Metrifonate: Update on a New Antidementia Agent

John M. Ringman, M.D., and Jeffrey L. Cummings, M.D.

Objective: To review preclinical and clinical studies of metrifonate, a cholinesterase inhibitor relevant to the treatment of Alzheimer's disease.

Data Sources: English-language literature identified by MEDLINE using the term *metrifonate* was reviewed, and bibliography-sorted searches were conducted.

Study Findings: Metrifonate is an organophosphate cholinesterase inhibitor effective in the treatment of the cognitive symptoms of Alzheimer's disease and currently under review by the U.S. Food and Drug Administration. The active metabolite of metrifonate, 2,2-dimethyldichlorovinyl phosphate (DDVP), irreversibly inhibits the acetylcholinesterase enzyme. Although the elimination half-life of DDVP is 2–3 hours, the half-life of cholinesterase inhibition by DDVP is stable (26 days). Metrifonate can be administered once daily. Animal studies demonstrate its efficacy in enhancing memory in animals that have cholinergic deficits. Double-blind, placebo-controlled studies have shown the benefit of metrifonate compared with placebo in improving scores on the Clinical Global Impression of Change scale, the Alzheimer's Disease Assessment Scale-cognitive subscale, and the Neuropsychiatric Inventory.

Conclusion: Metrifonate is a useful addition to our limited armamentarium of agents helpful against the cognitive deficits of Alzheimer's disease.

(J Clin Psychiatry 1999;60:776–782)

Received March 24, 1998; accepted Feb. 11, 1999. *From the Departments of Neurology (both authors), and Psychiatry & Biobehavioral Sciences (Dr. Cummings), University of California Los Angeles (UCLA) School of Medicine, Los Angeles.*

Supported by a National Institute on Aging Alzheimer's Disease Center grant (AG 10123), an Alzheimer's Disease Research Center of California grant, a grant from the Bayer Corporation, and the Sidell-Kagan Foundation (Dr. Cummings).

Reprint requests to: Jeffrey L. Cummings, M.D., Reed Neurological Research Center, UCLA School of Medicine, 710 Westwood Plaza, Los Angeles, CA 90095-1769 (e-mail: cummings@ucla.edu).

The personal and social costs of dementia are enormous. It is impossible to quantify the suffering endured by dementia patients and their families; on a societal level, the economic cost is staggering. Estimates of the direct and indirect annual financial burden of dementia in the United States range from $113 to $536 billion.[1,2] With the increasing number of elderly people in the world, the cost of dementia to society is certain to rise. It is estimated that the number of people over age 65 in the United States will increase by 105% between 1985 and 2025.

Alzheimer's disease is the most common cause of dementia in the elderly and thus has been a major focus of medical research in recent years. Important information regarding the etiology and pathogenesis of Alzheimer's disease has been amassed. Unfortunately, progression of the disease cannot be stopped, little progress in preventing it has been made, and "curing" Alzheimer's disease may be impossible. Much current research is therefore aimed at developing medications to ameliorate or slow the progression of Alzheimer's disease symptoms. Specifically, Alzheimer's disease is characterized by impairment in cognition, deterioration in the ability to perform activities of daily living, and the appearance of behavioral disturbances. These symptoms are among the principal targets of current Alzheimer's disease therapy.

DATA SOURCES

The MEDLINE computerized reference database was searched using the term *metrifonate*. In addition, bibliographies of articles located were used to identify additional relevant publications. The search was confined to English-language literature.

ALZHEIMER'S DISEASE

Etiology

Alzheimer's disease accounts for 70% of cases of dementia in the elderly. Although most cases are sporadic and of late onset, 2% to 5% are inherited in an autosomal dominant fashion, with the responsible mutations being localized on chromosomes 1, 14, and 21 in some pedigrees.[3] Alzheimer's disease occurs with increased frequency and earlier onset in the context of trisomy-type Down syndrome in which there are 3 copies of chromosome 21.[4]

Among the neuropathologic changes found in Alzheimer's disease brains are neuritic plaques, which are in part composed of β-amyloid protein. The progenitor of this protein is amyloid precursor protein (APP), the gene for which has been localized on chromosome 21. Overproduction of APP or abnormal posttranscriptional modification of this protein may lead to its aberrant depo-

sition in Alzheimer's disease brains.[5] Neurofibrillary tangles, which are helical protein aggregates composed of hyperphosphorylated tau protein, ubiquitin, and neurofilament protein, also are prevalent in Alzheimer's disease brains. Recent evidence for mutations in the tau protein gene on chromosome 17 in other familial dementias[6] has refocused research on tau and its interaction with β-amyloid in the neuropathology of Alzheimer's disease.

Epidemiologic studies have shown that other factors associated with an increased risk of sporadic Alzheimer's disease include a family history of Alzheimer's disease, head injury, and low educational level.[7] Apolipoprotein E (ApoE) genotype has been shown to affect the risk of developing Alzheimer's disease, with the ApoE-4 allele associated with an increased risk and the ApoE-2 allele possibly imparting a protective effect.[8] More recent studies suggest that factors associated with a decreased risk of Alzheimer's disease are use of nonsteroidal anti-inflammatory drugs (NSAIDs)[9] and estrogen replacement therapy in postmenopausal women.[10]

Neurochemistry

Reductions in levels of acetylcholine (ACh), norepinephrine, serotonin, γ-aminobutyric acid, substance P, corticotropin-releasing factor, and somatostatin levels have been reported in Alzheimer's disease.[11] Changes in the cholinergic system are the most consistent and extreme of these neurochemical changes.

Dramatically decreased amounts of choline acetyltransferase and acetylcholinesterase (AChE), enzymes responsible for the manufacture and degradation of ACh, respectively, occur in the hippocampus and in the mid-temporal, parietal, and portions of the frontal cortex in the brains of patients with Alzheimer's disease.[12] The deficiency of ACh activity is due to the loss of cholinergic projections from the nucleus basalis of Meynert. This nucleus, located ventral to the medial globus pallidus, is the major source of cholinergic innervation to the cortex, and there is marked atrophy of this nucleus in postmortem Alzheimer's disease brains.[13] The nucleus of Meynert receives projections from prepiriform, orbitofrontal, entorhinal, and medial temporal cortices as well as from the septal nuclei, nucleus accumbens-ventral pallidal complex, amygdala, and hypothalamus. Through these limbic afferents and neocortical efferents, the nucleus of Meynert may influence neocortical activity in relation to the emotional and motivational state of the organism.

Animal studies have shown that lesions of the nucleus of Meynert produce a memory disorder with properties similar to those seen in humans with Alzheimer's disease.[12] Administration of scopolamine, an anticholinergic drug, to healthy human volunteers causes a temporary memory deficit similar to the memory abnormalities in Alzheimer's disease. The deficit can be reversed by physostigmine, an AChE inhibitor.[14] Interruption of normal cholinergic activity can cause many neuropsychiatric changes in addition to memory deficits. Delirium can be induced by administration of drugs with anticholinergic properties, anticholinergics can exacerbate psychotic symptoms in schizophrenics,[15] and administration of scopolamine to patients with Alzheimer's disease increases their agitation and thought disorder.[16] These observations indicate that cholinergic deficiency contributes to both the memory deficits and behavioral disturbances of Alzheimer's disease. This hypothesis has provided a major impetus to develop drugs that enhance cholinergic transmission to treat the symptoms of Alzheimer's disease.[12]

Attempts have been made to treat Alzheimer's disease by improving cholinergic transmission with many different medications. Acetylcholine precursors, cholinergic receptor agonists, and AChE inhibitors have all been studied. Modest beneficial results have been obtained with receptor agonists and AChE inhibitors. Currently, there are no direct receptor agonists approved for use to treat Alzheimer's disease.

CHOLINESTERASE INHIBITORS

Enhanced neurotransmission at cholinergic synapses can be achieved through the inhibition of AChE, the enzyme that normally degrades ACh in the synaptic cleft. Inhibitors of this enzyme also have high affinity for AChE in red blood cells (RBCs) and variable affinity for butyrylcholinesterase, the type of cholinesterase present in free plasma and associated with the neuritic plaques of Alzheimer's disease brains.[17] Selectivity of a given drug for central nervous system (CNS) AChE might be anticipated to be an important factor in determining the ratio of its therapeutic effect to toxic side effects. However, there is no clear relationship between the selectivity of a particular AChE inhibitors for CNS AChE and its toxicity.[18] Properties of the drug independent of peripheral and central butyrylcholinesterase inhibition such as rapidity of onset of effect, specificity for different forms of AChE, and noncholinergic effects may be more important in determining toxicity.

Several classes of drugs exhibit cholinesterase inhibition. Agents from the acridine, piperidine, carbamate, and organophosphate classes all have been considered for clinical use. Preclinical and clinical experience with these medications varies greatly. These medications differ in regard to mechanism of action, duration of effect, side effect profile, and metabolism (Table 1).

Tacrine, a short-acting cholinesterase inhibitor, has been available since 1993 and was the first specific drug for palliative treatment of Alzheimer's disease to be widely used. In a 30-week prospective trial,[19] patients who tolerated the highest dose (160 mg/day) of tacrine experi-

Table 1. A Comparison of Acetylcholinesterase (AChE) Inhibitors in Use or in Development for the Treatment of Alzheimer's Disease[a]

Drug	Mechanism of Action	T_{max}[b]	Half-Life of Action	Dosing Schedule	Metabolism	Clinical Trial Drop-Out Rates
Tacrine	Reversible, noncompetitive	1–2 h	1–4 h	qid	CYP1A2, 2D6	Up to 55%
Donepezil	Reversible, mixed competitive/ noncompetitive	2–4 h	70 h	qd	CYP2D6, CYP3A3/4	5%–32%
Metrifonate	Irreversible, competitive	30–40 min	7–26 d	qd	Non-hepatic	4%–21%
Galantamine	Reversible, competitive, receptor agonist	2 h	5–10 h	tid	CYP2D6	Not available
Rivastigmine	Pseudo-irreversible competitive	1–2 h	10 h	bid–tid	Non-hepatic	7%–28%

[a]Based on data from Giacobini,[18] Knapp et al.,[19] Rogers et al.,[22] Corey-Bloom,[25] and Unni et al.[26]
[b]Time to maximal plasma concentration after oral administration.

enced a benefit in cognition compared with placebo (mean of 4.8 points) as assessed by the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog),[20] a widely used, validated cognitive test that assesses orientation, memory, language, and constructional praxis. Possible scores range from 0 to 70, with a higher score reflecting poorer performance. A follow-up study[21] of patients on tacrine treatment at 2 years showed a decreased likelihood of nursing home placement for patients maintained on greater than 80 mg/day of tacrine. Hepatotoxicity and other side effects resulted in a high rate of discontinuation. The observed hepatotoxicity has been related to the drug's acridine structure.

Donepezil, an intermediate-duration cholinesterase inhibitor of the piperidine class, was the second drug to be approved by the U.S. Food and Drug Administration (FDA) for use in treating the symptoms of Alzheimer's disease. In a 12-week trial,[22] 11% of patients on 5 mg/day of donepezil showed clinical decline, whereas 20% of placebo-treated patients did. This study was continued to 24 weeks,[23] at which time a statistically significant improvement over placebo on the ADAS-cog and the Clinician's Interview Based Assessment of Change-Plus (CIBIC-Plus, an evaluation founded on a structured interview with the caregiver) was evident. Sixty-eight percent of patients taking 10 mg/day completed the study compared with 80% taking placebo. Although tacrine and donepezil have not been compared directly with each other in a trial, the lower rate of adverse effects (including hepatotoxicity) of donepezil and its ease of administration (once-daily dosing as opposed to 4-times-daily dosing for tacrine) are distinct advantages.

Rivastigmine has completed phase 3 trials and is under review by the FDA. Rivastigmine is a carbamate and acts as a "pseudo-irreversible" AChE inhibitor, forming a short-lived covalent bond with AChE. The drug is degraded in the process and therefore does not depend on hepatic metabolism. It has been reported to have selectivity for the monomeric G_1 form of AChE, which is relatively spared in Alzheimer's disease compared with other forms of the enzyme.[24] In a double-blind, placebo-controlled trial[25] in which the maximum tolerated dose was employed, a mean improvement in ADAS-cog score of 4.9 was seen after 26 weeks. Sixty-five percent of patients completed the trial. Gastrointestinal side effects were common. Potential advantages of rivastigmine are increased activity against the form of AChE that is predominant in Alzheimer's disease and decreased liability to drug interactions.

Galantamine is an AChE inhibitor that also exerts nicotinic effects. It is currently available in Austria and is being studied for use in the United States. Other AChE inhibitors in various stages of development include metrifonate (discussed below), eptastigmine, and long-acting physostigmine.

The incidence and severity of side effects of a specific AChE inhibitor in a particular individual will vary depending on many factors, including fluctuations in concentration and degree of AChE inhibition, pharmacokinetic differences between patients, and possibly the relative degree of central and peripheral activity. The side effects that may be seen with any AChE inhibitor are those of hyperactivity at cholinergic synapses and include nausea, abdominal discomfort, vomiting, loose stools, muscle cramps, muscle weakness, increased sweating, and bradycardia. Some drugs (such as succinylcholine and cocaine) are catabolized by peripheral cholinesterase, and thus inhibition of this enzyme by AChE inhibitors can potentially prolong their activity. AChE inhibitors, therefore, should be discontinued prior to surgery to avoid prolonged paralysis with succinylcholine. AChE inhibitors should be used with caution in patients with asthma, chronic obstructive pulmonary disease, and gastric ulcers, as they may exacerbate these conditions.

METRIFONATE

Metrifonate (*O,O*-dimethyl-[1-hydroxy-2,2,2-trichloroethyl]phosphonate, or trichlorfon) is an organophosphate compound that has been used as an antihelminthic in the treatment of schistosomiasis since 1960. It is a prodrug that is metabolized nonenzymatically to 2,2-dimethyldichlorovinyl phosphate (DDVP or dichlorvos). Because of the anticholinesterase properties of its metabolite, metrifonate has been studied for its potential utility in Alzheimer's disease.

Pharmacokinetics and Pharmacodynamics

As a prodrug with the active metabolite functioning as an irreversible AChE inhibitor, the pharmacology of metrifonate is unique. It is readily absorbed from the gut, with peak plasma levels of both metrifonate and DDVP occurring 30 minutes after oral administration in drug-naive elderly human subjects.[26] Protein binding is reported to be 20% for metrifonate and 50% for DDVP. The plasma level of DDVP has been reported to be about 1% that of metrifonate in young subjects but higher (2%–7%) in older adults.[26,27] Both metrifonate and DDVP are highly metabolized, accounting for their short half-life in plasma (metrifonate through glucuronidation and DDVP by *O*-demethylation).[28] In a study of elderly subjects,[29] the plasma half-life was 1.5 to 2.1 hours for metrifonate and 2 to 3 hours for DDVP. Because of this extensive metabolism, urinary excretion of unchanged metrifonate and DDVP is insignificant.

DDVP covalently binds to AChE, thus causing irreversible inhibition. Its duration of action is prolonged, depending on the time required to synthesize new AChE. The half-life of RBC cholinesterase inhibition in the study of elderly patients with Alzheimer's described above[26] was 26 days. Some effect was still present 8 weeks after the last dose in one study.[29] The onset of plasma cholinesterase inhibition is almost instantaneous after metrifonate administration, whereas RBC AChE inhibition peaked at 60% 1 to 3 hours after oral administration of 7.5 mg/kg in elderly patients.[26] A study[30] in rats showed that metrifonate is rapidly though incompletely distributed to the brain and that peak brain AChE inhibition occurs 30 minutes after intramuscular administration. This study demonstrated a correlation between RBC and brain AChE inhibition and suggested that RBC AChE activity may be used as an estimate of CNS AChE activity. In humans, cerebrospinal fluid (CSF) cholinesterase activity was ascertained in 2 patients who had received a 5-mg/kg dose of metrifonate.[31] CSF AChE activity of 37% and 47.5% respectively corresponded to RBC AChE activity of 50% and 80%.

Clinical Pharmacology

In the setting of schistosomiasis, metrifonate is usually administered to children in 7.5- to 15-mg/kg doses at 2- to 4-week intervals for 3 doses and is generally well tolerated. The dosage required for an appropriate and constant level of AChE inhibition was not studied until this decade. In an open trial[31] of multiple doses of metrifonate in patients with Alzheimer's disease, the dose at which maximal cognitive improvement occurred was 5 mg/kg/week. This dose corresponded to a 45% reduction of RBC AChE activity. Sixty percent of patients reported adverse effects. The most common of these were nausea, vomiting, and diarrhea, accounting for 55% of all adverse events reported. Relative bradycardia and other electrocardiogram changes were reported as well, but none of these were considered clinically significant. Side effects were more common with increasing doses; none of the 20 patients in this 3-month study withdrew owing to adverse events.

A double-blind, placebo-controlled study[29] of 27 patients on 4 separate once-daily doses of metrifonate examined the pharmacokinetics and pharmacodynamics of the drug. A loading-dose plus maintenance-dose regimen was used in this study. The degree of RBC AChE inhibition increased with increasing dose, with 82% inhibition obtained in the high-dose group (loading dose of 4 mg/kg/day for 6 days followed by a maintenance dose of 1 mg/kg/day for 15 days) after 3 weeks of treatment. Over one half of the steady-state inhibition activity was still present 4 weeks after discontinuation of the drug. Side effects were gastrointestinal in nature.

It has been suggested that efficacy of AChE inhibitors may be limited by the degree of CNS cholinesterase inhibition that can be achieved. Because the degree of RBC cholinesterase inhibition that can be achieved with metrifonate is dose dependent,[29] a study was performed[32] in an attempt to establish the maximum dose of metrifonate that could be tolerated. Six of 8 patients with Alzheimer's disease given 2.5 mg/kg/day for 14 days followed by 4 mg/kg/day for 3 days and then 2 mg/kg/day developed side effects (including muscle cramps, weakness, and abdominal distress) severe enough to warrant discontinuation of the medication by day 28. In this group, RBC AChE inhibition was nearly complete, ranging from 88% to 94%. A comparable level of AChE inhibition was achieved in a second group on 2.5 mg/kg/day for 14 days followed by 1.5 mg/kg/day without undue side effects. It was concluded that 1.5 mg/kg/day (75–135 mg/day) is the maximum tolerated chronic dose.

Toxicity

Both metrifonate and DDVP were used as insecticides prior to their use as antihelminthics in humans, so there is extensive toxicologic information both in animals and in humans. In vitro mutagenesis studies of both metrifonate and DDVP have been contradictory.[33] Studies in mice, rats, hamsters, and guinea pigs showed a teratogenic effect of metrifonate at high doses.[34] Two studies employing high-dose metrifonate (15–30 mg/kg 2–3 times weekly for at least 700 days) in rats revealed increased forestomach malignancies, hepatic necrosis, and myeloproliferative changes, while other studies in mice have failed to show such carcinogenesis.[33] Tests with DDVP have shown evidence of carcinogenic activity in rats and mice, with elevated rates of forestomach tumors. No evidence of carcinogenicity in humans has been identified. The LD_{50} for metrifonate ranges from 400 to 800 mg/kg for laboratory animals,[33] with death due to respiratory failure accompanied by other signs of cholinergic toxicity.

Cases of aplastic anemia in humans have been associated with the agricultural use of DDVP and other organo-

phosphates as pesticides.[35] A case-control study[36] indicated a role for organophosphates in contributing to the risk of non-Hodgkin lymphoma. Doses used in Alzheimer's disease therapy are much lower than those resulting from agricultural exposure, and a 7-month follow-up study[37] of 18 Alzheimer's disease patients taking metrifonate failed to reveal any changes in erythrocyte, leukocyte, or platelet quantity or quality.

Acute poisoning with metrifonate, whether as the result of an industrial accident or purposeful suicide attempt, has been reported to cause a delayed distal motor neuropathy. Since these cases come mostly from the former Soviet Union, it is unclear whether this is an effect of metrifonate or of a contaminant peculiar to their preparation.[33] Delayed neurotoxicity is known to occur because of poisoning with other organophosphate compounds.

Despite years of data demonstrating the safety of metrifonate in the treatment of schistosomiasis, the effects of chronic administration of the drug in the elderly are not entirely known. The reason for this lack of knowledge is 2-fold: those generally treated for schistosomiasis belong to the younger population, and the course of treatment for this condition is short term. Several patients with Alzheimer's disease experienced muscle weakness during the phase 3 trials of metrifonate—it is unclear why this syndrome developed in a select minority of patients.

If overdosage is suspected in patients taking metrifonate, it should be managed as organophosphate poisoning. Specifically, atropine should be administered to counteract the presence of excessive acetylcholine present in synapses. In addition, pralidoxime, which reacts with phosphorous at the active site of AChE, thus regenerating its active form, should be given promptly.[31] AChE, which is irreversibly inhibited, will remain so until more is synthesized (days to weeks); therefore prolonged life support may be required.

Effects on Cognitive Function in Animals

Several studies have demonstrated the efficacy of metrifonate in enhancing cognition in both experimental animals and humans. The effects of metrifonate on learning and memory have been studied in normal young and old animals, as well as in animals with experimentally induced memory impairment.

In the passive avoidance paradigm in which a rat is shocked when entering the dark portion of a cage, the latency to enter (the step-through latency) after initial learning can be used as a measure of memory. Rats remembering the shock will remain for longer periods of time in the lighter portion of the cage. In normal rats, metrifonate at doses of 2.5 or 5 mg/kg increased the step-through latency. Rats with basal forebrain or medial septal lesions, as well as those pretreated with scopolamine, have a decreased step-through latency. Metrifonate at doses of 5 to 15 mg/kg reversed this change in basal-forebrain–lesioned and scopolamine-treated rats,[38] and another study[39] employing rats with medial septal lesions and scopolamine at slightly higher doses showed that metrifonate up to 100 mg/kg was effective in improving memory. In normal older rats, doses of 10 and 30 mg/kg were shown to facilitate retention in passive avoidance tests.[39]

The possibility that metrifonate has this effect in the passive avoidance paradigm due to decreased locomotion is unlikely, since metrifonate did not affect the step-through latency in the acquisition trial. Further evidence against this explanation is that metrifonate at doses of 12.5 mg/kg was associated with an increased number of responses in an active avoidance paradigm.[39] This experiment involved conditioning rats to move from one compartment to another in response to a light and tone paired with an electric shock.

In the Morris water escape task, the amount of time it takes a rat to swim to the previously learned location of an invisible underwater platform in a tank of water is a measure of memory. Metrifonate at daily doses of 10 to 30 mg/kg significantly shortened the time young, old, and basal-forebrain–lesioned animals took to find the platform. This was confirmed in scopolamine-treated and medial-septral–lesioned rats.[39]

Other studies suggest that metrifonate improves object recognition in old rats and that it can improve associative learning in a conditioned eye-blink paradigm in rabbits.[39] Animal studies provide support for the efficacy of metrifonate in enhancing memory function. Many clinical trials in patients with Alzheimer's disease have now been performed as well.

Use in Alzheimer's Disease

In the open-label trial discussed above,[31] the efficacy of different weekly doses of metrifonate was studied in 20 patients with Alzheimer's disease. Metrifonate at the 5-mg/kg/week dose was associated with a significant reduction (improvement) in scores on the ADAS-cog but not on a number of other scales (Hamilton Rating Scale for Depression, Brief Psychiatric Rating Scale, Clinical Global Impression of Change scale, Caregiver Burden Interview, an activities of daily living scale). When all patients receiving different doses were analyzed together, evidence of efficacy on the ADAS-cog was lacking. Whether the data revealed an inverted U-shaped dose-response curve (where efficacy is absent at doses either too high or too low) as the authors speculated or the study lacked the statistical power to show efficacy at different doses could not be ascertained. In a continuation portion of this study, improvement was maintained in 4 of 9 patients who had experienced initial benefit in cognition.

Subsequently, a double-blind, placebo-controlled study[40] of metrifonate in 50 patients with Alzheimer's disease was performed. This study lasted 3 months and involved a loading dose of 5 mg/kg/week for 2 weeks

followed by a single dose of 4.9 mg/kg followed by a weekly maintenance dose of 2.1 mg/kg/week. The goal of this dosing regimen was to achieve a 40% to 60% steady-state inhibition of RBC AChE, a level that an earlier study[31] suggested correlated with cognitive benefit. The ADAS-cog, ADAS noncognitive subscale, Mini-Mental State Examination (MMSE), Global Improvement Scale (GIS), and Activities of Daily Living Checklist were used as outcome measures and were recorded initially and at 1 and 3 months of treatment. Fifty-one patients were randomly assigned to treatment, but 1 dropped out secondary to uncooperative behavior, leaving 23 in the placebo group and 27 in the metrifonate group. At baseline, the placebo and treatment groups did not differ in ADAS-cog scores. They did differ subsequently in that the placebo group had a significant 1.1-point deterioration in scores, while the treated group had a nonsignificant improvement of 0.75 points. The 2 groups differed significantly in their scores on the GIS as well, with the treated group showing less worsening than the placebo group. Side effects were generally mild, and no patient withdrew during the 3-month, double-blind phase. Of the 50 patients eligible for enrollment in an extended open-phase trial, 46 did so. During follow-up, another 6 withdrew from the study. There were 2 incident cases of lymphoma thought by the authors to be unrelated to metrifonate because the patients had an advanced stage of the disease but had been taking the drug for only a short time.

To establish whether the difference between the metrifonate and placebo groups was due to an improvement in memory or reflected an effect on slowing the decline of Alzheimer's disease, these same authors[41] performed a 6-month double-blind, placebo-controlled study involving 47 patients. A significant difference between the 2 groups in ADAS-cog scores and MMSE scores was seen at 6 months, largely due to a smaller degree of deterioration in the metrifonate-treated group. This study suggested that metrifonate was effective in slowing cognitive decline in Alzheimer's disease and paved the way for larger studies.

Two large prospective randomized placebo-controlled, double-blind studies employing daily dosing have been performed. In the first study,[42] 480 patients were randomly assigned to receive placebo or 1 of 3 doses of metrifonate. Primary outcome measures at 3 months were the ADAS-cog and the CIBIC-Plus. Patients taking all metrifonate doses demonstrated a statistically significant difference from placebo in ADAS-cog scores, with the highest dose (2-mg/kg/day loading dose for 2 weeks, followed by 0.65 mg/kg/day for 10 weeks) showing an improvement of 2.38 points. The placebo group showed a mean decline of 0.56 points, so the difference between placebo and the highest dose of metrifonate was 2.94 points. A statistically significant difference in scores on the CIBIC-Plus was seen in the mid- and high-dose metrifonate subgroups. These results were maintained in both the intent-to-treat analysis and the valid-for-efficacy analysis. The most common effects reported were diarrhea (occurring in 19% of patients in the high-dose metrifonate group), abdominal pain, flatulence, nausea, and leg cramps. These effects tended to occur toward the end of the loading phase and were generally transient. Adverse events leading to withdrawal occurred in 4% of patients on placebo and in 7% of patients in the mid- and high-dose metrifonate groups. Three patients were withdrawn from the study because of asymptomatic bradycardia. There were no significant changes in hepatic enzymes and no reported cases of malignancy. RBC AChE inhibition was measured at 2, 8, and 12 weeks and found to be stable over time, with high-dose metrifonate causing inhibition of 68% to 72%.

A 6-month prospective, double-blind, placebo-controlled study[43] involving 408 patients was performed as well. In this study, patients were randomly assigned to receive either placebo or metrifonate at the high dose described in the previous study. Besides significant improvement on the ADAS-cog (2.86 difference from placebo) and the CIBIC-Plus, treatment differences were seen in scores on a secondary outcome, the Neuropsychiatric Inventory. The Neuropsychiatric Inventory[44] is a caregiver-based structured interview that surveys 10 different types of behavioral abnormalities (e.g., depression, agitation) and assigns scores to each of these areas and provides a total score. There were differences from placebo in a number of realms, with only the total score and the hallucinations subscore reaching statistical significance. Adverse events in this study were similar to those in other studies, and the discontinuation rate due to these was 4% in the placebo group and 12% in the metrifonate group. Again, no abnormalities of hepatic enzymes or incidences of malignancy were reported.

Pooled data from multiple studies at different centers reveal significant differences from placebo on other subscores on the Neuropsychiatric Inventory (depression, anxiety, and apathy) as well as improvement on a measure of ability to perform activities of daily living (Disabilities Assessment for Dementia).[45,46]

SUMMARY AND CONCLUSIONS

Metrifonate is a cholinergic drug that may become available to augment the current armamentarium of anti–Alzheimer's disease drugs. In common with existing anticholinesterase medications is its proven efficacy. It also shares with other anticholinesterase medications the limitations inherent in acting on a damaged system; that is, the efficacy is modest and cognitive function is not normalized. Cholinesterase inhibition by metrifonate is irreversible, which makes once-daily dosing possible and avoids rapid fluctuations in levels of AChE inhibition. Clinical trials indicate that metrifonate is useful in treating the

cognitive deficits in Alzheimer's disease. The beneficial effects on behavior and activities of daily living suggest that metrifonate may be valuable in managing these aspects of Alzheimer's disease.

Drug names: atropine (Donnatal and others), donepezil (Aricept), pralidoxime (Protopam), scopolamine (Isopto Hyoscine and others), succinylcholine (Anectine and others), tacrine (Cognex).

REFERENCES

1. National Foundation for Brain Research. The Cost of Disorders of the Brain. Washington, DC: National Foundation for Brain Research; 1992
2. Ernst RL, Hay JW. The US economic and social costs of Alzheimer's disease revisited. Am J Public Health 1994;84:1261–1264
3. Levy-Lahad E, Bird TD. Genetic factors in Alzheimer's disease: a review of recent advances. Ann Neurol 1996;40:829–840
4. Olson MI, Shaw C-M. Presenile dementia and Alzheimer's disease in mongolism. Brain 1969;92:147–156
5. Selkoe DJ. Physiological production of the beta-amyloid protein and the mechanism of Alzheimer's disease. Trends Neurosci 1993;16:403–409
6. Poorkaj P, Bird TD, Wijsman E, et al. Tau is a candidate gene for chromosome 17 frontotemporal dementia. Ann Neurol 1998;43:815–825
7. Cummings JL. Dementia: the failing brain. Lancet 1995;345:1481–1484
8. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 1993;43:1467–1472
9. Stewart W, Kawas C, Corrada M, et al. Risk of Alzheimer's disease and duration of NSAID use. Neurology 1997;48:626–632
10. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 1997;48:1517–1521
11. Cummings JL, Benson DF. Dementia: A Clinical Approach. 2nd ed. Stoneham, Mass: Butterworth-Heinemann; 1992
12. Cummings JL, Kaufer D. Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. Neurology 1996;47:876–883
13. Whitehouse PJ, Price DL, Clark AW, et al. Alzheimer's disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. Ann Neurol 1981;10:122–126
14. Drachman DA. Memory and cognitive function in man: does the cholinergic system have a specific role? Neurology 1977;27:783–790
15. Singh MM, Kay SR. Therapeutic antagonism between anti-cholinergic anti-parkinsonism agents and neuroleptics in schizophrenia: implications for a neuropharmacological model. Neuropsychobiology 1979;5:74–86
16. Sunderland T, Tariot PN, Cohen RM, et al. Anticholinergic sensitivity in patients with dementia of the Alzheimer type and age-matched controls. Arch Gen Psychiatry 1987;44:418–426
17. Geula C, Mesulam M. Special properties of cholinesterase in the cerebral cortex of Alzheimer's disease. Brain Res 1989;498:185–189
18. Giacobini E. The second generation of cholinesterase inhibitors: pharmacological aspects. In: Becker R, Giacobini E, eds. Cholinergic Basis for Alzheimer Therapy. Boston, Mass: Birkhauser; 1991:247–262
19. Knapp MJ, Knopman DS, Soloman PR, et al. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group [see comments]. JAMA 1994;271:985–991
20. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364
21. Knopman D, Schneider L, Davis K, et al. Long-term tacrine (Cognex) treatment: effects on nursing home placement and mortality, Tacrine Study Group [see comments]. Neurology 1996;47:166–177
22. Rogers SL, Friedhof LT, and the Donepezil Study Group. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicenter randomized double blind placebo controlled trial. Dementia 1996;7:293–303
23. Rogers SL, Farlow MR, Doody RS, et al, and the Donepezil Study Group. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 1998;50:136–145
24. Atack JR, Perry EK, Bonham JR, et al. Molecular forms of acetylcholinesterase and butyrylcholinesterase in the aged human central nervous system. J Neurochem 1986;47:263–277
25. Corey-Bloom J, Anand R, Veach T, for the ENA 713 B352 Study Group. Randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new cholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Geriatr Psychopharmacol 1998;1:55–65
26. Unni LK, Womack C, Hannant ME, et al. Pharmacokinetics and pharmacodynamics of metrifonate in humans. Methods Find Exp Clin Pharmacol 1994;16:285–289
27. Nordgren I, Bengtsson E, Holmstedt B, et al. Levels of metrifonate and dichlorvos in plasma and erythrocytes during treatment of schistosomiasis with Bilarcil. Acta Pharmacol Toxicol 1981;49(suppl 5):79–86
28. Lamb HM, Faulds D. Metrifonate. Drugs Aging 1997;11:490–496
29. Pettigrew LC, Bieber F, Lettieri J. Pharmacokinetics, pharmacodynamics, and safety of metrifonate in patients with Alzheimer's disease. J Clin Pharmacol 1998;38:236–245
30. Hallek M, Giacobini E. A comparison of the effects of two inhibitors on brain cholinesterase. Neuropharmacology 1987;26:521–530
31. Becker RE, Coller J, Elble R, et al. Effects of metrifonate, a long-acting cholinesterase inhibitor, in Alzheimer disease: report of an open trial. Drug Dev Res 1990;19:425–434
32. Cutler NR, Jhee SS, Cyrus P, et al. Safety and tolerability of metrifonate in patients with Alzheimer's disease: results of a maximum tolerated dose study. Life Sci 1998;62:1433–1441
33. Holmstedt B, Nordgren I, Sandoz M, et al. Metrifonate: summary of toxicological and pharmacological information available. Arch Toxicol 1978; 41:3–29
34. Holmstedt BR, Nordgren I. Toxicological limitations to cholinomimetic therapy. In: Becker R, Giacobini E, eds. Cholinergic Basis for Alzheimer Therapy. Boston, Mass: Birkhauser; 1991:155–161
35. Fleming LE, Timmeny W. Aplastic anemia and pesticides: an etiologic association? J Occup Med 1993;35:1106–1116
36. Hoar Zahm S, Blair A. Pesticides and non-Hodgkin's lymphoma. Cancer Res 1992;52(suppl):5485S–5488S
37. Moriearty PL, Womack CL, Dick BW. Stability of peripheral hematological parameters after chronic acetylcholinesterase inhibition in man. Am J Hematol 1991;37:280–282
38. Itoh A, Nitta A, Katono Y, et al. Effects of metrifonate on memory impairment and cholinergic dysfunction in rats. Eur J Pharmacol 1997;322: 11–19
39. Schmidt BH, Hinz VC, Van der Staay FJ. Cognition enhancement by metrifonate: evidence from animal studies. In: Iqbal K, Winblad B, Nishimura T, et al, eds. Alzheimer's Disease: Biology, Diagnosis and Therapeutics. New York, NY: John Wiley & Sons; 1997:784–786
40. Becker RE, Colliver JA, Markwell SJ, et al. Double-blind, placebo-controlled study of metrifonate, an acetylcholinesterase inhibitor, for Alzheimer's disease. Alzheimer Dis Assoc Disord 1996;10:124–131
41. Becker RE, Colliver JA, Markwell SJ, et al. Effects of metrifonate on cognitive decline in Alzheimer disease: a double-blind, placebo-controlled, 6-month study. Alzheimer Dis Assoc Disord 1998;12:54–57
42. Cummings JL, Cyrus PA, Bieber F, et al. Metrifonate treatment of the cognitive deficits of Alzheimer's disease. Neurology 1998; 50:1214–1221
43. Morris JC, Cyrus PA, Orazem J, et al. Metrifonate benefits cognitive, behavioral, and global function in patients with Alzheimer's disease. Neurology 1998;50:1222–1230
44. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314
45. Cummings JL, Cyrus PA, Ruzicka BB, et al. The efficacy of metrifonate in improving the behavioral disturbances of Alzheimer's disease patients. Neurology 1998;50(suppl 4):A251
46. Gelinas I, Gauthier S, Cyrus PA, et al. The efficacy of metrifonate in enhancing the ability of Alzheimer's disease patients to perform basic and instrumental activities of daily living. Neurology 1998;50(suppl 4): A90–A91