The presence of leuko-araiosis in patients with Alzheimer's disease predicts poor tolerance to tacrine, but does not discriminate responders from non-responders

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Abstract

Background: approximately one-third of patients with Alzheimer's disease (AD) respond favourably to the anticholinesterase tacrine, but the drug's usefulness is marred by a high incidence of side-effects.

Objective: to discover if AD patients with white matter low attenuation (WMLA) represents a subgroup that responds differently to tacrine from those with no WMLA.

Design: the results come from a combination of double-blind and open studies. Seventy-two AD patients prescribed tacrine in our centre were divided into two groups according to the presence or absence of WMLA on brain CT scans. We compared the rate of response to and withdrawal from tacrine between the groups. Response was defined as an improvement in the Mini-Mental State Examination score of three or more points at 3 months.

Results: 18 of the 72 patients were found to have WMLA. There was no significant difference in the proportion of patients responding to tacrine in each group (28.5% in those with WMLA and 31% in those without), but the rate of withdrawal from tacrine did differ: 11 patients with WMLA (61%) had to be withdrawn prematurely, compared with 14 patients (26%) in the group without evidence of WMLA ($P = 0.015$).

Conclusion: AD patients with WMLA can still respond to tacrine, although the rate of withdrawal from treatment is much higher in such patients.

Keywords: anticholinesterase, leuko-araiosis, tacrine, white matter low attenuation

Introduction

The anticholinesterase drug tacrine (tetrahydroamino-acridine) has been shown to improve cognitive function in between 30 and 40% of patients with Alzheimer's disease (AD) [1, 2]. Although this improvement is only modest, it is the only drug so far that has been shown to benefit a proportion of sufferers with this condition. Its usefulness is however limited by a high incidence (30–50%) of adverse effects, particularly affecting the liver [3]. It is not clear why some patients with AD but not others respond to tacrine, but it is important to try and identify any factors that would help to predict which patients are more or less likely to benefit, thus avoiding the risk of side-effects in those unlikely to respond.

White matter low attenuation (WMLA), also called leuko-araiosis, is seen as periventricular hypodense areas on the brain CT scans of some normal elderly subjects [4, 5]. They are reported to be present in approximately 30% of AD patients, as well as other dementias, especially vascular-type dementia where they are present in approximately 70% of patients [6, 7, 16]. Although the exact aetiology is unknown, WMLA is thought to be caused by ischaemia to the white matter [8, 9]. Pathological examination shows WMLA to represent areas of demyelination, axonal loss, gliosis and hyalinization of the supplying arterioles [10].

It is possible that this subgroup of AD patients, i.e. AD patients with WMLA, could respond differently to tacrine. Theoretically they may be less likely to respond...
Table 1. Demographic features of the patients with Alzheimer's disease

<table>
<thead>
<tr>
<th>WMLA</th>
<th>Total</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% of total)</td>
<td>72</td>
<td>18 (25)</td>
<td>54 (75)</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>71.9 (7.0)</td>
<td>74.6 (6.5)</td>
<td>70.8 (7.0)</td>
</tr>
<tr>
<td>Male/female</td>
<td>37/35</td>
<td>8/10</td>
<td>29/25</td>
</tr>
<tr>
<td>Mean MMSE score (SD)</td>
<td>14.7 (6.5)</td>
<td>13.5 (7.2)</td>
<td>15.1 (6.3)</td>
</tr>
</tbody>
</table>

WMLA, white matter low attenuation; MMSE, Mini-Mental State Examination.

Materials and methods

Among 72 patients included in this study who were prescribed tacrine, 42 were part of a double-blind placebo-controlled study and the remaining 30 were prescribed it in an open study. None of the patients included in this study participated in both the double-blind and open studies. We were able to retrieve the original brain CT scans on 48 patients and these were reassessed by one of the investigators (K.A.) and an experienced neuroradiologist (T.L.) who commented on the presence or absence of leuko-araiosis in the absence of the clinical information.

WMLA was defined as periventricular hypodense areas which may be limited to the frontal and/or occipital areas, or be more extensive, spreading toward the centrum semiovale. The degree and severity of white matter involvement was also graded on a seven-point scale (0–6). A further 24 patients were added to the analysis on the basis of a full CT report which commented clearly and specifically on the presence or absence of WMLA. In these patients, we were unable to retrieve the original CT scans and could not therefore grade the severity of white matter involvement.

Patients referred to our centre are assessed with a full history and examination, including cardiovascular and neurological examination and a psychometric test battery. A biochemical dementia screen and brain CT, and in some patients magnetic resonance imaging and SPECT scans, are performed. All patients in this study fulfilled the diagnosis of probable AD according to McKhann's criteria [11]. Patients prescribed tacrine were assessed clinically and neuropsychologically before starting treatment (at baseline), and after 1 and 3 months of treatment. They were cognitively assessed with the Mini-Mental State Examination, (MMSE), together with either the CAMDEX cognitive examination (CAMCOG) or the AD assessment scale, ADAS-cog [11, 12, 13]. Patients were closely monitored in order to detect any adverse effects.

Statistical analysis

The computer package for social science research (SPSS, release 6.1) was used to analyse the data. Levene's student t-test for equality of variances was used to compare means, while Pearson's $\chi^2$ with Yates' continuity correction was used to compare groups.

Results

Of the 72 patients included in this study, 18 (25%) were found to have leuko-araiosis, and this varied from 20% (six patients) in the open-ended study to 29% (12 patients) in the double-blind study. Half the patients with WMLA (nine patients) were included on the basis of clear CT reports rather than the actual CT scans. Table 1 presents the demographic features of the patients with and without WMLA. There were no significant differences between the two groups with regard to sex or mean MMSE score. Although the patients with WMLA were older, this did not reach statistical significance. There was also no significant difference with regard to age, sex, rate of response to tacrine or withdrawal between the groups of patients who were prescribed tacrine on a double-blind basis and those prescribed tacrine openly. The mean MMSE was, however, significantly lower in the open group.
Leuko-araiosis in patients with Alzheimer's disease

Table 3. Number of patients withdrawn from each group and the reason for withdrawal

<table>
<thead>
<tr>
<th>No. of patients withdrawn</th>
<th>With WMLA</th>
<th>Without WMLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>11 (61%)</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Developed a stroke</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

WMLA, white matter low attenuation

*P = 0.015 (Pearson's χ² followed by Yates' continuity correction).

The importance of trying to predict response to tacrine has been well recognized by many investigators, yet so far has only met with limited success [17–19]. Schneider et al. found that responders to tacrine were more likely to be older and have a greater degree of postural drop in their blood pressure compared with non-responders [20]. Pamora et al. reported the opposite, i.e. responders were younger and had less postural hypotension, when they compared AD patients' responses to the anticholinesterase drug Velnacrine (a metabolite of tacrine) [21]. Alhainen et al. reported that responders to tacrine were more likely to be mildly demented [22].

Although there is evidence in favour of a role for WMLA as a contributory factor to the production and development of cognitive impairment [23, 24], the presence of WMLA in our study did not help to discriminate potential responders from non-responders. This can be interpreted in one of two ways: either WMLA has not made a significant contribution to those cognitive deficits that are susceptible in some subjects to improvement by tacrine, or these ischaemic-related cognitive deficits can also respond to anticholinesterase treatment.

The most interesting finding in this study is that significantly fewer patients with WMLA were able to tolerate tacrine for the full 3 months of treatment. The rate of withdrawal of patients with WMLA from tacrine was more than twice that of patients with no visible white matter disease. Although patients with WMLA were a little older than those without WMLA, and therefore possibly more frail and more susceptible to side-effects, it is unlikely that this is enough to explain the great discrepancy in the incidence of side-effects between the two groups. Also, the higher rate of withdrawal in the WMLA group was not associated with a higher dosage and therefore a greater chance of developing side-effects, since both groups received similar dosage regimes.

Patients included in the open study were significantly more cognitively impaired than patients included in the double-blind study (mean MMSE 12.7 compared with 16.1 in the double-blind group, P = 0.027).

Response to tacrine was defined as an improvement in the MMSE score of three or more points which was maintained at 3 months. In patients with no WMLA, 12 patients (31%) who tolerated the treatment were classified as responders, compared with two out of seven (28.5%) in the group with WMLA. This did not change when the definition of a response was altered by changing the cut-off points on the MMSE (Table 2). Assessments with the CAMCOG and the ADAS-cog gave similar results to the MMSE.

The rate of withdrawal from tacrine was, however, significantly higher in the group of patients with WMLA. Eleven patients (61%) with white matter disease were withdrawn prematurely, compared with 14 (26%) of those with no visible white matter lesions (P = 0.015). As can be seen from Table 3, the higher rate of withdrawal in the WMLA group is accounted for by a higher rate of cholinergic side-effects, i.e. nausea and vomiting (two patients), together with a higher incidence of agitated behaviour (two patients), and one patient who developed a stroke.

Discussion

WMLA has been reported in 26–61% of AD patients [5, 6, 15]. In a previous report we discovered a WMLA incidence of 52% in our AD patients [16]. The lower than expected incidence of WMLA in this study (25%) could simply be due to bias caused by differential difficulty in retrieving the CT scans for some patients. It could also reflect extra caution on our part in prescribing tacrine to patients with WMLA which may cast doubt on the diagnosis of AD by pointing more to a vascular aetiology. However, the presence of leuko-araiosis is fully compatible with a diagnosis of AD and we are not aware of having been influenced in this way. The higher age of the patients with WMLA (Table 1) is to be expected, since the incidence of leuko-araiosis is known to rise with increasing age [5].

(mean MMSE 12.7 compared with 16.1 in the double-blind group, P = 0.027)

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compared with 16.1 in the double-blind group). This would suggest that they were more severely demented and therefore less likely to tolerate the treatment or respond favourably. The rate of withdrawal from the open study, however, was similar to that in the double-blind study (36 and 33% respectively).

Although the commonest cause for withdrawal was an elevation of liver transaminases (20% of patients without WMLA and 22% of patients with WMLA), the main difference between the two groups was caused by a higher rate of withdrawal because of agitated behaviour, nausea and vomiting, and symptomatic cerebrovascular disease in the WMLA group. The reason for the higher incidence of agitation is not clear. Demented patients with leuko-araiosis often display subcortical features such as mental slowness, apathy and poor concentration [25]. Harrell et al. postulated that patients with white matter lesions could be more susceptible to developing depression, possibly due to disruption of some of the fibre systems that traverse the white matter [26].

One possibility therefore is that the low threshold for developing agitated behaviour in patients with WMLA given tacrine could be due to an early depressive illness, which was not otherwise detected clinically. This is unlikely as agitation accompanying depression usually occurs in moderate to severe depression and we are not aware that any of the patients who withdrew because of agitation developed clinical depression on follow-up. Recently, Binetti et al. reported a correlation between frontal leuko-araiosis and delusions. It is therefore possible that patients with leuko-araiosis could have a lower threshold for developing other psychiatric symptoms [27]. The possibility of a direct pharmacological effect by tacrine causing increased arousal and activation in susceptible individuals cannot be discounted.

Interestingly, in the group without WMLA, no patients were withdrawn solely because of gastrointestinal cholinergic side-effects (nausea and vomiting), although some had cholinergic side-effects accompanying deranged liver function tests, which was the main reason for their withdrawal. By contrast, two patients with WMLA had to be withdrawn because of nausea and vomiting. It is known that cholinergic side-effects are dose-dependant but in these two patients the dose of tacrine (50 mg) was not high.

It is not surprising that one patient with WMLA had to be withdrawn from tacrine because of a stroke. It has been reported that AD patients with leuko-araiosis are more likely to develop clinically significant cerebrovascular disease on follow-up [28]. Also, patients with lacunar infarcts and WMLA are reported to have a worse prognosis on follow-up compared with those without WMLA. Following their first stroke they have a higher incidence of further strokes and dementia [29].

In conclusion, although the small number of patients studied precludes firm conclusions, it appears that response to tacrine of AD patients with WMLA differs from that of AD patients without white matter lesions. The risk of adverse effects is more than doubled in AD patients with leuko-araiosis. This finding may be relevant to other anticholinesterase treatments being evaluated for AD, and merits further investigation in clinical trials.

Key points

- Approximately one-third of Alzheimer's disease patients prescribed tacrine show mild improvement in cognitive function.
- About one-third develop adverse effects, the commonest being abnormal liver function tests.
- The presence of white matter low attenuation does not discriminate responders to tacrine from non-responders.
- Alzheimer's disease patients with white matter low attenuation have a significantly higher rate of withdrawal from tacrine.

References


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