 48, 42 and 10%, respectively, while the A allele frequency was 69% and the G allele frequency was 31% for the two groups. The genotype and allele frequencies were not significantly different ($P>0.05$) (Table IV).

Correlation between the genotype of G-3113A locus and theophylline clearance rate of CYP1A2 gene in the two groups. In this study, logarithmic methods were used for theophylline clearance to make it more consistent with the normal distribution. The results showed that there were significant differences in the number of theophylline clearance ($P<0.05$) in the G-3113A locus of the *CYP1A2* gene in the Han nationality group and the ethnic group (Table V).

Correlation between CYP1A2 gene G-3113A allele and theophylline clearance in the two groups. The number of theophylline clearance for the G-3113A locus A (AA+GA genotype) of the *CYP1A2* gene of the Han group was -1.23±0.10. The number of theophylline clearance for the G allele (GG genotype) was -1.32±0.06. There was a significant difference between the two groups ($P<0.05$). The number of theophylline clearance of the *CYP1A2* gene G-3113A locus A allele (AA + GA genotype) was -1.22±0.10, while the number for the G allele (GG genotype) was -1.33±0.08. There was a significant difference between the two groups ($P<0.05$) (Table VI).

Correlation between the G-3860A genotype and theophylline clearance rate of CYP1A2 gene in the two groups.

Table I. Comparison of characteristic data between the two groups.

Characteristics	Groups		χ^2	P-value
	Han n =50	Ethnic n =50		
Age (years)	56.18±8.75	55.96±8.87	1.075	>0.05
Weight (kg)	59.59±7.33	60.02±8.05	1.038	>0.05
COPD (n)	28	26	1.236	>0.05
Asthma (n)	22	24	2.085	>0.05
Sex (n)				
Male	32	30	2.221	>0.05
Female	18	20		
Smoking (n)				
Yes	28	29	1.149	>0.05
No	22	21		
Total (n)				
Hypertension	9	8	2.417	>0.05
Gout	2	1		
Rheumatoid arthritis	1	2		

Table II. Comparison of steady-state serum theophylline concentration and theophylline clearance rate between the two groups.

Groups	Steady-state serum theophylline concentration (mg/l)	Theophylline clearance rate
Han (n=50)	3.52±0.46	0.058±0.010
Ethnic (n=50)	3.48±0.48	0.059±0.009
χ^2	1.075	2.331
P-value	>0.05	>0.05

Logarithmic methods were used for theophylline clearance to make it more consistent with the normal distribution. The results showed that there was no significant difference in the selectivity of theophylline corresponding to the genotype of the *CYP1A2* gene G-3860A in the Han nationality and ethnic groups (P>0.05) (Table VII).

Correlation between CYP1A2 gene G-3860A allele and theophylline clearance in two groups. The number of theophylline clearance of the G-3860A locus A allele (AA + GA genotype) of the *CYP1A2* gene of the Han nationality group was -1.40±0.20, while that of G allele (GG genotype) was -1.42±0.19. No significant difference was identified between the two groups (P<0.05). The number of theophylline clearance of the *CYP1A2* gene G-3860A locus A allele (AA+GA genotype) was -1.41±0.20, while that of the allele carrier (GG genotype) was -1.43±0.22. No significant difference was identified between the two groups (P<0.05) (Table VIII).

Discussion

The *CYP1A2* gene is located on human chromosome 15 and contains 7 exons and 6 introns. The expression of CYP1A2 mRNA and protein in liver was 15- to 40-fold higher than that between individuals, and the activity of CYP1A2 in females was significantly lower than that in males (9-11). Differences between species can also lead to differences in CYP1A2 activity. Relevant reports found that the CYP1A2 activity of Africans and Asians is significantly lower than occidental individuals, for example, the CYP1A2 activity of Swedish is 1.5-fold higher than that of Korean patients (12). In addition, CYP1A2 activity among individuals is also affected by environmental factors, for example, oral contraceptives can cause a decrease in CYP1A2 activity, while the consumption of cruciferous vegetables, smoking and the use of omeprazole can cause increased activity of CYP1A2.

However, the difference in CYP1A2 from 35 to 75% was due to genetic factors. At present, 41 CYP1A2 alleles and corresponding mutants have been identified. Of these, more studies have been conducted on CYP1A2*1C, *1D, *1E and *1F (13,14). CYP1A2*1C was able to reduce the effect of cigarettes on CYP1A2 activity in smokers because it reduced the expression level of the enzyme. However, CYP1A2*1F can increase the effect of certain inducing substances on CYP1A2 activity. There is a difference in the frequency of alleles between different ethnicities. The CYP1A2*1C mutation frequency in the Chinese population is 22%, while that in the Japanese population is 23%. The CYP1A2*1K mutation frequency in the Saudi Arabian population is 3.6%, 3% in the Ethiopian population and 0.5% in the Spanish population. CYP1A2*3, *4, *7, *11, *15 and *16 reduce the activity of CYP1A2 in the identified CYP1A2 allele mutations, but not in the remaining CYP1A2. There is no definite report on

Table III. Comparison of genotype distribution of G-3113A locus of *CYP1A2* gene between the two groups.

Groups	Genotype (n, %)			Allele (n, %)	
	AA	GA	GG	A	G
Han (n =50)	41 (82.00)	8 (16.00)	1 (2.00)	90 (90.00)	10 (10.00)
Ethnic (n =50)	40 (80.00)	9 (18.00)	1 (2.00)	89 (89.00)	11 (11.00)
χ^2		3.061			0.084
P-value		>0.05			>0.05

Table IV. Comparison of genotype distribution of G-3860A locus of *CYP1A2* gene between the two groups.

Groups	Genotype (n, %)			Allele (n, %)	
	AA	GA	GG	A	G
Han (n =50)	23 (46.00)	22 (44.00)	5 (10.00)	68 (68.00)	32 (32.00)
Ethnic (n =50)	24 (48.00)	21 (42.00)	5 (10.00)	69 (69.00)	31 (31.00)
χ^2		2.187			1.443
P-value		>0.05			>0.05

Table V. Correlation between the genotype of G-3113A locus and theophylline clearance rate of *CYP1A2* gene in the two groups.

Groups	Genotype	Lg (1,3 DU/TP)	χ^2	P-value
Han	AA	-1.23±0.09	8.446	<0.05
	GA	-1.22±0.09		
	GG	-1.32±0.06		
Ethnic	AA	-1.22±0.10	8.349	<0.05
	GA	-1.24±0.08		
	GG	-1.33±0.08		

Table VI. Correlation between *CYP1A2* gene G-3113A allele and theophylline clearance in the two groups.

Groups	Allele	Lg (1,3DU/TP)	χ^2	P-value
Han	AA+ GA	-1.23±0.10	9.012	<0.05
	GG	-1.32±0.06		
Ethnic	AA+ GA	-1.22±0.10	8.746	<0.05
	GG	-1.33±0.08		

the association between allele polymorphism and enzyme activity (15,16).

The serum concentration of theophylline used for relieving asthma was 10-20 mg/l, bid, the dose is generally 200 to 400 mg (17). However, the use of theophylline is more likely to produce some side effects and the anti-asthmatic effect of β-agonists is more rapid and effective than theophylline. Therefore, in the GOLD guidelines, theophylline is already a second-line preparation for COPD asthma treatment (18). A recent study found that low concentrations of theophylline (5-10 mg/l) can produce anti-inflammatory and immunomodulatory effects, with <5 mg/l concentration of theophylline playing a role in enhancing hormone sensitivity (19). Previous findings have shown that the daily administration of 250-375 mg of theophylline and 40 g of budesonide compared to only 800 mg dose of budesonide administered for moderate asthma does not yield a significant difference, even though the combination of theophylline and budesonide is cost-effective (19). In a multicenter comparison study conducted by the Chung Nanshan team (20), it was

Table VII. Correlation between the genotype of G-3860A genotype and theophyl-line clearance rate of *CYP1A2* gene in the two groups.

Groups	Genotype	Lg (1,3 DU/TP)	χ^2	P-value
Han	AA	-1.45±0.16	0.775	>0.05
	GA	-1.38±0.24		
	GG	-1.42±0.19		
Ethnic	AA	-1.40±0.19	1.450	>0.05
	GA	-1.42±0.20		
	GG	-1.43±0.22		

Table VIII. Correlation between *CYP1A2* gene G-3860A allele and theophylline clearance in the two groups.

Groups	Allele	Lg (1,3 DU/TP)	χ^2	P-value
Han	AA+ GA	-1.40±0.20	1.022	>0.05
	GG	-1.42±0.19		
Ethnic	AA+ GA	-1.41±0.20	1.016	>0.05
	GG	-1.43±0.22		

observed that the duration of acute exacerbation of COPD patients and the duration of acute attack were significantly higher than those of placebo in patients with COPD compared with placebo at a dose of 100 mg twice daily. By contrast, the effect of treatment with 100 mg of theophylline twice a day to reach the number of body concentration remains to be determined. Additionally, use of this dose as a target *in vivo* plasma concentration has not been previously reported. Previous findings have shown that for a theophylline dose of 250 mg twice daily, steady-state plasma concentration of theophylline was 6.1 mg/l. However, conclusions of that study are discrepant from our study, which showed that the theophylline metabolism of Han and ethnic minorities was slower than that of occidental populations. Thus, the prescribed dose should be less than that for occidental populations (21). It can be seen that the drug concentration of theophylline between different ethnicities is quite different and appropriate attention should be paid in the use of theophylline between different regions and ethnic groups. In this study, the difference between the scavenging rates of the Han population and the minorities was not found, and the effect of body weight on the plasma concentration of theophylline was not excluded. The metabolism of theophylline *in vivo* may be more susceptible to the clearance rate of theophylline. The genotype and allele frequencies of the *CYP1A2* gene G-3113A and G-3860A in the Han and ethnic groups were significantly different from those of the reported Caucasian mutations, which was associated with CYP1A2*. Genetic polymorphisms have the same ethnicity as racial differences (3,22,23). Differences in the frequency of mutations in these functional sites may be one of the causes of ethnic differences in CYP1A2 activity and the resulting CYP1A2 metabolic drugs also have racial differences (24-27). Thus, the individualized administration of the drug requires consideration of the genetic characteristics of the region. However, there was no difference in genotype and allele frequencies between the G-3113A and G-3860A loci in *CYP1A2* gene between Han and minority groups in this study.

In this study, the frequency of G-3113A mutation in the Chinese Han and ethnic minority groups was approximately 10 and 11%, respectively. However, in the experiment on gene polymorphism in the Korean and Swedish population, the mutation frequency of the G-3113A locus was 2.7% in the population and 2.3% in the Swedish population (28), which was much lower than the conclusion of the study. In this study, it was observed that the clearance rate of theophylline was slower than that of the G-3113A mutation, which may explain the metabolism of theophylline in the Chinese population. However, this conclusion requires a large number of samples from different ethnicities to be studied.

By studying the clearance rate of theophylline and the mutation of the G-3860A function site, we found that the clearance rate of theophylline did not affect the mutation between the genotypes. The conclusion is different from other reports. Japanese researchers have observed the relationship between the plasma concentration of theophylline and the mutation of the G-3860A site of the CYP1A2 gene in asthmatic patients (29). It has been observed that the selenium clearance of G-3860A site was decreased. A decrease was observed for Korean workers in the rate of CYP1A2-3860 (G/A) G-A theophylline metabolism of 1,3-dimethyluric acid. However, it has been reported that the level of theophylline clearance between G-3860A genotypes is similar, and our findings also reveal that the metabolism of theophylline *in vivo* is not affected by the genetic polymorphism of the locus. The production of such differences may be related to racial differences, or because the sample size is slightly smaller (30-32). Therefore, the ability of such sites to affect the metabolism of theophylline requires more samples and studies between different ethnicicites.

In conclusion, the results have shown that there was no significant difference between the *CYP1A2* gene G-3113A and G-3860A genotypes in the Han and ethnic minorities. Compared with the GG genotype, the clearance rate of the main body of the *CYP1A2* gene in the G and 3113A loci of the Han and ethnic minorities was decreased. The clearance rate of theophylline in the genotype of the *CYP1A2* gene G-3860A in the Han and ethnic minorities was decreased, with significant differences.

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