Switching from donepezil to galantamine: a double-blind study of two wash-out periods

David G. Wilkinson¹* and Ian Howe² on behalf of the GAL-GBR-1 Study Group

¹Memory Assessment and Research Centre, Moorgreen Hospital, Southampton, UK
²Shire Pharmaceuticals Ltd, Hampshire, UK

INTRODUCTION

Currently, the most commonly prescribed acetylcholinesterase inhibitor (AChEI) for treatment of patients with mild to moderate Alzheimer’s disease (AD) is donepezil. However, clinicians who initiate treatment with donepezil may wish to consider an alternative AChEI if it is felt that the patient is not tolerating donepezil or has failed to respond. In one donepezil to galantamine ‘switching’ trial, an overnight switch with no washout and subsequent dose escalation (8 mg/day to 24 mg/day) over three weeks resulted in an increase in gastrointestinal (GI) adverse events (AEs) (Rasmusen et al., 2001). Another trial showed that either fast (weekly increments of 8 mg/day) or slow (monthly increments of 8 mg/day) galantamine dose titration after a seven-day donepezil washout period was well tolerated (Rasmusen et al., 2001).

Because donepezil has a longer half-life than galantamine (~70 vs ~7 h), there will be a slow drop in blood levels after stopping donepezil which could dovetail with galantamine titration. Consequently patient’s switching may tolerate a new one better than patient’s who are AChEI-naive. The need for a washout period between two AChEIs to prevent over-inhibition and increased AEs is generally accepted in clinical practice but a break in treatment may result in loss of efficacy and relatively rapid cognitive decline back to that pre-treatment (Farlow, 2001). This study explored the optimum length of the wash-out period in patients switching from donepezil to galantamine.

MATERIALS AND METHODS

Subjects were included if they had mild to moderate probable AD, had been taking donepezil for ≤12 weeks and were considered to be in need of alternative anti-dementia medication. All subjects had a Mini-Mental State Examination (MMSE) score of 10–25, and an Alzheimer’s Disease Assessment Scale total score of ≤12 (ADAS-cog/11).

Subjects continued to take donepezil during a two-week run-in/screening period. Those entering the four-week double-blind washout/dose escalation period were randomised to a washout period of four days or seven days, after which they began treatment with galantamine 4 mg twice daily. The total daily dose was increased by 8 mg/week to a maximum of 24 mg/day. By the end of week 4 all subjects were taking 12 mg twice daily and continued on that dose in the open phase for the next 48 weeks.

Safety and efficacy (ADAS-cog/11) assessments were conducted during the double-blind and open-label phases. An open-label ‘rescue arm’ was available for those subjects who could benefit from galantamine escalated at a slower rate.

RESULTS

Fourteen UK centres enrolled 105 subjects (45 men, 60 women); 53 were randomised to a four-day washout period and 52 to a seven-day period. Demographic/
baseline characteristics were similar between the groups: all were Caucasian, with a mean age of 75 years, median MMSE 18, and median ADAS-cog/11 of 27.

Ninety-eight subjects (93.3%) completed the double-blind phase (Discontinuations: 4, ‘rescue arm’ 3), 97 (50 and 47 subjects in four- and seven-day groups, respectively) entered the open-label phase, and 71 (73.2%) completed the study (38 and 33 subjects in four- and seven-day groups, respectively). Discontinuation in the open-label phase was mainly for AEs, which was greater in the seven-day group than in the four-day group (5, 10.6% vs 2, 4.0%).

Changes in ADAS-cog/11 from screening to baseline and to the end of week 4 were <1 point and, after 52 weeks were similar in both groups (mean change ± SD: from baseline, four-day group, 4.9 ± 6.69; seven-day group, 4.6 ± 6.45) and from week 4 (four-day group, 5.4 ± 6.83, seven-day group, 5.7 ± 7.56).

Findings from the double-blind phase suggested that there was no difference in the safety profile of galantamine between a four-day and seven-day wash-out period; the incidence of individual AEs events was low.

During the double-blind phase, 22 subjects in the four-day group and 24 in the seven-day group had at least one treatment-emergent adverse event/worsening of an ongoing pre-treatment event. The number of occurrences of selected GI events by week during the washout/dose escalation period suggests a trend towards an increase in GI events alongside the increase in dose (Figure 1). The overall number of events remained low, except at week 4 in the seven-day group when the dose increased from 16 mg to 24 mg galantamine. There was no comparable increase in GI events at week 3 when the dose was increased from 16 mg to 24 mg in the four-day group. During the open-label phase the incidence of nausea and vomiting (8%) was comparable between the groups.

DISCUSSION

Independent of a four- or seven-day washout period, findings confirm that patients with AD who had been receiving donepezil for at least 12 weeks and were in need of alternative anti-dementia medication were subsequently switched successfully to galantamine. Reductions from baseline in ADAS-cog/11 over the 52 weeks (~5 units) compare favourably with the average annual rate of cognitive decline for untreated patients with AD (~8 units) (Stern et al., 1994).

Previous studies have shown that there may be an increase in GI AEs at the time of dose escalation of galantamine to maintenance dosages (Scott and Goa, 2000). But their relative frequency has been shown to reduce with each dose increase. The somewhat higher incidence of GI AEs observed on escalation from 16 mg to 24 mg daily following a seven-day washout from donepezil may tentatively suggest this had caused brain acetylcholine concentrations to return close to no-treatment levels thus potentially exposing the seven-day group to rapidly increased levels of acetylcholine at week 4. This could suggest that after stopping the pharmacodynamic effect of donepezil lasts 3–4 weeks for some patients and is lost by week 4. Dose escalation of galantamine in this study is considerably faster than that specified in the product label and would potentiate any tendency towards an increase of GI AEs. However, these results must be interpreted with caution due to the small number of reported GI events.

CONCLUSION

Galantamine is generally well tolerated; there was no evidence of a loss of symptomatic benefit or changes in cognitive performance with either a four-day or seven-day washout period. AEs are consistent with previous findings but suggest that patients switching from donepezil to galantamine may experience fewer GI AEs if the washout period is four days rather than seven days.

ACKNOWLEDGEMENT

The study was funded by Shire Pharmaceuticals Ltd and Janssen-Cilag Ltd.
REFERENCES


