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Safety and tolerability of once-daily versus twice-daily memantine: a randomised, double-blind study in moderate to severe Alzheimer's disease

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SUMMARY

Objective To assess the safety and tolerability of three different dosing schedules of memantine in patients with moderate to severe Alzheimer's disease (AD).

Method This 12-week, randomised, double-blind study, investigated three dosing schedules of memantine: OD1 (20 mg once daily with a 1-step up-titration); OD3 (20 mg once daily with a 3-step up-titration); and BID3 (10 mg twice daily with a 3-step up-titration as currently recommended in the memantine labelling). The study comprised 78 patients with moderate to severe AD (DSM-IV-TR criteria; MMSE score $\leq$18), 70% of whom were on stable dosing of acetylcholinesterase inhibitor (AChEI) initiated $\geq$3 months prior to study start. Safety and tolerability were assessed by the number of withdrawals, adverse events (AEs) and monitoring of vital signs.

Results The number of patient withdrawals was low: 3 of 27 in OD1, 1 of 25 in OD3 and 2 of 26 in BID3. One or more AEs were reported in 9 patients in OD1, 7 patients in OD3 and 12 patients in BID3. Most AEs were mild or moderate, and typical for the population studied; no clinically important differences in AEs or vital signs were observed between the different dosing schedules. There were no between-group differences in efficacy, as assessed by clinical global severity and clinical global change. These results are consistent with the good safety profile of memantine observed in larger studies.

Conclusions Although relatively small in size, the study indicates that once-daily dosing and twice-daily dosing of memantine are similar in terms of safety and tolerability.

KEY WORDS — memantine; Alzheimer's disease; once-daily dose; simplified titration; NMDA

INTRODUCTION

Memantine is an uncompetitive NMDA receptor antagonist with moderate affinity and rapid voltage-dependent kinetics (Parsons *et al*., 1999). Placebo-controlled studies have demonstrated the efficacy and safety of memantine in the treatment of moderate to severe AD (Winblad and Poritis, 1999; Reisberg *et al*., 2003; Tariot *et al*., 2004). Currently, the recommended daily dose of memantine is 20 mg (10 mg twice daily), achieved by a 3-week, 3-step, twice-daily titration [Memantine Tablets. Summary of Product Characteristics (SPC), 2005]. However, pharmacokinetic studies demonstrate a mean plasma half-life of 60–100 h, with monoexponential elimination [Memantine Tablets. Summary of Product Characteristics (SPC, 2005)], suggesting that memantine could be dosed at 20 mg once daily. Such a strategy would be of benefit to patients and their caregivers, optimising ease of use and promoting treatment compliance.

The aim of this study was to evaluate the safety and tolerability of a 20 mg once-daily dose of memantine

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in moderate to severe AD in comparison with a 10 mg twice-daily strategy, and with a simplified (1-step) titration scheme. Further objectives included assessment of clinical global severity (CGI-S) and clinical global change (CGI-C).

METHODS

Patient selection

The study population comprised outpatients from five study centres in the UK, with patient visits falling between 23 June 2003 and 13 April 2004. In total, the study planned to enrol 75 patients aged ≥ 50 years, with a diagnosis of dementia of the Alzheimer's type consistent with DSM-IV-TR criteria (American Psychiatric Association, 2000). In addition, patients had a Mini-Mental State Examination (MMSE) score of ≤ 18 at screening, indicating moderate to severe disease (Folstein *et al*., 1975). Patients eligible for entry into the study also had to be ambulatory (with or without a walker or cane), have a reliable carer to supervise medication during the study and, aside from AD, be in a good state of health. Both patient and carer were required to provide informed consent for entry into the study. Concomitant treatment with stable doses of acetylcholinesterase inhibitors (AChEIs) initiated ≥ 3 months prior to screening was permitted, provided that the dose remained constant during the study period.

Exclusion criteria included: previous treatment with memantine; concomitant use (≤ 30 days prior to screening) of any investigational drugs, NMDA antagonists, unstable doses of AChEIs, traditional/typical antipsychotics, or atypical antipsychotics; or concomitant use (≤ 6 months prior to screening) of depot antipsychotics. Patients likely to be placed in a care-home within 6 months of screening, according to the investigator's judgement, were also excluded.

Study design

This multicentre, randomised, double-blind study was conducted in compliance with the principles of good clinical practice. Patients who met selection criteria at screening and baseline visits were randomised to one of three treatment groups (Figure 1):

- Memantine 20 mg once daily, with 1-step up-titration (OD1)
- Memantine 20 mg once daily, with 3-step up-titration (OD3)
- Memantine 10 mg twice daily, with 3-step up-titration (BID3) (schedule currently recommended in the memantine SPC).

At their baseline visit, eligible patients were allocated randomisation numbers consecutively and, using a computer-generated randomisation code and a

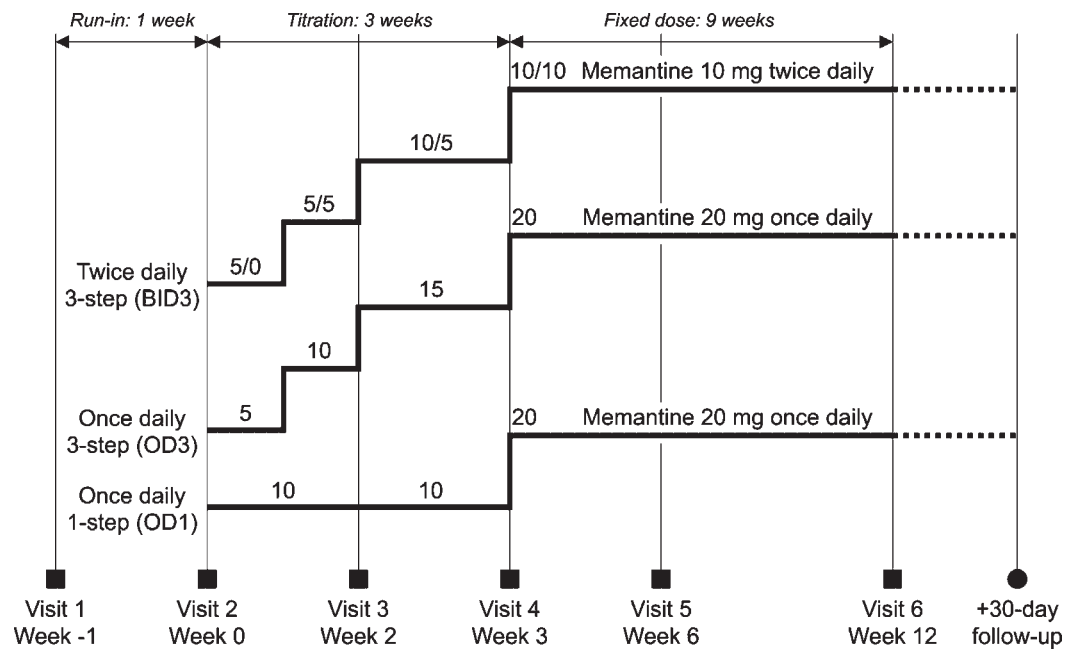

Figure 1. Study design.

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block size of 6 patients, assigned (1:1:1) to the three treatment groups.

Eligible patients entered a 12-week double-blind treatment phase consisting of a 3-week up-titration period followed by 9 weeks at a fixed dose of memantine 20 mg/day. Study medication was supplied as 5 mg and 10 mg tablets. Blinding was maintained by the use of matching placebo tablets where necessary so that each patient received tablets twice per day (morning and evening) throughout the study. Blinding was not broken for any patient during the study.

Study visits took place at screening, baseline and at weeks 2, 3, 6 and 12 of the double-blind study period. An additional safety follow-up contact was made 30 days after study completion. Patients who withdrew from the study for any reason were asked to attend an early withdrawal visit.

Outcome measures

Safety and tolerability. The primary objective of the study was the assessment of the safety and tolerability of memantine 20 mg administered once daily, in comparison with the currently recommended dosing schedule of memantine 10 mg given twice daily (OD3 *vs* BID3). A secondary objective was evaluation of the safety and tolerability of two dose-titration schedules (simplified 1-step *vs* 3-step; OD1 *vs* OD3), in patients receiving memantine 20 mg once daily.

Safety and tolerability analyses included details of study withdrawals, adverse events (AEs), vital signs and weight. AEs were recorded at baseline, weeks 2, 3, 6 and 12 and at the follow-up visit; vital signs at screening, baseline, and weeks 2, 3, 6 and 12; and weight at baseline and week 12 only. ECGs and clinical safety laboratory tests were performed at screening only, to assess patient eligibility.

All AEs observed by the investigator or reported by the patient (spontaneously or following investigator questioning) were recorded. The intensity (mild, moderate or severe) and causality (probably, possibly or not related to study medication) of AEs were assessed by the investigator.

Efficacy. Efficacy analysis was a secondary objective of the study.

Investigators rated efficacy on the Clinical Global Impression—Change (CGI-C) and Clinical Global Impression—Severity (CGI-S) scales. CGI-C is a single-item rating system that evaluates a patient's total improvement or worsening relative to baseline on a seven-point scale from 1 (very much improved) to 7 (very much worse) (National Institute for Mental Health, 1976). CGI-S is a single-item rating system, evaluating patient status on a seven-point scale from 1 (normal, not ill) to 7 (extremely ill) (National Institute for Mental Health, 1976). In this study, efficacy ratings were recorded at baseline (CGI-S only), and at weeks 2, 3, 6 and 12 (or at early withdrawal).

Statistical analysis

All analyses were performed according to the intention-to-treat (ITT) principle.

Analysis of AEs was descriptive. Although the study was not powered to detect a statistically significant difference in AE reporting, an overall sample size of 75 patients was considered appropriate to detect any major changes in the frequency of adverse events reported between the treatment arms.

Efficacy analyses were based on treatment differences in least squares means obtained from ANCOVA, with treatment and centre as factors. Parameters were analysed per visit using both observed cases (OC) and last observation carried forward (LOCF) methods.

RESULTS

Of 83 patients screened, five were screening failures and 78 patients were randomised to the three study groups (Figure 2). All patients received treatment and all patients had at least one valid post-baseline assessment of CGI-C or CGI-S. Treatment duration was similar for the three study groups, with a mean exposure to memantine of approximately 80 days—nearly all patients (96%) were treated for more than 40 days.

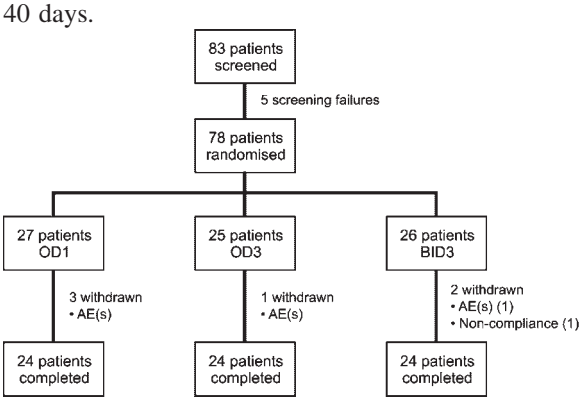

Figure 2. Patient flow through study.

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Table 1. Summary of patient baseline characteristics

	OD1	OD3	BID3	Total
No. patients	27	25	26	78
No. female (%)	17 (63.0)	14 (56.0)	11 (42.3)	42 (53.8)
Mean age, years (SD)	78.4 (8.2)	73.4 (8.1)	76.2 (8.2)	76.1 (8.3)
Race, % Caucasian	100.0	96.0	96.2	97.4
Mean BMI (SD)	25.7 (4.3)	26.1 (3.8)	26.2 (4.8)	26.0 (4.2)
Mean MMSE score (SD)	12.2 (4.9)	11.4 (4.6)	12.5 (4.3)	12.1 (4.6)

Baseline characteristics

The mean age of patients was approximately 76 years, and nearly all were Caucasian (Table 1). Overall, the male to female ratio was approximately 1:1, although the OD1 treatment group included proportionally more women and the BID3 group proportionally more men. The BMI of all three groups was similar (~26) (Table 1). The mean MMSE (SD) score at screening was 12.1 (±4.6), which is consistent with a patient population with moderate to severe AD. Mean MMSE scores were similar in the three treatment groups (Table 1). There were no clinically relevant differences between groups in baseline assessments of clinical laboratory values, ECG or measurements of vital signs.

During the study period, stable doses of AChEIs were taken by 74% of patients in the OD1 group, 68% of patients in OD3, and 69% of patients in BID3.

Safety

Memantine was well tolerated in all treatment groups, with no notable differences between the groups receiving memantine in once-daily or twice-daily administration regimens (OD3 *vs* BID3). The incidence of AEs was low (Table 2), and the type of AEs generally typical, given the patient population studied. The majority of AEs reported were classed as mild or moderate in severity, with only one AE (urinary tract infection) reported in more than one group, and no single AE reported by more than two patients per treatment group. The AEs occurring twice in the OD1 group were urinary tract infection, and rhinitis; the AE occurring twice in the OD3 group was headache; and AEs occurring twice in the BID3 group were pneumonia, upper respiratory tract infection, and urinary tract infection. There was no indication of any differences in emergence of early AEs (during the 3-week titration period) in association with the different titration schedules (Table 2).

Table 2. Incidence of adverse events*

	OD1	OD3	BID3
No. patients	27	25	26
No. patients reporting at least one AE during:			
Whole study period	9	7	12
3-week titration phase	5	5	3
9-week fixed-dose phase	6	3	10
No. patients with AEs leading to withdrawal	3	1	1
No. patients with SAEs	1	1	1
Total number of AEs	20	15	20
Total number of SAEs	1	1	1

*Each patient may report more than one AE.

Serious adverse events (SAEs) were reported by three patients, one in each of the three treatment groups (Table 2), leading to study withdrawal in each case. Only one SAE—increased anxiety in a patient in the BID3 group—was judged by the investigator as possibly related to treatment. Two patients died during or shortly after the study. One patient was an 86-year-old man in the OD1 group who had a stroke (cerebrovascular accident) during the study. The other death occurred in a 67-year-old man in the OD3 group who had an accidental fall during the 30-day safety follow-up period, was hospitalised, and died of pneumonia 3 months later. Both deaths were judged to be unrelated to treatment.

To enable comparison between the two once-daily titration schedules (3-step *vs* 1-step; OD3 *vs* OD1), AEs were subdivided according to whether they started during the initial 3-week titration phase or the 9-week fixed-dose phase. There were no obvious trends regarding the incidence or nature of the AEs reported during these two phases of the study (Table 2).

Overall rates of withdrawal and rates of withdrawal due to AEs were low for all three treatment schedules (Table 2). No specific AE led to withdrawal in more than one patient. However, in the OD1 group, two patients accounted for five of the six adverse events, and these five events were psychiatric symptoms (apathy, confusion, delusion, depression, hallucination). The onset of these adverse events occurred on Day 17 (titration phase) and Day 22 (start of the fixed-dose phase), suggesting that they may have been related to the 1-step titration regimen.

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There were no clinically relevant differences between the treatment groups in terms of vital signs or weight changes.

Efficacy

At week 12 there were no statistically significant differences between treatment groups in least-squares means of the CGI-C score. There were no apparent differences between the once- and twice-daily memantine dosing regimens (OD3 *vs* BID3), or between the once-daily, 3-step and 1-step schedules (OD3 *vs* OD1). For all three treatment groups, the mean CGI-C score (OC and LOCF) improved slightly over the course of the study.

In the measure of disease severity, there were no clinically relevant differences between the three treatment groups in terms of CGI-S score at baseline, or in terms of least-squares means change from baseline over the study period.

DISCUSSION

Alzheimer's disease (AD) is a chronic, progressive disorder, which develops from stages of mildly impaired cognition to increasingly severe disruption of daily function, behaviour and cognition. Patients with AD are usually elderly and frequently take a number of medications. Simplifying dosing regimens is an important strategy for improved compliance that can help patients as well as their families/caregivers, who may be required to administer this medication. Therefore, ease of dosing and simple titration regimens are a key element of developing AD treatment strategies.

Memantine is indicated for the treatment of moderate to severe AD. Its safety and efficacy is supported by several large-scale, controlled clinical studies (Winblad and Poritis, 1999; Reisberg *et al*., 2003; Tariot *et al*., 2004). The current recommendation is that memantine should be administered at a dose of 20 mg, taken as 10 mg twice daily, with a 3-week, 3-step up-titration phase. Memantine already has a relatively simple administration (without regard to time of day or to food), but due to its plasma half-life, it has also been suggested that a 20 mg once-daily dosing strategy would be possible.

The present double-blind, fixed-dose study in moderate to severe AD assessed the safety and tolerability of a memantine 20 mg once-daily regimen compared with a 10 mg dose taken twice daily, and with a simplified 1-step, once-daily, dose titration schedule. As this was primarily a safety study, no active or inactive comparator arm was deemed necessary. Publication of additional data from three clinical studies (MEM-MD-03, MEM-MD-11, MEM-MD-12) documenting the memantine once-daily regimen, is expected, and a summary of these results is already available on the Forest Clinical Trial Registry website (Forest Clinical Trials Registry, 2006).

Although this was a relatively small study ($n = 78$), results suggest that once-daily dosing of memantine is as well tolerated as twice-daily dosing. In addition, a simplified 1-step once-daily dose titration schedule was well tolerated. However, based on the number of patients who withdrew due to adverse events (3 *vs* 1), the standard 3-step up-titration regimen may be slightly better tolerated than the 1-step up-titration regimen. Once-daily dosing would be a beneficial and more practical option for patients with AD.

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