Kaohsiung Journal of Medical Sciences (2017) 33, 277–283

Available online at www.sciencedirect.com

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journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

Factors affecting therapeutic response to Rivastigmine in Alzheimer's disease patients in Taiwan

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Received 29 September 2016; accepted 14 April 2017
Available online 22 May 2017

KEYWORDS
Alzheimer's disease;
Apolipoprotein E;
Mini-Mental Status Examination (MMSE);
NAP 226-90;
Rivastigmine

Abstract Rivastigmine has been widely used in mild-to-moderate Alzheimer's disease (AD), but the therapeutic response rate varies from 20 to 60%. A dose-dependent effect has been suggested, but the plasma concentration of rivastigmine and its metabolite, NAP 226-90, were not measured in previous studies. The influencing factors of therapeutic response are complicated and discordant in various studies among different ethnic groups. Hence, we analyzed the therapeutic responses of rivastigmine, measured by neuropsychological assessments, among 63 clinically diagnosed AD patients taking a daily dosage of 6–9 mg in relation to their plasma concentration of rivastigmine and NAP 226-90, apolipoprotein E (APOE) genotype and demographic characteristics. Our reports revealed that 41.3% of recruited AD patients had improvement in cognition, measured by Mini-Mental Status Examination (MMSE), and 63.5% in global status, by Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score. In cognition, the clinically improving group had a significantly higher rivastigmine concentration [$p = 0.049$, odds ratio (OR) = 1.029, 95%CI = 1.000–1.058], lower initial MMSE score ($p = 0.010$, OR = 0.708, 95%CI = 0.546–0.920), and lower initial CDR-SB score ($p = 0.003$, OR = 0.552, 95% CI = 0.372–0.817). The patients with APOE ε4 allele had worsening cognition ($p = 0.037$,

Conflicts of interest: All authors declare no conflicts of interest.

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http://dx.doi.org/10.1016/j.kjms.2017.04.006

OR = 3.870, 95%CI = 1.082—13.840). In global status, only higher education (p = 0.043, OR = 1.222, 95%CI = 1.007—1.484) was significantly associated with clinical improvement. In conclusion, high concentrations of rivastigmine may benefit cognitive function of AD patients, especially in APOE ε4 (−) carriers.

Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by a reduction of cholinergic transmission. Therefore, inhibitors of cholinesterase, including acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), have emerged as effective drugs for AD [1]. Rivastigmine acts as a carbamate-type dual inhibitor of AChE and BuChE in the treatment of mild to moderate AD [1,2]. However, the patients exhibited individual variation in drug response, ranging from 20 to 60% [3,4]. The predictive factors of therapeutic response are very sophisticated and remain limited.

Rivastigmine is extensively metabolized to (S)-3-(1-dimethylaminoethyl) phenol, NAP 226-90, by cholinesterase-mediated decarbamylation. This is the main step required for cholinesterase inhibition [5], and hence, the concentration of NAP 226-90 is a reliable indicator of the extent of enzyme inhibition [6]. Previous literature has proposed a dose-dependent effect of rivastigmine in the treatment of AD [2,3]. However, the measurements of the plasma concentration of rivastigmine and NAP 226-90 in AD patients are lacking in most studies [5,7,8].

It would be ideal in clinical practice to start drug therapy only in those patients whose effects are expected because the adverse events are more obvious under higher dosage [3]. However, it is presently unclear which characteristics identify the responders. Most studies adopted Mini-Mental Status Examination (MMSE) and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) as cognitive outcomes [9,10] to cholinesterase inhibitors (ChEI) therapy. The patients with improved cognitive response after treatment were those taking higher dosage [3] and being cognitively impaired at baseline [11,12]. Nevertheless, conflicting findings were observed regarding gender [13,14] and apolipoprotein E (APOE) genotype [14—17]. On the other hand, the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) score is a qualitative instrument to stage the severity of dementia and to assess the global function, but few scholars have adopted this global severity score as therapeutic outcome in spite of its validation [18,19]. Moreover, the plasma concentration of rivastigmine and its metabolite NAP 226-90 were not measured in these published studies, but they were important data to reflect the real effects of rivastigmine in comparison with the reported dosage taken by AD patients.

Apolipoprotein E (APOE) polymorphisms have been regarded as principal genetic factors in AD [20]. The APOE ε4 allele may be associated with various cerebral pathologic features, such as neurofibrillary tangles, amyloid deposition, and senile plaques, which may accelerate the progression of AD [21—23]. It has been shown that APOE ε4 carriers have an earlier onset and a higher risk of developing AD [20]; nevertheless, some authors have proposed that the carriers with the APOE ε4 allele may deteriorate at a slower rate after the diagnosis of AD [15]. Various studies have been carried out for exploring the differences of therapeutic responses to acetylcholinesterase inhibitors (AChEIs) between APOE ε4 carriers and non-carriers, but inconsistent findings were found [14—17].

We conducted this pilot study to investigate the possible factors which might be associated with therapeutic outcome of rivastigmine, including the plasma concentration of rivastigmine and NAP 226-90, APOE genotype, and clinical characteristics of AD patients. Our aim was to identify optimal patients for rivastigmine treatment.

Methods

Patients

The AD patients under the treatment of rivastigmine 6—12 mg/day were recruited from the Neurological Department of Kaohsiung Medical University Hospital, a medical center in southern Taiwan, from January 2005 to December 2006. The optimal treatment dosage of rivastigmine for each recruited patient was decided on and titrated up by the physician according to the clinical condition of patient. AD was diagnosed according to the NINCDS-ADRDA criteria [24] referring to a series of tests, including the Mini-Mental Status Examination (MMSE) [25], Cognitive Assessment Screening Instrument (CASI) [26], Neuropsychiatric Inventory (NPI) [27] and Clinical Dementia Rating (CDR) scale [28]. Patients with other diseases which may contribute to the diagnosis of AD were excluded. In addition, the patients who had ever been treated with memantine or other AChEIs at any time before enrollment were also excluded. Only the patients who had regularly received a stable dosage of rivastigmine for at least 6 months were included for the purpose of maintaining steady state plasma concentrations of rivastigmine and its metabolite, NAP 226-90.

Evaluation

All procedures were approved by the Kaohsiung Medical University Hospital Institutional Review Board, and written informed consent was obtained from all participants or their legal representatives. Every recruited AD patient should receive a series of tests, including MMSE and CDR, at initial enrollment and at 6-month follow-up in order to