

Piracetam, Rivastigmine and Their Joint Consumption Effects on MMSE Score Status in Patients with Alzheimer's Disease

FARAD IRANMANESH^{1*}, ALIREZA VAKILIAN², FARANAK GADARI³, AHMADREZA SYADI³, MILAD MEHRABIAN⁴, MARYAM MORADI³, ELAHE RAESY³

For author affiliations, see end of text.

Received January 25, 2012; Revised May 18, 2012; Accepted June 4, 2012

This paper is available online at <http://ijpt.iuums.ac.ir>

ABSTRACT

Alzheimer's disease is considered the most common cause of dementia. At present, no definite cure is available for healing the disorders and stopping the disease progress. The aim of this study is to study the effects of piracetam, rivastigmine and their joint consumption on MMSE score status in patients with Alzheimer disease. This interventional study was carried out on 64 patients with Alzheimer's disease. They were randomly divided into four groups. The first group was treated with piracetam 800 mg daily. The second group was treated with rivastigmine 3 mg daily. The third group used a combination of both drugs; and the fourth group has taken placebo. At the beginning of the experiment and at the end of the third month, all patients underwent MMSE. The results were statistically analyzed. In this study 32 patients were male. A significant difference was found between rivastigmine group and control group ($p < 0.01$) and between control group and the group who had received a combination of both drugs ($p < 0.02$). In summary, the findings of this study showed that treatment with rivastigmine or combination of rivastigmine and piracetam can improve clinical symptoms in these patients, but piracetam alone has no effect in the patients.

Keywords: *Alzheimer's disease, MMSE, Rivastigmine, Piracetam*

Alzheimer's disease is the most common cause of dementia and the most important degenerative disease which results in ongoing disorder of memory, other brain activities and consequently disability and impairment of the person [1]. Nowadays, no strong documents have been found regarding the effectiveness of treatments employed for Alzheimer's disease including acetylcholinesterase inhibitors, brain vasodilators, nootropic combinations, L-dopa, vitamins C and E [2].

Concerning the above-mentioned cases and high incidence of this disease in old people, many studies have been carried out to find the preventive methods for this disease [3-4]. Rivastigmine and piracetam are the most common drugs used frequently in this disease. However, there is no unanimous agreement concerning

their level of efficiency. In a study carried out in New Zealand, it was shown that nootropic combinations cause the improvement of clinical symptoms [5]. In another study performed in Budapest in 2000, consumption of piracetam in patients resulted in improvement of clinical symptoms within several weeks after taking this drug [6]. Also, some research has shown that piracetam can cause increased learning level, improved memory and increased brain metabolism [7]. In a number of researches carried out in England and Spain on patients who used rivastigmine, it was shown that this drug can improve patients' memory [8,9]. On the contrary, in a study carried out in Germany, the beneficial effects of cholinesterase inhibitors such as rivastigmine were not supported [10]. Similarly, in an Australian study, piracetam was shown

Table 1. Comparison of average MMSE scores before and after consumption of Rivastigmine Piracetam, both drugs and Control group

	Group	No.	MMSE Score	ANOVA Test result
Before treatment	Rivastigmine	16	16/3750 ± 3/82753	<i>p</i> = 0.746
	Piracetam	16	16/3125 ± 3/75444	
	Both	16	14/9375 ± 4/63995	
	control	16	15/8750 ± 4/27200	
Total		64	15/8750 ± 4/08054	
After treatment	Rivastigmine	16	18/3750 ± 3/36403	<i>p</i> = 0.009
	Piracetam	16	17/1875 ± 4/46047	
	Both	16	18/1875 ± 3/50654	
	control	16	14/1250 ± 3/87943	
Total		64	16/9688 ± 4/10949	

to have no therapeutic effects [11]. Considering the above-mentioned controversies and since no similar research has been carried out in Iran, this research aimed to study the effect of piracetam, rivastigmine and their joint consumption on MMSE status of patients with Alzheimer's disease.

MATERIALS AND METHODS

The present study is a double blind clinical experiment (Iranian Randomized Clinical Trial number was IRCT201112198430N2) in which 64 patients aged more than 40 were selected. Alzheimer's disease had been diagnosed by the physicians based on standard criteria (DSM-IV) and other causes of dementia had been excluded using MRI and laboratory measures such as, TSH, T4, T3, ESR, liver function tests, BUN, creatinine, FBS and CBC. Those who had the history of consuming drugs (except for drugs used for controlling hypertension, heart ischemia, hyperlipidemia and diabetes) or field diseases were excluded. This study was approved by Medical Ethics Committee of Rafsanjan University. All participating patients signed the written informed consent. At first, all patients underwent MMSE and the results were recorded. Then, the patients were randomly divided into four groups using random table of numbers method. The first group was treated by piracetam 800 mg daily. The second group received rivastigmine 3 mg daily. The third group used a combination of both drugs; and the fourth used placebo. MMSE were performed again at the end of the third month. After data collection, information was analyzed using SPSS 16 Software. statistical tests of Paired T, Chi-Square, Wilcoxon and Kruskal-wallis was used.

RESULTS

In this study, 32 patients were male. Male and female Mean age was 75.3±2.25 and 77.21±2.25 respectively. No significant difference was found between men and women's Mean age (Table 1). A

meaningful difference was found between MMSE score of rivastigmine group and control group (*p* < 0.01) and between control group and the group who had received a combination of both drugs (*p* < 0.02). An statistically-significant difference was found between rivastigmine group and control group (*p* < 0.01) and between control group and the group who had received a combination of both drugs (*p* < 0.02) after interference.

DISCUSSION

Many years have passed since Alzheimer's disease was first described. Alzheimer's disease is characterized by memory disorders; it has many negative effects on the patient's family and it imposes huge mental and financial burden on the society. Since life expectancy increases in most countries, the prevalence of disease has increased consequently. Numerous attempts have been made to identify preventive and treatment methods for this disease. Exercising, using low-fat diets and having more mental activities in old people are among the guidelines recommended to prevent this disease [12]. Concerning treatment, despite various drugs like acetylcholinesterase inhibitors, brain vasodilators and nootropic combinations have been widely used, no definite treatment is available for healing or stopping the disease progress and every day new results are reported [1,2].

Piracetam is one of the drugs that has been highly taken into consideration. Studies show that it can cause increased learning level and increased memory and brain metabolism. Also, it has anti-coagulating and neuro-protective properties and can improve changes appeared in hippocampal membrane in patients with Alzheimer's disease [2,7,13,14]. In this study, no significant relationship was found between consumption of piracetam at the end of this treatment period and improvement in electroencephalography and MMSE score. In other words, no positive effects were found in those who consumed piracetam. In their study in Australia, Fliker et al reviewed the results of piracetam therapy in various studies and concluded that although

this drug lacks side effects, it does not have any positive effects on treatment of Alzheimer's disease [11]. A systematic review carried out in Germany in 1997 represented the same findings [15]. Dislike the above findings, Vins et al showed that this drug can increase memory of patients and can control their restlessness [16]. A study performed in Budapest showed that using this medicine can cause increased memory and increased speed in doing psychomotor tests [6].

Rivastigmine (commercially called Exelon) is another medicine which is used very widely among these patients. It belongs to acetylcholinesterase inhibitors group and can maintain the effects of acetylcholine. Since this neurotransmitter shows the highest disorder during disease, this mechanism can improve the disease symptoms [17]. In this research, consumption of this drug had no useful effect on improving EEG changes but it was meaningfully accompanied by increased MMSE score which reflects improvement in clinical symptoms. However, a German study showed no positive effect in these patients [10]. Enormous clinical documents exist concerning the efficiency of these drugs. In a systematic review of studies carried out until to 2005 on those who consumed acetylcholinesterase inhibitors, Brex showed that these drugs improved the clinical symptoms and there was no difference between them concerning efficiency level [18]. In his study in Italy, Imbimo showed that rivastigmine was effective in reducing disease symptoms and has some slight side effects such as nausea, vomiting, and diarrhea, which are mainly related to the initial level of drug at the beginning of treatment [19]. It seems that therapeutic effect of this drug was good in mild and moderate diseases and in severe cases it was useless [20,21]. Also, it seems that the efficiency of rivastigmine is, to some extent, related to its dose and treatment period. In his study in Italy, Mossello revealed that improvement appears in the third month and the best condition appears in the ninth month [22]. Gavrilva in Russia emphasizes on treatment which is based on patients' genotype, and drugs may be selected according to patients' genotype [23].

The only study carried out on comparing therapeutic effects of piracetam and rivastigmine in Australia had a 6-7 week follow-up and showed that rivastigmine was more effective [24]. Some of negative results in this study may result from short treatment period, low drug level or jointly evaluation of patients with severe and mild disease. In this research, consumption of these two drugs together caused improved clinical symptoms which should be evaluated in further studies. Generally, findings of this research showed that rivastigmine or combination of rivastigmine and piracetam can improve clinical symptoms. This finding is not the case for treatment with piracetam alone.

ACKNOWLEDGEMENT

We would like to acknowledge the contributions of Rafsanjan University of Medical Sciences.

REFERENCES

1. Sicras-Mainar A, Vergara J, Leon-Colombo T, Febrer L. Retrospective comparative analysis of antidementia medication persistence patterns in Spanish Alzheimer's disease patients treated with donepezil, rivastigmine, galantamine and memantine. *Rev Neurol* 2006; 43:449-53.
2. Jelic V, Kivipelto M, Winblad B. Clinical trials in mild cognitive impairment: lessons for the future. *J Neurol Neurosurg Psychiatry* 2006; 77:429-38.
3. Seshadri S, Zornberg GL, Derby LE, Myers MW, Jick H, Drachman DA. Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease. *Arch Neurol* 2001; 58:435-40.
4. Knopman D. Pharmacotherapy for Alzheimer's disease. 2002. *Neuropharmacology* 2003; 26: 93-101.
5. Vernon MW, Sorkin EM. Piracetam. An overview of its pharmacological properties and a review of its therapeutic use in senile cognitive disorders. *Drugs Aging* 1991; 1:17-35.
6. Tariska P, Paksy A. Cognitive enhancement effect of piracetam in patients with mild cognitive impairment and dementia. *Orv Hetil* 2000; 141:1189-93.
7. Winnicka K, Tomasiak M, Bielawska A. Piracetam-an old drug with novel properties? *Acta Pol Pharm* 2005; 62:405-9.
8. Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, Clegg A. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. *Health Technol Assess* 2006; 10:1-160.
9. Gonzalez-Gutierrez JL, Gobartt AL. Rivastigmine solution prescribing habits in patients with Alzheimer-type dementia in Spain (RIVASOL study). *Rev Neurol* 2007; 44:705-10.
10. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomized clinical trials. *Evid Based Med* 2006; 11:23.
11. Flicker L, Grimley EJ. Piracetam for dementia or cognitive impairment. *Cochrane Database Syst Rev* 2001; 2:CD001011.
12. Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, Cohen C, Fisk JD, Forbes D, Man-Son-Hing M, Lancôt K, Morgan D, Thorpe L. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. *CMAJ* 2008; 179:1019-26.
13. Eckert GP, Cairns NJ, Müller WE. Piracetam reverses hippocampal membrane alterations in Alzheimer's disease. *J Neural Transm* 1999; 106:757-61.
14. Gabryel B, Trzeciak HI. Nootropics: pharmacological properties and therapeutic use. *Pol J Pharmacol* 1994; 46:383-94.
15. Ihl R' Kretschmar C. Nootropic drug evaluation for general practice. *Nervenarzt* 1997; 68:853-61.
16. Weiner MF, Womack KB, Martin-Cook K, Svetlik DA, Hynan LS. Levetiracetam for agitated Alzheimer's disease patients. *Int Psychogeriatr* 2005; 17:327-8.
17. Ventura M, Sternon J. Anticholinesterases in Alzheimer's disease. *Rev Med Brux* 2001; 22:43-9.
18. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev* 2006; 1:CD005593.
19. Imbimo BP. Pharmacodynamic-tolerability relationships of cholinesterase inhibitors for Alzheimer's disease. *CNS Drugs*. 2001; 15(5):375-90.
20. López-Pousa S, Turon-Estrada A, Garre-Olmo J, Pericot-Nierga I, Lozano-Gallego M, Vilalta-Franch M, Hernández-Ferrándiz M, Morante-Muñoz V, Isern-Vila A, Gelada-Batlle E, Majó-Llopert J. Differential efficacy of treatment with acetylcholinesterase inhibitors in patients with mild and moderate Alzheimer's disease over a 6-month period. *Dement Geriatr Cogn Disord* 2005; 19:189-95.

21. Burns A, Spiegel R, Quarg P. Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. *Int J Geriatr Psychiatry* 2004; 19:243-9.
22. Mossello E, Tonon E, Caleri V, Tilli S, Cantini C, Cavallini MC, Bencini F, Mecacci R, Marini M, Bardelli F, Sarcone E, Razzi E, Biagini CA, Masotti G. Effectiveness and safety of cholinesterase inhibitors in elderly subjects with Alzheimer's disease: a "real world" study. *Arch Gerontol Geriatr Suppl* 2004; 9:297-307.
23. Gavrilova SI. Pharmacological approaches to the therapy of Alzheimer's disease. *Vestn Ross Akad Med Nauk* 2006; 9-10:30-4.
24. Rainer M, Mucke HA, Krüger-Rainer C, Kraxberger E, Haushofer M, Jellinger KA. Cognitive relapse after discontinuation of drug therapy in Alzheimer's disease: cholinesterase inhibitors versus nootropics. *J Neural Transm* 2001; 108:1327-33.

CURRENT AUTHOR ADDRESSES

Farad Iranmanesh, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran. Email: fpp_farhad@yahoo.com (Corresponding author)

Alireza Vakilian, Department of Neurology, Rafsanjan University of Medical Sciences Rafsanjan, Iran

Faranak Gadari, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

Ahmadreza Syadi, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

Milad Mehrabian, Physiology and Pharmacology Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

Maryam Moradi, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

Elahe Raesy, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.