Evaluating Response to Metrifonate

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Metrifonate, administered orally to patients with probable Alzheimer's disease in a once-daily dose, readily enters the brain and inhibits brain acetylcholinesterase (AChE) activity in a dose-dependent fashion. Metrifonate is a prodrug, converted non-enzymatically to 2,2-dichlorovinyl dimethyl phosphate, a long-acting inhibitor of AChE that produces stable enzyme inhibition over time. In combination, these pharmacologic characteristics lead to a reduced side effect profile in comparison with several other cholinesterase inhibitors. Both preliminary and confirmatory pivotal studies have shown that significant cognitive improvement is achieved with this medication in comparison with placebo in patients with probable Alzheimer's disease. Moreover, these studies also have demonstrated that metrifonate benefits the global function—a measure comprising domains of cognition, function, activities of daily living, and behavior—of patients with Alzheimer's disease. The medication is generally well tolerated, and no significant laboratory abnormalities occur. Therefore, metrifonate is a useful treatment for the symptoms of Alzheimer's disease.

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At present, there are 2 Alzheimer's disease therapies on the market in the United States. By the end of 1999, there are likely to be as many as 4, and that number will probably increase in the years to come. In order to appreciate the significance of any new form of antidementia therapy, it is useful to briefly review the major conceptual approaches to antidementia treatment. These include improving cognition, treating behavioral disturbances, minimizing decline in activities of daily living, slowing the progression of the illness, delaying the onset of illness, preventing the illness, and repairing neuronal damage.

A large number of agents have been investigated over the years in pursuit of these conceptual treatment approaches.[1] These investigations can be categorized as efforts to enhance cerebral blood flow, improve neurotransmitter function, reduce effects of endogenous or exogenous toxins, modulate immune system function, modulate the activity of nerve growth factors, alter processing of abnormal proteins, and stabilize membranes.

Improvement of cognition is the current standard therapy for dementia. It is conceivable to imagine future therapies that reflect each of the treatment approaches individually (e.g., improving cognition without altering disease course) or in combination. The major strategy for cognition enhancement is the use of cholinergic agents to augment cholinergic neurotransmission. The basis for this has been outlined in the article by Peskind (this supplement).[2] In brief, the evidence in support of the "cholinergic hypothesis" of Alzheimer's disease is as follows: cholinergic neurotransmission is critical for cognition in humans and animals; the blocking of cholinergic neurotransmission impairs cognition in animals and humans; cholinergic markers are decreased in Alzheimer's disease in a fashion that correlates with neuropathology; and patients with probable Alzheimer's disease are particularly sensitive to cholinergic blockade.[1,3] These data collectively suggest that cholinergic replacement may improve cognition. Four strategies to augment cholinergic transmission are available, namely, administration of (1) precursors to acetylcholine (ACh) synthesis (e.g., lecithin or choline), an approach that is ineffective; (2) cholinesterase (ChE) inhibitors to block enzyme activity, an approach that has been proved to be effective and is the best studied and only one approved by the U.S. Food and Drug Administration (FDA); (3) partially selective muscarinic or nicotinic receptor agonists, a strategy that is still in development; and (4) indirect cholinergic receptor agonists, another strategy that is in development.

Cholinesterase inhibition may not be the only mechanism by which cholinergic stimulation with agents such as metrifonate may be beneficial in Alzheimer's disease. These agents may also protect against the neurotoxic effects of *N*-methyl-D-aspartate receptor stimulation and increase soluble amyloid precursor protein secretion.[4–8] Indeed, recent evidence suggests that 2,2-dichlorvinyl

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dimethyl phosphate (DDVP) increases the levels of soluble amyloid precursor protein.[9]

The first-generation ChE inhibitors include physostigmine and tacrine, reviewed by Peskind (this supplement).[2] Second-generation cholinesterase inhibitors include donepezil, available in the United States since early 1997, metrifonate, rivastigmine, galanthamine, and eptastigmine.

With this general introduction in mind, the remainder of the paper will focus on metrifonate, a second-generation ChE inhibitor that has been studied extensively for the treatment of Alzheimer's disease. Understanding its special place in the hierarchy of ChE inhibitors begins with a review of its pharmacokinetic and pharmacodynamic properties.

PHARMACOLOGIC PROPERTIES

Metrifonate is rapidly absorbed in the gastrointestinal (GI) tract and readily enters the brain.[10,11] It is not a ChE inhibitor itself, but rather, acts as a prodrug. It is converted nonenzymatically by dehydrochlorination to DDVP. DDVP binds at the catalytic or active site of acetylcholinesterase (AChE), yielding a stable drug-enzyme complex. The binding of DDVP to the enzyme complex is long-lasting, since recovery of enzyme activity parallels new enzyme synthesis.[12] However, this binding is pharmacologically reversible by the administration of pralidoxime, an agent that reactivates the enzyme.[13]

There are several implications of this pharmacologic profile. One consequence of the nature and pattern of metrifonate metabolism to DDVP is that the inhibition of AChE occurs in a gradual, time-dependent manner, a property believed to be related to the relatively high tolerability of the medication.[14] Another is that the inhibition of brain AChE occurs in a dose-dependent fashion, meaning that greater levels of inhibition can be achieved by using increasing doses of the medication. The resulting changes in ACh levels are stable and long-lasting, an outcome of AChE inhibition that has been hypothesized to be necessary for cholinergic neurons to accommodate the increased levels of ACh, and also to prevent inhibition of ACh release.[15] This characteristic contrasts with the relatively rapid fluctuation in ACh levels seen with other cholinergic agents such as tacrine or physostigmine.

This pharmacologic profile (Table 1) was deemed ideal for a clinically useful ChE inhibitor by Becker and Giacobini in 1988.[16] They underscored the importance of the achievement of high levels of AChE inhibition and showed that tacrine and physostigmine used at tolerable doses produced less than 30% AChE inhibition, a level of inhibition that was not associated with significant efficacy. However, higher doses of such agents achieved higher levels of enzyme inhibition and greater efficacy, but also produced more side effects.[10] The researchers suggested that the ideal agent should produce high levels of AChE inhibition in a gradual fashion with a low incidence of side effects; they proposed metrifonate as a candidate for development as an Alzheimer's disease therapeutic.

Table 1. Pharmacologic Profile of Metrifonate*

Once-daily dosing
Oral administration
Rapid absorption from gastrointestinal tract
Linear pharmacokinetics
Enters central nervous system readily
Increases extracellular acetylcholine concentration in brain
Cholinomimetic effects are gradual (leading to low risk of side effects); dose-dependent (high doses can be achieved safely); reflected in changes in red blood cell enzyme activity (i.e., easily measurable); stable; and long-lasting
Possible effects on secretion of amyloid precursor protein

*Based on data from reference 16.

PRECLINICAL EVIDENCE

A major limitation to the use of most ChE inhibitors is the high risk of cholinergic side effects. Becker et al.[15] argued that cholinergic side effects were related more to the rapid rate of AChE inhibition, rather than to drug levels or absolute levels of enzyme inhibition. Animal studies confirmed this by showing that high levels of enzyme inhibition (associated with high levels of ACh in the central nervous system) could be achieved with metrifonate administration, with relatively low rates of cholinergic side effects.[14,17] This contrasted with the observed effects of directly acting AChE inhibitors such as physostigmine and tacrine. At the same time, cognitive performance as assessed with a variety of animal models was shown to be improved after metrifonate administration.[11,14,18] Finally, extensive preclinical studies showed that prolonged metrifonate therapy was safe and associated with tolerability that increased over time.[19] The significance of these preclinical data is that a wide range of AChE inhibition can be achieved with a broad therapeutic window.

INITIAL CLINICAL EVIDENCE

Metrifonate has been used widely for the treatment of schistosomiasis in humans since 1960, achieving marked and long-lasting AChE inhibition with a relatively high degree of safety. It is important to note, however, that these patients were different from those with Alzheimer's disease. Moreover, metrifonate formulation also differed significantly from that administered to patients with Alzheimer's disease. This clinical experience is, nonetheless, reassuring.

On the basis of the pharmacologic profile of metrifonate, Becker et al.[15] undertook a series of investigations to define its clinical properties in patients with Alzheimer's disease. In 1990, they reported results from a complex pre-

liminary open-label study of 20 patients with probable Alzheimer's disease.[15] Patients received metrifonate in 1 of 4 weekly doses for variable periods of time, with intermittent drug-free intervals, followed by a 2-month washout, and then best-dose treatment for 1 to 3 months. The best dose was that associated with an individual's greatest improvement on the Alzheimer's Disease Assessment Scale, cognitive portion (ADAS-cog).[20] A change of 4 or more points was defined for the purposes of this study as a significant improvement. Fifteen patients met this criterion; the mean change in the ADAS-cog score for the best-dose phase was 7.7 points. The authors also examined the levels of red blood cell (RBC) AChE inhibition at the different metrifonate doses. Since the RBC AChE activity level mirrors that in the brain, the degree of RBC AChE inhibition can be used as a marker of metrifonate action in the brain. The authors found a range of RBC AChE inhibition levels across the different metrifonate doses; cognitive benefit occurred in the 30% to 80% inhibition range. They concluded that the AChE inhibition level was approximately 55%. The authors found no metrifonate effects on secondary outcome measures of activities of daily living, behavior, caregiver burden, or global impressions of change. There were, however, compelling anecdotes from families indicating that some individuals showed significant improvement in the ability to complete activities of daily living and in socialization. Additionally, adverse events were few, mild, and chiefly dose-related cholinergic effects (nausea, vomiting, diarrhea). These occurred in a minority of patients. Tolerability remained relatively high during prolonged therapy for up to 3 months. The authors concluded that metrifonate administered in this fashion produced the expected high-level, and sustained, inhibition of acetylcholinesterase. The investigated dose range suggested that cognitive benefit could occur with relatively few side effects. They concluded that further development of the drug was warranted.

Some researchers reported results from a double-blind, placebo-controlled study of metrifonate in patients with probable Alzheimer's disease.[21] Twenty-seven patients with probable Alzheimer's disease received single daily doses of placebo or oral loading doses of metrifonate for 6 days, followed by single oral maintenance doses for 15 days. (A daily dosing regimen, as opposed to the weekly dosing regimen employed by Becker and colleagues,[15] had been shown to reduce the peak-trough fluctuations in AChE inhibition levels, and consequently improve the safety profile [Bayer Corp., data on file].) Maintenance doses for the different groups, and total dose ranges, were as follows: 0.25 mg/kg/day (range, 7.5–13.5 mg/day), 0.4 mg/kg/day (range, 12.5–22.5 mg/day), 0.65 mg/kg/day (range, 30.0–60.0 mg/day), and 1.0 mg/kg/day (range, 50.0–90.0 mg/day). There were no discontinuations in this dose-ranging study. A linear relationship was found between dose and level of RBC AChE inhibition. Mild, transient, and dose-related side effects, chiefly GI symptoms, were observed somewhat more frequently with metrifonate than placebo. There was also a slight and clinically insignificant lowering of pulse rate and blood pressure with the highest dose. Unspecified improvement in cognitive function was noted. This preliminary study also supported further development of the compound.

CONFIRMATORY CLINICAL TRIALS

In 1996, Becker et al.[10] reported the first detailed results of a double-blind, placebo-controlled trial of metrifonate in 50 patients with probable Alzheimer's disease. Doses were selected on the basis of their pilot work and that of others showing that such doses would produce stable, high-level, steady-state AChE inhibition that was likely to be associated with cognitive improvement.[15,21] There was a 3-week, single-blind, placebo lead-in followed by double-blind therapy for 3 months, followed by a 1-month washout, and open treatment for up to 18 months.

The mean reduction in AChE activity was found to be 52%. At the end of the double-blind treatment period, the mean drug-placebo difference in ADAS-cog scores was 2.6 points ($p < .01$) in favor of metrifonate. This was associated with improvement on a global function scale ($p < .02$). A difference of approximately 1 point was found between drug and placebo on the Mini-Mental State Examination (MMSE) score, which was not statistically significant. Adverse events associated with metrifonate therapy were remarkably few in the double-blind phase. In fact, placebo patients demonstrated significantly more GI events (11 events, including nausea, vomiting, and diarrhea) than did patients given metrifonate therapy (2 individuals experienced upset stomach). No withdrawals or dose changes due to adverse experiences occurred. Forty-six patients continued with open therapy for up to 18 months. These patients, too, rarely experienced side effects. In addition, the authors estimated an annual rate of decline in MMSE scores with metrifonate therapy of 1.68 points per year, less than the expected range of 2 to 4.5 points per year reported in the literature.[15] This study, although relatively small, demonstrated fairly convincingly that short-term therapy with metrifonate was well tolerated and associated with improvement in cognitive function, and raised the possibility of long-term slowing of disease progression.

Pivotal trials were conducted according to recently adopted criteria (reviewed in detail elsewhere).[3] These regulatory criteria emphasize the improvement in cognition as a critical outcome, along with improvement in nonspecific global terms in the opinion of an experienced, blinded clinician. The current gold standard for assessing change in cognition is the ADAS-cog; for the global impression of change, it is any one of a variety of semistructured interviews. These regulatory guidelines have shaped

the design of recent clinical trials and our interpretation of them. As a consequence, the studies do not clarify other effects that may occur with the use of "cognition enhancers." As evidence accrues that other outcomes may be beneficial—for instance, slowing disease progression—it is likely that regulatory guidelines will evolve. At present, however, the current standard of therapeutic efficiency is enhancement of cognition.

The pivotal metrifonate studies were completed only recently; to date, there are few published data. What follows is a preview of results from a 12- and a 26-week trial, based on partial review of data on file with the manufacturer and abstracts presented during 1997.

The first pivotal metrifonate trial[22] was conducted in 480 outpatients with Alzheimer's disease who received daily oral placebo for 12 weeks or daily oral loading doses of metrifonate for 2 weeks, followed by 1 of 3 daily oral maintenance doses of metrifonate—10 to 20 mg, 15 to 25 mg, or 30 to 60 mg, all based on weight—for 10 weeks. These different doses resulted in an inhibition of RBC AChE activity of 34%, 52%, and 75%, respectively. The overall completion rate was high (89%), with a discontinuation rate of 4% in the placebo group (all due to adverse experiences), and 7% in the group receiving 30 to 60 mg metrifonate (of which 6% were due to adverse experiences). There were no discontinuations in the other metrifonate treatment arms. Tolerability was reported as excellent, with mild, transient, GI symptoms occurring in a small percentage of patients. Both the 15- to 25-mg and 30- to 60-mg doses were associated with significant drug-placebo differences in scores on the ADAS-cog.[20] Using an intent-to-treat analysis with last-observation-carried-forward data from week 12, the mean difference in scores between drug and placebo at the highest dose was 2.94 ($p < .001$). This was associated with a mean difference of 0.35 points on a Clinician's Interview-Based Impression of Change that also permitted interview of family members or caregivers (CIBIC-Plus, $p \leq .006$). The investigators also retrospectively examined the effects of a variety of clinical and demographic variables on outcome. They found minimal to no effects of these variables, leading to the conclusion that the drug appears to be suitable for the treatment of a diverse group of patients with Alzheimer's disease.

The second pivotal metrifonate trial[23] was conducted in 408 outpatients with probable Alzheimer's disease who received either daily oral placebo for 26 weeks or a loading dose of metrifonate for 2 weeks followed by metrifonate 30 to 60 mg for 24 weeks. Discontinuation rates for this study were slightly higher than the above study (placebo = 12%; metrifonate = 21%), consistent with its longer duration (about twice the length of the earlier study). Among the discontinuations, 4% of the placebo patients terminated the study prematurely owing to adverse experiences versus 12% of the metrifonate-treated patients, who discontinued for the same reason. Side effect data were generally consistent with prior trials, with respective rates for placebo and drug of 8% and 19% for diarrhea, 1% and 10% for cramps, and 1% and 6% for rhinitis. There were no other side effects that occurred substantially more often with drug than placebo. There was a clinically insignificant decrease in mean pulse rate with drug versus placebo. Using week 26 data with last observation carried forward, the intent-to-treat analysis showed a drug-placebo difference in the ADAS-cog score of 2.74 points ($p < .001$) and a difference in the CIBIC-Plus score of 0.27 ($p < .004$). Thus, metrifonate was shown to be safe, well-tolerated, and efficacious in the symptomatic treatment of Alzheimer's disease.

SUMMARY

Metrifonate has several characteristics that render it unique among the AChE inhibitors currently available for the symptomatic treatment of Alzheimer's disease. It has a gradual onset of action and achieves a stable and long-lasting AChE inhibition. Its use is associated with comparatively good tolerability in both animals and humans. Preliminary clinical trials were encouraging, demonstrating metrifonate efficacy with respect to both cognition (ADAS-cog) and global function (CIBIC-Plus), the latter reflecting the domains of cognition, function, activities of daily living, and behavior. Side effects were rated as mild and were generally transient. Time-limited loading was used, although dose titration is not necessary. Laboratory surveillance proved to be unnecessary, in contrast to the monitoring required for tacrine.

Subsequent review of secondary outcome measures from these trials will be important. While not significant from a current regulatory standpoint, data regarding changes in behavior and capacity to perform activities of daily living will certainly be important clinically. Clinicians using these agents are faced with the need to go beyond a change in performance on cognitive test batteries or global impressions and should focus on how the individual has responded to therapy across all the domains of potential interest.

As an example of 1 approach to clinical practice, the goal would be to delineate target symptoms prior to the initiation of therapy, addressing the key domains of relevance: cognition (e.g., has trouble finding words, forgets phone messages), neurologic function (e.g., incontinence, apraxia), activities of daily living (e.g., needs assistance with dressing, cannot do household chores), and behavior (e.g., agitation, delusions, apathy, depressive symptoms). After initiation of therapy, target symptoms in each of these domains, along with side effects, would be monitored. The onset of new medical problems would be addressed vigorously. Liver-function testing would be required with tacrine use. Scales can also be useful. Using

this approach, therapy could be considered successful if significant clinical benefit occurred in 1 or more of the domains of relevance (preferably in all 4 domains), with satisfactory tolerability. Further, if the patient's condition stabilized over a period of 3 to 6 months, this also would be considered a favorable therapeutic outcome. A decline in clinical condition that is viewed as being slower than expected for the patient's particular course would require a subjective judgment as to whether this represented a therapeutic success. However, no impact on course or symptoms whatsoever would clearly be a therapeutic failure.

This general therapeutic approach will be refined in the future as secondary clinical trial data become available regarding the impact of cholinomimetic agents on the 4 symptom domains. Likewise, postmarketing experience will be a major determinant of clinical practice with respect to cholinomimetic agents, by virtue of gradual clarification of the following: relative efficacy, tolerability, and safety of different agents; the importance of pharmacokinetic and pharmacodynamic profiles with attendant effects on drug-drug interactions; need for dose titration; and requirement for laboratory surveillance. Given metrifonate's pharmacologic profile, it would seem likely that we will have a new safe and effective therapeutic option to offer patients in the near future.

Drug names: pralidoxime (Protopam), tacrine (Cognex).

REFERENCES

1. Tariot PN. Neurobiology and treatment of dementia. In: Salzman C, ed. Clinical Geriatric Psychopharmacology. 2nd ed. Baltimore, Md: Williams & Wilkins; 1992:277–299
2. Peskind ER. Pharmacologic approaches to cognitive deficits in Alzheimer's disease. J Clin Psychiatry 1998;59(suppl 9):22–27
3. Schneider L, Tariot PN, Small GW. Update on treatment for Alzheimer's disease and other dementia. Psychiatric Clinics of North America: Annual of Drug Therapy 1997;4:135–166
4. Koh J-Y, Palmer E, Cotman CW. Activation of the metabotropic glutamate receptor attenuates *N*-methyl-D-aspartate neurotoxicity in cortical cultures. Proc Natl Acad Sci U S A 1991;88:9431–9435
5. Nitsch RM, Slack BE, Wurtman RJ, et al. Release of Alzheimer amyloid precursor derivatives stimulated by activation of muscarinic acetylcholine receptors. Science 1992;258:304–307
6. Buxbaum JD, Oishi M, Chen HI, et al. Cholinergic agonists and interleukin 1 regulate processing and secretion of the Alzheimer B/A4 amyloid protein precursor. Proc Natl Acad Sci U S A 1992;89:10075–10078
7. Eckols K, Bymaster FP, Mitch CH, et al. The muscarinic M1 agonist xanomeline increases soluble amyloid precursor protein release from Chinese hamster ovary M1 cells. Life Sci 1995;57:1183–1190
8. Wolf BA, Wertkin AM, Jolly YC, et al. Muscarinic regulation of Alzheimer's disease amyloid precursor protein secretion and amyloid beta-protein production in human neuronal NT2N cells. J Biol Chem 1995;270: 4916–4922
9. Mori F, Lai CC, Fusi F, et al. Cholinesterase inhibitors increase secretion of APPs in rat brain cortex. Neuroreport 1995;6:633–636
10. Becker RE, Colliver JA, Markwell SJ, et al. Double-blind, placebo-controlled study of metrifonate, an acetylcholinesterase inhibitor, for Alzheimer disease. Alzheimer Dis Assoc Disord 1996;10:124–131
11. Schmidt BH, Hinz VC, van der Staay F-J. 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. In press
12. Taylor P. Anticholinesterase agents. In: Gilman AG, Rall TW, Nies AS, et al, eds. The Pharmacological Basis of Therapeutics. 8th ed. New York, NY: Pergamon Press; 1990:100–119
13. Hinz V, Grewig S, Schmidt BH. Metrifonate and dichlorvos: effects of a single oral administration on cholinesterase activity in rat brain and blood. Neurochem Res 1996;21:339–345
14. Schmidt BH, Hinz VC, Blokland A, et al. Preclinical pharmacology of metrifonate: a promise for Alzheimer therapy. In: Becker RE, Giacobini E, Roberts P, eds. Alzheimer Disease: From Molecular Biology to Therapy. Boston, Mass: Birkhauser; 1996:217–221
15. Becker RE, Colliver J, Eible 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
16. Becker RE, Giacobini E. Mechanisms of cholinesterase inhibition in senile dementia of the Alzheimer type: clinical, pharmacological, and therapeutic aspects. Drug Dev Res 1988;12:163
17. Hallak M, Giacobini E. A comparison of the effects of two inhibitors on brain cholinesterase. Neuropharmacology 1987;26:521–530
18. 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
19. Holmstedt B, Nordgren I, Sandoz M, et al. Metrifonate: summary of toxicological and pharmacological information available. Arch Toxicol 1978; 41:3–29
20. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364
21. Pettigrew LC, Bieber F, Lettieri J, et al. Pharmacokinetics, pharmacodynamics, and safety of metrifonate in patients with Alzheimer's disease. J Clin Psychopharmacol 1998;38:236–245
22. Cummings JL, Cyrus P, Bieber F, et al, and the Metrifonate Study Group.Metrifonate treatment of the cognitive deficits of Alzheimer's disease. Neurology 1998;50:1214–1221
23. 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