The Effects of Metrifonate on the Cognitive, Behavioral, and Functional Performance of Alzheimer's Disease Patients

Murray A. Raskind, M.D.; Pamela A. Cyrus, M.D.;
Bianca B. Ruzicka, Ph.D.; and Barbara I. Gulanski, M.D.,
for the Metrifonate Study Group

Background: The objective of this study was to evaluate the efficacy and safety of metrifonate, a long-acting acetylcholinesterase inhibitor, in patients clinically diagnosed with probable Alzheimer's disease of mild-to-moderate severity.

Method: This was a prospective, multicenter, 26-week, double-blind, parallel group study. The 264 randomized patients met diagnostic criteria of the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association for probable Alzheimer's disease. Patients had Mini-Mental State Examination (MMSE) scores of 10–26 and ischemic scores (Rosen modification) of < 4. Metrifonate-treated patients received a single 50-mg dose once daily. The efficacy of metrifonate was investigated with respect to 3 symptom domains. Cognitive performance was analyzed using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and the MMSE. Psychiatric and behavioral disturbances were analyzed using the Neuropsychiatric Inventory (NPI) and the ADAS-Noncognitive subscale (ADAS-Noncog). The ability to perform instrumental and basic activities of daily living was evaluated using the Disability Assessment for Dementia (DAD) scale. Additionally, global state was assessed using the Clinician Interview-Based Impression of Change with Caregiver Input (CIBIC-Plus) scale.

Results: After 26 weeks of metrifonate therapy, a statistically significant benefit of metrifonate was observed in the cognitive performance of Alzheimer's disease patients (ADAS-Cog, $t = 2.55$, $df = 237$, $p = .012$; MMSE, $t = 4.60$, $df = 237$, $p = .0001$). Metrifonate also significantly attenuated the deterioration in activities of daily living of the patients (DAD total score, $t = –2.11$, $df = 233$, $p = .036$) and relieved patients' psychiatric and behavioral disturbances (NPI total score, $t = 2.51$, $df = 233$, $p = .013$). In addition, metrifonate significantly improved the scores for the global state of the patients (CIBIC-Plus, $t = 2.07$, $df = 232$, $p = .039$). Metrifonate was well tolerated; adverse events were predominantly mild in intensity, and no hepatotoxicity was observed.

Conclusion: In this study, metrifonate was safe and well tolerated. It benefited the cognitive decline, psychiatric and behavioral disturbances, impaired ability to perform instrumental and basic activities of daily living, and global state of patients diagnosed with mild-to-moderate Alzheimer's disease.

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A complete list of the members of the Metrifonate Study Group appears at the end of this article.

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Reprint requests to: Murray A. Raskind, M.D., VA Puget Sound Health Care System (116), 1660 South Columbian Way, Seattle, WA 98108.

Alzheimer's disease is a neurodegenerative disease that is newly diagnosed in 0.6% of persons aged 60–65 years,[1] and the prevalence of which is 30% to 50% of persons aged 85 years or older.[2] Alzheimer's disease is characterized clinically by a gradual impairment in cognition, psychiatric and behavioral disturbances,[3] and a decline in the ability to perform instrumental and basic activities of daily living. Pathologically, Alzheimer's disease is defined by the presence of intracellular neurofibrillary tangles and extracellular aggregations of β-amyloid protein in the form of plaques.[3] The etiology of Alzheimer's disease still has not been clearly defined. However, a consistent biochemical feature of the disease is a presynaptic cholinergic deficiency that reflects a loss of cholinergic neurons, predominantly those of the basal forebrain pathways.[4,5]

Several studies of normal elderly and Alzheimer's disease patients have explored the relationship between cholinergic neurotransmission and cognition. Such studies have shown a direct correlation between the reduced activity of choline acetyltransferase, the enzyme responsible for catalyzing acetylcholine (ACh) synthesis, and the cognitive impairment in Alzheimer's disease patients[6,7]; an enhanced sensitivity of Alzheimer's disease patients to the adverse cognitive effects of anticholinergic therapy[8]; and a cognitive deficit similar to that observed in Alzhei-

mer's disease produced by the pharmacologic antagonism of cholinergic transmission.[9] Thus, the cholinergic deficiency appears to contribute to the cognitive impairment associated with Alzheimer's disease.

Considerable evidence also exists to support a relationship between cholinergic neurotransmission and certain psychiatric and behavioral features of Alzheimer's disease (reviewed by Cummings and Kaufer[10]). Many types of behavioral disturbances are associated with Alzheimer's disease.[11] For example, delusions, agitation, and apathy are observed in 30% to 70% of Alzheimer's disease patients.[11–13] Delusions typically occur sporadically at some point in the course of the disease, agitation is more prevalent in the late stages of the disease, and apathy may be experienced early in the disease and become more apparent with disease progression.[12–14] Generally, anticholinergic agents exacerbate these features, whereas cholinomimetic agents have been found to ameliorate them.[15–20] Therefore, the cholinergic deficiency in Alzheimer's disease may contribute to certain aspects of the psychiatric and behavioral symptoms typical of this disorder.

Recently, therapeutic strategies for the treatment of Alzheimer's disease have focused on augmenting cholinergic transmission and improving the cognitive deficits in afflicted patients. However, therapies consisting of ACh precursor loading, facilitation of ACh release, and the use of cholinergic receptor agonists have met with variable degrees of success.[21] Currently, tacrine and donepezil, 2 inhibitors of acetylcholinesterase (AChE), the enzyme responsible for ACh catabolism, are available for the treatment of Alzheimer's disease symptoms.[22–24] Tacrine and donepezil have been shown to enhance cognition in Alzheimer's disease patients.[22–24]

Metrifonate is an AChE inhibitor that has been developed as an Alzheimer's disease therapeutic. Metrifonate is a prodrug that is converted nonenzymatically to the active metabolite, 2,2-dichlorovinyl dimethyl phosphate (DDVP).[25,26] This metrifonate metabolite forms a stable drug-enzyme complex, resulting in a long-lasting enzyme inhibition.[27,28]

Metrifonate was first investigated as an Alzheimer's disease therapeutic by Becker and colleagues[29] who conducted an open trial in 20 patients. The cognitive benefit from metrifonate treatment reported in this study also was observed in a subsequent 3-month, randomized, double-blind, placebo-controlled, dose-finding study of metrifonate administered to Alzheimer's disease patients in a once-daily dosing regimen.[30] Moreover, preliminary data from the 3-month study demonstrated that metrifonate improved not only cognition, but also the global state of the Alzheimer's disease patients. More recently, a 6-month, randomized, double-blind, placebo-controlled trial of metrifonate in Alzheimer's disease patients revealed that a single daily dose of metrifonate (30–60 mg based on patient weight) benefited cognition, certain psychiatric and behavioral features, and the global state of these patients.[31]

The present 6-month, randomized, double-blind, placebo-controlled study was designed to examine the safety and efficacy of a fixed dose (50 mg/day) of metrifonate in patients diagnosed with Alzheimer's disease of mild-to-moderate severity, using outcome measures for cognition, psychiatric and behavioral disturbances, activities of daily living, and global state.

METHOD

Study Design

We conducted a prospective, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of metrifonate in patients with probable Alzheimer's disease of mild-to-moderate severity. The study included a 2-week screening period, a 26-week double-blind treatment period, and an 8-week posttreatment follow-up period.

Patient Selection

Inclusion criteria. Patients were evaluated by clinical interview, psychiatric assessment, physical and neurologic examinations, and laboratory studies. All participants met the criteria of the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable Alzheimer's disease.[32] Patients had Mini-Mental State Examination (MMSE)[33] scores between 10 and 26, modified ischemia scale scores[34] of less than 4, and weighed between 43 and 98 kg (95–215 lb). All participating patients had caregivers with whom they were in contact at least 4 times a week.

Exclusion criteria. Patients were excluded from study if they had a dementia other than probable Alzheimer's disease. Patients underwent a computed tomography or magnetic resonance imaging scan to exclude vascular dementia, hydrocephalus, and intracranial mass lesions. Patients with cognitive impairment attributable to toxic or alcoholic causes or a history of cognitive deficits following head trauma were excluded. Patients also were prevented from study participation if they had a history of seizure disorder, encephalitis, or other disorders associated with dementia, including Parkinson's disease, Huntington's disease, Pick's disease, abnormal thyroid hormone levels, B_{12} deficiency, neurosyphilis, or a current major depressive disorder, bipolar disorder, schizophrenia, or mental retardation according to the *Diagnostic and Statistical Manual, Fourth Edition* (DSM-IV)[35] criteria. Patients were excluded if they had clinically significant cardiovascular problems, including conduction defects, bradycardia (< 50 beats per minute [bpm]), myocardial infarction within the preceding 4 months, significant arrhythmias, supine or standing systolic blood pressure 180 mm Hg or greater or 100 mm Hg or lower, or ventricular

rate (by electrocardiogram [ECG]) less than 50 bpm or greater than 110 bpm. Additionally, patients with other clinically significant medical problems, including cancer within the preceding 5 years, poorly controlled diabetes, asthma or chronic obstructive pulmonary disease, gastrointestinal obstruction, or clinically significant hepatic, renal, cardiac, or pulmonary insufficiency were not included in the study. Lastly, patients were excluded from the study if they had taken metrifonate in the past for the treatment of Alzheimer's disease or were taking any of the following medications: psychotropic drugs, potential cognition-enhancing agents (any choline-containing compound, lecithin, any ergoloid derivative, tacrine, donepezil), drugs with significant cholinomimetic or anticholinergic activity, anticonvulsants, antacids or cimetidine (chronic use), or any investigational drug (within 30 days of screening).

The study was conducted in accordance with institutional review board guidelines at the participating centers. It was fully explained to all patients and their caregivers, and informed consent for participation was given by the patient as well as his or her legal representative or family caregiver.

Metrifonate Dosing

The 264 patients enrolled in this study were randomly assigned to the placebo (N = 87) or the metrifonate (N = 177) group according to a computer-generated randomization code. The investigators were blinded as to random code assignment. The metrifonate-treated patients received a single 50-mg tablet once each day before breakfast. The placebo-treated patients received matching placebo tablets once daily.

Outcome Measures

Efficacy evaluations. The efficacy of metrifonate was evaluated by using scales that assessed cognition, psychiatric and behavioral disturbances, instrumental and basic activities of daily living, and global state. The ability of metrifonate to improve cognition was analyzed using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)[36] and the MMSE.[33] The ability of metrifonate to benefit psychiatric and behavioral disturbances was assessed using the Neuropsychiatric Inventory (NPI)[37] and the ADAS-Noncognitive subscale (ADAS-Noncog).[36] The NPI is a validated and reliable instrument that evaluates the severity and frequency of 10 psychiatric and behavioral disturbances common in dementia (delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, and aberrant motor behaviors). The ADAS-Noncog is also a validated and reliable measure of mood and behavioral changes. The effect of metrifonate on the ability to perform activities of daily living was evaluated using the Disability Assessment for Dementia (DAD) scale.[38,39] The DAD scale is a validated and reliable measure designed specifically for community-dwelling individuals afflicted with Alzheimer's disease; it examines instrumental, basic, and leisure activities. The ability of metrifonate to improve global state was determined using the Clinician Interview-Based Impression of Change with Caregiver Input (CIBIC-Plus) scale.[40] Lastly, the severity of the manifested symptoms was evaluated using the Clinician Interview-Based Impression of Severity with Caregiver Input (CIBIS-Plus)[40] and the Global Deterioration Scale (GDS).[41]

Safety evaluations. Treatment groups were compared with respect to the incidence rates of premature termination, treatment-emergent adverse events, mortality, laboratory abnormalities, ECG findings, and neurologic examination abnormalities. Changes from baseline in vital signs (blood pressure and pulse rate), weight, ECG cardiac cycle measurements, and ECG heart rate also were summarized for both treatment groups. Adverse events were rated by the clinician as mild, moderate, or severe, based on the degree of discomfort and disability induced by the event. Adverse events in disfavor of metrifonate (i.e., selected adverse events) were defined as those for which the rate in the metrifonate group differed from that in the placebo group by at least 5%. The 5% threshold for the selection of adverse events was based on the need to identify, using a relatively conservative approach, adverse events that were drug-related and of clinical importance. All adverse events were reported according to an encoding system (the Coding Symbols for Thesaurus of Adverse Reaction Terms [COSTART]).[42]

Data Analyses

The target sample size specified in the protocol was 156 randomized patients in the metrifonate group and 78 randomized patients in the placebo group. The sample size was determined as that required to provide 90% dual outcome power, where dual outcome power refers to the probability of observing a significant metrifonate versus placebo comparison with respect to both the ADAS-Cog and the CIBIC-Plus. Computer simulations of the analysis of variance (ANOVA) methodology for the efficacy analyses were used to estimate the required sample size.

Patients were included in the safety analyses if they took at least one dose of study medication and underwent any postbaseline safety assessments. Patients were included in the intent-to-treat (ITT) analyses of efficacy if, in addition to being valid for the safety analysis, they also had any postbaseline efficacy data collected.

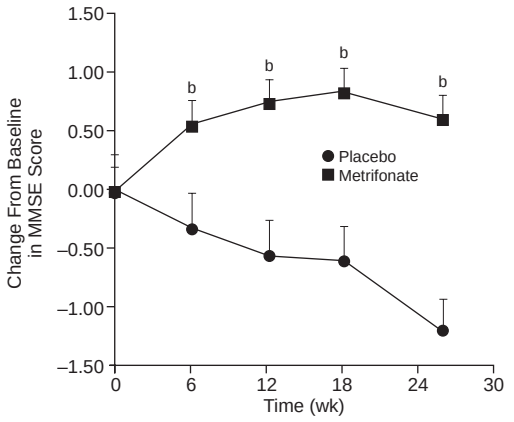
All efficacy variables were analyzed as a change from baseline, except for the CIBIC-Plus, for which the value itself was analyzed. The method of handling assessments missing owing to premature study discontinuation consisted of last-observation-carried-forward (LOCF) analyses based on the ITT population.

Table 1. Baseline Demographic Characteristics of Patients[a]

Variable	Placebo	Metrifonate
Total patients randomized, N[b]	87	177
Age (y, mean ± SD)	74.5 ± 7.5	74.6 ± 8.3
Weight (kg, mean ± SD)	66.7 ± 14.8	66.9 ± 12.4
Height (cm, mean ± SD)	163 ± 11	164 ± 10
Gender, N (%)		
Male	28 (32.2%)	67 (37.9%)
Female	59 (67.8%)	110 (62.1%)
Race, N (%)		
White	79 (90.8%)	157 (88.7%)
African-American	3 (3.4%)	7 (4.0%)
Asian	1 (1.1%)	0 (0.0%)
Hispanic	4 (4.6%)	10 (5.6%)
American Indian	0 (0.0%)	1 (0.6%)
Missing	0 (0.0%)	2 (1.1%)
Education level, N (%)		
Postgraduate	6 (6.9%)	14 (7.9%)
College or equivalent	21 (24.1%)	27 (15.3%)
High school or equivalent	38 (43.7%)	94 (53.1%)
Grammar school	22 (25.3%)	41 (23.2%)
No schooling	0 (0.0%)	1 (0.6%)
Baseline MMSE score (mean ± SD)	18.7 ± 4.97	18.7 ± 4.76

[a]Abbreviation: MMSE = Mini-Mental State Examination.
[b]Patients were those valid for the safety analysis.

Figure 1. Least Squares Mean Change From Baseline in MMSE Scores (last-observation-carried-forward) of Intent-to-Treat Patients as a Function of Time[a]



[a]Abbreviation: MMSE = Mini-Mental State Examination. Positive changes in MMSE scores indicate improvement.
[b]$p < .05$ when compared with the placebo group.

Efficacy variables were analyzed using 2-tailed statistical tests conducted at the 5% level. For continuous efficacy variables, a main effects ANOVA model with terms for center and treatment was used to estimate and test effects. Secondarily, the ANOVA model formed by adding the treatment-by-center interaction to the main effects model was used to determine the existence of any such interaction. If the treatment means for an efficacy variable obtained at baseline indicated a substantial imbalance across groups, an analysis of covariance (ANCOVA) model with terms for center, treatment, and the baseline value was used in a secondary analysis of the variable. Regarding the efficacy variables analyzed using the ANOVA model, treatment groups were summarized using least squares means and standard errors obtained from the model. With respect to the analysis of NPI scale subitems, a multivariate analysis of variance (MANOVA) was employed. For the other variables, treatment groups were compared using descriptive statistics (sample size, standard deviation, minimum and maximum for continuous variables, and cell counts and percentages for categorical variables).

RESULTS

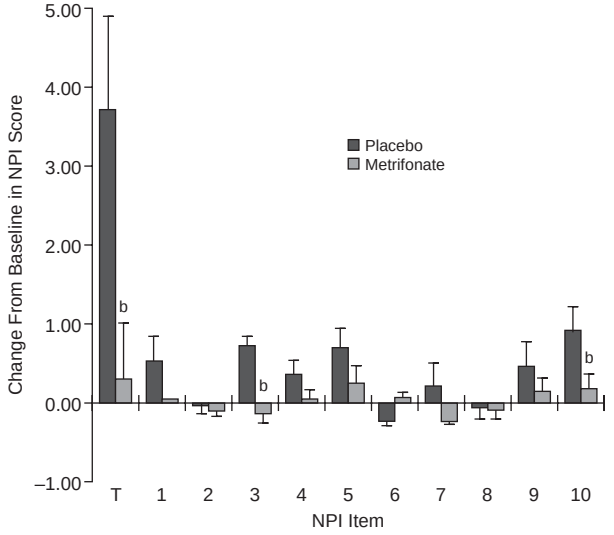
Table 1 presents the baseline demographic data for the patients valid for the safety analysis. No significant differences were noted between the 2 groups with respect to the mean age, height and weight, or distributions according to gender, race, and education level. Patients in the 2 treatment groups also had similar baseline MMSE scores, suggesting that the level of cognitive impairment was comparable between the 2 groups.

Efficacy Evaluations

The effects of metrifonate on cognition were evaluated using the ADAS-Cog and the MMSE. In the ITT patient population at week 26, a mean drug-placebo difference (i.e., treatment difference) in the ADAS-Cog score in favor of metrifonate was observed ($t = 2.55$, $df = 237$, $p = .012$). For the MMSE, the placebo-treated patients in the ITT population showed a mean 1.24 point decline in cognitive performance at week 26, whereas the metrifonate-treated patients were characterized by a 0.61 point improvement, resulting in a treatment difference in favor of metrifonate of 1.85 ($t = 4.60$, $df = 237$, $p = .0001$) (Figure 1). Therefore, metrifonate benefited cognitive performance in the Alzheimer's disease patients as assessed by both the ADAS-Cog and the MMSE.

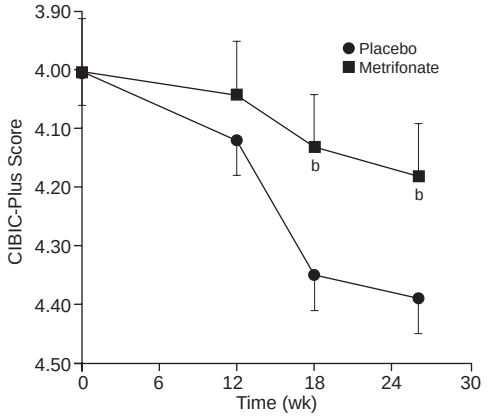
The influence of metrifonate on the psychiatric and behavioral disturbances of Alzheimer's disease patients was assessed using the NPI and the ADAS-Noncog. The ITT analysis revealed that, at week 26, the metrifonate-treated Alzheimer's disease patients exhibited a mean change in the total NPI score of 0.32 points, whereas the placebo-treated patients were more severely behaviorally disturbed with a mean change of 3.74 points ($t = 2.51$, $df = 233$, $p = .013$) (Figure 2). Prior to an analysis of the individual NPI subitems, a MANOVA was performed on these items and found to yield a statistically significant result ($F = 2.11$, $df = 10,244$; $p = .024$). An analysis of the individual NPI subitems revealed that metrifonate significantly reduced the degree of agitation and aggression ($t = 11.38$, $df = 233$, $p = .001$), and aberrant motor behavior ($t = 3.95$, $df = 233$, $p = .048$). The metrifonate-treated patients also tended to manifest a decreased degree of delusions when compared with their placebo-treated coun-

Figure 2. Least Squares Mean Change From Baseline in NPI Scores (last-observation-carried-forward) of Intent-to-Treat Patients at Week 26 of Treatment[a]



[a]Abbreviations: NPI = Neuropsychiatric Inventory, T = total NPI score. A negative value reflects improvement relative to the baseline. NPI Item scores are presented for (1) delusions, (2) hallucinations, (3) agitation and aggression, (4) depression and dysphoria, (5) anxiety, (6) elation and euphoria, (7) apathy, (8) disinhibition, (9) irritability and lability, and (10) aberrant motor behavior.
[b]$p < .05$ when compared with the placebo group.

Figure 3. Least Squares Mean Change From Baseline in CIBIC-Plus Scores (last-observation-carried-forward) of Intent-to-Treat Patients as a Function of Time[a]



[a]Abbreviation: CIBIC-Plus = Clinician Interview-Based Impression of Change with Caregiver Input. CIBIC-Plus scores below 4.0 indicate an improvement relative to baseline status.
[b]$p < .05$ when compared with the placebo group.

terparts, but the treatment difference for this particular subitem did not reach statistical significance ($t = 2.73$, $df = 233$, $p = .100$). The ADAS-Noncog assessment of behavioral disturbances revealed that, although metrifonate-treated patients tended to receive better scores than the placebo-treated patients, this effect was not statistically significant ($t = 1.33$, $df = 237$, $p = .185$). Therefore, metrifonate favorably influenced certain behavioral features of the Alzheimer's disease patients as evaluated by the NPI.

The ability of metrifonate to benefit the performance of instrumental and basic activities of daily living of Alzheimer's disease patients was determined using the DAD. Metrifonate had a favorable effect on the activities of daily living of these patients as represented by a mean drug-placebo difference of 4.07 ($t = -2.11$, $df = 233$, $p = .036$) in the total DAD score.

The ability of metrifonate to improve the overall global state of the Alzheimer's disease patients was evaluated using the CIBIC-Plus scale. In the ITT patient population at week 26, metrifonate ameliorated the decline in the global state of the Alzheimer's disease patients as reflected by a mean drug-placebo difference of 0.20 ($t = 2.07$, $df = 232$, $p = .039$) in the CIBIC-Plus score (Figure 3).

The effect of metrifonate on the severity of manifested symptoms of Alzheimer's disease patients was determined using the CIBIS-Plus and the GDS. The ITT analysis at week 26 showed that, on both scales, the metrifonate-treated patients received comparable scores, on average, to those of the placebo-treated patients. In regard to the CIBIS-Plus, the mean drug-placebo difference was 0.05 ($t = 1.13$, $df = 232$, $p = .260$). For the GDS measure, the mean drug-placebo difference was 0.04 ($t = 0.57$, $df = 225$, $p = .570$).

Safety Evaluations

Eighty-four percent of placebo-treated patients and 82% of metrifonate-treated patients completed the 6-month treatment. Few patients discontinued treatment owing to adverse events: the placebo discontinuation rate due to adverse events was 9%, while that for the metrifonate-treated patients was 11%.

Table 2 presents the data related to the incidence of adverse events. Adverse events experienced with metrifonate treatment tended to be predominantly mild in intensity. Selected adverse events (encoded using COSTART), defined as those for which the metrifonate rate differed from the placebo rate by at least 5%, included abdominal pain, leg cramps, rhinitis, and agitation.

The metrifonate-treated patients exhibited no clinically relevant laboratory abnormalities, including liver function abnormalities. Similarly, the metrifonate-treated patients showed no clinically significant changes in weight; at the end of treatment, the patients in the placebo group showed a least squares mean increase from baseline weight of 0.46 kg, whereas those in the metrifonate group showed a mean increase of 0.26 kg ($t = 0.76$, $df = 241$, $p = .447$).

Metrifonate produced no clinically significant changes from the baseline values in the mean supine or standing

Table 2. Incidence of Adverse Events With Placebo and Metrifonate Treatment

	Placebo		Metrifonate	
Variable	N	%	N	%
Patients valid for safety analysis	87	100	177	100
Patients completing treatment	73	84	146	82
Patients experiencing any mild adverse event	58	67	127	72
Patients experiencing any moderate adverse event	20	23	76	43
Patients experiencing any severe adverse event	6	7	13	7
Patients discontinuing due to adverse events	8	9	19	11
Selected adverse events[a]				
Abdominal pain	2	2	17	10
Leg cramps	2	2	18	10
Agitation	2	2	14	8
Rhinitis	2	2	17	10

[a]Selected adverse events (encoded by the Coding Symbols for Thesaurus of Adverse Reaction Terms) are those for which the metrifonate rate differed from the placebo rate by at least 5%.

diastolic and systolic blood pressures. At the end of treatment, the least squares mean supine systolic pressure was increased by 2.21 points in the placebo group and by 3.20 points in the metrifonate group ($t = –0.39$, $df = 241$, $p = .697$); the mean supine diastolic pressure was increased by 2.40 points in the placebo group and decreased by 0.17 points in the metrifonate group ($t = 2.09$, $df = 241$, $p = .037$). Similarly, the least squares mean standing systolic blood pressure was 1.45 points higher than baseline in the placebo group and 1.99 points higher in the metrifonate group ($t = –0.23$, $df = 241$, $p = .815$), and the mean standing diastolic pressure was 1.06 points higher in the placebo group and 0.11 points lower in the metrifonate group ($t = 0.97$, $df = 241$, $p = .332$).

At the end of treatment, metrifonate was found to decrease the mean heart rate (as measured by ECG) when compared with placebo. Metrifonate-treated patients manifested a least squares mean 4.92 bpm reduction in heart rate from the baseline value, whereas the placebo-treated patients exhibited a mean 1.20 bpm increase in this rate. Therefore, at the end of treatment, metrifonate-treated patients were characterized by a mean heart rate that was approximately 6 bpm lower than that of their placebo-treated counterparts ($t = 4.51$, $df = 234$, $p = .0001$). These changes in heart rate generally were considered to be clinically unimportant by the study investigators, and no patients were discontinued from treatment due to these heart rate changes.

DISCUSSION

In this study, we examined the efficacy and safety of a once-daily fixed dose (50 mg) of metrifonate to benefit the cognitive decline, the psychiatric and behavioral disturbances, the impaired ability to perform instrumental and basic activities of daily living, and the global state of Alzheimer's disease patients. Metrifonate significantly benefited all 3 symptom domains and possessed a benign side effect profile.

Previously, a 6-month, double-blind, randomized, placebo-controlled study showed that metrifonate, administered in a once-daily dose of 30–60 mg based on weight (0.65 mg/kg), positively influenced cognitive performance in Alzheimer's disease patients as assessed by the ADAS-Cog.[31] In the current study, metrifonate also produced a significant treatment difference in the ADAS-Cog score. Therefore, the results of the current 6-month study confirm the findings of the previous study and demonstrate that metrifonate favorably influenced cognitive performance in Alzheimer's disease patients as assessed by the ADAS-Cog.

Consistent with the positive ADAS-Cog result of this study, metrifonate also benefited cognition as measured by the MMSE. The MMSE score treatment difference in favor of metrifonate was 1.85 points, representing a 1.24-point worsening of the score for placebo patients and a 0.61-point improvement in the score for metrifonate-treated patients. It has been reported that a 3-point decrease in the MMSE score represents the degree of cognitive decline manifested by an Alzheimer's disease patient over a 1-year period.[43] Thus, the approximate 2-point difference in the MMSE scores of the placebo- and metrifonate-treated patients in this study may reflect their different rates of cognitive deterioration and may be viewed as a metrifonate-mediated reversal of 8 months of cognitive decline.

An analysis of the activities of daily living using the DAD and of the psychiatric and behavioral disturbances using the NPI revealed that metrifonate produced a significant treatment difference with respect to both the performance of daily activities and the psychiatric and behavioral disturbances of the Alzheimer's disease patients. In both the previous[31] and the current 6-month studies of metrifonate efficacy, metrifonate relieved the psychiatric and behavioral disturbances of the Alzheimer's disease patients. The results of the NPI analyses in both studies demonstrated a statistically significant metrifonate-mediated reduction in the composite score of 10 common psychiatric and behavioral symptoms experienced by Alzheimer's disease patients. Therefore, these findings suggest that metrifonate significantly benefits the psychiatric and behavioral disturbances in addition to the cognitive deficits and the performance of daily activities of Alzheimer's disease patients.

Metrifonate exerts its effects by increasing central cholinergic transmission. Cholinergic transmission has been found to play a role in both learning and memory.[44] Cholinergic fibers from the basal forebrain also are involved in the regulation of cerebral activation, sensory informa-

tion processing, and motor behavior.[45,46] Therefore, the effect of a metrifonate-mediated increase in cholinergic transmission on these functions may contribute to the observed benefit on cognitive performance, relief of psychiatric and behavioral disturbances, and the ability to conduct activities of daily living.

Effective therapeutic strategies for Alzheimer's disease ideally should address all 3 domains of impairment (cognition, psychiatric and behavioral disturbances, and activities of daily living) in Alzheimer's disease patients. Although a deterioration in cognitive performance is the most consistent clinical feature of Alzheimer's disease, the manifestation of psychiatric and behavioral disturbances and an impaired ability to perform instrumental and basic activities of daily living are integral components of the disease that can have a profound effect on caregiver burden, institutionalization, and caregiver and patient quality of life.[47–49] Indeed, neuropsychiatric complications in Alzheimer's disease patients may be the primary contributor to the feelings of burden experienced by caregivers.

In spite of the recognition by clinicians and researchers that Alzheimer's disease is more complex than a loss of cognitive abilities, therapeutic strategies historically have focused on enhancing cognitive performance. Relatively recently, tacrine and donepezil were shown to benefit the cognition and global state of Alzheimer's disease patients.[22–24] In a preliminary open-label study (N = 28)[16] and in an exploratory analysis of a selected subsample of subjects in a placebo-controlled trial,[20] tacrine was found to attenuate some of the psychiatric and behavioral disturbances of Alzheimer's disease patients. Xanomeline, a cholinergic muscarinic receptor agonist, also benefited certain behavioral disturbances of Alzheimer's disease patients.[19] These reports of positive behavioral effects of cholinomimetic agents are consistent with the findings of the current study with metrifonate.

The selected adverse events in disfavor of metrifonate were limited to abdominal pain, leg cramps, rhinitis, and agitation. Although the possibility that these adverse events are central in etiology cannot be excluded, it is likely that they are peripheral in origin. In this regard, abdominal pain may result from an overstimulation of gastrointestinal muscarinic cholinergic receptors, and leg cramps may reflect the hyperactivation of nicotinic cholinergic receptors localized at the neuromuscular junction. The occurrence of rhinitis as an adverse event may be a consequence of increased secretions following excessive muscarinic receptor activity. Interestingly, agitation appeared as both an adverse event and a behavioral feature responsive to metrifonate treatment. Although the explanation for this is not clear, it should be noted that, as a behavioral feature assessed by the NPI, agitation is categorized along with aggression as a single item, whereas as an adverse event, agitation is encoded as several types of "agitation-like" events. Thus, the possibility that the agitation terms defining behavior and adverse events actually reflect different manifestations cannot be dismissed. Additionally, the NPI item of "agitation and aggression" does not distinguish between these 2 behavioral components. Therefore, that the aggression component, and not the agitation component, may be the more responsive to metrifonate treatment also must be considered.

The pharmacokinetics profile of metrifonate includes a rapid and almost complete absorption, leading to an increase in brain ACh levels within 1 hour of oral administration.[50] Metrifonate undergoes little protein binding (< 15%), a property that serves to minimize potential drug-drug interactions. Metrifonate and DDVP both have a serum half-life of approximately 2 hours.[50] Although both metrifonate and DDVP undergo extensive biotransformation, they are metabolized independently of the hepatic cytochrome P450 enzyme system, a property that favors the absence of drug-drug interactions involving this system.

Given its benefit on the cognitive decline, the psychiatric and behavioral disturbances, the impaired ability to perform instrumental and basic activities of daily living, and the global state of Alzheimer's disease patients, coupled with its low incidence of adverse effects, metrifonate is a promising cholinomimetic therapeutic option for the treatment of Alzheimer's disease symptoms.

Drug names: cimetidine (Tagamet), donepezil (Aricept), lecithin (PhosChol), tacrine (Cognex).

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Geoffrey L. Ahern, M.D., Ph.D., University of Arizona Health Sciences Center, Tucson, Ariz.; Peter Bailey, M.D., P.A.B. Professional Corporation, Saint John, New Brunswick, Canada; Barry Baumel, M.D., Neuromedical Research Associates, Miami Beach, Fla.; Howard Chertkow, M.D., Jewish General Hospital, Montreal, Quebec, Canada; Carl W. Cotman, M.D., University of California-Irvine, Irvine; Neal R. Cutler, M.D., California Clinical Trials Medical Group, Beverly Hills; Eugene DuBoff, M.D., Center for Behavioral Medicine, Denver, Colo.; Larry Eisner, M.D., Neuromedical Research Associates, Tamarac, Fla.; Martin R. Farlow, M.D., University Hospital Alzheimer's Clinic, Indianapolis, Ind.; Michael Jann, Pharm.D., Mercer University, Atlanta, Ga.; David I. Margolin, M.D., Fresno, Calif.; Peter McCracken, M.D., Glenrose Rehabilitation Hospital, Edmonton, Alberta, Canada; Ali Rajput, M.D., Royal University Hospital, Ottawa, Ontario, Canada; Murray A. Raskind, M.D., VA Puget Sound Health Care System, Seattle, Wash.; Frederich Schaerf, M.D., Ph.D., Medical Studies Florida, Fort Myers; Alan L. Schneider, M.D., Pharmacology Research Institute, Northridge, Calif.; Lon Schneider, M.D., USC School of Medicine, Los Angeles, Calif.; Paul Solomon, M.D., Memory Disorders Clinic, Bennington, Vt.; Mahmood Usman, M.D., Alzheimer's Center of Pittsburgh, Pittsburgh, Pa.; Jonathan Wilmer, M.D., Elisabeth Bruyere Health Center, Ottawa, Ontario, Canada.

