Effects of cholinesterase inhibitors appear greater in patients on established antihypertensive therapy

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SUMMARY

Introduction There is increasing evidence that hypertension may contribute to the development of dementia. Studies show that blood pressure lowering therapy might protect against cognitive deterioration and that antihypertensive treatment reduce the incidence of dementia.

Aim We hypothesize that administration of cholinesterase inhibitors (AChEis) to patients with Alzheimer’s Disease (AD) receiving antihypertensive medications therapy would result in clinical benefits for a period of 40 weeks in routine clinical practice.

Methods and materials Patients with possible or probable AD were enrolled from 16 Alzheimer evaluation units (UVA) of Brescia and Cremona (Northern Italy). Patients treated with donepezil, rivastigmine and galantamine for 40 weeks independently of dosages were selected. Patients were evaluated at baseline (T0), 4 weeks (T1), 16 weeks (T2) and 40 weeks (T3).

Results 416 patients completed the study at 40 weeks; of these 255 were ‘non users’ while 161 utilized antihypertensive drugs (‘users’). The mean change in MMSE score from baseline to week 40 demonstrate that antihypertensive-treated patients improved by 0.7 points while patients receiving only AChEis remain stables. Analyzing separately patients (n = 183) that ameliorate (responders) on cognition at T3 (> 1 point MMSE score increase) a significant differences in favor of ‘users’ antihypertensive drugs over ‘non users’ on cognition at weeks 16 and 40 has been demonstrated. In particular, at T2 the mean change of MMSE from baseline in ‘users’ was 3.2 ± 2.6 vs ‘non users’ 2.2 ± 2.3 (p = 0.016) and at T3 was 3.5 ± 2.5 vs ‘non users’ 2.0.2.7 ± 1.6 (p = 0.018). Antihypertensive drugs were independently associated with cognitive improvement in responder patients treated with AChEis (95% CI: 0.41–1.79; p = 0.002).

Conclusion Antihypertensive medications in AD patients treated with AChEis are associated with an independent improvement on cognition after 40 weeks of treatment. Copyright © 2005 John Wiley & Sons, Ltd.

Key words—cholinesterase inhibitors; antihypertensive drugs; Alzheimer’s disease; cognition; real world study; functional status

INTRODUCTION

There is increasing evidence that hypertension may contribute to the development of cognitive impairment and dementia (Skoog et al., 1996; Birkenhager et al., 2004; Staessen et al., 2004). It follows that blood pressure lowering therapy might protect against cognitive deterioration. The Syst-Eur trial (Forette et al., 2002) observed that antihypertensive treatment, compared with placebo, reduced the incidence of dementia by 50% from 7.7 to 3.8 cases by 1000 patient-years and the Rotterdam study (in’t Veld et al., 2001) demonstrated that dementia may be prevented by antihypertensive treatment.

However, to our knowledge the joint effects of antihypertensive medications and AChEis in demented patients has never been studied.

On the base of our data, we hypothesize that administration of AChEis to patients with mild to moderate AD receiving antihypertensive medications would
result in clinical benefit for a period of 40 weeks in routine clinical practice.

METHODS

This 40-week, multicenter study was conducted in 16 Alzheimer Evaluation Units of the Italian ‘Cronos project’. This project was enacted by the Italian Ministry of Health (September, 2000) to address the issue of Alzheimer’s disease treatment in Italy. Global cognitive function was assessed using the Mini Mental State Examination (MMSE; Folstein et al., 1975), while functional capacity was assessed with the Basic Activity of Daily Living (BADL; Katz et al., 1970) and the Instrumental Activity of Daily Living Scale (IADL; Lawton and Brody, 1969). Patients considered in our study had mild to moderate AD (MMSE score from 10 to 26); we excluded from the analysis patients that stopped the treatment before the end of the planned observation period. At baseline, all participants were asked whether or not they had a history of hypertension and the specific treatment. We assumed that drugs with antihypertensive proprieties were used chronically. All patients were considered at the baseline (T0) (starting with donepezil, rivastigmine, or galantamine) and were re-evaluated after 4 weeks (T1), 16 weeks (T2) and 40 weeks (T3).

Statistical methods

Statistical analysis was performed with the Statistical Package for the Social Sciences, release 11.5.1. Descriptive statistics are presented as mean values and standard deviation or percentages, according to the nature of the variable. T-test was used to compare continuous variables and chi-square test for dichotomous ones. All tests were two-tailed at a probability level 0.05. The significance of change from baseline to 4, 16 and 40 weeks for MMSE was evaluated through the General Linear Model (GLM). Linear regression model was used to identify whether variables were independently associated with cognitive improvement (≥1 point MMSE score increase indicate improvement) in patients treated with AChEis at T3.

RESULTS

Four hundred and sixteen patients with mild to moderate Alzheimer’s disease were included in the present study and completed the observation at T3. Patients were divided in ‘users’ (n = 161) and ‘non users’ (n = 255) antihypertensive drugs (Table 1). The number of disease (p = 0.000) was significantly higher in ‘users’, female gender was more represented in ‘users’ (p = 0.05), while age, MMSE, level of education and the activities of daily living (BADL and IADL) were comparable between groups. At baseline, of the 161 demented patients taking antihypertensive medication, 48% reported use of Angiotensin Converting Enzyme (ACE) inhibitors, 16% of diuretics, 15% of calcium antagonist, 12% of beta-blockers; 9% used two or more drugs or other antihypertensives (alpha-blockers or angiotensin II receptor antagonists). Patients received at baseline donepezil (n = 282; 67.8%), rivastigmine (n = 100; 24.0%) and galantamine (n = 34; 8.2%) as per the clinician’s judgment at different dosages (Donepezil 5–10 mg/daily; Rivastigmine 1.5–3 mg/b.i.d. or higher; Galantamine 4–8 mg/b.i.d. or higher). In all patients we observed a mean improvement from baseline of the MMSE score at weeks 40 (MMSE mean change 0.2 ± 3.2; p = 0.08).

Table 1. General characteristics of participants (n = 416) divided in ‘non users’ and ‘users’ of antihypertensive drugs

<table>
<thead>
<tr>
<th></th>
<th>Non users (n = 255)</th>
<th>Users of antihypertensive drugs (n = 161)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Sex, female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>76.8</td>
<td>6.6</td>
</tr>
<tr>
<td>Education, years</td>
<td>5.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Duration of the disease, months</td>
<td>25.9</td>
<td>12.9</td>
</tr>
<tr>
<td>MMSE</td>
<td>19.4</td>
<td>3.7</td>
</tr>
<tr>
<td>IADL (functions maintained)</td>
<td>3.7</td>
<td>2.7</td>
</tr>
<tr>
<td>BADL (functions maintained)</td>
<td>4.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Number of diseases*</td>
<td>0.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

NS = not significant; MMSE = Mini Mental State Examination; IADL = Instrumental Activities of Daily Living; BADL = Basic Activities of Daily Living; *excluding dementia.
Significant differences in favor of antihypertensive ‘users’ over ‘non users’ were observed for the mean change from baseline on the MMSE at week 16 (Mean change MMSE 1.1 ± 2.8 vs 0.4 ± 2.9; \( p = 0.02 \)). Furthermore, at T3 observed a significant functional decline was not observed, characterized by the loss of ability to perform activities of daily living (BADL and IADL), in patient ‘users’ and ‘non users’ antihypertensive medications, responders and non-responders to AChEis.

Analyzing separately patients (\( n = 183 \)) that ameliorate (responders) on cognition at T3 (\( \geq 1 \) point total MMSE score increase, indicating responders) significant differences in favor of ‘users’ over ‘non users’ on cognition at weeks 16 and 40 have been found (Figure 1). In particular, at T2 the mean change of MMSE from baseline in ‘users’ was \( 3.2 \pm 2.6 \) vs ‘non users’ \( 2.2 \pm 2.3 \) \(( p = 0.016 \)) and at T3 was \( 3.5 \pm 2.5 \) vs ‘non users’ \( 2.7 \pm 1.6 \) \(( p = 0.018 \)).

Also, in patients that worsen (0 or 1 point total MMSE score decrease, indicating non-responders) we did not observe significant differences on MMSE change at T2 between ‘user’ and ‘non user’ antihypertensive drugs \((0.52 \pm 2.04 \text{ vs } 0.87 \pm 2.6; \ p = \text{NS})\), while at T3 it has been found a significant worsening in patients who did not assume antihypertensive medications (mean change of MMSE from baseline ‘users’ \( -1.6 \pm 1.6 \) vs ‘non users’ \( -2.3 \pm 2.3 \); \( p = 0.036 \)) was found.

To determine the variables independently associated with cognitive improvement after 40 weeks of treatment with AChEis, the association between cognitive improvement and potential determinants (age, sex, education, MMSE at baseline and higher dose of AChEis at T2) was calculated with a linear regression model. In responder patients the utilization of antihypertensive drugs \((95\% \text{ Confidence Intervals (CI): } 0.41–1.79; \ p = 0.002)\) was independently associated with cognitive improvement. In non-responder patients the same trend although not statistically significant \((95\% \text{ CI: } -0.32–0.93; \ p = 0.33)\) was found.

**DISCUSSION**

To our knowledge, this is the first published study examining the benefits of the joint effect of AChEis and antihypertensive medications on a real world representative population of mild to moderate Alzheimer’s disease patients. The effect exerted by AChEis use in this study is comparable to previously reported randomized and open-label placebo controlled trials. In fact, the majority of these trials, using either donepezil, rivastigmine or galantamine, demonstrate an initial improvement in cognitive performances during the first 12 weeks, returning to close to or baseline levels at the end of the treatment period (Farlow et al., 2000; Raskind et al., 2000; Rogers et al., 2000; Tariot et al., 2001). These studies show that the mean effect of the drug over placebo represents an improvement in cognition roughly equivalent to stemming 6–12 months of natural decline in untreated patients (O’Brien and Ballard, 2001). Our findings confirm a similar pattern, even if the study environment is different from the clinical trials. In fact, cognitive performances changed by 0.2 MMSE points from baseline to 40 weeks, a rate which was very similar to previous studies that used MMSE score as an outcome measure (Rogers et al., 1998; Winblad et al., 2001).

In our study we found strong joint effect of antihypertensives and AChEis. To date, literature analysis does not clarify whether the cognitive improvement due to these treatments is a synergic or an independent effect. Recent findings indicate that AChEis, above all rivastigmine, are effective particularly in patients with vascular risk factors (Kumar et al., 2000), in line with other data (Erkinjunti et al., 2003) showing that additional apparent benefit in Alzheimer’s disease patients treated with AChEis may be linked to drug effect on cerebrovascular factors. Experimental data on antihypertensive medications, particularly ACE inhibitors and calcium channel-blockers, hypothesized a
function on cognition of these drugs. In fact, studies (Hirawa et al., 1999; Savaskan et al., 2001; Ohru et al., 2004) have reported elevated levels of ACE in the hippocampus, parahippocampal gyrus, frontal cortex, and caudate nucleus of AD patients. The increased ACE activity may be directly responsible for cognitive impairment in AD because the enhanced formation of angiotensin II would result in an increased inhibitory effect on acetylcholine release (Barnes et al., 1991). On the same line Sudilovsky et al. (1987) suggest that ACE may have a role in the modulation of cognitive memory processes in rat and in humans. They found that angiotensin II impairs performance on various learning and memory paradigms in animals (Melo et al., 1975; Morgan and Routtenberg, 1977) and that the effect is prevented by captopril administration.

Recently, Parihar and Hennani (2004) underlined the role of calcium channel blockers as a possible therapeutic approach to AD. This hypothesis is supported by Pierrot et al. (2004) demonstrating that calcium channel blockers, through reduction of cytosolic calcium concentration, inhibit the production of calcium channel blockers, through reduction of cytosolic calcium. They concluded that verapamil significantly improved both types of learning, even when associated with physostigmine.

Our study has limitations. Firstly, we do not have informations on temporal relation between the use of antihypertensive drugs and cognitive decline and we not provide data on potential differential cognitive effects associated with various antihypertensive agents.

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