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A randomized trial of memantine as treatment for spasticity in multiple sclerosis

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Abstract

We report the results of a single center randomized, double-blind, placebo-controlled, parallel group trial of memantine in adults with multiple sclerosis and spasticity conducted over 12 weeks. Eligible MS patients had to have an Ashworth spasticity rating of 2 or higher in at least one lower extremity muscle group. Subjects were randomized to receive either placebo or memantine 10 mg twice a day. The primary outcome measure for efficacy was the change in Ashworth Spasticity Scale Score. Although well tolerated, memantine treatment did not demonstrate efficacy in treatment of spasticity in this 12-week small exploratory study.

Keywords

Ashworth scale, memantine, multiple sclerosis, MSSS-88, spasticity, toe-tapping test

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Introduction

Spasticity is characterized by muscular hyper-excitability and spasm, and is a source of discomfort and diminished quality of life for patients with multiple sclerosis (MS).[1] Experimental models of spasticity in animals have shown that blockade of the N-methyl-D-aspartic acid glutamate receptor with memantine reduces muscle tone.[2,3] We report the results of a single center, randomized, double-blind, placebo-controlled, parallel group clinical trial to assess the effect of memantine on MS spasticity.

Methods

Patients with clinically definite MS or MS according to the McDonald criteria,[4] ages ranging from 18 to 70 years, a minimum score of 2 on the Ashworth spasticity scale[5] in at least one lower extremity muscle group, a total score of at least 4 in the lower extremity muscles tested, estimated creatinine clearance >50 ml/min and able to complete a timed 25 foot walk in <3 minutes were included. Concomitant spasmolytics were allowed provided that participants had been on such medications at stable dosages for at least one month prior to screening. Medication changes were prohibited during the study period. Subjects were excluded if they had received prior memantine treatment for any condition. All subjects provided written informed consent. The protocol was approved by the Institutional Review Board at URMC (Trial registration number: NCT00638027).

Participants were randomized to receive either memantine or matching placebo in a 1:1 ratio using a computer generated randomization plan prepared independently by a programmer at our institution. This was stratified by Expanded Disability Status Scale (EDSS) score (<6, ≥6) and incorporated permuted blocks to promote balance in allocation. The dosage of study medication was titrated in the following manner: 5 mg per day for the first week, then 5 mg twice per day for the second week, then 5 mg every am and 10 mg every pm for week three, then 10 mg twice per day for the duration of the study.

The primary outcome variable for efficacy was the change in Ashworth Spasticity Scale Score[5] from

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Table 1. Baseline characteristics of study participants and changes from baseline to Week 12 in outcome variables for efficacy

Baseline characteristics of study participants

Variable	Placebo (n = 10)	Memantine (n = 11)
Age	52.1 (12.2)	52.9 (7.5)
Female Gender (%)	50	54.6
concomitant spasmolytics	5	6
EDSS†	5.3 (4.5, 6.0)	5.5 (3.5, 6.5)
Ashworth Spasticity Scale	9.7 (4.4)	9.5 (5.0)
Toe Tapping Test	12.2 (4.7)	8.8 (4.2)
Lower Extremity MMT	4.3 (0.8)	4.4 (0.6)
Time to Walk 25 Feet (sec)†	8.9 (6.1, 11.7)	7.2 (5.3, 10.5)
9 Hole Peg Test†	26.5 (25.9, 43.1)	27.2 (22.1, 33.9)
PASAT-3†	38.5 (29.0, 48.0)	48.0 (33.0, 55.0)
MSSS-88		
Muscle Stiffness	32.0 (8.9)	34.1 (7.6)
Pain/Discomfort	20.0 (6.9)	24.0 (8.0)
Muscle Spasms	27.0 (7.1)	31.8 (11.0)
Activities of Daily Living	22.6 (7.3)	23.1 (6.8)
Walking	29.8 (6.2)	29.5 (7.8)
Body Movements	30.0 (4.8)	30.6 (9.1)
Emotional Health	26.1 (10.3)	29.0 (14.0)
Social Function	16.6 (5.3)	17.4 (7.6)

Changes from baseline to Week 12 in outcome variables for efficacy

Variable	Placebo (n = 10)	Memantine (n = 11)	Treatment Effect	95% CI	P-value
Ashworth Spasticity Scale	−1.00 (2.67)	−1.55 (2.81)	0.55	(−1.96, 3.05)	0.65
Toe Tapping Test	−1.45 (2.69)	0.32 (2.00)	−1.77	(−3.92, 0.39)	0.1
Lower Extremity MMT	0.14 (0.53)	0.09 (0.19)	0.05	(−0.31, 0.41)	0.76
MSFC (Z-Scores)					
Overall	−0.04 (0.20)	0.02 (0.26)	−0.06	(−0.27, 0.16)	0.58
T25FW	−0.06 (0.20)	−0.01 (0.18)	−0.05	(−0.22, 0.12)	0.52
9 Hole Peg Test	−0.15 (0.38)	−0.02 (0.34)	−0.13	(−0.46, 0.20)	0.42
PASAT-3	0.10 (0.50)	0.09 (0.58)	0.01	(−0.49, 0.50)	0.97
MSSS-88					
Muscle Stiffness	−3.33 (7.07)	−5.55 (7.89)	2.21	(−4.91, 9.33)	0.52
Pain/Discomfort	−3.00 (5.43)	−5.91 (5.68)	2.91	(−2.35, 8.17)	0.26
Muscle Spasms	−3.78 (6.51)	−7.55 (12.60)	3.77	(−6.00, 13.54)	0.43
ADL	−1.78 (6.50)	−1.09 (5.80)	−0.69	(−6.47, 5.09)	0.81
Walking	−3.44 (5.36)	−6.36 (7.49)	2.92	(−3.34, 9.18)	0.34
Body Movements	−2.78 (9.61)	−7.64 (10.95)	4.86	(−4.94, 14.66)	0.31
Emotional Health	−2.67 (7.35)	−6.18 (10.60)	3.52	(−5.26, 12.29)	0.41
Social Function	−1.67 (4.00)	−4.46 (6.73)	2.79	(−2.58, 8.15)	0.3

Values are mean (standard deviation) unless otherwise indicated.
†Values are median (25^{th} and 75^{th} percentiles).
Treatment effect is the group difference (placebo – memantine) in mean response.
CI, Confidence Interval; MMT, Manual Muscle Test; MSFC, Multiple Sclerosis Functional Composite; T25FW, Timed 25-Foot Walk; PASAT-3, Paced Auditory Serial Addition Test; MSSS-88, Multiple Sclerosis Spasticity Scale; ADL, Activities of Daily Living.

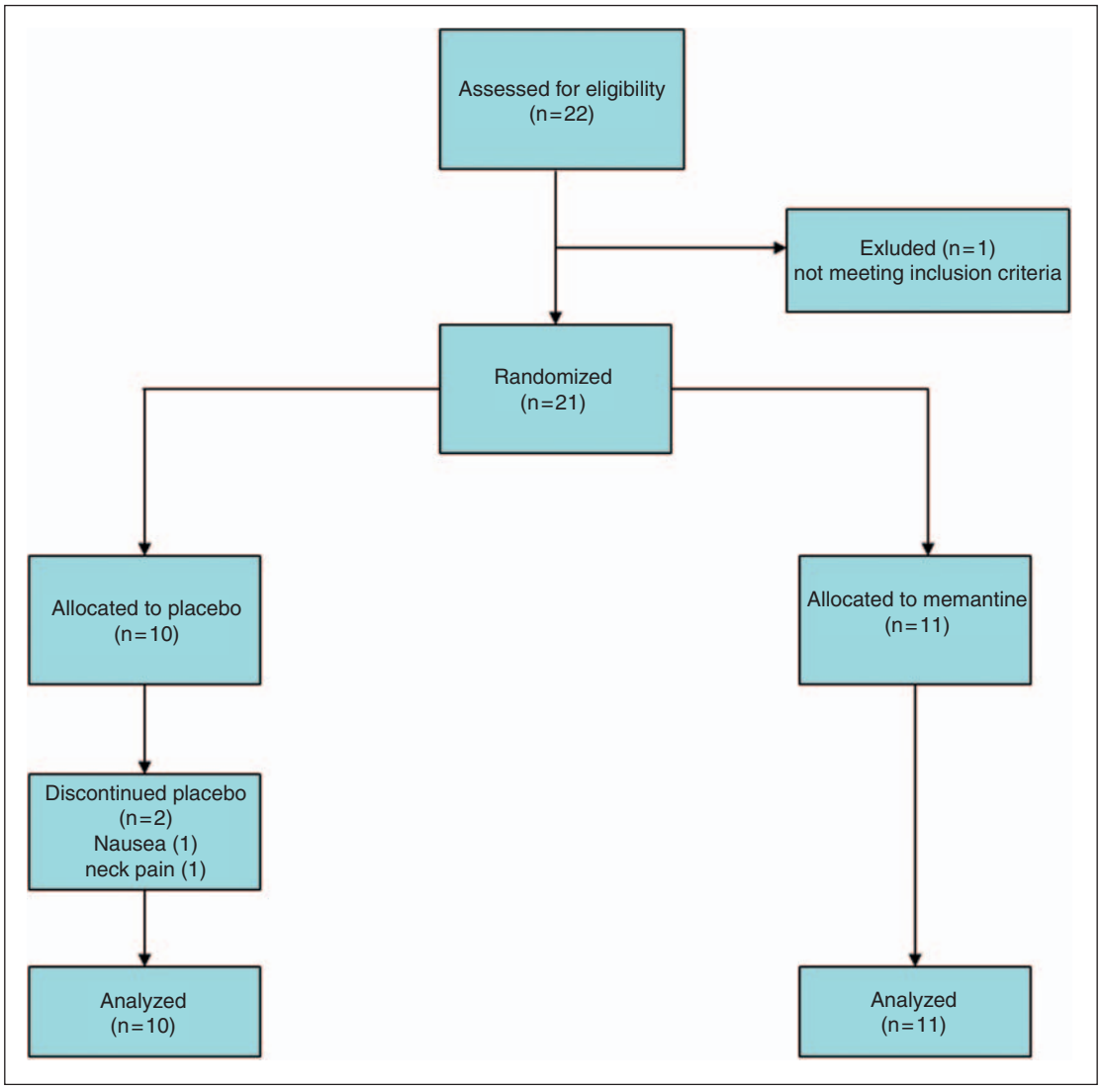

Figure 1. Flow diagram of clinical trial.

baseline to Week 12. Secondary outcome measures included changes from baseline to Week 12 in the Multiple Sclerosis Functional Composite Scale (MSFC) (overall *z*-score and individual components: timed 25 foot walk, paced auditory serial addition test, and 9 hole peg test),[6] the toe-tapping test (averaged across both sides),[7] lower extremity manual muscle test score,[8] and the 88-item Multiple Sclerosis Spasticity Scale (MSSS-88) subscale scores.[9] The same examiner performed all the testing throughout the entire trial.

Statistical considerations

We chose a sample size of 20 subjects based largely on practical considerations. The trial was designed as a small exploratory study to inform the design of future studies of memantine in MS. To assess efficacy, *t*-tests were used to compare the mean changes from baseline to Week 12 between the treatment groups. Ninety-five percent confidence intervals were also computed for the differences in group means. A two-tailed p value <0.05 was considered significant. For the two participants who withdrew from the trial, the last available observation was carried forward for purposes of statistical analysis. The data were analysed using SAS software, Version 9.1.

Results

Recruitment for the trial began in June 2006 and ended in June 2008. The last subject formally completed the trial in September 2008. Baseline characteristics of the two groups were generally comparable (Table 1). Of those receiving concomitant spasmolytics, five subjects were in the placebo group and six subjects were in the memantine cohort. Participant flow is schematically illustrated in Figure 1. Two subjects who were in the

placebo arm dropped out of the study. Memantine was generally well tolerated with no serious adverse events identified. Relapses occurred equally in both treatment groups (two in each arm).

Changes from baseline to Week 12 are described by treatment group in Table 1. No statistically significant treatment effects were detected for the Ashworth scale ($p = 0.65$) nor for any of the secondary outcome variables, including the MSFC and its individual components. Those treated with memantine (mean change = 0.32) tended to perform better on the toe-tapping test at 12 weeks than those on placebo (mean change = −1.45, $p = 0.10$). Although the mean reductions in MSSS-88 scores favored memantine for seven of the eight subscales, these reductions were not statistically significant.

Discussion

In this small exploratory study, we did not detect any significant benefit of memantine 20 mg per day for treatment of spasticity in MS. Aside from the lack of adequate power, there are several other possible explanations for this result. The 95% confidence interval for the treatment effect on the Ashworth scale (−1.96, 3.05) indicates that treatment effects in favor of memantine of as much as 3 points are consistent with the data and cannot be ruled out by our small trial. Although easy to administer, the Ashworth scale may not be sufficiently sensitive to detect small differences in spasticity or functional change in MS patients as noted in other studies.[10] Being an ordinal scale, it is difficult to interpret small differences in Ashworth scores. We also cannot exclude the possibility that higher doses of memantine could have significantly reduced spasticity.

This pilot study did provide information that can be useful in the design of future trials assessing MS spasticity. This validated scale was easily administered in a trial setting. It can provide the MS patient's perspective in capturing the impact of spasticity across eight dimensions.[9] Since the MSSS-88 has eight different subscales and does not yield an overall total score, an appropriately chosen subscale would have to be specified in advance as the outcome variable of primary interest for a given clinical trial. Table 1 provides information on the variability of changes in various outcome measures, which can be valuable in calculating the required sample sizes for future trials of treatments for spasticity in MS. More research is needed to determine the smallest magnitudes of treatment effects that would be worthwhile to try to detect in a clinical trial.

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