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The Therapeutic Effects of Oral and Transdermal Rivastigmine for the Treatment of Alzheimer's Disease

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Abstract

Objectives: To conduct a preliminary assessment of the effects of the oral and transdermal pharmaceutical forms of rivastigmine tartrate

Methods: Forty patients with AD were treated with cholinesterase inhibitors (ChE-Is), evaluated using the MMSE and NPI, and simultaneously sampled to determine their serum levels of AChE and BuChE for 180 days.

Results: The differences obtained between the oral and transdermal forms, as assessed by the MMSE and NPI scores of the AD patients, were not significantly different at the three time points examined (0, 90, and 180 days). However, the serum BuChE levels of the transdermal group were significantly different ($p < 0.0004$) than those of the oral group at 90 days.

Conclusion: The use of a transdermal ChE-I, rivastigmine tartrate, significantly reduced the levels of BuChE in the AD patients.

Key Words: *Alzheimer's disease; Rivastigmine; Acetylcholine; MMSE; NPI; Esterases*

Introduction

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].

Cholinesterase inhibitors (ChE-Is) are among the main drugs approved for the treatment of AD. Their use is based on the assumption that cholinergic deficits occur during the disease and function to increase the availability of synaptic acetylcholine (ACh) by inhibiting its key catalytic enzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) [3,4]. ChE-Is represent the most promising therapeutic agents and are the only therapeutic class of drugs that has been developed and has produced significant cognitive improvement in AD patients [5]. In 2003, 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]. 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. The combination of a ChE-Is with an NMDA receptor antagonist in the treatment of AD may result in improved results when compared to non-pharmacological therapies. However, the potential adjuvant effects of suppressing auxiliary psychotropic drug therapy still needs to be addressed, because it is known that rivastigmine, one of the ChE-Is, reduces or eliminates the need to take these other drugs. 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]. Furthermore, in 1998, it became the first approved ChE-I to be sold in Brazil. 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].

Forlenza showed that second-generation ChE-Is, (i.e., rivastigmine, donepezil, and galantamine) have the same pharmacological properties, and their side effects (nausea, vomiting, diarrhea, increased acid secretion, dyspepsia, anorexia, and abdominal pain) are similar [3].

Our study aimed to evaluate the neurocognitive and 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. Hence, we demonstrated a possible relationship between pre-diagnostic blood levels of AChE and BuChE and the cognitive and behavioral scores 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.

The biological quantification of these substances, in addition to their activities, may establish parameters to determine the rivastigmine levels that reduce the neuropsychiatric symptoms associated with this disease.

Methods

We evaluated 40 individuals of both sexes with mild- to moderate-stage AD, which were diagnosed at the beginning of our experiment. The patients were grouped according to the type of rivastigmine tartrate treatment; 20 patients were in the oral group (OG), 20 patients were in the patch group (PG), and neurocognitive surveys and biological blood analyses were performed over a period of 180 days. The rating determined in the Neuropsychiatric Inventory (NPI) enabled the tracking of the effectiveness of the treatments, and the severity of the disease was classified as either 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 Alzheimer's Disease and Related Disorders Association (ADRDA, 2008). The instruments used to assess neurocognition during the experiment were the Mini-Mental State Examination (MMSE) and the NPI. AChE and BuChE were analyzed according to the Accreditation Program for Clinical Laboratories (PALC) standards from the Brazilian Society of Clinical Analyses (SBAC). The study was approved by the Ethics and Research Committee of the UNIBAN BRASIL (protocol no. 292/08). For the statistical analyses, we used ANOVA, Student's t-test, and the Kruskal-Wallis test in GraphPad Prism 5.

Results

Neurocognitive evaluation

Evaluation of the Mini-Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI) results at the start of the treatment

The patients were clinically evaluated using the NINCDS inclusion and exclusion criteria, and the patients were grouped according to the form of the treatment. The OG consisted of patients who were treated with 6.0-mg doses rivastigmine tartrate every 12 hours, and the PG consisted of patients who were treated with a transdermal patch containing a 9.5-mg dose of rivastigmine tartrate every 24 hours. In the preliminary analysis of the patients' clinical statuses, we found similar neurocognitive statuses. The patients exhibited no significant differences in their MMSE scores ($p = 0.30$). There were also no significant differences in their NPI scores ($p = 0.43$). Thus, we had patients with identical neurocognitive function at the initiation of treatment, and no significant differences were found between the two groups.

In the MMSE assessment, we found that, after 180 days, the OG had significantly decreased scores compared to day 0. Nevertheless, the MMSE for the PG in the same period exhibited an insignificant decrease when compared to day 0 (Table 1). In the NPI assessment, we observed that, after 180 days, the OG had significantly decreased scores compared to day 0. However, in the same period, the PG exhibited a significant decrease compared to day 0 (Table 2).

	Day 0 (zero)	Day 180
Oral	19.4 ± 4.1	14.1 ± 7.0***
Patch	20.2 ± 7.0	16.2 ± 6.8[A]

***p < 0.0002, decrease compared to the day-0 group (paired t-test).

[A]p < 0.0006, decrease compared to the day-0 group (paired t-test).

Table 1: *Evaluation of Mini-Mental State Examination at various time periods.*

Day	Day 0	Day 180
Oral	33.4 ± 11.2	27.1 ± 12.3*
Patch	40.4 ± 20.2	29.3 ± 18.0**

*p < 0.01, decrease compared to the day-0 group (paired t-test).

**p < 0.001, decrease compared to the day-0 group (paired t-test).

Table 2: *Evaluation of the neuropsychiatric inventory at various time periods.*

Biochemical assessment

AChE levels

The results of the biochemical measurements of the AChE levels in the OG and PG patients (Table 3) revealed no significant changes (p > 0.05) from 0 to 180 days across the three time periods examined.

	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 3: *Evaluation of AChE levels at various time periods.*

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 4) 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.

	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).

Table 4: *Evaluation of BuChE level at various time periods (values in U/L).*

Discussion

Our results showed that, at day 0, the MMSE scores of the OG and the PG were equal (Table 1), with a score of 19.4 for the OG and 20.2 for the PG.

In 2007, the IDEAL [13] study described the MMSE as an assessment tool for evaluating AD (scores from 10-20).

These values are similar to those already described by Almeida and Crocco, who analyzed the institutionalized elderly in the Santa Casa de São Paulo. These patients had a mean MMSE score of 14.93 (CI, 12.68 to 17.18) [14].

In 2003, Laks et al. found an MMSE score of 22.34 in literate and 17.08 in illiterate individuals [15]. These data reinforce the correlation between schooling and MMSE performance [16]. Some studies have suggested setting a score of 17 as the MMSE cutoff point for individuals with low education [17]. Similarly, Almeida suggested that 20 is the optimum cutoff score for diagnosing AD in elderly individuals with no schooling [18].

From these evaluations, we can conclude that schooling has a decisive impact on cognitive performance, as assessed by the MMSE. However, if stratification were present these populations, it would be possible to clarify any possible interference.

The MMSE is a screening tool, and it has been suggested that individuals with low scores and possible eventual functional losses undergo more detailed neuropsychological evaluation [19].

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 [10,20,21].

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.

As shown in Table 2, by examining the NPI assessments at the beginning of the treatment, we found that the patients in the OG had a score of 33.4, and the patients in the PG had a score of 40.4. This indicates a balanced behavioral situation.

The NPI is used to detect and quantify changes arising from psychiatric disorders caused by dementia [22]. The NPI is an interview that is designed to assess ten behavioral areas: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, and aberrant motor behavior. Two other areas may be studied in this assessment: nighttime behavioral disturbances and appetite and eating abnormalities [23]. Therefore, 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. However, the decline in the NPI scores of the PG patients with respect to the OG patients is associated with a major decrease in their behavioral assessment. The score was 27.1 in the OG and 29.3 in the PG; this difference was not statistically significant.

Importantly, we discovered a relationship between AD and inflammation and identified AChE and BuChE as possible markers for low-grade inflammation [20]. AChE is found at high levels in the brain, nerves, and red blood cells, whereas BuChE (pseudocholinesterase) is found in the blood, pancreas, liver, and central nervous system (CNS) [24,25]. In a study by Giacobini et al., 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]. The biochemical assessment of blood from patients with AD conducted in the present work confirmed the importance of ChE-Is as a potential treatment strategy, because ChE-Is can change the serum esterase levels of patients with AD, which enables the monitoring of this disease by measuring the concentrations of these enzymes. We observed no significant changes in the blood AChE level from day 0 (the start of sample collection) to day 180 (final sampling); its value remained stable. In the patients treated with the oral form of the drug for six months, the differences showed a p-value of > 0.05, and the AChE blood levels in the OG patients had a slight decrease during the latter 90 days of treatment (between day 90 and day 180). In addition, for the patch form of drug treatment, the samples showed differences with a p-value of > 0.05, with a slight decrease at treatment day 180 compared with day 0.

The BuChE levels (Table 4) of the OG and PG were significantly different at day 0. The patients who used the patch form of the drug were different ($p > 0.0004$) from the patients who used the oral form. The mean BuChE level of the patients who used the oral form was 4,179.5 U/L, compared to 6,618.6 U/L in the patients who used the patch form. During the experiment, we observed that the patients who used the patch form for 90 days continued to exhibit a significant difference ($p > 0.003$), and at the end of the experiment, the two groups were statistically similar, which may reflect the inhibition of rivastigmine tartrate, which strongly influences BuChE levels. The findings of this study confirm the pharmacological effects of rivastigmine on esterases, specifically as an inhibitor of BuChE, and its effects were observed by sample analysis.

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.

In the biochemical BuChE analysis, the fluctuations were significant, indicating that BuChE levels can be monitored using this test and may be used as a parameter for disease evolution and treatment and may also serve as a support for the clinical monitoring of patients with AD.

Although the results of our study suggest that biomarkers can be used as potential AD diagnostic tools, as previously described in literature [28F], some limitations were found during the research. The sample size of 40 patients limits the observational scope of the effects of rivastigmine. In addition, we believe that our cholinesterase determination method may not have accurately quantified the concentrations of these substances in the evaluated patients. However, in this experiment, these limitations were not thought to have interfered with any of the other drugs that were used by the patients.

Therefore, further studies are necessary to evaluate the use of biological markers as monitoring and evaluation tools. In conclusion, the transdermal form of rivastigmine (compared to the oral form) showed a significant difference in the reduction of BuChE, confirming its ability to inhibit this enzyme, which usually is elevated in the advanced stages of AD. In addition, the use of patch technology yields similar or even better results than oral administration, offering more convenience to patients.

Disclosure: The authors report no conflits of interest.

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