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Effect of CYP2D6 and CYP3A4 Genotypes on the Efficacy of Cholinesterase Inhibitors in Southern Chinese Patients With Alzheimer's Disease

Suk Ling Ma, PhD[1], Nelson Leung Sang Tang, MD[2,3,4], Karen Hong Yun Wat, MBChB[5], Jenny Hoi Yin Tang, MBChB[5], Ka Hin Lau, FHKAM[6], Chun Bon Law, MBBS[7], John Chiu, MBBS[7], Cindy Chi Woon Tam, MBChB[8], Tin Keung Poon, MBBS[9], Ka Leung Lin, MBBS[10], Carolyn Poey Lyn Kng, MBBS[10], Hing Leung Kong, MBBS[10], Tak Yeung Chan, MBBS[11], Wai Chi Chan, MBChB[6], and Linda Chiu Wa Lam, MD[1]

Abstract

Alzheimer's disease (AD) is the most prevalent form of dementia, and age is strongly associated with the incidence of AD. This study aimed to investigate the association between the genotypes of CYP2D6, CYP3A4, and CYP2C9 genes to the clinical efficacy and tolerability of cholinesterase inhibitors (ChEIs) in Chinese patients with AD. One hundred seventy-nine patients with AD with newly prescribed with ChEIs were recruited. The clinical response and tolerability were evaluated at baseline, 3rd-, 6th-, and 12th-month follow-ups and were compared according to their genotypes of CYP2D6, CYP3A4, and CYP2C9. Among patients prescribed with donepezil/galantamine, CYP2D6*10 carriers showed significantly less side effects ($P = .009$). CYP2D6*10 carriers responded better to ChEIs and resulted in better improvement in Alzheimer's Disease Assessment Scale-Cognitive subscale ($P = .027$) and Mini-Mental State Examination ($P = .012$). Further study is required to replicate the finding, and it might be useful for clinicians to decide the medication based on the patients' CYP genotypes.

Keywords

Alzheimer's disease, donepezil, efficacy, pharmacogenetics, tolerability

Introduction

Cholinesterase inhibitors (ChEIs) is the commonest medicine prescribed to patients with mild-to-moderate Alzheimer's disease (AD). Cholinesterase inhibitors included donepezil, rivastigmine, and galantamine which are the approved drugs for management of AD. Cholinesterase inhibitors act by inhibiting the activity of acetylcholinesterase, the enzyme responsible for breaking down acetylcholine and compensating the reduced cholinergic transmission. The group efficacies of ChEIs for symptomatic improvement in AD had been well replicated. However, the efficacy for individual patient varied.[1,2]

Among the 3 ChEIs commonly prescribed, donepezil and galantamine are metabolized by cytochrome P450 (CYP) enzymes to clinically inactive metabolites.[3,4] On the other hand, rivastigmine is metabolized primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite, and

[1] Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, China
[2] Department of Chemical Pathology, Faculty of Medicine, The Chinese University of Hong Kong, China
[3] Functional Genomics and Biostatistical Computing Laboratory, Shenzhen Research Institute, The Chinese University of Hong Kong, Hong Kong, China
[4] Laboratory of Genetics of Disease Susceptibility, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China
[5] Kwai Chung Hospital, Hong Kong, China
[6] Queen Mary Hospital, Hong Kong, China
[7] Princess Margaret Hospital, Hong Kong, China
[8] North District Hospital, Hong Kong, China
[9] Kowloon Hospital, Hong Kong, China
[10] Ruttonjee Hospital and Tang Shiu Kin Hospital, Hong Kong, China
[11] Kwong Wah Hospital, Hong Kong, China

Corresponding Author:
Suk Ling Ma, PhD, Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong.
Email: suklingma@cuhk.edu.hk

CYP450 enzymes are minimally involved in the metabolism of rivastigmine. The clinical responsiveness of donepezil and galantamine had been associated with genotypes of CYP2D6.[4] Studies showed patients with AD having additional copies of CYP2D6*1 allele were less responsive to ChEIs.[3] The CYP enzymes are known for its function in drug metabolism. Polymorphisms in major CYP-related genes involved in the metabolism of ChEIs, such as CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, resulted in variation in drug metabolism and efficacy in medication.[3-6] Studies reported the association of CYP2C9*2, CYP2C19*2, CYP3A4*1b, and extra copies of CYP2D6*1 and CYP2D6*2 with reduced efficacy of ChEIs.[4] In Caucasians, over 80% of the population had normal CYP2D6 metabolism, but the frequencies differed among populations.[4] In addition, the correlation between CYP2D6 enzyme activities and polymorphisms may vary among different populations. A study showed that, despite the same CYP2D6 allele, the CYP2D6 enzyme activity of African Americans was significantly lower than the Caucasians.[7] On the other hand, CYP2D6*1 and CYP2D6*2 are the most common alleles in Caucasians, but CYP2D6*10 is the most common allele in Chinese.[8] This suggested that different drug dosage recommendations may be required for different populations with variable genetic predispositions.

In this study, we aimed to investigate the association of CYP polymorphism and the clinical efficacy and tolerability of ChEIs in Southern Chinese patients with AD. Our result may have implication on the prescription practice in the future to increase the efficiency of treatment.

Methods

Patients Recruitment

One hundred seventy-nine Chinese patients with AD with NINCDS-ADRDA diagnosis for probable and possible AD were recruited from psychogeriatric and geriatric clinics of 11 hospitals under Hospital Authority of Hong Kong. Patients with AD were clinically indicated for ChEIs to manage cognitive symptoms. This is in accordance with the update prescription guidelines of the Hospital Authority of Hong Kong. During recruitment, the psychiatrists/clinicians explained the procedure and obtained the informed consent from the patients and/or their caregivers. The study has been approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong, and it was performed in accordance with the latest version of the Declaration of Helsinki.

Study Design

This was a naturalistic observational study. Participants were prescribed with ChEIs as decided by the attending clinicians. The regime of dose adjustment followed the standard guidelines and clinical response. Clinical efficacy assessments included Clinical Dementia Rating (CDR), Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Mini-Mental State Examination (MMSE), and Neuropsychiatric Inventory (NPI), and side-effect checklist were performed at baseline, 3 months, 6 months, and 1 year.

Selection of Polymorphisms of CYP2D6, CYP2C9, and CYP3A4

It is known that the frequencies of CYP alleles differed significantly among different populations. The CYP2D6 alleles found in Chinese population with frequencies over 1% were *1, *2, *5, *10, *14, and *41.[9] For CYP2C9, *1 and *3 were the allele with frequencies over 1% in the Chinese.[10] For CYP3A4, *1G, *6, and *18 were the major alleles in the Chinese.[11] The polymorphisms accounting for each allele were retrieved from The Human CYP Allele Nomenclature Database (now transitioned to Pharmacogene Variation [PharmVar] Consortium).[12] By comparing the polymorphisms among the frequently occurring alleles in each CYP gene, a list of polymorphisms that could be used to predict the allele were sorted out for genotyping. Five single-nucleotide polymorphism (SNPs) of CYP2D6 (rs1080989, rs1065852, rs1081003, rs1135840, and rs16947), 2 SNPs of CYP2C9 (rs1057910 and rs4918758), and 6 SNPs of CYP3A4 (rs2740574, rs34784390, rs55901263, rs59715127, rs201821708, and rs2242480) were chosen for genotyping and identifying the patients' allele.

Genotyping

Buccal swabs were collected from patients with Catch-All Buccal Swab (Epicentre Biotechnologies, Madison, Wisconsin) during the patients' baseline home visit, after obtaining the written consent. DNA extraction was performed according to the manufacturer's instructions. Genotyping of apolipoprotein E (ApoE), CYP2D6, CYP2C9, and CYP3A4 were performed by melting curve genotyping protocols. In brief, this genotyping method utilized a set of 3 primers that were composed of 2 allele-specific primers and a common reverse primer. The 2 allele-specific primers contained additional sequence of different length at 5′ end which will produce a different melting temperature due to differences in GC composition in additional 5′ sequence. For example, a long 14-bp 5′ GC sequence (5′-GCGGGCAGGGCGGC-3′) was added to one of the allele-specific primer, while a short 5′ 8-bp GC tail (5′GATTACCG-3′) was attached to the other allele-specific primer. By attaching 5′ GC tails of different lengths onto the 5′ end of each pairs of allele-specific primers, genotypes at the SNP can be inferred from the melting profile of the polymerase chain reaction (PCR) products, as the different GC 5′ tail will generate a 3°C to 4°C difference in Tm between the allele-specific PCR products. This method was used in our group's study and it is well validated.[13] Both positive and negative controls were included in each assay as quality controls.

Statistical Analysis

Data analysis is based on intention-to-treat population, which included patients who received baseline and at least 1 post-baseline assessments. Student *t* test was used for normally distributed variables while for ordinal variables, the Wilcoxon and the Mann-Whitney *U* tests were used. Chi-square test was used for categorical variables. Age and gender were included as covariates for the analysis. Test results in which *P* value was smaller than .05 were declared significant.

Results

Study Population

At baseline, 124 (69.3%) patients were prescribed with donepezil, 30 (17%) patients were prescribed with rivastigmine patch, 14 (8%) patients were prescribed with rivastigmine pill, and 11 (6%) patients were prescribed with galantamine. Rivastigmine is metabolized via cholinesterase-mediated hydrolysis. The elimination bypasses the hepatic system, and hepatic CYP450 isoenzymes are not involved. As there had been no significant differences in clinical efficacy between different types of ChEIs reported,[14] patients on rivastigmine were regarded as the control group for comparison of expected clinical response in patients prescribed with donepezil and galantamine, as these 2 drugs will be metabolized by CYP450 enzymes. All patients were assessed with CDR, Montreal Cognitive Assessment (MoCA), and ADAS-Cog at baseline, 3 months, 6 months, and 1 year. At baseline, the score of MoCA for patients prescribed with donepezil or galantamine and rivastigmine patch or pill were 13.1 and 12.6, respectively. The ADAS-Cog score were 22.0 and 23.1, respectively, for patients prescribed with donepezil or galantamine and rivastigmine patch or pill. For MMSE score, patients prescribed with donepezil or galantamine and rivastigmine patch or pill were 19.1 and 18.7, respectively. There were no significant differences for the scores of cognitive measures between patients with different medication. The CDR of the patients ranged from 0.5 to 2.0, and there was no significant difference in the distribution of CDR between groups of patient prescribed with different ChEIs and across the course of the study (Table 1).

Genotyping of CYP2D6, CYP2C9, and CYP3A4

A number of polymorphisms for CYP2D6, CYP2C9, and CYP3A4 were chosen for genotyping to determine the major group of CYP2D6, CYP2C9, and CYP3A4. For CYP2D6, 10a/10b and 10b/10b were the most frequent genotypes (26.8% and 33.7%, respectively). For CYP2C9, 81.8% of the patients were 1/1 and 99.4% of patients were *1 allele carrier. For CYP3A4, 1/1 and 1/1G were the major genotypes (61.8% and 36.2%, respectively) and only 1 patient was *1 allele noncarrier. There was no significant difference in the distribution of genotypes of CYP2D6, CYP2C9, and CYP3A4 between the patients prescribed with donepezil/galantamine and rivastigmine.

Table 1. Table Showing the Demographic Characteristics of the Patients Recruited in This Study.

	Patients Prescribed With Donepezil or Galantamine	Patients Prescribed With Rivastigmine
Age, mean (SD)	79.4 (5.9)	80.6 (6.4)
Gender		
Male	42 (32.1%)	9 (21.4%)
Female	89 (67.9%)	33 (78.6%)
Education, year, mean (SD)	3.9 (5.2)	3.1 (4.4)
ApoE ε4 carrier	34 (29.8%)	9 (23.1%)
MoCA, mean (SD)	13.1 (5.2)	12.6 (4.9)
ADAS-Cog, mean (SD)	22.0 (7.1)	23.1 (8.1)
MMSE, mean (SD)	19.1 (4.8)	18.8 (5.2)
CDR		
0.5	29 (22.1%)	10 (23.8%)
1	79 (60.3%)	23 (54.8%)
2	20 (15.3%)	9 (21.4%)

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; ApoE, apolipoprotein E; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; SD, standard deviation.

Adverse Side Effect

This study was a naturalistic observational study and the type of ChEIs or dosage were prescribed by clinicians according to patients' condition; therefore, the data analysis was based on the intent-to-treat population. Intent-to-treat population is defined as patients who received at least baseline medication and some post-baseline on-treatment assessment. At baseline, 29.3% patients prescribed with rivastigmine and 34.1% patients prescribed with donepezil or galantamine reported adverse side effects ranging from 1 to 4 symptoms, and the commonest complains included nausea, dizziness, and fatigue. No serious adverse side effect was reported. There was no significant difference on the occurrence of side effect between medication groups. Patients who were carrier of CYP2D6*10 showed significantly less side effect when compared to non-carrier of CYP2D6*10 at baseline ($P = .009$; Table 2). For NPI scoring, no significant changes were associated with the allele of CYP in both medication groups.

Clinical Efficacy

According to the National Institute for Health and Clinical Excellence requirements, a responder was defined as a patient who showed improvement or no deterioration in cognition as evaluated by means of ADAS-Cog and MMSE. Overall, 62% of patients prescribed with rivastigmine were responders and 48.3% of patients prescribed with donepezil or galantamine were responders. However, the difference is not statistically significant. In the group of patients who were prescribed with donepezil or galantamine, their genotypes of CYP2D6, CYP3A4, and CYP2C9 were further analyzed with the clinical efficacy by Pearson χ^2 test. The result showed that carrier of CYP2D6*10 allele was significantly associated with better

Table 2. Cytochrome P450 (CYP) Genotypes and Adverse Side Effects.[a]

	Side-Effect		
	0	≥1	*P* Value
(A)			
CYP2D6 *10			
Carrier	47 (77%)	14 (23%)	.009
Noncarrier	9 (45%)	11 (55%)	
(B)			
Genotype			
CYP2D6*10 noncarrier & CYP3A4*1G carrier	2 (25.0%)	6 (75.0%)	.013
Others	45 (72.6%)	17 (27.4%)	

[a](A) Association between CYP2D6 *10 and adverse side effect in patients prescribed with donepezil or galantamine. (B) Association between CYP2D6 *10 and CYP*3A4 and the occurrence of side effect in patients prescribed with donepezil or galantamine.

Table 3. Cytochrome P450 (CYP) Genotypes and Clinical Efficacy.[a]

	Responder	Nonresponder	*P* Value
(A)			
CYP2D6*10		ADAS-Cog	
Carrier	23 (60.5%)	15 (39.5%)	.027
Noncarrier	4 (26.7%)	11 (73.3%)	
(B)			
Genotype		ADAS-Cog	
CYP2D6*10 noncarrier & CYP3A4*1G noncarrier	0 (0%)	5 (100%)	.019
Others	24 (58.5%)	17 (41.5%)	
(C)			
Genotype		MMSE	
CYP2D6*10 carrier & CYP3A4*1G noncarrier	11 (64.7%)	6 (35.3%)	.012
Others	10 (27.8%)	26 (72.2%)	

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; CYP, cytochrome P450; MMSE, Mini-Mental State Examination.
[a](A) Carrier of CYP2D6*10 allele and ADAS-Cog responder in patients prescribed with donepezil or galantamine. (B) Association between CYP2D6 *10 and CYP*3A4 and performance of ADAS-Cog in patients prescribed with donepezil or galantamine. (C) Carrier of CYP2D6*10 allele and response in MMSE.

improvement in clinical efficacy, which was reflected by the score of ADAS-Cog at third follow-up when compared to baseline assessment ($P = .027$). Further analysis with CYP3A4 and CYP2C9 genotypes showed that patients who were noncarrier of CYP2D6*10 allele and noncarrier of CYP3A4*1G allele were all nonresponders (Table 3; $P = .019$). From baseline to first follow-up, both groups of patient showed slight improvement in ADAS-Cog score, but patients who were noncarrier of CYP2D6*10 allele and noncarrier of CYP3A4*1G allele showed clinical decline from second follow-up while this is not observed in other patients.

Effect of ApoE

No significant difference was found in the distribution of ApoE ε4 carrier between patients prescribed with donepezil or galantamine and patients prescribed with rivastigmine (Table 1). Apolipoprotein E genotype was not associated with the outcome of cognitive measure, either in the whole sample set or patients prescribed with donepezil or galantamine.

Discussion

Cholinesterase inhibitors are prescribed to patients with AD to slow down the progression of the disease and relieves the symptoms. Cholinesterase inhibitors were prescribed at a starting dosing and gradually increased to the highest dosage recommended by the respective drug company if there is no adverse effect encountered. A meta-analysis comparing the outcome of cognitive function by the dosage of donepezil was performed and the result showed that 5 mg/d was associated with worse cognitive function as revealed by ADAS-Cog. On the other hand, it showed there was no significant improvement in the efficacy outcome when the dose was increased from 10 to 23 mg/d, which was the maximum dosage recommended by the drug company.[15] The result further showed that there was less adverse side effects experienced by the 10 mg/d group when compared to the 23 mg/d group. Increasing the dosage of ChEIs might provide beneficial outcome on the efficacy; however, balancing with the adverse side effect experienced and the compliance of medication will also be important.

In this study, we aimed to investigate the association between CYP genotypes and the clinical efficacy and side effects of ChEIs in patients with AD. Since donepezil or galantamine were metabolized by the hepatic CYP450 enzymes, CYP genotypes is hypothesized to be associated with the outcomes. On the other hand, rivastigmine is metabolized via cholinesterase-mediated hydrolysis and does not involve hepatic CYP450 enzymes, it is assumed that the genotypes of CYP is not associated with the outcomes. Previous studies showed CYP2D6*3, CYP2D6*4, and CYP2D6*5 accounted for up to 98% of the poor metabolizers in Caucasians. However, in Asians, the occurrence of CYP2D6*3 and CYP2D6*4 were negligible, and CYP2D6*5 only accounted for about 5% in the population. On the other hand, CYP2D6*10 is associated with reduced CYP2D6 activity and it is the commonest allele in Chinese.[8,16] In our current study, 72% of the patients were CYP2D6*10 carriers, which is consistent with other studies in Asians. Due to the ethnic difference on the frequency of CYP genotypes and the outcome on the drug metabolism, studies in different populations is required to elucidate the correlations.

At baseline of the study, there was no significant difference in the score of MoCA, MMSE, and ADAS-Cog between patients prescribed with donepezil/galantamine or rivastigmine. Since the metabolism of rivastigmine is not via CYP enzymes, CYP genotypes of the patients would not affect the pharmacokinetics of rivastigmine. The clinical efficacy and side-effect on CYP genotypes were compared in the group of

patients prescribed with donepezil/galantamine, as we hypothesized that CYP genotypes would affect the metabolism of donepezil/galantamine. Interestingly, we found that CYP2D6*10 carriers were significantly associated with better improvement in ADAS-Cog. In all, 60.5% CYP2D6*10 carriers responded to the treatment, while there only 26.7% CYP2D6*10 noncarrier, showed no cognitive decline or improvement. The responsiveness was supported by improvements in both MMSE and ADAS-Cog. A recent study also reported the association between CYP2D6*10 and responsiveness in donepezil.[17] On the other hand, a study from India showed association of different CYP2D6 alleles and responsiveness to donepezil.[18]

Our findings showed that CYP2D6*10 carriers had fewer complains on side effects. CYP2D6*10 is the most common allele in Asians, and it is associated with lower metabolic activity due to the formation of unstable enzyme. This finding might be associated with lower metabolic rate of donepezil and therefore fewer side effects were reported. On the other hand, our results showed patients who were noncarriers of CYP2D6*10 and carrier of CYP3A4*1G had more complaints on adverse side effect. However, patients who were either carrier of CYP3A4*1G did not show increased occurrence of adverse side effect. This phenomenon suggested there might be additive or interaction effect for these 2 genotypes. Serious adverse effect, associated with CYP genotypes were not reported in ChEI users, but it was reported in other medication such as clopidogrel.[8]

In this naturalistic observation study, we were unable to control for the medication switch and this is the major limitation for this study. In addition, patients may drop out of the study due to unpleasant adverse side effect and failure to get obvious improvement after medication. This made it difficult to maintain a consistent sample number throughout the study. Further studies with larger sample size will be required to validate the result from the current study. Identifying CYP genotypes that are associated with clinical efficacy and adverse effect will be useful to improve the outcome and compliance of the therapy. It is hoped that personalized medication will become possible with the help of CYP genotyping to determine the best medication.

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Declaration of Conflicting Interests

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ORCID iD

Suk Ling Ma https://orcid.org/0000-0001-6175-5691

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