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ASSESSMENT OF BRAIN ESTERASE LEVELS IN PATIENTS WITH ALZHEIMER'S DISEASE

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ABSTRACT

Objectives: To prove the therapeutic efficacy of rivastigmine tartrate in transdermal form, for the reduction of blood esterase levels, in patients with Alzheimer's disease. Methods: Forty AD patients were treated with Rivastigmine and evaluated for serum levels of AChE and BuChE esterases for 180 days. Results: We found that serum levels of BuChE in the transdermal group were significantly different ($p < 0.0004$) than in the oral group at 90 days. Conclusion: Rivastigmine significantly reduced BuChE levels in patients with AD.

Key Words: Alzheimer's disease, rivastigmine, acetylcholine, esterases.

INTRODUCTION

Among the main drugs approved for the treatment of AD are esterase inhibitors. We justify its use because of the cholinergic deficits that occur during the disease. These drugs can increase the availability of synaptic acetylcholine (ACh) and inhibit its main catalytic enzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)[3,4]. ChE-Is are the only therapeutic class of drugs that was developed to treat Alzheimer's and produce significant cognitive improvement in patients with AD, in addition to being very promising[5]. In 2003, Trinh et al.6 stated that studies that examined AD treatments focused on reducing cognitive decline using Cholinesterase inhibitors (ChE-Is). Cummings endorsed ChE-Is as the first class of drugs that are currently used for this purpose[7].

The development of Alzheimer's disease (AD) is marked by a gradual or progressive deterioration of intellectual function, a significant decline in the ability to perform everyday activities, and changes in personality and behavior, resulting in impaired memory, attention, executive function, language, and ability to perform calculations and create abstractions. Personality changes are frequent, with patients becoming more passive or aggressive and less spontaneous[1,2].

In addition to ChE-Is, there are non-competitive glutamate receptor antagonists (N-methyl d-aspartate), such as memantine, which block the pathological effects of high glutamate levels[8] and were the first of a novel class of drugs designed to treat moderate to severe AD. Trinh et al.[6] stated that studies examining AD treatments have focused on reducing cognitive decline by using ChE-Is. Cummings endorsed ChE-Is as the first class of drugs that are currently used for this purpose[7].

Rivastigmine is a well-tolerated drug that improves cognition and participation during the everyday life activities of patients in the mild to moderately severe stages of AD[9]. It is one of the most widely used drugs for the treatment of AD because it is capable of inhibiting both AChE and BuChE and, consequently, is more effective at increasing brain levels of ACh[4]. Rivastigmine in a transdermal patch is the preferred delivery method of caregivers of AD patients because it ensures increased treatment compliance[10]. This ChE-I represents, from a clinical perspective, an effective treatment for people with AD[11]

Our study aimed to evaluate the biological effects of administering oral and transdermal rivastigmine tartrate to individuals with dementia associated with AD. We sought to identify a possible marker for assessing this treatment outcome using biochemical results and behavioral and cognitive evaluations of AD patients.

Therefore, to investigate the influence of rivastigmine tartrate using the aforementioned evaluations, we assessed the effectiveness of various formulations of rivastigmine in the pharmacological treatment of patients with AD.

METHODS

Forty participants were evaluated, with mild to moderate AD, of both sexes. All were diagnosed with Alzheimer's Disease at the beginning of our experiment, that is, before collections.

Patients were separated into groups, according to the type of treatment / pharmaceutical form of Rivastigmine Tartrate.

20 patients were in the oral group (OG), 20 patients were in the patch group (PG); Biological analyzes were based on collections of blood samples over a period of 180 days. The classification determined in the Neuropsychiatric Inventory (NPI) made it possible to track the effectiveness of treatments and the severity of the disease was classified as mild, moderate or severe[12]. To determine the inclusion and exclusion criteria, we used a script from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Association of Alzheimer's Disease and Related Disorders (ADRDA, 2008). AChE and BuChE esterases were analyzed according to the standards of the Clinical Laboratory Accreditation Program (PALC) of the Brazilian Society of Clinical Analyzes (SBAC). The study was approved by the Ethics and Research Committee of UNIBAN BRASIL (protocol nº 292/08). For statistical analysis, we used ANOVA, Student's t test and the Kruskal-Wallis test in GraphPad Prism 5.

RESULTS

Biochemical assessment

AChE levels

The results of the biochemical measurements of the AChE levels in the OG and PG patients (Table 1) revealed no significant changes ($p > 0.05$) from 0 to 180 days across the three time periods examined.

When comparing the AChE levels after 90 days of rivastigmine tartrate treatment, we observed that the PG exhibited a small change in AChE levels; however, this difference was not statistically significant ($p = 0.1764$; nonparametric t-test).

BuChE levels

The results of biochemical measurements of the BuChE levels of the OG and PG patients (Table 2) revealed altered levels after 180 days of treatment when comparing the scores at day 0 using an ANOVA. A significant difference between the OG and PG patients was observed at both experimental days 0 and 90. The same difference between the groups was not observed after 180 days.

DISCUSSION

In general, studies have shown that the use of rivastigmine has been beneficial for patients with AD. These studies have emphasized the improvement of cognition and global performance[10,20]

We believe that this significant improvement contributes to the stabilization of the patient's state for several months. However, there are no beneficial effects in the more advanced stages of the disease.

Based on the scores obtained, we found a possible correlation between the results of the neurocognitive assessment and the AChE and BuChE levels, as described below. In the groups selected for this research, we found that the

differences between the oral and patch treatments were not significant after 180 days. We discovered a relationship between AD and inflammation and identified AChE and BuChE as possible markers for low-grade inflammation[20]. BuChE (pseudocholinesterase) is found in the blood, pancreas, liver, and central nervous system[24,25]. AChE is found at high levels in the brain, nerves, and red blood cells. Giacobini et al. claims that AChE was found at cholinergic nerve terminals, whereas BuChE was associated with glial cells or neurons[26]. Clearly establishing the role of BuChE in the normal brain or in brains with AD is still difficult[27]. Our work confirmed the biochemical evaluation of ChE-Is as a possible treatment strategy, which makes it possible to monitor this disease by assessing the concentrations of these enzymes. The study did not find significant changes in blood levels of AChE between the day of the start of collections and the end after 180 days; the AChE value remained stable. We found that in patients treated with the oral form of the drug for six months, the differences showed a p-value> 0.05, and blood AChE levels in OG patients had a slight decrease during the last 90 days of treatment (between day 90 and day 180). We point out that for the drug treatment patch form, the samples showed differences with a p-value of> 0.05, with a slight decrease on treatment day 180 compared to day 0.

There was an important difference in the levels of BuChE GO and GP on day 0. The patients who used the adhesive form were different (p> 0.0004) from the patients who used the oral form. We found that the levels of average BuChE of patients who used the oral form was 4,179.5 U / L, compared to 6,618.6 U / L in patients who used the patch form. It was possible to observe during the research that patients who used the adhesive form for 90 days continued to show significant difference (p> 0.003) and, at the end of the experiment, the two groups were statistically similar, which may mean that the inhibition provoked by tartrate rivastigmine strongly influences BuChE levels. Our results confirm the pharmacological effects of rivastigmine on esterases, mainly as a BuChE inhibitor. These results were of interest because no previous study had found a correlation between the biochemical and behavioral data. Given the small changes observed in the MMSE and NPI scores, there were no significant cognitive differences.

The fluctuations were significant in the biochemical analysis of BuChE, indicating that the levels of this enzyme can be monitored by means of tests and used as a parameter in the evolution and treatment of the disease. This means support for the clinical follow-up of patients with AD.

The results of our study suggest that biomarkers can be used as potential diagnostic tools for AD, however, as previously described in the literature[28], some limitations were found during the research. The sample of only 40 patients limits the scope of observation of the effects of rivastigmine. We believe that our method of determining cholinesterases may not have accurately quantified the concentrations of these substances in the evaluated patients, so more tests should be performed.

We concluded that the transdermal form of rivastigmine (compared to the oral form) demonstrated a significant difference in

the reduction of BuChE, confirming its ability to inhibit this enzyme, normally elevated in the advanced stages of AD. The use of the pharmaceutical patch form produces similar or even better results than oral administration, in addition to providing greater convenience to patients.

Table 1. Evaluation of AChE levels at various time periods.

	0 dd	90 dd	180 dd
Oral	3.20 ± 0.58	2.99 ± 0.87	3.39 ± 0.69
Patch	3.25 ± 0.62	3.31 ± 0.52	3.47 ± 0.49

Table 2. Evaluation of BuChE level at various time periods (values in U/L).

	0dd	90dd	180dd
Oral	4179.5 ± 1799.2	3782.9 ± 1798.1	5544.6 ± 2109.5*
Patch	6618.2 ± 2095.6**	6165.5 ± 2090.5***	6339.4 ± 2451.1

*p < 0.05, compared to the oral group at day 90 (ANOVA test).
**p < 0.003, compared to the oral group at day 0 (nonparametric t-test).
***p < 0.0004, compared to the oral group at day 90 (nonparametric t-test).

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