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Evaluation of Multiple Doses of Milacemide in the Treatment of Senile Dementia of the Alzheimer's Type

Neal R. Cutler, MD; T. Daniel Fakouhi, PhD, MBA; Ward T. Smith, MD; Hugh C. Hendrie, MD; Fumisuke Matsuo, MD; John J. Sramek, PharmD; Robert L. Herting, MD, PhD

Abstract

A multicenter, double-blind, placebo-controlled, parallel group study was conducted to assess the safety and efficacy of three doses of milacemide in the treatment of patients with senile dementia of the Alzheimer type of mild to moderate severity. Patients were randomly assigned to receive one of three dosages of milacemide (400, 800, or 1200 mg/day) or placebo for 4 weeks followed by a single-blind 4-week placebo period. One hundred forty-eight men and women older than 50 years of age were enrolled, and 129 patients completed the study. The differences among treatment groups were not statistically different with respect to total scores on the Alzheimer's Disease Assessment Scale or any items and subscales that were examined, nor were significant differences on the Clinical Global Impression Scale found. Clinically significant increases in liver function tests, specifically aspartate aminotransferase and alanine aminotransferase (AST and ALT), were reported for five of the patients receiving milacemide, requiring their withdrawal from the study. (*J Geriatr Psychiatry Neurol* 1993;6:115–119).

Senile dementia of the Alzheimer type (SDAT) is a progressive condition that is principally manifested by memory deficits and loss of other intellectual abilities of sufficient severity to interfere with social or occupational functioning.[1–5]

Neurochemical studies have identified several neurotransmitter systems that are known to have an impact on memory processes, primarily the cholinergic system, as evidenced by loss of cholinergic neurons in the nucleus basalis in Alzheimer's patients, as well as the adrenergic-dopaminergic, γ-aminobutyric acid (GABA)-ergic, and glutamatergic systems.[6–11] In several studies glutamate binding to *N*-methyl-D-aspartate (NMDA) receptor sites was significantly reduced in Alzheimer's disease patients,[12–14] although negative studies also demonstrated no reduction in NMDA receptor sites despite apparent reduction of glutamate uptake.[15–17] Marked decreases in glutamate levels were also found in a dissection of the perforant pathway zone.[18] Coupling in the glycine recognition site in the NMDA-receptor may also be impaired.[19]

It has been reported that activation of the NMDA subtype of glutamate receptors leads to long-term potentiation in the postsynaptic neurons when stimulated by either NMDA or the natural agonist, the excitatory amino acid glutamate.[20,21] Because long-term potentiation has been suggested as a mechanism for memory formation, positive modulation of NMDA-receptors should lead to memory and learning enhancement.

Milacemide (2-*n*-pentylaminoacetamide hydrochloride), a monoamine oxidase–B inhibitor and a prodrug for glycine, has been shown to have a

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unique action in several tests that evaluate short-term memory. Milacemide was able to reverse memory impairment induced by electroshock in the passive avoidance task in rats, as well as memory loss by scopolamine and diazepam in the spontaneous alternation test in mice.[22] It also facilitated memory consolidation in the passive avoidance model in rats.[23] These results in animal studies indicate that milacemide may have beneficial effects on cognition. They are consistent with the hypothesis that milacemide exerts stimulatory effects through the newly discovered supraspinal glycine receptors associated allosterically with NMDA-receptors.[24–26] Glycine does not readily cross the blood-brain barrier, but milacemide does and is then metabolized to glycinamide and glycine.[27] Because this biotransformation results in a marked increase in glycine concentration in the central nervous system, milacemide may be considered a prodrug for glycine. Thus, milacemide was identified as one of the first drugs modulating these supraspinal glycine receptors positively, with the consequence of offering benefit in the treatment of memory impairment and, possibly, learning deficiencies. Because of these properties, it seemed justified to objectively evaluate the efficacy and safety of milacemide in the treatment of the cognitive and memory disorders that occur in patients suffering from SDAT.

Methods

Men and women, aged 50 years or older, with Alzheimer's disease were enrolled into the study at 10 sites. The presence of SDAT was determined by clinical evaluation supported by NINCDS criteria, a Mini-Mental State Examination score between 10 and 27, a Dementia Rating Scale score less than 20, a Global Deterioration Scale score of 3 to 5, a Hachinski Cerebral Ischemia Scale score of 4 or less, and a history of progressive worsening of memory and other cognitive functions documented for at least 1 year before enrollment. A computed tomographic or magnetic resonance imaging scan within 1 year of enrollment must have been compatible with a diagnosis of SDAT. Patients were excluded if they had evidence of cerebral ischemia or other brain disorders; neurologic, substance abuse, or psychiatric disorders (other than SDAT); or significant cardiovascular, thyroid, hepatic, renal, pulmonary, gastrointestinal, or other clinically significant medical conditions as determined by physical examination, electrocardiogram, and laboratory tests (including triiodothyronine, thyroxine, folic acid, and vitamin B_{12} determinations). Patients who had participated in an investigational drug trial within the last 30 days before entering this study were also excluded. Concomitant psychoactive medication was prohibited unless prescribed by the physician or investigator on a prn basis. Calcium channel blockers, angiotensin-converting enzyme inhibitors, β-blockers, and anticholinergic drugs were also prohibited.

Study Design

This was a multicenter, randomized, double-blind, parallel group, dose-response study of milacemide in patients with SDAT. After screening determination of eligibility, patients received milacemide in single oral doses of 400, 800, or 1200 mg/day or matching placebo for 4 weeks during the double-blind treatment period, which was followed by a 4-week placebo washout period. All patients (or their family member or legal guardian) provided oral and written signed consent.

Efficacy was assessed by the subject's performance using the Alzheimer's Disease Assessment Scale (ADAS),[28] the Clinical Global Impression Scale (CGI), the Patient Global Improvement Rating,[29] the Physical Self-Maintenance Scale, and the Instrumental Activities of Daily Living Scale (IADL).[30] Efficacy measures were evaluated at the screening visit (visit 1) and biweekly during the double-blind period (at visits 3 and 5) and during the placebo washout period (at visits 7 and 9). A 17-item Hamilton Depression Scale was administered at baseline and at the end of the double-blind drug administration period to rule out any major depressive state. Safety measures, including electrocardiogram, hematology and biochemistry screens, and urinalysis were performed weekly.

Statistical Methods

Treatment groups were compared with respect to age by a two-way analysis of variance (ANOVA) using study site and treatment group as factors in the model. A power calculation yielded sample groups of 30 patients (total 120) based on a standard deviation of 15 and a 5-point drop in the ADAS from baseline with an α of .05 and power slightly greater than .90. Treatment groups were compared with respect to sex and race using the Cochran-Mantel-Haenszel test. At the screening visit, eligibility for enrollment in the study was assessed with the Mini-Mental State Examination, the Dementia Rating Scale, the Global Deterioration Scale, and the Hachinski Cerebral Ischemia Scale. Treatment groups were compared with respect to total scores on these scales by

two-way ANOVA using study site and treatment group as factors.

The primary measure used in determining efficacy was the cognitive behavior score of the ADAS, which consists of 21 items. Eleven of these items combine to form a cognitive behavior subscale, and the other 10 form a noncognitive behavior subscale. Two items that form part of the cognitive subscale are also intended to be analyzed separately. These are the word recall score and the word recognition score. The primary measure used in statistical tests of efficacy is the sum of the cognitive behavior item scores. Tests were also done on the word recall score, the word recognition score, the orientation score, and the sum of noncognitive behavior item scores. Means and standard deviations of the total ADAS score and each subscale were calculated by treatment group and visit. ADAS scores taken at the screening visit were submitted to a two-way ANOVA with investigator and dose level as factors in the model to establish baseline comparability of treatment groups. To ensure the validity of the ANOVA, ADAS scores were examined for heterogeneity of variance among treatment groups, using the F_{max}-test.[24] Where significant heterogeneity of variance was found, the Kruskal-Wallis test was used to verify the results of the ANOVA.

To examine the effect of withdrawal from milacemide, changes in total ADAS score and in cognitive behavior score from the last available double-blind treatment period total score to the last available washout period score were submitted to an ANOVA using treatment and study site as factors in the model. The Cochran-Mantel-Haenszel test was used in comparing the proportion of patients in the milacemide groups showing at least a one-point improvement on the Severity of Illness scale to the proportion in the placebo group, controlled for effects of study sites. The IADL Scale consists of ratings on 10 everyday activities. Individual ratings are on a scale of 1 to 3, 1 to 4, or 1 to 5, with lower numbers representing greater disability. Differences from baseline for each scale were submitted to ANOVA as described under methods for the ADAS.

Results

One hundred forty-eight patients (75 men and 73 women; mean age, 71.5 years; age range, 52 to 91 years) were randomized to treatment with milacemide, 400 mg (n = 40), 800 mg (n = 38), 1200 mg (n = 33), or placebo (n = 37). One hundred twenty-nine patients completed the study. Nineteen patients withdrew or were withdrawn before the end of the study because of adverse events (n = 10), treatment failure (n = 7), or noncompliance (n = 2). Treatment groups were not statistically different with respect to age, sex, height, and weight. However, of a total of five black patients randomized, four were randomized to the 1200 mg group; the other was in the placebo group. All other patients were white (n = 143).

Efficacy Analysis

At visit 1, the treatment groups did not differ significantly with respect to total score or with respect to noncognitive behavior score, word recognition, word recall, or orientation subsection scores. Study sites differed with respect to baseline total scores and subscale scores; however, study site–treatment interaction on the baseline scores was not significant. The total ADAS scores are summarized in Table 1. No significant changes from baseline were observed between treatments for total or subsection scores of the ADAS (total ADAS, P = .97; cognitive behavior, P = .93, noncognitive behavior, P = .57; word recognition, P = .61; word recall, P = .59; and orientation, P = .93).

As a group, the placebo patients tended to be less severely ill (Table 2). The CGI severity of illness ratings showed no differences between treatments in the proportion of patients showing improvement (P = .39). A greater proportion of patients on milacemide had improved scores at the end of the treatment (10% to 13% on milacemide versus 3% on

TABLE 1
Alzheimer's Disease Assessment Score: Total Scores

		Milacemide		
	Placebo	400 mg	800 mg	1200 mg
Screening (visit 1)				
Mean	30.0	33.8	29.4	28.6
SD	14.2	10.8	13.0	13.0
n	37	40	36	32
Day 14 (visit 3)				
Mean	27.3	33.6	26.9	29.8
SD	14.3	13.4	13.0	16.3
n	37	39	35	31
Day 28 (visit 5)				
Mean	28.3	32.6	26.4	26.9
SD	13.4	12.4	11.5	14.0
n	33	38	31	30
Washout				
Mean	28.8	34.7	25.8	26.9
SD	16.2	15.1	11.3	15.6
n	35	37	32	28

TABLE 2
Clinical Global Impression Severity of Illness Rating

	Placebo	Milacemide 400 mg	Milacemide 800 mg	Milacemide 1200 mg
Baseline (visit 1)				
Mean	3.57	4.10	3.76	3.85
SD	0.69	0.71	0.75	0.79
n	3.7	40	38	33
Day 14 (visit 3)				
Mean	3.62	4.07	3.75	3.84
SD	0.64	0.73	0.73	0.77
n	37	40	36	32
Day 28 (visit 5)				
Mean	3.69	4.05	3.68	3.41
SD	0.68	0.71	0.68	0.81
n	35	40	34	32
Washout				
Mean	3.78	4.10	3.80	3.72
SD	0.72	0.79	0.76	0.92
n	36	39	35	29

placebo), but the difference was not statistically significant ($P = .10$).

No significant differences between treatments were found on the Patient Global Improvement Rating, the Physical Self-Maintenance Scale, or the IADL, either by visit or at endpoint. Although the Hamilton Depression Scale scores of the study sites differed with respect to baseline, the differences with respect to change from baseline were not statistically significant.

Of the 148 enrolled patients, seven were withdrawn from the study because of treatment failure. All were on active drug. Three were receiving 400 mg/day, and two each received 800 mg/day and 1200 mg/day. These patients were judged to range from "minimally worse" to "much worse" on the CGI. Two patients were also withdrawn because of noncompliance, and 10 withdrew because of adverse events.

Adverse Events

A total of 255 adverse events rated as mild (160), moderate (84), and severe (11) for milacemide and 74 events of mild (57) and moderate (17) severity for placebo were reported during the study. The overall frequency of adverse events was similar between milacemide (43.5%) and placebo (50.0%); however, a pattern differentiating milacemide from placebo could be seen. The most frequent drug-related treatment-emergent adverse events were fatigue, headache, dizziness, and nausea, whereas the most frequent placebo-related events were headache, rhinitis, dizziness, back pain, diarrhea, and nervousness.

Clinical Laboratory Values

Clinically significant increases in liver function tests, specifically aspartate aminotransferase and alanine aminotransferase (AST and ALT), were reported for five patients receiving milacemide. In three of the five patients, elevations were judged to be severe (one patient receiving 1200 mg/d and two patients taking 400 mg/d); however, all liver function test elevations were reversible on drug discontinuation. With the exception of the abnormalities in liver function tests and a single patient with blood in urine, none of the clinical laboratory values constituted an adverse event.

Discussion

None of the milacemide groups showed a statistically significant increase in efficacy ratings over placebo. The results of this placebo-controlled double-blind trial are in contrast to those reported by Schwartz et al,[31] who found that milacemide had a significant effect on the speed and accuracy of verbal retrieval in normally functioning young and elderly volunteers. Cognitive behavior values were highly nonsignificant ($P = .93$).

Reasons for lack of efficacy in this trial may be a relative nonresponsiveness of NMDA-receptor activation in the population itself, or the time period of active drug administration (4 weeks) may be too brief to begin to see acute changes or improvements. Also, given the slow progression of the disease, some clinical trials in SDAT patients are conducted for 6 months or longer to evaluate for changes in disease progression over time.[32] Although milacemide administration was associated with a tendency ($P = .10$) toward improvement of CGI severity scores, no clear dose-response relationship between tendencies for improvement and milacemide dosages used in this study was found. Nonetheless, it is unlikely that future long-term trials with milacemide will be planned because of the effects on hepatic enzymes seen in our study and in a previous milacemide (1200 mg/d) study in SDAT (Dysken et al, in preparation). Enzyme elevations requiring drug discontinuation were observed in our study at low (400 mg/d) and at high dosages (1200 mg/d).

Other promising approaches for stimulating NMDA receptors in SDAT patients include partial agonists for the glycine-B site, such as D-cycloserine, which can stimulate NMDA-receptors in a low-glycine environment while blocking excess stimulation in a high-glycine environment.[33] The latter is important because excessive stimulation of NMDA-

receptors can potentially lead to tachyphylaxis and/or neurotoxicity.

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