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Contents

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

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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

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