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CONSENT TO PARTICIPATE IN RESEARCH

Name of the study: A study of polymorphism of hepatic drug metabolism enzymes in a South Indian population.

Institute: Jawaharlal Institute of Post-graduate Medical Education and Research, Pondicherry.

Name of the Investigator: Benny K. Abraham

Name of the Supervisor: Dr. C. Adithan

Introduction: We would like you to take part in study being conducted by us at JIPMER. Before you decide whether or not to participate, we would like to call your attention to three matters. First your participation is entirely voluntary, your own personnel choice. Second, if at any time you want to withdraw from the study, you may do so. Your withdrawal would in no way result in JIPMER withholding goodwill or normal medical care. Finally we would like to point out that, although we accept this study to produce knowledge that might generally benefit others, this indirectly may be beneficial for you to understand your cytochrome P-450 2D6 (CYP2D6) activity. Below is a brief description of the nature and purpose of the study including its possible risks, inconveniences or discomfort. Please feel free to ask any question you may have about this study.

Purpose: To understand the prevalence of CYP2D6 enzyme polymorphism in South Indian population.

Method: You may be asked to take syrup dextromethorphan (equivalent to 30mg, single dose) before going to bed after voiding your bladder. Overnight (8 hours) urine will be collected and around 20ml of that will be stored for the study.

Risks, Inconveniences and Discomforts: In therapeutic dose (10 to 30mg, 5 to 6 times a day) no major adverse effects reported. But extremely high dose may produce CNS depression. Other possible side effects are dizziness, gastro-intestinal disturbances, excitation and confusion.
Expected benefits: Since you are a healthy volunteer, no direct benefit will accrue from this study. However it may be gratifying to know that your contribution is indispensable for the advancement of medical knowledge. Indirectly it may be helpful for you to know about your CYP2D6 activity.

The details of the study have been explained to me and I consent to participate in the study outlined above.

Date: 

Signature

Name:
Address:

Witnessed by:
Annexure-V

Proforma

GENETIC POLYMORPHISM OF CYP2D6 IN SOUTH INDIAN POPULATION

Number: Date:

Name:

Age: Sex: Address: State:

Height: Weight:

Religion: Subdivision:

Alcoholic: Yes/No (Duration_________________)

Smoker: Yes/No (Duration__________Quantity_____/day)

Food: Vegetarian/Non-vegetarian

Drug history: Yes/No

Drug Name: Duration:

History of allergy:

History of chronic illness:

General physical examination:

BP: Temperature: Pulse:

Adverse reaction with test drug (if any):

Volume of urine:

REPORT:

C. No. DM= DT= DM/DT=

Phenotype:
Annexure-VI:

PUBLICATIONS

A. Research papers presented in the conferences and awards won:

1. ABRAHAM BK, Adithan C, Shashindran CH, Vasu S, Alekutty NA. Genetic polymorphism of CYP2D6 in Keralite (South India) population. Southern regional conference of Indian Pharmacological Society, 1999, Perundurai, Tamilnadu

   Won the Best scientific paper award


   Won The Servier Young Investigators' Award Instituted by Institutet de Recherches Internationales Servier, France


B. Research Papers published:


**Reviews**

1. ABRAHAM BK, Adithan C. Genetic polymorphism of *CYP2D6* (Submitted for publication).
Genetic polymorphism of CYP2D6 in a Keralite (South India) population

CYP2D6, which exhibits genetic polymorphism, is involved in the metabolism of more than 40 drugs especially neuroleptics, antidepressants, certain anti-arrhythmics and lipophilic β-adrenergic receptor blockers as well as opioids such as codeine [1]. Pronounced interethnic differences in the prevalence of this polymorphism are known to exist. The poor metaboliser (PM) phenotype is present in, for example, 5–10% of European-derived Caucasians [2], less than 1% of Chinese [3] and Japanese [4], 1% of Saudi Arabians [5], 0–2% of black populations [2] 1% of Thais [6] and 0–2% of Sinhalese in Sri Lanka [7]. However, the CYP2D6 polymorphism in Indian populations has not been studied extensively. A study among subjects resident in Bombay, which is on the west coast of the central part of India, reported 2% PM with respect to CYP2D6 [8]. A much more recent study shows a frequency of 3% PM in a North Indian population [9]. Since CYP2D6 polymorphism has not been studied in a Keralite population, the present study was undertaken.

The study was performed in 104 volunteers residing in Kerala, who were mostly students and staff from Mahatma Gandhi University, Kottayam, Kerala. Sixty-four were males and 39 were females in the age range of 17–44 years (mean ± s.d age: 23.5 ± 3.7 years). The mean body mass index ± s.d was 20.7 ± 2.6. All subjects gave their informed consent and the study was approved by the Ethics committee, JIPMER, Pondicherry. All subjects were judged to be in good health as determined by a medical history, physical examination and blood pressure measurement. They were on no medication and drank no alcohol for at least 2 weeks before the study.

After voiding their bladder prior to bedtime, participants ingested 30 mg dextromethorphan (5 ml of Lactura-EA, cough suspension, FDC Limited, Aurangabad, India). Urine was collected overnight for 8 h. A 20 ml aliquot was stored at −20 °C until analysis for dextromethorphan (DM) and dextrorphan (DT) by hplc [11]. The inter and intraday coefficient of variation for assay of DM and DT (50–8000 ng ml⁻¹) were less than 10% and 5%, respectively. The least quantifiable amount was 20 ng ml⁻¹ for both DM and DT.

The oxidative phenotype assignment was based on the value of the molar urinary ratio of DM to DT (metabolic ratio) in relation to the population antmode. Subjects with a metabolic ratio greater than 0.3 were classified as poor metabolisers with respect to the CYP2D6 enzyme [12]. Nineteen subjects (92.6%) had metabolic ratios between 0.005 and 0.192 and were classified as extensive metabolisers (EM). Five subjects were identified as PM, four males and one female. They had metabolic ratios between 0.315 and 3.14 (Figure 1). This corresponds to a prevalence of the PM phenotype of 4.8% with a 95% confidence interval of 1.6–10.9%. Three subjects (two males and one female) who had very low metabolic ratios between 0.0034 and 0.0039 may be identified as ultra extensive metabolisers (UEM) with very high enzyme activity [1].

The distribution of the metabolic ratio was not significantly different between male and female subjects (P > 0.05). No side-effects or any adverse drug reactions were observed. The body mass index of the subjects did not significantly influence the metabolic ratio (P > 0.05).

The prevalence of PM in the Keralite population is more than the mean value of approximately 1% observed in other Asian populations [3–7]. The metabolic ratio is determined by factors such as renal drug clearance as well as enzyme activity. Environmental factors may modify these variables which may give rise to differences in the antmode of the metabolic ratio between ethnic groups [6]. However, the prevalence of PM with respect to CYP2D6 in the Dravidian population of Kerala differs from that reported in the Indo-Aryan subjects of Sri Lanka, Bombay and North India [10].

There is a rightward shift in the frequency distribution curve of dextromethorphan in the Keralite population compared with the Caucasian population studied by Christman et al. (P < 0.001) [13]. However, the frequency distribution pattern of the Keralite population is comparable with that reported in North Indian populations (P > 0.05). A similar intratissue difference in the frequency distribution of the metabolite metabolic ratio has also been observed between Chinese and Japanese populations [14]. Differences between white subjects and subjects from Kela in lifestyle, dietary habits, and/or occupation may contribute to the ethnic difference in the activity of CYP2D6.

This is the first study of the pattern of CYP2D6 enzyme activity in the Keralite population. Since this ethnic group has migrated widely to different parts of the world, these results may serve as a basis for further studies to test the relationship between drug oxidation polymorphism and drug-induced adverse reactions or diseases of unknown aetiology in Keralites. Further study in other South Indian states can give a clearer picture of the CYP2D6 polymorphism in this region.

We are grateful to Dr Eva Rasmussen, Department of Clinical Pharmacology, University hospital, Uppsala and Dr S V Shanbhag, Boehringer Mannheim India Ltd.
Figure 1 Distribution of the dextromethorphan metabolite ratios among 104 healthy subjects in Maharashtra, India for their generous gift of dextromethorphan and dextromethorphan respectively. We thank all the volunteers who participated in the study.

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10 Roland JP, Breton F. Idi of the language and ethnic communities of South Asia. Naya publication. New Delhi, India 1992 39

Excretion of fluvoxamine into breast milk

Treatment with antidepressants is regularly demanded in post partum women due to the high prevalence of mood and anxiety disorders during this period. In general treatment with selective serotonin reuptake inhibitors (SSRIs) have been considered to be compatible with breast feeding [1, 2] although some concern has been alleged about the use of fluoxetine because of reports of possible adverse effects in sucking infants whose mothers were treated with fluoxetine [3–5].

The subject of this report is a 31 yr old woman with a history of panic disorder but no somatic disease as assessed by medical history, physical examination and routine blood chemistry. Height and body weight were 175 cm and 90 kg respectively. The study was performed 3 months post partum and the subject was treated with fluvoxamine for 6 months with the present dosage 100 mg twice daily. After intake of 100 mg fluvoxamine (Favam), anti-coated fluvoxamine was detected by Solvay Pharma (Brussels, Belgium) at 08:00 h venous blood samples (10 ml) and milk samples (5 ml) from both breasts were collected every hour during a 12 h period.
Genetic polymorphism of CYP2D6 in Karnataka and Andhra Pradesh population in India

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KEY WORDS cytochrome P-450 CYP2D6; human; India; high pressure liquid chromatography; dextromethorphan; phenotype; polymorphism(genetics)

ABSTRACT

AIM: To study the prevalence of cytochrome P-450 2D6 (CYP2D6) polymorphism in Karnataka (KA) and Andhra Pradesh (AP) population. METHODS: Two hundred and eleven healthy human volunteers participated in the study (100 from KA and 111 from AP). At bed time, after voiding their bladder, the volunteers ingested 30 mg of dextromethorphan hydrobromide (DM). Urine samples were collected for 8 h. DM and its metabolite dextrorphan (DT) were estimated in the urine using HPLC. The metabolic ratio (DM/DT) was used for phenotyping. RESULTS: The prevalence of poor metabolisers (PM) in KA is 4 % and AP is 1.8 %. CONCLUSION: The frequency of PM phenotype in South Indian population is in between the Western and Oriental population.

INTRODUCTION

Polymorphism in CYP2D6 has been studied intensively in recent years with respect to both effects on drug metabolism and a possible role in susceptibility to certain diseases[1]. The CYP2D6 polymorphism has become one of the most important pharmacogenetic differences involved in clinical drug efficacy and undesirable drug reactions[2].

CYP2D6 is responsible for the metabolism of more than 40 commonly used drugs especially neuroleptics, antidepressants, certain antiarrhythmics and lipophilic β-adrenergic blockers etc[1-4]. Because of the potentially large inter-phenotypic differences in metabolism, determination of this genetic polymorphism may be of clinical value in predicting adverse or inadequate response to certain therapeutic agents and in predicting increased risk of environmental or occupational exposure-linked disease. Thus genotyping/phenotyping of CYP2D6 activity may lead to increased therapeutic efficacy and more cost-effective medication[1,5,6].

Several studies are already reported from different parts of the world regarding the polymorphism of CYP2D6 isoenzyme. The frequency of this polymorphism is dependent on the ethnic origin of the study subjects. The poor metaboliser (PM) phenotype is reported in about 5 % - 10 % of Caucasians[7], less than 1 % of Chinese[8] and Japanese[9], 1 % of Saudi Arabians[10], 0 - 2 % of black population[7], 1.2 % of Thais[11] etc. The studies on the polymorphism of the CYP2D6 from Indian population are very few. A study among subjects residing in Bombay, which is in the west coast of central part of India, reported 2 % PM with respect to CYP2D6[12]. In North Indian subjects, 3 % frequency of PM phenotype has been reported[13]. The study on the debrisoquin oxidation in Sinhalese residing in Sri Lanka observed the PM frequency of about 0 - 2 %[14]. Subjects from Kerala state, which is in the west coastal area of South India showed 4.8 % of PM phenotype[15]. A recent study shows 3.2 % PM in subjects from Hyderabad city (Andhra Pradesh) population[16]. Since Hyderabad is a metropolitan city, this study population is not
METHODS

Subjects The study was performed in 211 unrelated healthy volunteers (111 from AP and 100 from KA) in the age group of 15 to 45 years. The subjects from KA were mostly students and staff from Krupanidhi College of Pharmacy, Bangalore, KA and the volunteers from AP were mainly students and staff from Rengaraya Medical College, Kakinada, AP. The demographic characteristics of the volunteers are given in Tab 1. All subjects were judged to be in good health as determined by a medical history, physical examination and blood pressure measurement. Individuals were excluded if they were receiving any medications on a chronic basis, or even receiving concomitant therapy with drugs known to induce or inhibit the cytochrome P-450. None of the subjects were regular alcohol users. All subjects gave their informed consent and the study was approved by the Ethics Committee, JIPMER, Pondicherry.

Protocol for phenotyping The dextromethorphan metabolic ratio (MR) was determined from the ratio of the molar recovery of dextromethorphan (DM) to that of dextrophan (DT) in the urine collected for 8 h. After emptying the bladder, each subject received an oral dose of 30 mg of dextromethorphan hydrobromide (5 mL of Lactuss-LA, cough suspension; FDC Limited, Aurangabad, India) at bed time. Urine was collected overnight for 8 h. A 20-mL aliquot was stored frozen (−20 °C) until analysis for dextromethorphan and dextrophan by HPLC method[12]. In brief, 0.5 mL of urine sample was incubated with 0.5 mL of β glucuronidase (8 000 kU/L) at 37 °C for 16 h. The samples were then extracted with an organic solvent mixture (20:9:1 of diethyl ether; chloroform;2-propanol). The organic layer was vortexed with 400 μL of HCl 0.2 mol/L. The acid layer was aspirated and 200 μL was injected into the HPLC with cyano column. The mobile phase consisted of methanol, acetonitrile and triethylamine (16; 3:0.06, vol;vol;vol) in water at pH 2.8. A fluorescence detector was used with excitation wavelength at 230 nm and emission wavelength at 330 nm. The inter and intra-day coefficient of variation for assay of DM and DT (50–8 000 mg/L) were less than 10 % and 5 % respectively. The least quantifiable amount was 20 mg/L for both DM and DT.

The oxidative phenotype assignment was based on the value of the subject's molar urinary ratio of dextromethorphan to dextrophan (metabolic ratio, MR) in relation to the population antimode. Dextromethorphan metabolic ratio of 0.3 was considered as the antimode[18]. Subjects with a metabolic ratio greater than or equal to the antimode were classified as poor metabolisers of the CYP2D6 enzyme.

Statistical analysis Statistical analysis were performed using INSTAT computer software. Data are presented as x ± s. Analysis of inter-individual variations in CYP2D6 activity to metabolise dextromethorphan was expressed by computing a frequency distribution histogram between log MR on the abscissa and number of subjects on the ordinate. The shift in the frequency

Tab 1. Description of Karnataka (KA) and Andhra Pradesh (AP) study population. *P < 0.05 vs AP subjects.

<table>
<thead>
<tr>
<th></th>
<th>KA</th>
<th>AP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100</td>
<td>111</td>
<td>211</td>
</tr>
<tr>
<td>Male</td>
<td>83*</td>
<td>72</td>
<td>155</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>39</td>
<td>56</td>
</tr>
<tr>
<td>Age (s)</td>
<td>24.05(4.9)</td>
<td>23.42(6.7)</td>
<td>23.72(5.9)</td>
</tr>
<tr>
<td>BMI (s)</td>
<td>20.54(3.4)</td>
<td>20.36(3.0)</td>
<td>20.45(3.2)</td>
</tr>
<tr>
<td>EM</td>
<td>0.057(0.03)</td>
<td>0.057(0.04)</td>
<td>0.057(0.04)</td>
</tr>
<tr>
<td>PM</td>
<td>3.206(2.34)</td>
<td>0.859(0.28)</td>
<td>2.423(2.18)</td>
</tr>
<tr>
<td>Phenotype</td>
<td>96(96)</td>
<td>109(98.2)</td>
<td>205(97.2)</td>
</tr>
<tr>
<td>BMI (%)</td>
<td>4(4)</td>
<td>2(1.8)</td>
<td>6(2.8)</td>
</tr>
</tbody>
</table>
distribution histogram of the study population to that of other ethnic group is analysed by comparing the mean log metabolic ratios (SD) of extensive metabolisers (EM) using unpaired t-test. Rest of the data was analysed by two tailed t-test and Fisher's exact test. A P value < 0.05 was considered to be statistically significant.

RESULTS

Out of the 211 study subjects, 6 subjects (2.8%) with a 95% confidence interval of 1.06% to 6.09% had metabolic ratios exceeding their population antmode and were classified as poor metabolisers of dextromethorphan. The distribution of IgMR in the 0-8 h urine of the 100 subjects from Karnataka and 111 subjects from AP are shown in Fig 1 and 2 respectively.

In Karnataka 4 subjects (4% with a 95% confidence interval of 1.1% - 9.93%) and in Andhra Pradesh 2 subjects (1.8% with a 95% confidence interval of 1.06% to 6.08%) were identified as poor metabolisers with respect to CYP2D6. In Karnataka population 96 subjects (96%) had metabolic ratio between 0.005 and 0.205 and were classified as extensive metabolisers (EM). In Andhra Pradesh subjects, the metabolic ratio of 100 EM phenotype (96.2%) ranged from 0.0053 to 0.194. There was no demographic difference with the PM when compared to the EM. Out of six PM, 4 were males and 2 were females. No side effects or any adverse drug reactions were observed.

The mean age or body mass index was not significantly different between the KA and AP subjects. The mean metabolic ratio of the EM subjects was also not significantly different between the two groups (Tab 1).

DISCUSSION

In the present study, 4 poor metabolisers were identified among the 100 Karnataka subjects. This represented a PM frequency of about 4% in this population. The frequency of PM in Andhra subjects (1.8%) is comparatively less than Karnataka population. The incidence of PM in Karnataka population is more than that observed in other Asian populations (less than 1% in Chinese and Japanese, 1% in Saudi Arabian, 1.2% in Thai population etc). However the low frequency of PM in Andhra Pradesh population is comparable to that of Orientals.

Based upon the genetic distance, the people of India have been broadly classified into four main ethnic groups; Caucasoid Aryans, Caucasoid Dravidians, Australoids, and Mongoloids. The non-tribal population of India consists mainly of Caucasoid Aryans in North India and Caucasoid Dravidians in South India. The population in Karnataka is of Dravidian origin and the present study is the first to be conducted in this population.

Andhra Pradesh consists of three distinct regions. (i) Coastal region generally called Andhra, (ii) the interior region known as Rayalaseema and (iii) Telengana region, consisting of the capital Hyderabad and adjoining districts. The present study population is from Andhra region. The earliest mention of the Andhras is said to be in Aixerana Brahmana (2000 BC). It indicates that
Andhras originally an Aryan race, living in North India, migrated to the south of Vindhyas and later mixed with non-Aryan stocks\textsuperscript{[20]}. The low frequency of PM in Andhra Pradesh population can be compared with the other studies conducted in populations of migrated Indo-Aryan races. The subjects of Bombay and Sinhalese from Sri Lanka also show a low prevalence of PM phenotype (0 - 2\%)\textsuperscript{[12,14]} like Andhra population.

A similar study conducted by the same authors in 168 subjects from Kerala observed a frequency of 4.8\% PM in Keralite population\textsuperscript{[15]}. Kerala is another South Indian state where the population is of Dravidian origin. The studies in Karnataka and Keralite subjects shows that the Dravidian population has a higher frequency of PM phenotype when compared to other Oriental races.

There is a marked rightward shift in the frequency distribution histogram of the metabolic ratio of South Indian population compared to Caucasian population (\(P < 0.001\))\textsuperscript{[21]}. This shift is comparatively less when compared to the Chinese population\textsuperscript{[22]}. However the frequency distribution of the present study population is comparable with that reported in North Indian population (\(P > 0.05\))\textsuperscript{[13]}. Hori et al\textsuperscript{[21]} reported that the frequency distribution curve for metoprolol metabolic phenotype in Chinese population was skewed to the right compared with that in the Japanese population. A similar inter-ethnic difference in the distribution histograms of debrisoquin EMs and metoprolol EMs has also been observed between two non-Oriental (British and Nigerian) populations\textsuperscript{[24]}. Environmental factors may modulate genetic expression, which may give rise to differences in the titrination of the metabolic ratio between ethnic groups\textsuperscript{[11]}. The differences between White subjects and South Indian subjects in life style, dietary habits and/or occupation might have influenced the CYP2D6 isoenzyme in Andhra Pradesh and Karnataka population. This may be the reason for the difference in the mean metabolic ratios of these ethnic groups.

Unlike Western population none of our female participants were smokers or alcoholics. This may be because of the strict social restrictions in this region. In males chronic alcoholism was one of the exclusion criteria, so that only occasional social drinkers participated in the study. Their alcohol consumption was less than 20 units per month.

It has been proven that pregnancy can induce CYP2D6 enzyme activity, so pregnancy was an exclusion criteria while selecting the female subjects\textsuperscript{[25]}. However the menstrual cycle phase has not been considered in females during study because of the lack of influence of menstrual cycle phase on dextromethorphan metabolic ratio\textsuperscript{[20]}. The present study shows that subjects of pure Dravidian origin have a higher frequency of PM compared to the migrated Aryan subjects. However the mean metabolic ratio or frequency distribution histograms of Karnataka and Andhra subjects were not significantly different. Further studies including the genotyping of the subjects may give a more clear picture about the genetic polymorphism in this region.

ACKNOWLEDGMENT We are grateful to Hoffman-La Roche, Switzerland and Mr K N Bopanna, Astra-IDL Ltd, Bangalore, India for their generous gift of dextromethorphan and dextromethorphan respectively. We thank Mr Remesh Raju for arranging the volunteers for the study and Mr Balakrishnan, Mrs Thamijarrassy M, and Miss Immaculate E for their technical assistance.

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CYP2D6在印度卡纳塔克邦和安得拉邦人群中的遗传多态性

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关键词 细胞色素 P-450 CYP2D6; 人类; 印度; 高血压药物; 双光子; 衣型; 多态现象 (遗传学)

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