Int J Clin Exp Med 2015;8(2):2944-2948
www.ijcem.com /ISSN:1940-5901/IJCEM0004028

Original Article

Comparison of the efficacy of four cholinesterase inhibitors in combination with memantine for the treatment of Alzheimer's disease

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Received November 21, 2014; Accepted January 28, 2015; Epub February 15, 2015; Published February 28, 2015

Abstract: Background: Combined use of memantine and acetylcholinesterase inhibitors (AChEIs) has shown improved outcomes in patients with Alzheimer's disease (AD). However, it is not clear which AChEI is the optimal for the combined treatment with memantine. Methods: A total of 110 AD patients were randomized to receive memantine and one of the following add-on drugs: placebo, donepezil, rivastigmine, galantamine, and huperzine A for 24 weeks (n=22). At baseline, 12 weeks, and 24 weeks, the patients were evaluated using mini-mental state examination (MMSE) and Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scales. Adverse events were recorded to analyze the safety profile. Results: The MMSE scores were significantly increased and the ADL scores were significantly decreased at 12 weeks and 24 weeks in all five groups compared with baseline (all $P<0.01$). At 24 weeks, patients treated with memantine+huperzine A showed better MMSE and ADL scores than those treated with memantine+placebo. Conclusions: Huperzine A may be an optimal choice for the combined therapy with memantine in treating AD.

Keywords: Alzheimer's disease, memantine, huperzine A, drug therapy

Introduction

Alzheimer's disease (AD) is the most common reason of dementia, and its prevalence is increasing globally [1]. It is estimated that there will one AD patient in every 85 individuals by the year 2050 [2]. In addition, AD causes significant emotional and financial burdens to the patient's family and society. The pathogenic mechanisms of AD are still not clear. It has been shown that various factors are involved in the development of AD, such as genetic background, environment, behavior, and developmental components.

Currently, there are four acetylcholinesterase inhibitors (AChEIs) approved by the U.S. Food and Drug Administration for the treatment of AD, including tacrine, donepezil, rivastigmine, and galantamine. However, tacrine has been rarely used due to its hepatotoxicity [3]. Huperzine A is a natural product isolated from the Chinese moss shrub (Huperziaserrata) with acetylcholinesterase inhibiting effects [4]. It has shown promising safety profile in a phase II trial in patients with mild to moderate AD [5]. Another drug, memantine, is approved for clinical use in moderate to severe AD with convincing evidence of efficacy [6, 7]. However, its role in early AD is unclear.

The combined use of memantine and AChEI has shown improved efficacy and patient outcome in the treatment of AD [8-14]. However, there is no report comparing the efficacy of different AChEI in combination with memantine for the treatment of AD. In this trial, we investigated the outcome of AD patients treated with memantine combined with one of the four AChEIs, donepezil, rivastigmine, galantamine, and huperzine A.

Materials and methods

Patients

This clinical trial included 110 consecutive patients treated at our hospital from October 2009 to September 2013. The diagnosis of AD

Table 1. Doses of the drugs

Drugs	Week 1	Week 2	Week 3	Week 4	Week 5-24
Memantine	5 mg in the morning	5 mg, twice daily	10 mg in the morning, 5 mg in the afternoon	10 mg, twice daily	10 mg, twice daily
Donepezil	5 mg before bed	5 mg before bed	5 mg before bed	5 mg before bed	10 mg before bed
Rivastigmine	1.5 mg, twice daily	1.5 mg, twice daily	1.5 mg, twice daily	1.5 mg, twice daily	3 mg, twice daily
Galantamine	2 mg, twice daily	2 mg, twice daily	4 mg, twice daily	4 mg, twice daily	6 mg, twice daily
Huperzine A	100 μg, twice daily	100 μg, twice daily	100 μg, twice daily	100 μg, twice daily	100 μg, twice daily
Placebo	One tablet, twice daily	One tablet, twice daily	One tablet, twice daily	One tablet, twice daily	One tablet, twice daily

Table 2. Patient demographics

	Memantine+placebo (n=22)	Memantine+donepezil (n=22)	Memantine+rivastigmine (n=22)	Memantine+galantamine (n=22)	Memantine+huperzine A (n=22)
Male/female	11/11	10/12	11/11	11/11	10/12
Age (year)	73.04±7.10	73.40±6.04	73.13±7.08	73.36±7.81	72.90±7.17
Disease course (year)	3.59±2.15	3.45±1.99	3.68±2.16	3.31±1.67	3.36±2.25
MMSE	15.27±1.60	15.09±1.77	15.40±1.73	15.36±1.76	15.45±1.73
ADL	35.45±1.84	35.13±2.09	35.40±2.08	35.04±1.91	35.27±1.98

Table 3. MMSE and ADL scores at 24 weeks

	Memantine+placebo (n=22)	Memantine+donepezil (n=22)	Memantine+rivastigmine (n=22)	Memantine+galantamine (n=22)	Memantine+huperzine A (n=22)
MMSE at base line	15.27±1.60	15.09±1.77	15.40±1.73	15.36±1.76	15.45±1.73
MMSE at 12 weeks	17.72±2.09	18.00±2.37	18.09±2.34	18.50±2.54	18.36±2.44
MMSE at 24 weeks	18.90±2.54	19.27±2.22	19.31±2.80	19.72±2.18	22.18±1.81*
ADL at base line	35.45±1.84	35.13±2.09	35.40±2.08	35.04±1.91	35.27±1.98
ADL at 12 weeks	32.77±2.32	31.86±2.39	32.00±2.63	31.04±2.64*	31.54±2.17*
ADL at 24 weeks	32.04±1.81	31.40±2.36	31.86±2.37	30.90±2.61	28.04±3.21*

MMSE, mini-mental state examination; ADL, Alzheimer Disease Cooperative Study-Activities of Daily Living. *, vs memantine+placebo.

Table 4. Incidence of adverse effects

	Memantine+placebo (n=22)	Memantine+donepezil (n=22)	Memantine+rivastigmine (n=22)	Memantine+galantamine (n=22)	Memantine+huperzine A (n=22)
Patients with adverse effects (n)	5	7	8	6	7
Incidence of adverse effects	22.72%	31.81%	36.36%	27.27%	31.81%

was made according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* [15]. All patients had mild to moderate symptoms with mini–mental state examination (MMSE) scores of 10-24. Patients with the following conditions were excluded from this study: vascular or mixed dementia; epilepsy; depression; schizophrenia; administration of other psychotropic drugs within prior two weeks; allergy to memantine or AChEIs. This study was approved by the Ethics Committee of our hospital. Written informed consent was obtained from the patients or their families.

Treatment

All patients were randomly assigned into five groups (n=22) and treated with memantine (XinyiJiufu, Shanghai, China) and one of the following add-on drugs: placebo, donepezil (Haosen, China), rivastigmine (Novartis, China), galantamine (Tianpu, China), and huperzine A (Fuhua, China). The doses of the drugs are listed in **Table 1**. All patients underwent a washout period of one week before the initiation of treatment. The treatment lasted for 24 weeks

Outcome measurement

At baseline, 12 weeks, and 24 week, the patients were evaluated using the MMSE [16] and Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) [17] scales.

Safety profile

Adverse effects such as nausea, vomiting, and dizziness were recorded. Electrocardiography and blood and urine biochemistry were performed at baseline and every four weeks during the treatment.

Statistical analysis

Continuous data were represented as mean ± standard deviation (SD) and compared with one-way ANOVA. Categorical data were compared with X^2 test. Statistical analysis was performed using SPSS 12.0 software (SPSS, Chicago, IL). A *P*-value less than 0.05 was considered statistically significant.

Results

Patient demographics

This study included 53 males and 57 females with a mean age of 73.17±6.94 years (range 56-84 years). The mean disease course was 3.48±2.02 years (range 1-9 years). No significant difference was found in sex, age, disease course, and MMSE/ADL at baseline between the five groups (**Table 2**).

Treatment outcomes

The MMSE scores were significantly increased and the ADL scores were significantly decreased at 12 weeks and 24 weeks in all five groups compared with baseline (all $P<0.01$). At 12 weeks, no significant difference in MMSE scores was found among the groups. At 24 weeks, patients treated with memantine plus huperzine A showed significantly higher MMSE scores than those treated with memantine plus placebo ($P<0.05$). At 12 weeks, both galantamine and huperzine A as add-ons to memantine significantly decreased the ADL scores compared with memantine alone (both $P<0.05$). However, only memantine plus huperzine A showed significantly decreased ADL in comparison with memantine alone at 24 weeks ($P<0.05$). These results indicate that memantine plus huperzine A is superior to other drug combinations in terms of MMSE and ADL scores at 24 weeks (**Table 3**).

Adverse effects

During the 24-week treatment, three patients withdrew due to severe adverse effects, including two patients with severe nausea and vomiting in the memantine+rivastigmine group, and one patient with hepatotoxicity in the memantine+donepezil group. Other patients had experienced mild adverse effects and resolved spontaneously. No remarkable changes were noticed in blood pressure, heart rate, electrocardiography, and biochemistry during the treatment. The incidence of adverse effects did not differ significantly among the five groups (**Table 4**).

Discussion

In this preliminary trial, we compared the efficacy of four AChEIs in combination with memantine in the treatment of AD. The results showed that memantine+huperzine A was superior to other three AChEIs in combination with memantine in improving MMSE and ADL scores at 12 and 24 weeks.

The cholinergic neurons are the main neurotransmitter system involved in AD and basal

forebrain cholinergic loss is an important pathologic process. These neurons maintain cortical activity, cerebral blood flow, modulate cognition, learning, task and memory related activities, and regulation of sleep-wake cycles [18, 19]. Considering the many functions of the cholinergic neurons, the symptom complex in AD can at least be partially understood. AChEI enhance cholinergic neurotransmission through inhibition of acetylcholinesterase, thus decreasing the breakdown of acetylcholine. Various short term trials with AChEI monotherapy have shown clinically apparent and encouraging improvement in cognitive function, slowed the pace of functional decline or clinical worsening compared with placebo and reduced behavioral symptoms in mild-to-moderate and moderate-to-severe AD patients; data from meta-analyses also attest to the same fact [20].

In the pathological state of AD, there is a low and persistent state of N-methyl-D-aspartate (NMDA) activation even at resting periods; in such states, Mg^{2+} ions are excluded from the channel, thereby, allowing continuous Ca^{2+} flow across the membrane. Memantine is an uncompetitive NMDA antagonist, has voltage dependency, rapid blocking kinetics, moderate affinity, and blocks the channel by trapping it in open conformation [21]. The moderate affinity and voltage dependency property of memantine allows it to block the persistent NMDA activation and is thus, beneficial in AD. The three main studies that have seen the role of memantine in mild to moderate AD show there are some beneficial effects on cognitive and global functioning status, but it does not impede the progression of disease [11, 22, 23]. A recent meta-analysis also indicates the same [24]. Memantine's lack of benefit in the early stages is not well understood yet. The involvement of cholinergic neurons probably occurs early in the disease but, damage to glutamatergic system and excitotoxicdegeneration occurs late in the course of disease [25]. However, a combined use of memantine and AChEIs has shown improved outcomes in AD patients [8-14].

In our study, all the four AChEIs in combination with memantine can significantly improve the MMSE and ADL scores of AD patients at 12 and 24 weeks. Among them, only huperzine A showed better efficacy compared with other AChEIs. Huperzine A, derived from the Chinese herb Huperziaserrata, was identified by scientists in China in the 1980s as a potent, reversible, selective inhibitor of acetylcholinesterase [26], which has a mechanism of action similar to donepezil, rivastigmine and galantamine. A large number of preclinical studies and clinical trials had shown the potential effect of huperzine A in treating AD.

In conclusion, huperzine A may be an optimal choice for the combined therapy with memantine in treating AD. However, due to the relatively small sample size, this conclusion needs further investigation.

Disclosure of conflict of interest

None.

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