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INFLUENCE OF CYP2D6*3, CYP2D6*9 AND CYP2D6*14 POLYMORPHISM ON DONEPEZIL METABOLISM AMONG DEMENTIA PATIENT IN MEMORY CLINIC, HOSPITAL KUALA LUMPUR

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ABSTRACT

Introduction: In Malaysia, the Alzheimer's disease (AD) approximately reached more than 500 000 people in 2050**.** Donepezil is one of Acetylcholinesterase inhibitor used to treat Alzheimer's disease (AD) that metabolized by CYP2D6 isoenzyme. The isoenzyme was found to be highly polymorphic which may affect the metabolism of donepezil. **Objective:** The main objectives of this research is to identify genotype-phenotype correlation and clinical implication of Donepezil metabolism in dementia due to influence of polymorphism *CYP2D6*3*, *CYP2D6*9* and *CYP2D6*14*. **Methods:** This was a retrospective study of 21 Malaysian diagnosed with dementia according to Diagnostic and Statistical Manual of Mental Disorders, Fourth (DSM-IV) and Fifth Edition (DSM-V). Patients were treated with 5-10mg/daily of Donepezil for a year. Cognitive and functional statuses were evaluated using Neuropsychiatric Inventory (NPI), Instrumental Activity of Daily Living (IADL) and Mini Mental State Examination (MMSE). Pharmacokinetic parameters, drug interaction, drug-related side effects and tolerability status were also evaluated. The analysis identifying *CYP2D6* polymorphism was performed in double blinded fashion. **Results:** After a year follow-up, 21 of 54 patients were responders and succeeded until genotyping procedure completed. The mean age of our population are 76.14±7.492 years ($p = 0.513$) showed that the result is normally distributed. Almost half of the population had Mixed Dementia (47.6%) which consists of Alzheimer's disease and vascular dementia. 50% of the population is extensive metabolizer (EM). The result also showed the MMSE score changes from upon treatment until a year after treatment is -1.0952±3.375 with normally distributed data according to Shapiro Wilk Test ($p = 0.343$). **Conclusions:** The MMSE value changes among *CYP2D6*-UM showed changes from -7 to 7 (n=6). The analysis of CYP2D6 polymorphism may

CHAPTER 1

INTRODUCTION

1.1 Overview of Dementia treatment with donepezil influenced by *CYP2D6* polymorphism

The prevalence of Alzheimer's disease (AD) in Malaysia keeps increasing over the years. In 2050, the expected number Malaysian diagnosed with dementia is approximately 590 000 people (Prina & Wimo, 2014). The number keep increasing since some studies showed one of major risk of Alzheimer's disease is aging. The deposition of beta amyloid is believed to interrupt neuron function and subsequently cause cell death in the brain. The depletion of cholinergic in brain due to aging proved the increasing risk of Alzheimer's disease among elderly (Thies & Bleiler, 2011).

Acetylcholinesterase inhibitor drugs are one of the best choices in controlling Alzheimer's disease. It is proved to improve cognitive function among Alzheimer patients and showed better effect on advanced AD that have higher deficit cholinergic function (Small & Bullock, 2011). Donepezil is one of Acetylcholinesterase inhibitor group that more preferable than other drugs in Acethylcholinesterase inhibitor group due to less side effects and a better bioavailability than others such as rivastigmine and galantamine (Cacabelos, 2007). Donepezil is hepatically metabolized by *CYP2D6* and *CYP3A4* of CYP isoenzyme. There are numerous of metabolites formed according to the