The impact of anticholinergic burden in Alzheimer’s Dementia-the Laser-AD study

Cris Fox1,2, Gill Livingston3, Ian D. Maidment4, Simon Coulton4, David G. Smithard5,6, Malaz Boustan7,8, Cornelius Katona3

1Dementia Research Innovation Group, Norwich School of Medicine, Norwich Research Park, University of East Anglia, Norwich NR4 7TJ, UK
2Norfolk and Waveney Mental Health NHS Foundation Trust, Hellesdon Hospital, Drayton High Road, Norwich NR6 5BE, UK
3UCL, London, UK
4Centre for Health Service Studies, University of Kent, Canterbury, UK

© The Author 2011. Published by Oxford University Press on behalf of the British Geriatrics Society.
All rights reserved. For Permissions, please email: journals.permissions@oup.com

Received 10 December 2010; accepted in revised form 14 May 2011

© The Author 2011. Published by Oxford University Press on behalf of the British Geriatrics Society.
Impact of anticholinergic burden in Alzheimer’s dementia

Abstract

Objective: to examine the effect of medications with anticholinergic effects on cognitive impairment and deterioration in Alzheimer’s dementia (AD).

Methods: cognitive function was measured at baseline and at 6- and 18-month follow-up using the Mini-Mental State Exam (MMSE), the Severe Impairment Battery (SIB) and the Alzheimer’s Disease Assessment Battery, Cognitive subsection (ADAS-COG) in a cohort study of 224 participants with AD. Baseline anticholinergic Burden score (ABS) was measured using the Anticholinergic Burden scale and included all prescribed and over the counter medication.

Results: the sample was 224 patients with Alzheimer’s dementia and 71.4% were women. Their mean age was 81.0 years [SD 7.4 (range 55–98)]. The mean number of medications taken was 3.6 (SD 2.4) and the mean anticholinergic load was 1.1 (SD 1.4, range 0–7). The total number of drugs taken and anticholinergic load correlated (rho = 0.44; P < 0.01). There were no differences in MMSE and other cognitive functioning at either 6 or 18 months after adjusting for baseline cognitive function, age, gender and use of cholinesterase inhibitors between those with, and those without high anticholinergic load.

Conclusions: medications with anticholinergic effect in patients with AD were not found to effect deterioration in cognition over the subsequent 18 months. Our study did not support a continuing effect of these medications on people with AD who are established on them.

Keywords: cognitive impairment, dementia and anticholinergic burden, elderly

Introduction

There is increasing evidence that medications with anticholinergic effects may adversely affect cognitive function [1, 2]. Older people are particularly sensitive to anticholinergic effects due to the significant age-related decrease in cholinergic neurons or receptors in the brain, the reduction in hepatic and renal clearance of medications and the increase in blood–brain barrier permeability particularly in acute physical illness [3]. Older people are at high risk of exposure to medications with anticholinergic effects, due to medical morbidity, frequent use of prescribed and over-the-counter medications; those that take such medication are more likely to be cognitively impaired than those who do not [4]. An estimated 20–50% of patients with dementia in the USA, take at least one medication with anticholinergic activities [5–7]. Such medications are used in a variety of conditions, for example psychiatric conditions, cardiac disease and bladder illnesses and people with dementia take these medications because of multiple illness comorbidities [7].

Cholinergic mechanisms have been implicated in the aetiology of delirium, to which older people are also vulnerable [8]. People with Alzheimer’s disease (AD) may be at particular risk of cognitive deterioration secondary to medications with anticholinergic effects because of marked reduction in the functioning of central cholinergic pathways [9].

The aim of this study was to examine whether anti-cholinergic burden was associated with the magnitude of current cognitive impairment or predicted the rate of future cognitive deterioration in a cohort of people with established AD.

Methods

The study is part of a larger longitudinal cohort study of 224 participants with AD, the London and South East Region AD (LASER-AD) study [10]. People with AD and their carers were approached through a variety of sources: their local community mental health team, dementia specialist nurses, the voluntary sector (including the Alzheimer’s Society), memory clinics, nursing and residential homes, day hospitals and inpatient units. Some of the participants had not received a diagnosis of AD, but the doctor in the research team screened and confirmed the diagnosis in all the participants. The participants from July 2002 to January 2003 were prospectively recruited purposely in order to be a sample of people with AD similar to that in the general population in terms of severity of cognitive impairment, gender and living situation [11].

The inclusion criteria were a standardised diagnosis of dementia [12] and fulfillment of criteria for possible or probable AD [13], being aged over 55 years, living in either...
C. Fox et al.

North London or Essex and being in contact with a family or statutory carer for at least 4 h a week. Interviewers were trained, experienced health professionals and collected socio-demographic details, a medical (including prescribed and non-prescribed medication) and psychiatric history and physical examination. Follow-up interviews were undertaken at 6 and 18 months. Cognitive function was measured at baseline and at follow-up using the following: (i) Mini-Mental State Exam (MMSE) [14]—scores range from 0–30; (ii) the Severe Impairment Battery (SIB) [15]—scores range from 0 to 100 [16, 17] and (iii) the Alzheimer’s Disease Assessment Battery Cognitive subsection (ADAS-COG) [18]—scores range from 0 to 75. For the MMSE and SIB lower score indicates greater dysfunction, whereas for the ADAS-Cog higher scores indicate greater dysfunction.

For the purposes of this study, each LASER-AD participant’s ‘anticholinergic burden’ was calculated using the Anticholinergic Burden scale (ABS) which we had previously developed [19–21]. The scale was developed through a systematic review of the literature to identify drugs with documented anticholinergic activity. The ABS scale focuses on central effects of medication with anticholinergic actions derived from reported serum anticholinergic assays and systematic evidence review of studies [19–21]. Content validity was tested by presenting the list to an expert interdisciplinary panel that included geriatricians, pharmacists, old age psychiatrists, general physicians, specialist geriatric nurses and ageing brain researchers. Using clinical and basic science expertise as well as the documentation provided, a consensus approach was used to classify the potential anticholinergic effects of individual drugs [19]. An individual’s ‘anticholinergic burden’ (ABS) can then be calculated by summing the scores for all the drugs that patient is taking. Its predictive validity of cognition as measured by the SIB and MMSE.

At baseline those with a greater ABS has a lower level of cognition as measured by the SIB and MMSE. The mean number of medications was 3.6 (SD 2.4) and the mean anticholinergic load was 1.1 (SD 1.4) with a range of 0–7. At baseline 47% of participants were on cholinesterase inhibitors; at 18 months this had risen to 56%. There was no effect of use of cholinesterase inhibitors on the results.

The results confirmed the expected correlation between total number of drugs taken and anticholinergic load (rho = 0.44; P < 0.01). There were no significant correlations between changes in cognitive score and the total number of medications taken (Table 2).

<table>
<thead>
<tr>
<th>Table 1. Baseline description of the sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Mean number of drugs (SE)</td>
</tr>
<tr>
<td>% Male</td>
</tr>
<tr>
<td>Mean age (SE)</td>
</tr>
<tr>
<td>Mean MMSE score (SE)</td>
</tr>
<tr>
<td>Mean ADAS-COG (SE)</td>
</tr>
<tr>
<td>Mean SIBTOT (SE)</td>
</tr>
<tr>
<td>% Taking CHEI</td>
</tr>
</tbody>
</table>

controlling for confounding covariates; baseline measures of cognition, age, gender and whether patients where receiving a cholinesterase inhibitor. Where necessary to meet the assumptions of analysis of covariance, outcomes were transformed with the results being transformed back for ease of interpretation.

Power calculation

Our sample size was sufficient to detect a clinically significant correlation between ABS and the cognitive measures—ADAS-COG, MMSE and SIB (conventionally taken as 0.4 or greater) at the 0.001% level (http://department.obg.cuhk.edu.hk/index.asp?scr=1280).

Results

We interviewed 224 people (160 women; 71.4%) with AD at baseline. One hundred and fifty-one were living at home and the remainder in institutional care. Their mean age was 81.0 years [SD 7.4 (range 55–98)]. At 18 months, 167 (74.6%) people completed follow-up. A total of 48 (21.4%) had died. Eight (3.6%) refused to take part. One (0.4%) had moved too far away to be interviewed. Participants who died were older [mean: 84.4 (SD 6.5) versus 80.20 (SD 7.5) P < 0.001] and more cognitively impaired on MMSE [mean: 11.0 (SD 8.3) versus 15.68, (SD 7.4)] and more likely to be living in 24-h care accommodation [24 (50.0%) versus 48 (28.7%), P < 0.01]. Participants, who refused were not significantly different demographically from the rest of the population. The description of the baseline population is shown in Table 1. At baseline those with a greater ABS has a lower level of cognition as measured by the SIB and MMSE.

The mean number of medications was 3.6 (SD 2.4) and the mean anticholinergic load was 1.1 (SD 1.4) with a range of 0–7. At baseline 47% of participants were on cholinesterase inhibitors; at 18 months this had risen to 56%. There was no effect of use of cholinesterase inhibitors on the results.

Any disagreement was resolved by discussion until a consensus was obtained.

Analysis

We report descriptive statistics and as appropriate parametric or non-parametric correlation coefficients of ABS load with cognitive outcome and possible confounders. To correct for multiple testing, we considered an alpha value of P < 0.01 as significant and to explore the impact of ABS load on cognition at 6 and 18 months, we conducted an analysis of covariance with a dichotomous fixed factor, ABS =0 and ABS = 0, with the ADAS-COG, MMSE and SIB at 6 and 18 months as the dependent variables.
A sensitivity analysis was undertaken using total number of drugs at baseline as an additional covariate. The results did not differ and were not statistically significant and this suggests that the number of drugs at baseline is not a mediator of outcome after other covariates have been adjusted for.

There was no significant correlation between ABS score and cognition using any of the three measures (ADAS-COG, MMSE and SIB) at baseline, 6 months or 18 months. ABS baseline scores were not normally distributed, with 101 participants having an ABS score of 0, 58 participants a score of 1 and 63 participants a score >1. In order to have large and similar numbers of people in both groups, we compared baseline cognitive scores between participants with ABS scores of 0 and those with ABS scores of 1 or more. For participants with information available at both time-points, we also compared cognitive scores at 6 and 18 months, adjusting for baseline cognitive scores, use of cholinesterase inhibitors, age and gender, between the groups with baseline ABS score of 0 and the group with a score ≥1. These results are summarised in Table 3. There was no significant difference between the groups on any of the cognitive measures.

There was no correlation between baseline anticholinergic load (as a continuous variable) and change in MMSE (rho = 0.03 NS), change in ADAS-COG (rho = 0.09 NS) or change in SIB (rho = 0.08 NS) at 18 months.

Discussion

This study of an Alzheimer naturalistic cohort considered the effect of cholinergic burden on cognition. Its strengths include that it had more than adequate power and used three different instruments to measure cognition to ensure there was no ceiling or floor limitation in measurement and to triangulate the findings. There was no effect on cognition at baseline, 6 or 18 months later. Psychotropics were the commonest group of medications in this sample with anticholinergic effects. The failure to show any effect contrasts with other studies which have looked at non-dementia samples where an effect has been found using the same assessment tool [20, 21]. In a previous paper from the LASER study, we have however reported the absence of

---

**Table 2. Correlations between change in cognitive score and total number of medications**

<table>
<thead>
<tr>
<th>Cognitive measure</th>
<th>Pearson correlation</th>
<th>Sig (two-tailed)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in MMSE BL to 6 months</td>
<td>0.14</td>
<td>0.054</td>
<td>163</td>
</tr>
<tr>
<td>Change in MMSE BL to 18 months</td>
<td>0.06</td>
<td>0.47</td>
<td>163</td>
</tr>
<tr>
<td>Change in SIB BL to 6 months</td>
<td>0.04</td>
<td>0.61</td>
<td>195</td>
</tr>
<tr>
<td>Change in SIB BL to 18 months</td>
<td>0.01</td>
<td>0.94</td>
<td>152</td>
</tr>
<tr>
<td>Change in ADAS-COG BL to 6 months</td>
<td>0.06</td>
<td>0.36</td>
<td>224</td>
</tr>
<tr>
<td>Change in ADAS-COG BL to 18 months</td>
<td>0.03</td>
<td>0.67</td>
<td>156</td>
</tr>
</tbody>
</table>

**Table 3. Baseline, month 6 and 18 and adjusted mean differences for cognitive measures categorised by ABS score 0 or 1 or more**

<table>
<thead>
<tr>
<th>Cognitive measure</th>
<th>Baseline mean (95% CI)</th>
<th>n</th>
<th>Month 6 mean (95% CI)</th>
<th>n</th>
<th>Month 18 mean difference (95% CI)</th>
<th>Month 18 P-value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS COG</td>
<td>29.67 (25.88-33.12)</td>
<td>224</td>
<td>31.57 (29.56-33.11)</td>
<td>224</td>
<td>33.72 (31.59-36.86)</td>
<td>0.02</td>
<td>156</td>
</tr>
<tr>
<td>ABS = 0</td>
<td>34.9 (31.15-38.47)</td>
<td>326</td>
<td>32.86 (31.25-34.47)</td>
<td>326</td>
<td>34.41 (32.88-36.01)</td>
<td>0.22</td>
<td>156</td>
</tr>
<tr>
<td>ABS 1</td>
<td>29.42 (26.60-32.20)</td>
<td>224</td>
<td>14.32 (13.70-15.94)</td>
<td>224</td>
<td>13.08 (11.98-14.18)</td>
<td>0.26</td>
<td>156</td>
</tr>
<tr>
<td>SIB</td>
<td>73.51 (65.18-81.84)</td>
<td>224</td>
<td>72.68 (71.75-83.62)</td>
<td>224</td>
<td>71.54 (70.61-82.47)</td>
<td>0.39</td>
<td>156</td>
</tr>
<tr>
<td>ABS = 0</td>
<td>75.41 (68.97-81.86)</td>
<td>139</td>
<td>75.41 (68.97-81.86)</td>
<td>139</td>
<td>75.41 (68.97-81.86)</td>
<td>0.39</td>
<td>156</td>
</tr>
<tr>
<td>ABS 1</td>
<td>75.34 (68.90-81.86)</td>
<td>224</td>
<td>75.34 (68.90-81.86)</td>
<td>224</td>
<td>75.34 (68.90-81.86)</td>
<td>0.39</td>
<td>156</td>
</tr>
</tbody>
</table>

Covariates included in the model are baseline values, age and gender.
correlation between exposure to (and dosage of) atypical psychotropic medication and cognitive decline when neuropsychiatric symptoms were taken into account [24].

The lack of an effect of ABS in this study [in contrast to the positive findings in a smaller but similar study [25]] may be because of the decreased sensitivity of patients with more advanced cognitive impairment or because participants had taken anticholinergic medication for significant time periods and therefore any impact on cognitive function had occurred prior to enrolment in the study. This is supported by the group with a clinically meaningful ABS at baseline having lower cognition scores (MMSE and SIB) at baseline. Alternatively, therapeutically the result could be interpreted as suggesting that medications with anticholinergic effects may not be as damaging to cognition as first thought in established dementia.

Limitations

There are a number of limitations to this study. It was not possible to collect serial ABS scores at baseline, 6, and 18 months and consider the impact of the potential change in ABS score over time, because the data set only contained drugs prescribed at a single timepoint. We did not include all potential confounders such as institutionalisation, diabetes, hypertension, smoking and alcohol use due to the risk of multi-collinearity which would have made the analysis impossible to interpret. We adjusted for baseline values on the appropriate outcomes and these in themselves should statistically adjust for the potential confounders. We took a dichotomous approach with two groups: anti-cholinergic burden present or absent. An alternative approach would have been to identify a number of groups depending on the magnitude of the anti-cholinergic burden. While we did not take this approach, due to the small sample size, our methods should be repeated in larger data sets.

The average anticholinergic load score and number of medications patients were taking were low. However, this and the number of medications with anticholinergic effects were in line with other studies in different population which showed an association [20, 21]. The duration of follow-up of 18 months may be seen as a limitation, but this is long enough to see a clinically relevant effect in this population. We only examined baseline medication, and the effect of compliance or the duration of use of anticholinergic medication prior to study entry was not measured.

It is possible we may have missed the stage of critical importance for anticholinergic effect beyond which damage to the cholinergic system had already occurred and may have passed a critical threshold before study entry so that the damage was already such that medication with anticholinergic effect may not have an impact in patients with more advanced dementia.

The ABS scale may lack sensitivity to detect an association. Additionally about half the people in our study were taking cholinesterase inhibitors which may have masked the cognitive effects of co-prescribed medications with anticholinergic effects. The lack of any association may have been due to the small sample size although our power calculation suggests that there were enough people in the sample to show a clinically significant effect. We did not have complete data on dosages of anticholinergic drugs and the duration that individuals were exposed to them.

The ABS scale has recently been validated as a predictor of cognitive impairment in two large samples of community-dwelling older people of patients without dementia [20–22]. Ideally it should also be validated against a biomarker ‘gold standard’. Reviews of the relevant literature concluded that radio-receptor assay may provide a reliable, reproducible and potent predictor of the impact of these medications on cognition [26, 27]. Such an approach would need to consider dose of medication and the effect of more than one drug with anticholinergic effects. Radio-ligand assays rely on serum samples and use rodent tissue. However, this may not represent in vivo effects for example the blood–brain barrier permeability can alter and the muscarinic receptor blockade in serum may not be representative of brain effects so such attempts at external validation may not be clinically relevant [19, 20, 28, 29].

The scale we used covers representative medication; however, there may be medication with anticholinergic effects which have a particularly potent effect. Such specific effects might have been lost with the present scale. Currently, a patient prescribed 5 mg of procyclidine daily will have the same burden score as a patient prescribed 30 mg and the scale needs to take into account the effect of dose of medication.

We conclude that, in this study of people with AD, that taking possibly a low dose of one medication with a low degree of anticholinergic activity (an ABS score of 1) does not predict more impaired cognition or a more rapid cognitive decline over the next 6 or 18 months. Further research is needed which includes people who are cognitively intact as well as those with dementia with a validated biomarker and the effect of medications with anticholinergic properties on outcomes of physical function, especially in frail older adults.

Key points

- Cognition in established dementia of moderate severity may not be affected by mildly anticholinergic medication.
- There is a need to assess impact of medication dose on potential cognitive impairment of anticholinergic medication.
- Use of assessment tools may offer greater clinical usefulness than current assays of anticholinergic effect.

Acknowledgement

We are grateful to the patients, their families and staff who took part in this study.
Impact of anticholinergic burden in Alzheimer's dementia

Conflicts of interest
None declared.

Funding
The original source of funding for this study was from Lundbeck Pharmaceuticals. C.F., C.K., I.D.M. and M.B. have received honoraria and educational grant support from the pharmaceutical industry.

References

Received 12 December 2010; accepted in revised form 14 July 2011