Galantamine improved cognition and global functioning in vascular dementia or Alzheimer’s disease with cerebrovascular disease


QUESTION: In patients with probable vascular dementia or Alzheimer’s disease (AD) with cerebrovascular disease, is galantamine more effective than placebo for improving cognitive ability and global functioning?

Design
6 month randomised (unclear allocation concealment*), blinded (clinicians and patients),* placebo-controlled trial.

Setting
Canada, Denmark, Finland, France, Germany, Ireland, Israel, The Netherlands, Poland, and the UK.

Patients
592 patients (mean age 75 y, 53% men) who met clinical criteria for probable vascular dementia or possible AD with radiological evidence of cerebrovascular disease. Additional inclusion criteria included a score of 10 to 25 on the Mini-Mental State Examination and ≥12 on the Alzheimer Disease Assessment Scale Cognitive subscale (ADAS-COG). Exclusion criteria included evidence of neurodegenerative disorders other than AD that might cause or contribute to dementia, and cognitive impairment resulting from cerebral trauma. Follow up was 82% and 77% at 3 and 6 months, respectively.

Intervention
Patients were allocated to receive galantamine, 24 mg/day (n = 396) or placebo (n = 196) once daily for 6 months.

Main outcome measures
Cognitive ability measured by the standard 11 item ADAS-COG (ADAS-COG11) and global functioning measured by the Clinician’s Interview-Based Impression of Change plus caregiver input assessed at baseline and 3 and 6 months.

Main results
At 6 months, improvement in cognitive ability was greater in the galantamine group than in the placebo group. More patients in the galantamine group remained stable or had improved global functioning at 6 months. More patients in the galantamine group than in the placebo group withdrew from the study because of adverse effects (20% v 8%, p < 0.01).

Conclusion
In a mixed population of patients with probable vascular dementia or Alzheimer’s disease and cerebrovascular disease, galantamine was more effective than placebo for improving cognitive ability and global functioning.

*See glossary.

Galantamine v placebo for probable vascular dementia or Alzheimer’s disease combined with cerebrovascular disease at 6 months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Galantamine</th>
<th>Placebo</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in ADAS-COG11</td>
<td>–1.7</td>
<td>1.0</td>
<td>2.7 (1.4 to 4.0)‡</td>
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<tr>
<td>scores from baseline</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RBI (CI)</td>
<td>74%</td>
<td>59%</td>
<td>25% (9 to 47)</td>
</tr>
</tbody>
</table>

| Patients with improvement or  |           |         |                     |
| no change on CIBIC-plus       | 74%        | 59%     | 25% (9 to 47)       | 7 (5 to 17)       |

‡The difference favours galantamine.

COMMENTARY

Acetylcholinesterase inhibitors are thought to partially correct the cholinergic deficit characteristic of AD. Benefits from these drugs are described as short term improvement or lack of decline in cognitive function. In this study by Erkinjuntti et al of older patients with vascular dementia and AD combined with cerebrovascular disease, about one-third (35.3%) of patients on galantamine compared with about one-fifth (22.2%) of patients on placebo improved by ≥4 points on a scale (ADAS-COG11) commonly used in AD drug trials. Patients with AD were most likely to improve.

Adverse events (predominantly nausea and vomiting) caused one-fifth (20%) of patients in the galantamine group to discontinue the drug. Erkinjuntti et al recommend a different dose escalation regimen to minimise this complication, but gastrointestinal toxicity, common to cholinesterase inhibitors, has to be weighed against the potential benefits of galantamine. Interpretation of this study is further complicated because more patients in the galantamine group than in the placebo group were taking antispasmodics and anticholinergics (domperidone 5% v 1%, and metoclopramide 3% v 0%) at baseline—a curious difference possibly relevant to the study outcome, which is left unexplained in the published paper.

This study confirms that such acetylcholinesterase inhibitors as galantamine probably have beneficial effects in some patients with AD, AD mixed with cerebrovascular disease, or clinically diagnosed vascular dementia. Recent pathologic studies have shown that AD mixed with other causes of dementia is common in older people in the community. Whether the benefits outweigh the adverse effects is best assessed in single patient trials using patient—and caregiver—valued clinical end points. Some patients may experience clinically meaningful improvement, but most will not.

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