CASE REPORT

RIVASTIGMINE IN WERNICKE-KORSAKOFF’S SYNDROME: FIVE PATIENTS WITH RIVASTIGMINE SHOWED NO MORE IMPROVEMENT THAN FIVE PATIENTS WITHOUT RIVASTIGMINE

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Abstract — Aims: To evaluate whether rivastigmine, an acetylcholinesterase inhibitor (AChEl), may be effective in restoring memory in Wernicke-Korsakoff’s syndrome (WKS). Methods: Five patients treated with rivastigmine for a period of 6 months were compared with five matched control patients, who received 6 months’ conventional treatment, but without rivastigmine. Memory tests were administered at baseline and after 6 months. Results: Slight improvements were observed in both rivastigmine and control patients, but no significant differences in improvements were found between the study groups. Conclusion: Treatment with rivastigmine may not be effective in restoring memory in WKS patients.

INTRODUCTION

Since 2001, case studies have reported on the beneficial effect of acetylcholinesterase inhibitors (AChEIs) in the persisting amnestic syndrome or Wernicke-Korsakoff’s syndrome (WKS) (Cochrane et al., 2005). On the contrary, one small and placebo-controlled cross-over study showed no improvement in memory after treatment with donepezil, an AChEl, in WKS caused by hunger pangs (Sahin et al., 2002). Clinically, the Korsakoff part of the WKS is characterized by a persistent anterograde episodic memory loss, while semantic memory, intelligence, and learned behaviour are preserved (Kopelman, 1995). As Wernicke’s syndrome, WKS is caused by thiamine deficiency. In a study, neurodegeneration of the hypothalamic mamillary nuclei and the mediodorsal thalamic nuclei appeared substantial in both Wernicke’s syndrome and WKS (Harding et al., 2000). However, neuronal loss of the anterior thalamic nuclei was found consistently only in WKS (Harding et al., 2000). The anterior nuclei of the thalamus are considered to be an integral part of the ‘extended hippocampal system’ (Aggleton and Saunders, 1997).

The cholinergic system plays a dominant role in the modulation of the activity of the cortex, thalamus, and hippocampus (Perry et al., 1999). The cholinergic system projects from groups of cells in the forebrain (nucleus basalis of Meynert) and the brainstem (pedunculopontine neurones) to the cortex, thalamus, and hippocampus (Perry et al., 1999). The projection from the nucleus basalis modulates selective attention. Together, these cholinergic cell groups modulate consciousness, waking, and REM sleep by synchronizing cortical activity (Perry et al., 1999).

In rats, persistent memory loss induced by alcohol is associated with loss of cholinergic forebrain cells and cholinergic dysfunction of the cortex and the hippocampus. No histological changes of the thalamus were found (Arendt et al., 1988), whereas such changes are apparent in humans. In rats, the memory impairment could be restored by placing fetal cholinergic implants in the cortex or the hippocampus (Arendt et al., 1988), or by supplying a cholinergic drug (Hodges et al., 1991). On the basis of these findings it was concluded that acetylcholine (ACh) plays a key role in the alcohol-induced loss of memory in rodents. In humans, cholinergic blockade causes a memory impairment as observed in Alzheimer’s disease and in WKS (Kopelman and Corn, 1988). However, a study comparing clinical and pathological anatomical states revealed only a similar and moderate loss of the ACh producing nucleus basalis of Meynert in Wernicke’s syndrome as well as in the combined WKS (Cullen et al., 1997). From this study it can be concluded that ACh deficiency in WKS is non-specific and limited in degree.

Moreover, it has been suggested that a relative deficiency of ACh does not primarily cause a memory impairment but rather a state characterized by impairment of attention and concentration, anxiety, restlessness, and hallucinations (Lemstra et al., 2003). So, the basis for an ACh deficiency in the WKS is questionable. Given these inconsistent findings, we tested the hypothesis that increased availability of ACh by rivastigmine, an AChEl, can improve alcohol-induced memory impairment in WKS, using a matched control design.

METHODS

Five WKS patients were consecutively selected from the department for Korsakoff’s patients from a psycho-medical centre in The Hague, The Netherlands. Four of these patients were recently admitted for diagnostic reasons; one patient was living in a Korsakoff home for 18 months. The diagnosis of WKS was firmly based on a history of severe drinking and...
a non-progressive mental condition of a persisting amnestic syndrome without another symptom indicative of dementia. Eligibility criteria consisted of (i) good physical health, (ii) no contra-indication for the use of rivastigmine, (iii) abstinence from alcohol for at least 2 months, and (iv) meeting the DSM-IV diagnostic criteria (American Psychiatric Association, 2000) for the persisting amnestic syndrome by alcohol.

The patients received rivastigmine in the following scheme: 1.5 mg 2 times a day in the first and second weeks, 3 mg 2 times a day in the third and fourth weeks, 4.5 mg 2 times a day in the fifth and sixth weeks, and 6 mg 2 times a day from the seventh week, and intentionally until the end of the trial. The treatment was supplied during 6 months analogous to the AChEI trials in Alzheimer’s disease. This experimental group was compared with a group of five patients from the same department, selected by the same criteria. The control group was compared with a group of five patients from the AChEI trials in Alzheimer’s disease. This experimental group completed the 6-month normal treatment regime.

Memory testing was conducted at baseline (i.e. before treatment) and after 6 months. Both groups were assessed with instruments that are generally regarded as specific for the experimental group of patients. The control group was matched with the experimental group in respect to gender (all male), age (median age being 46 years in the experimental group versus 47 years in the control group), time of abstinence (at least 2 months), psychotropic co-medication, and recent institutionalization. They did not receive rivastigmine, and followed the same treatment regime as the experimental group of patients.

Memory testing was conducted at baseline (i.e. before treatment) and after 6 months. Both groups were assessed with instruments that are generally regarded as specific for memory disturbances: a visual memory task, analogue to the Auditory-Verbal Learning Test (AVLT) (Lezac et al., 2004), called the ‘Word Image Learning Test’, the Verbal Fluency Test (Lezac et al., 2004), a verbal memory test, and the AVLTI, mentioned above. One experienced psychology assistant administered the tests.

<table>
<thead>
<tr>
<th>Memory test</th>
<th>Baseline mean (sd)</th>
<th>Follow-up mean (sd)</th>
<th>Baseline mean (sd)</th>
<th>Follow-up mean (sd)</th>
<th>P-value interaction effect</th>
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<tbody>
<tr>
<td>Word Image Learning Test:</td>
<td></td>
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<tr>
<td>- free recall</td>
<td>4.2 (0.18)</td>
<td>5.5 (0.56)</td>
<td>5.1 (0.83)</td>
<td>6.7 (0.96)</td>
<td>0.226</td>
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<td>- delayed recall</td>
<td>0.6 (0.89)</td>
<td>1.8 (0.84)</td>
<td>2.6 (1.14)</td>
<td>4.4 (2.41)</td>
<td>0.516</td>
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<td>Verbal Fluency Test:</td>
<td></td>
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<tr>
<td>- animals</td>
<td>15.4 (5.68)</td>
<td>16.6 (4.04)</td>
<td>16.6 (5.41)</td>
<td>17.2 (4.76)</td>
<td>0.769</td>
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<tr>
<td>- occupations</td>
<td>14.8 (6.06)</td>
<td>14.6 (5.98)</td>
<td>13.6 (5.46)</td>
<td>14.2 (4.92)</td>
<td>0.692</td>
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<tr>
<td>Auditory-Verbal Learning Test:</td>
<td></td>
<td></td>
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<tr>
<td>- direct recall</td>
<td>100th decile</td>
<td>100th decile</td>
<td>100th decile</td>
<td>100th decile</td>
<td></td>
</tr>
<tr>
<td>- delayed recall</td>
<td>&lt;100th decile</td>
<td>&lt;100th decile</td>
<td>&lt;100th decile</td>
<td>&lt;100th decile</td>
<td></td>
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<tr>
<td>- total recognition</td>
<td>23.8 (4.02)</td>
<td>24.6 (2.79)</td>
<td>24.4 (2.70)</td>
<td>25.8 (2.77)</td>
<td>0.757</td>
</tr>
</tbody>
</table>

All five patients of the medication group completed the 6-months treatment period of rivastigmine. Four patients tolerated the maximum daily dose of 12 mg, and one patient developed bradycardia. Consequently, the dose in this patient was reduced to 6 mg a day. All five patients of the control group completed the 6-month normal treatment regime.

For group, main effects were found for the scales ‘Free Recall’ [F(1, 8) = 6.64; P = 0.033] and ‘Delayed recall’ [F(1, 8) = 7.96; P = 0.022] of the Word Image Learning Test (Table 1). In addition, main Time effects were found for ‘Free recall’ [F(1, 8) = 92.56; P = 0.000] and ‘Delayed recall’ [F(1, 8) = 11.54; P = 0.009]. Although statistically significant, the post-treatment values remained far below the normal values found for ‘free recall’ (9.3) and ‘delayed recall’ (9.8). No significant main effects were observed on any of the other scales. Furthermore, no significant Group × Time interaction effects were observed on any of the scales. Hence, no significant differences in pre- to post-treatment patient changes on the memory scales were found between the two study groups (Table 1).
DISCUSSION

In this study, the effect of treatment with rivastigmine on memory in WKS patients was evaluated in ten patients. The results showed slight improvements in patients who received rivastigmine, and in control patients on visual short-term memory and learning capability (free recall), as well as on consolidation (delayed recall). No other improvement was found in these patients. Therefore, this change was validated as the result of the 6 months of abstinence, and as clinically insignificant.

In conclusion, this study did not find a positive effect of rivastigmine. Hence, treatment with rivastigmine may not be effective in restoring memory in WKS patients. The result can be seen as in line with the Cullen study (Cullen et al., 1997) and as confirmation of the controlled Sahin trial (Sahin et al., 2002). Although the pathogenesis of the serious memory disturbance in WKS is not fully unravelled, it is hypothesized that the lack of ACh is not a decisive feature of the WKS, contrary to the situation of the alcohol-induced memory disturbance in rodents.

Limitations

First, the study may have been limited by the small sample size. Nevertheless, although no significant interaction effects were found which obviously constitute the critical outcome of this study, significant main effects did occur, even in this small sample. Second, all patients in the present study had a severe amnestic syndrome, with possible serious structural damage in the thalamus. Therapy with rivastigmine may not be effective in this group, whereas patients with less severe forms of WKS may have benefited from it.

Further studies, for example, pharmacological functional magnetic resonance imaging (fMRI), could clarify the possible effect of an AChEi in the WKS.

CONFLICTS OF INTEREST

Disclosure: The authors have reported no conflicts of interest. NOVARTIS Pharmaceuticals Inc. provided rivastigmine.

REFERENCES


