Effects of a flexible galantamine dose in Alzheimer’s disease: a randomised, controlled trial

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Abstract

Objective—To assess the efficacy and safety of galantamine in Alzheimer’s disease at 3 months using flexible dose escalation.

Methods—A randomised, double blind, placebo controlled trial in 43 centres in the United States, Canada, Great Britain, South Africa, Australia, and New Zealand. Patients with probable Alzheimer’s disease (n=386; 171 women) with a score of 11–24 on the mini mental state examination, and a score ≥12 on the cognitive sub-scale of the Alzheimer’s disease assessment scale (ADAS-cog) were randomised to placebo, or galantamine escalated over 4 weeks to a maintenance dose of 24 or 32 mg/day. The primary outcome measures were the change in ADAS-cog score and the clinician’s interview based impression of change plus caregiver input (CIBIC-plus) score. Activities of daily living (ADL) and behavioural symptoms were secondary outcomes. To compare the effects of highest levels of dosing, an observed cases (OC) analysis was undertaken, with classic intention to treat (ITT) and ITT with last observation carried forward (LOCF) as confirmatory analyses.

Results—At 3 months, galantamine (24–32 mg/day) produced a significantly better outcome on cognitive function than placebo (treatment difference=1.9 points on ADAS-cog, p<0.002) and a significantly better global response than placebo, as measured by CIBIC-plus (deterioration in 21% of patients on galantamine v 37% on placebo; p=0.001). Galantamine produced significant benefits on basic and instrumental ADL. Behavioural symptoms did not change significantly from baseline levels in either group. Adverse events (primarily gastrointestinal) were of mild to moderate intensity. There were no important differences between the OC, ITT, and ITT/LOCF analyses. Most patients (82%) who were maintained on the higher dose of galantamine completed the study.

Conclusions—Patients on galantamine, compared with those on placebo, experienced benefits in cognitive function and instrumental and basic activities of daily living. Flexible dose escalation of galantamine was well tolerated.

Keywords: Alzheimer’s disease; galantamine; nicotinic receptors; acetylcholinesterase inhibition; activities of daily living

The enhancement of cholinergic function remains the most successful approach to date for ameliorating the symptoms of Alzheimer’s disease. This strategy is based on the cholinergic hypothesis, which proposes that degeneration of cholinergic neurons in the basal forebrain and the associated loss of cholinergic neurotransmission in the cerebral cortex contribute significantly to the cognitive decline seen in patients with Alzheimer’s disease. Acetylcholinesterase inhibition is currently the most established strategy for correcting cholinergic deficits in Alzheimer’s disease and improving cognitive symptoms. The development of newer cholinesterase inhibitors seems to have overcome the initial problem of hepatotoxicity, seen with tacrine and varenicline. Nevertheless, gastrointestinal symptoms, and other side effects, such as insomnia, sometimes reported with donepezil, and muscle weakness, reported with metrifonate, can be potentially troublesome side effects.

As the disease progresses, cognitive decline is accompanied by functional impairment, which increases patients’ dependence on caregivers and influences the decision to admit patients to long term care facilities. The precise benefits of cholinesterase inhibitors are still an issue of debate, with some commentators unconvinced that the reported improvements in cognition translate into clinically important effects on a patient’s functional ability.

Galantamine is a novel agent that modulates nicotinic receptors and potentiates nicotinic neurotransmission in addition to inhibiting acetylcholinesterase. Given the loss of nicotinic receptors that accompanies the impairment of presynaptic cholinergic function in Alzheimer’s disease, and their role in memory and learning, maintaining nicotinic activity may have therapeutic value. Galantamine binds to an allosteric binding site on nicotinic receptors, thereby potentiating the response of these receptors to the natural agonist, acetylcholine. This enhancement of nicotinic neurotransmission may be clinically relevant because activation of presynaptic nicotinic receptors has been shown to increase the release of acetylcholine and glutamate, which are deficient in Alzheimer’s disease and are thought to be involved in memory and learning. The beneficial effects of galantamine in patients with Alzheimer’s disease have already been demonstrated in two large 6 month placebo controlled trials that used a 4 week dose escalation period to achieve fixed maintenance doses of 24 or 32 mg/day.
more information becomes available on specific patterns of treatment effects with galantamine (perhaps, for example, early stabilisation of activities of daily living (ADL), lack of sleep disturbance, or improved attention) it may be that the clinical role of the nicotinic receptor might be better understood. As the tolerability of cholinesterase inhibitors is dose related,2 the present study was undertaken to test the efficacy and safety of galantamine using a flexible dose, in patients with mild to moderate Alzheimer’s disease, over 3 months.

Methods

Patients

Patients with a history of cognitive decline that had been gradual in onset and progressive for at least 6 months were included. Other inclusion criteria were:

- A diagnosis of probable Alzheimer’s disease according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA).24
- Presence of mild to moderate dementia (a score of 11–24 on the mini mental state examination (MMSE)25 and a score ≥2 on the standard cognitive subscale of the Alzheimer’s disease assessment scale (ADAS-cog).26
- Patients also had to have regular contact with a responsible caregiver. Those with concomitant diseases such as hypertension, congestive heart failure, non-insulin dependent diabetes mellitus, and hypothyroidism were included in the study provided the disease was controlled. Patients were excluded from the study if they had evidence of other neurodegenerative disorders; any cardiovascular disease thought likely to prevent completion of the study; clinically significant cerebrovascular, hepatic, renal, pulmonary, metabolic or endocrine conditions; clinically significant psychiatric disease, including moderate or severe or uncontrolled behavioural disturbances; urinary outflow obstruction; an active peptic ulcer; any history of epilepsy, or significant drug or alcohol misuse.

Patients previously treated with any cholinomimetic agent for Alzheimer’s disease, except muscarinic agonists, were also excluded. Any other medication being taken to treat dementia had to be discontinued. The use of other concomitant medication was permitted, except that, where possible, drugs with a psychotropic action were discontinued 48 hours before cognitive evaluation. Drugs with anticholinergic effects or cholinomimetic effects were avoided.

The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by ethics committees at each centre. The patient (or a representative), together with the carer, provided written informed consent to participate.

Design

This was a 3 month, parallel group, placebo controlled trial undertaken in 43 centres in six countries (Australia, Canada, Great Britain, New Zealand, South Africa, and the United States). After a 4 week, single blind, placebo run in phase, patients were randomised to receive galantamine or placebo in a 2:1 ratio using a computer generated code. The assignments were kept in sealed, opaque envelopes until the point of allocation. Patients treated with galantamine received 8 mg/day for 1 week, increasing to 16 mg/day for the 2nd week and to 24 mg/day (12 mg twice daily) for the 3rd week. During week 4, the galantamine or placebo dose could be increased (to 32 mg/day—that is, 16 mg twice daily for galantamine) at the discretion of the investigator, based on tolerance. By the end of the 4th week the investigator could reduce the dose (for galantamine from 32 mg/day to 24 mg/day).

Patients continued with their final dose of galantamine or placebo for a further 2 months. Throughout the study, all individual doses of galantamine and placebo were otherwise identical single tablets taken twice daily.

The primary efficacy variables were the standard, 11 item cognitive subscale of the Alzheimer disease assessment scale (ADAS-cog/11)20 to assess cognitive function, and the clinician’s interview based impression of change plus caregiver input (CIBIC-plus)37 to assess overall clinical response. The CIBIC-plus was scored by a trained clinician based on separate interviews with the patient and the caregiver; the clinician was blinded to other assessments. Scores ranged from 1 to 7 (1=markedly improved with respect to baseline, 7=markedly worse).

Secondary efficacy variables were:

- The expanded (13 item) version of the standard ADAS-cog subscale (ADAS-cog/13), with a score range of 0–85.26
- The proportions of responders (defined as improvements in ADAS-cog/11≥4 points from baseline).27
- Neuropsychiatric inventory (NPI), which assesses 10 domains of behavioural symptoms (score range of 0–120).30
- Disability assessment for dementia (DAD) scale, based on an interview with the caregiver, to assess basic and instrumental activities of daily living (ADL), initiation, planning and organisation, performance, and leisure; the DAD has a score range 0–100.21

All of the efficacy assessments were performed at baseline and after 1 and 3 months.

Safety evaluations throughout the study comprised physical examinations, ECG, vital sign measurements, standard laboratory tests, and monitoring for adverse events (classified according to World Health Organisation preferred terms). For the first 2 weeks, the investigator contacted the patient or caregiver by phone at weekly intervals to record any adverse events. Safety was further evaluated at monthly clinic visits at weeks 3 and 4, and after 2 and 3 months. Sleep patterns were assessed after 1 and 3 months using the seven item Pittsburgh sleep quality index (PSQI), which measures subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction; each item is scored from 0–3 (0 indicates no difficulty, 3 indicates severe difficulty).32
Using data from an earlier phase II trial, we calculated that 94 patients were needed to complete the study in the placebo group, and twice this number in the galantamine group, to achieve 80% power ($\alpha = 0.05$) for detecting a 2.5 point difference in the change in ADAS-cog/11 score between patients treated with placebo and with each of the maximum daily doses of galantamine.

All randomised patients who took at least one dose of trial medication were included in the analyses of baseline characteristics and safety data. As we were chiefly concerned with assessing the treatment effects of the maximum daily doses of galantamine (24–32 mg/day), a traditional “observed cases” (OC) analysis at 3 months was the primary efficacy analysis; this included patients who provided postbaseline data for ADAS-cog/11, CIBIC-plus, or DAD variables at the designated assessment times. More conservative 3 month, intention to treat (ITT) analyses were also performed to examine the robustness of the efficacy results. This included classic ITT analysis (according to assigned treatment and using the last observation available for each patient regardless of whether they took trial medication), and the traditional last observation carried forward (LOCF) analysis (using the last postbaseline observations available for each patient who received treatment). All results discussed are based on OC analysis unless otherwise stated.

Baseline characteristics of the three groups were compared using two ways of analysis: ANOVA for continuous variables and generalised Cochran-Mantel-Haenszel tests for categorical variables. Changes from baseline in efficacy variables, vital signs, and body weight were assessed using two tailed, paired $t$ tests. Comparisons of variables between the galantamine and placebo groups employed the following methods: ANOVA for changes from baseline in ADAS-cog subscales, DAD, PSQI, and vital signs; generalised Cochran-Mantel-Haenszel tests for ADAS-cog/11 response rates; and Van Elteren tests$^{33}$ for CIBIC-plus. The critical level of significance was set as $p \leq 0.05$. The statistical software used in these analyses was SAS version 6.12.

### Results

Five hundred and thirty four patients were screened for the study and 386 were randomised to trial medication, of whom 75% completed the study (fig 1). During week 4, 64 patients remained on the 24 mg/day dose of galantamine, whereas 165 were escalated to the 32 mg/day dose, of whom 40 (24%) reverted to the lower dose during that week. Of the 125 patients remaining on the higher dose by the end of week 4, 103 (82%) completed the study.

#### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=125)</th>
<th>Galantamine 24–32 mg (n=261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males/females</td>
<td>58/67</td>
<td>113/148</td>
</tr>
<tr>
<td>Age ($\text{y}$)*</td>
<td>74.6 (0.68)</td>
<td>75.2 (0.45)</td>
</tr>
<tr>
<td>Clinical:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>68.5 (1.37)</td>
<td>66.1 (0.86)</td>
</tr>
<tr>
<td>Smokers</td>
<td>9 (7.2)</td>
<td>21 (8.0)</td>
</tr>
<tr>
<td>Other active medical conditions</td>
<td>112 (89.6)</td>
<td>235 (90.0)</td>
</tr>
<tr>
<td>ApoE $\epsilon 4$ genotype:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygous</td>
<td>14 (13.0)</td>
<td>38 (16.7)</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>56 (51.8)</td>
<td>111 (48.9)</td>
</tr>
<tr>
<td>Total MMSE score*</td>
<td>19.6 (0.32)</td>
<td>19.7 (0.24)</td>
</tr>
<tr>
<td>ADAS-cog/11 score*</td>
<td>24.7 (0.85)</td>
<td>25.6 (0.65)</td>
</tr>
<tr>
<td>Total NPI score*</td>
<td>9.4 (1.01)</td>
<td>9.2 (0.66)</td>
</tr>
<tr>
<td>Total DAD score*</td>
<td>73.0 (1.91)</td>
<td>69.1 (1.42)</td>
</tr>
<tr>
<td>Time since cognitive problem diagnosed ($\text{y}$)*</td>
<td>3.22 (0.19)</td>
<td>3.8 (0.20)</td>
</tr>
<tr>
<td>Time since probable Alzheimer's disease diagnosed ($\text{y}$)*</td>
<td>0.69 (0.1)</td>
<td>0.71 (0.07)</td>
</tr>
</tbody>
</table>

Data are number (%) of patients, except those marked * which denotes mean (SE).
Of the patients who continued on, or reverted to, the lower dose during week 4, 72 (69%) completed the study. The baseline characteristics of the treatment groups were comparable (table 1). The proportions of patients taking concomitant medication (most commonly analgesics) during the double blind phase of the study were comparable between treatment groups (89%, placebo and 88%, galantamine). A slightly greater proportion of patients in the galantamine group (33% (85/261)) compared with those receiving placebo (25% (31/125)) took concomitant psychotropic medications.

Protocol deviations occurred in 38 (10%) of randomised patients. Use of prohibited medications (20 cases) was the most common problem.

**Efficacy**

Galantamine treated patients showed significantly superior cognitive function when compared with placebo treated patients, the mean treatment effect in favour of galantamine being 1.1 points ($p<0.05$) at 1 month and 1.9 points ($p=0.002$) at 3 months on the ADAS-cog/11 subscale (fig 2). These treatment differences were due to ADAS-cog/11 scores significantly improving from baseline in galantamine treated patients at both time points ($p<0.001$ in both cases), while not changing significantly in the placebo group (table 2). At 3 months, there was no difference in those who received 32 mg/day or 24 mg/day galantamine in improvement from baseline in ADAS-cog/11 during the fixed dose treatment period (mean (SE) 1.4 (0.57), n=99, and 1.5 (0.54), n=71, ADAS points respectively). All of these findings were confirmed by both ITT analyses. Galantamine also produced a significantly better outcome than placebo on the ADAS-cog/13 subscale ($p=0.004$) and ADAS-cog/11 responder rates ($p=0.02$, table 2).

The overall clinical response to galantamine at 3 months, as measured by CIBIC-plus, was significantly better than with placebo ($p=0.003$; significance confirmed by both ITT analyses, table 2). Only 21% of patients on galantamine (n=170) deteriorated compared with 37% (n=111) of those in the placebo group. Furthermore, galantamine produced significant benefits on activities of daily living as indicated by a drug–placebo difference in the mean change from baseline of 4.3 points in the total DAD score ($p=0.004$; significance confirmed by both ITT analyses, table 2). Functional performance was preserved in galantamine treated patients, as indicated by a DAD score that was not significantly different from baseline. This preservation of functional activity was seen regardless of whether patients completed the study on a dose of 32 mg/day or 24 mg/day (mean (SE) changes of 0.6 (1.21), n=99, and −0.5 (1.24), n=73, respectively). By contrast, the decline in total DAD score for the placebo group was statistically significant ($p<0.001$ for OC and ITT analyses). At 3

**Table 2  Efficacy outcomes after 3 months**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Placebo</th>
<th>Galantamine 24–32 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Classic ITT</td>
<td>ITT (LOCF)</td>
</tr>
<tr>
<td>ADAS-cog/11 (mean (SE) change from baseline)</td>
<td>+0.7 (0.47)</td>
<td>+0.6 (0.45)</td>
</tr>
<tr>
<td>(n=125)</td>
<td>(n=120)</td>
<td>(n=108)</td>
</tr>
<tr>
<td>ADAS-cog/13 (mean (SE) change from baseline)</td>
<td>+0.7 (0.52)</td>
<td>+0.7 (0.51)</td>
</tr>
<tr>
<td>(n=123)</td>
<td>(n=120)</td>
<td>(n=108)</td>
</tr>
<tr>
<td>No (% ADAS-cog/11 responders)</td>
<td>+4 points improvement</td>
<td>27 (22.0)</td>
</tr>
<tr>
<td>(n=124)</td>
<td>(n=123)</td>
<td>(n=111)</td>
</tr>
<tr>
<td>CIBIC-Plus (No (% patients in each category))</td>
<td>&gt; ADAS-cog/11 (mean (SE) change from baseline)</td>
<td>+0.7 (0.47)</td>
</tr>
<tr>
<td>(n=125)</td>
<td>(n=120)</td>
<td>(n=108)</td>
</tr>
<tr>
<td>&gt; ADAS-cog/11 (mean (SE) change from baseline)</td>
<td>−0.4 (0.65)</td>
<td>−0.3 (0.7)</td>
</tr>
<tr>
<td>(n=261)</td>
<td>(n=241)</td>
<td>(n=172)</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.001 v placebo.

ITT = Intention to treat analysis; LOCF = Last observation carried forward analysis; OC = Observed cases analysis.
Effects of a flexible galantamine dose in Alzheimer’s disease

...effects, especially given the contribution of costs of care. In our view, the short duration was the study’s main limitation. However, the duration of galantamine treatment was long enough to demonstrate a therapeutic effect, even with a fairly rapid dose escalation, and to test our primary hypothesis about the effects of flexible dosing on tolerability. We used the OC analysis at 3 months as the primary analysis so that we could capture the effect of treatment on completers who had been maintained on 24 or 32 mg/day galantamine, thus reflecting experience in clinical practice in patients who comply with treatment recommendations. Although the OC analysis may bias the results towards a larger treatment effect, especially as the drop out rate was higher in the galantamine group than in the placebo group, our findings are confirmed by more conservative ITT analyses.

Hitherto the lack of impact of cholinesterase inhibitors on function has been used to undermine the clinical importance of their cognitive effects, especially given the contribution of functional decline to caregiver burden and the cost of care. The general consensus view...
is changing as functional improvement has been reported in other studies of galantamine and, at least for instrumental ADL, with donepezil. Whether the preservation of basic ADL seen in this study constitutes an advantage of galantamine over other treatments cannot be established without direct comparative studies, but evidence now exists that functional benefit can be demonstrated with cholinesterase inhibition.

The adverse events associated with galantamine in this study were generally those expected from cholinergic stimulation, and similar to those reported with other cholinesterase inhibitors.6–10 The adverse events were of mild to moderate severity, with the exception of patients taking 32 mg/day who received 24 mg/day (mean ADAS-cog improvement over baseline 1.4 and 1.5 points respectively). This is consistent with a 6 month placebo controlled study that did not show any clinically or statistically significant differences on primary efficacy variables between the 24 and 32 mg/day doses of galantamine.6–10

This randomised, placebo controlled trial shows that galantamine produces cognitive and functional benefit in patients with mild to moderate Alzheimer’s disease. Galantamine was well tolerated with no evidence of hepatotoxicity, muscle weakness, or sleep disturbance. These results suggest that galantamine will have a useful role in the treatment of Alzheimer’s disease.


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