CASE REPORT

An N-of-1 randomized controlled trial (‘N-of-1 trial’) of donepezil in the treatment of non-progressive amnestic syndrome

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Abstract

Introduction: a professional man sustained a residual, persisting, isolated impairment of short-term memory secondary to severe carbon monoxide poisoning. Informal, open trial of the cholinesterase inhibitor donepezil resulted in uncertain benefit.

Protocol: an N-of-1 randomized, double-blind controlled trial of donepezil against placebo. Placebo-induced headache permitted evaluation of donepezil at only the 5 mg dose.

Results: there was no improvement in short-term memory.

Conclusion: the trial excluded significant benefit of donepezil 5 mg in this patient, preventing long-term unnecessary prescription. Beneficial effects in other similar patients or at higher dosage cannot be excluded.

Keywords: randomized controlled trials, cholinesterase-inhibitors, drug therapy, amnesia

Introduction

A 50 year-old professional man had, 15 years earlier, been found close to death following severe carbon monoxide (CO) poisoning. After resuscitation and rehabilitation he made a complete recovery of physical functions, but a residual isolated impairment of short-term memory persisted, a common sequela of CO poisoning [1]. Attention and executive function were unaffected, but work performance was impaired. There were no other neurological symptoms or signs. He did not feel able to return to his previous demanding profession, but held several less challenging, short-term posts. Cognitive function did not improve, and ultimately he was referred to the Oxford Memory Assessment Clinic for consideration of treatment options.

In view of the similarity in anatomical location of the damage associated with the amnestic syndrome in CO poisoning and in Alzheimer’s disease, an open trial of treatment with donepezil was discussed and agreed with the patient. Although at first he felt there was some improvement in memory function this became less clear over two to three months. Moreover, since the underlying impairment was permanent, there were concerns over possible lifelong prescription of a drug of uncertain benefit for an unlicensed indication and for which long-term safety data were not available. After discussion and explanation of the study design, the patient welcomed the suggestion of participating in a formal N-of-1 randomized, double-blind controlled trial of donepezil against placebo. In addition to evaluating benefit for the patient it was recognized that the trial would be of broader interest in initiating an exploration of possible uses for donepezil in contexts other than Alzheimer’s disease. The trial protocol was approved by the Chairman of the Central Oxford Research Ethics Committee as not requiring formal scrutiny by the Committee.

Protocol

The dosage schedule was discussed and agreed with the Medical Advisory Division of Eisai-Pfizer, the
manufacturers and marketers of donepezil. The schedule consisted of six modules of either treatment or placebo, each of six weeks duration. Each treatment module was to consist of four weeks of donepezil at 5 mg daily, followed by 2 weeks of 10 mg daily. Six-week periods were chosen as long enough to provide ‘washout’ on placebo and to attain measurable effect on active treatment. The trial was double-blind. Placebo modules used matching non-active tablets.

Eisai-Pfizer provided drugs and matching placebo and devised the randomization sequence without involvement of the investigators. The sealed randomization schedule was held in the hospital pharmacy until completion. The Medicines Control Agency granted special exemption permitting donepezil to be used outside its existing product licence.

The Mini-Mental State Examination (MMSE) was performed at baseline only. At baseline and at the end of each six-week study period, the same clinician applied the following validated psychometric instruments:

1. Hopkins Verbal Learning Test-Revised (HVLT-R) [2]; a brief, clinician-administered assessment of verbal recall and recognition. The HVLT-R was chosen partly because of its availability in six equivalent but different versions, so avoiding specific learning effects in repeated testing.

2. Hamilton Rating Scale for Depression (HRSD) [3]; a self-administered, 17-item questionnaire useful for measurement of depression.

3. Short Form 36 Health Survey questionnaire—UK version (SF-36) [4]; a self-administered, generic measure of health status.

4. Patient-Generated Index (PGI) [5]; one of several recently developed, self-administered instruments that ‘allows individuals to nominate, weigh and assess those domains of greatest relevance to their quality of life’ [6].

Beneficial or ill effects possibly attributable to the medication were noted and the assessing clinician made a simple qualitative assessment of change in the patient’s short-term memory in comparison with baseline.

### Results

Persistent headache occurred during the first module following dose increase to 10 mg. The dose was reduced to 5 mg and fixed at 5 mg throughout subsequent six-week treatment modules. The trial was not unblinded at that stage, but at analysis it was apparent that the headache had occurred during a placebo phase.

Baseline MMSE was 28/30, with points lost on recall only. The results of the other psychometric assessments are presented in Table 1.

At the end of the study the randomization schedule was revealed as having comprised alternating placebo and treatment phases. Results were inspected visually. There was no discernible effect of donepezil on memory, mood or wellbeing. However, mood and wellbeing deteriorated markedly during the second half of the trial, concurrently with unrelated adverse life events.

### Discussion

The trial demonstrated no worthwhile clinical benefit of donepezil for this patient, providing clinician and patient with high quality information that facilitated a definitive decision that further drug prescription was not worthwhile. Given that there were only three replications of each treatment, the power of the trial to detect small differences was weak, but the lack of any sign of benefit in the scores presented in Table 1 was regarded by investigators and patient as sufficiently convincing to justify no further use of donepezil. It has to be noted that owing to the episode of headache during the first placebo phase the dosage of donepezil was not raised to the intended 10 mg daily during the last two weeks.

### Table 1. Results of psychometric assessments

<table>
<thead>
<tr>
<th>Instrument (maximum possible score)</th>
<th>Baseline</th>
<th>Placebo module 1</th>
<th>Treatment module 1</th>
<th>Placebo module 2</th>
<th>Treatment module 2</th>
<th>Placebo module 3</th>
<th>Treatment module 3</th>
<th>Placebo modules mean</th>
<th>Treatment modules mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVLT-R total recall (36)</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>15</td>
<td>13</td>
<td>20</td>
<td>22</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>HVLT-R learning measure (12)</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>3.3</td>
<td>2.3</td>
</tr>
<tr>
<td>HVLT-R percent retained (100)</td>
<td>43</td>
<td>84</td>
<td>33</td>
<td>57</td>
<td>20</td>
<td>67</td>
<td>60</td>
<td>69.3</td>
<td>37.7</td>
</tr>
<tr>
<td>HVLT-R discrimination index (12)</td>
<td>7</td>
<td>11</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>7.3</td>
</tr>
<tr>
<td>PGI (100)</td>
<td>50</td>
<td>56</td>
<td>67</td>
<td>50</td>
<td>45</td>
<td>20</td>
<td>20</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>HRSD (50)</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>13</td>
<td>14</td>
<td>20</td>
<td>6.7</td>
<td>11.7</td>
</tr>
<tr>
<td>SF-36 (143)</td>
<td>109</td>
<td>129</td>
<td>130</td>
<td>128</td>
<td>122</td>
<td>84</td>
<td>114</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Clinician assessment</td>
<td>–</td>
<td>Improved</td>
<td>No change</td>
<td>Improved</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>–</td>
</tr>
</tbody>
</table>

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of each phase. Maximum benefit of the drug may not therefore have been attained.

As expected [2], there were no discernible practice effects from serial application of the HVLT-R. The HRSD, SF-36 and PGI proved sensitive to the patient’s low mood during the second half of the trial. Memory was no worse during this period, confirming the organic nature of the impairment.

The lack of therapeutic effect of donepezil for this patient does not exclude the possibility of benefit for other people with a similar clinical syndrome. In this trial, placebo-induced headache prevented trial of donepezil at the 10 mg dose at which response is most likely. Further N-of-1 trials of cholinesterase inhibitors in clinical contexts other than Alzheimer’s disease would be a logical approach to identifying new indications for these drugs.

**Key points**

- N-of-1 randomized controlled trials provide empirical evidence for the effectiveness of treatments for individual patients. Such trials are acceptable to patients and clinicians.
- Donepezil 5 mg was ineffective in a patient with non-progressive amnestic syndrome. However, other patients may benefit, at this or higher dose.

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**Acknowledgements**

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**References**

5. Ruta DA, Garratt AM, Leng M, Russell IT, MacDonald LM. A new approach to the measurement of quality of life. The Patient-Generated Index. Med Care 1994; 32: 1109–26.