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The Selective Muscarinic Agonist Xanomeline Improves Both the Cognitive Deficits and Behavioral Symptoms of Alzheimer Disease

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Summary: The therapeutic effects of selective cholinergic replacement using oral xanomeline, an m1/m4 receptor agonist, were assessed in a multicenter study of 343 patients with Alzheimer disease (AD). Patients were randomized to parallel treatment arms (placebo, 25, 50, and 75 mg t.i.d. xanomeline) and followed through 6 months of double-blind therapy and 1 month of single-blind placebo washout. Completer analysis, using the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), revealed a significant treatment effect (75 mg t.i.d. vs. placebo; $p = 0.045$). Similar assessment of global status, using the Clinician's Interview-Based Impression of Change, was also significant (75 mg t.i.d. vs. placebo; $p = 0.022$). Treatment Emergent Signs and Symptoms analysis of the Alzheimer's Disease Symptomatology Scale, revealed highly significant ($p \leq 0.002$) dose-dependent reductions in vocal outbursts, suspiciousness, delusions, agitation, and hallucinations. On end-point analysis, the Nurses' Observational Scale for Geriatric Patients also showed a significant dose–response relationship ($p = 0.018$). The improvement in ADAS-Cog provides the first clinical evidence of involvement of the m1 muscarinic receptor in cognition. Furthermore, the favorable effects of xanomeline on disturbing behaviors suggest a novel approach for treatment of the noncognitive symptoms of AD. Although adverse effects (mainly gastrointestinal) associated with the oral formulation appear to limit its use, a large-scale study investigating the safety and efficacy of transdermal xanomeline is under way. **Key Words:** Alzheimer disease—Xanomeline—Muscarinic—Cognition—Behavior.

Alzheimer Disease (AD) represents a major public health problem; the disease affects approximately 10% of the adult population of the United States over the age of 65 years and 30–40% of the population over the age of 85 years (Katzman, 1976; Evans et al., 1989). AD is associated with the relatively selective degeneration of cholinergic neurons of the nucleus basalis of Meynert (Coyle et al., 1983; Giacobini, 1990), which project to regions of the forebrain (the cerebral cortex and hippocampus) critical to learning and memory (Bartus et al., 1982). The primary cognitive symptoms of AD include deficits of memory and abstract thinking, and pharmacotherapy currently involves attempts to improve cognitive function through enhancement of cholinergic neurotransmission. To date, inhibitors of acetylcholinesterase, the major catabolic enzyme for acetylcholine, have shown some efficacy in improving cognition in AD patients (Davis et al., 1992; Farlow et al., 1992; Knapp et al., 1994), but the clinical relevance of this effect is unclear (Growdon, 1992).

In addition to deficits in cognitive function, patients with AD manifest a host of behavioral signs and symp-

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toms, including psychosis and aggression/impulsivity (Reisberg et al., 1987; Teri et al., 1989; Wragg and Jeste, 1989; Gilley et al., 1991; Rosen and Zubenko, 1991; Patterson and Bolger, 1994). The clinical importance of these symptoms is increasingly recognized as a source of stress for the caregiver (Reisberg et al., 1986, 1987; Teri et al., 1992; Patterson and Bolger, 1994) and as a major precipitant to institutionalization of AD patients (Ferris et al., 1985; Reisberg et al., 1987). Amelioration of psychotic symptoms may be of consequence in deferring institutionalization and therefore in reducing the substantial economic burden of AD. Nevertheless, the behavioral symptoms of AD have largely been ignored in experimental therapy and drug development (Raskind and Peskind, 1994).

Within the cholinergic system, five muscarinic receptor subtypes (m1–m5) have been characterized on molecular and pharmacologic bases (Bonner et al., 1987). Of these, two have emerged as targets for replacement therapy treating the symptoms of AD. The m1 muscarinic receptor in the cerebral cortex and hippocampus is preserved or increased in AD (Giacobini, 1990; Svensson et al., 1992), despite the loss of presynaptic cholinergic input from the nucleus basalis of Meynert (Giacobini, 1990). The m4 receptor has been identified in the cortex, striatum, hippocampus, and substantia nigra, (Bernard et al., 1992; Yasuda et al., 1993), and immunoprecipitated m4 receptor protein is elevated in the frontal, temporal, and parietal cortices in AD (Levey et al., 1991; Flynn et al., 1995).

It has also been postulated that muscarinic agonists may also be effective in attenuation of the disease process. The amyloid-β (Aβ) peptide, a major constituent of senile plaques characteristic of the neuropathology of AD (Selkoe, 1994), is processed by proteolysis of a larger transmembrane amyloid precursor protein (APP) and, in its aggregated form, is highly toxic to neurons (Lorenzo and Yankner, 1994). Recent studies have shown that muscarinic receptor agonists can increase the synthesis of the secreted (nonamyloidogenic) forms of APP, perhaps reducing the tissue levels of the Aβ peptide itself (Nitsch et al., 1992; DeLapp et al., 1995).

Xanomeline is a m1/m4-selective muscarinic receptor agonist now under development for AD. It has high affinity for m1 and m4 receptors in transfected cells but substantially less or no affinity for other members of the muscarinic cholinergic receptor family (Bymaster et al., 1994). Initial clinical studies in healthy male subjects have shown that an oral formulation is rapidly absorbed and extensively biotransformed. The elimination half-life of the oral formulation is approximately 3.6 h. Recent studies on the tissue distribution of ^{11}C-labeled xanomeline, measured with positron emission tomography in healthy male volunteers, have shown that 6% of the radioactivity is in the brain 5 min after administration, and the resulting concentrations in the cerebral cortex and corpus striatum are two- to threefold higher than those found in the cerebellum (Farde et al., 1993). In a small inpatient study, patients with AD tolerated doses of 100 mg t.i.d. with food, although dose-dependent side effects, including abdominal pain, diarrhea, dyspepsia, nausea, vomiting, and sweating, were observed (Bodick et al., 1994; Cutler et al., 1994).

The results of a double-blind, placebo-controlled study of the oral formulation of xanomeline in patients with mild to moderate AD are presented. The complete report of this study has been published previously (Bodick et al., 1997).

METHODS

Study Design

Outpatients of both sexes, who were at least 60 years old and had a reliable caregiver, were selected according to the following entry criteria: a diagnosis of probable mild to moderate AD as defined by National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) guidelines (McKhann et al., 1984), a score of 14–24 on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), and a score of 4 or lower on the modified Hachinski Ischemia Scale. In addition, all patients had undergone CT or MRI scans within the previous 12 months that were interpreted as compatible with AD. Informed consent was obtained from all patients, and an Institutional Review Board Approved Caregiver Agreement was signed by the caregiver. The trial was conducted at 17 sites in the United States and Canada.

After baseline evaluation, 343 patients who satisfied entry criteria proceeded through a 2-week lead-in period without treatment, followed by random assignment to one of four treatment arms: placebo, 25, 50, and 75 mg t.i.d. xanomeline tartrate. Approximately 85 patients were enrolled in each of the four arms. Clinic visits were scheduled at the end of weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28. Home visitation for adverse-event monitoring occurred twice weekly for the first 3 weeks, once weekly for weeks 3 through 12, and every other week thereafter through to week 28. Treatment was double-blind, lasted up to 6 months (visits 5 through 33), and was followed by a 1-month single-blind, placebo washout (visits 34 through 36).

Cognitive and Behavioral Assessment

The cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) (Mohs and Cohen, 1988), was used to assess severity of cognitive deficits (particularly memory, language, and motor skills). The ADAS-Cog was performed at weeks 0, 4, 8, 12, 24, 28, and at early termination. The Clinician's Interview-Based Impression of Change (CIBIC+) is an evaluation of the clinical status of the patient relative to baseline. It was assessed in semistructured interviews with the patient and caregiver (Knapp et al., 1994) conducted at baseline and at weeks 4, 8, 12, 24, and 28, or at early termination. The baseline CIBIC+ interview was videotaped and reviewed immediately before each subsequent CIBIC+ interview. The CIBIC+ interviewer was blinded to all other data in the study. The Alzheimer's Disease Symptomatology Scale (ADSS), which was developed for this study, is a caregiver assessment of 20 behavioral symptoms that are commonly found in AD patients: vocal outbursts, suspiciousness, delusions, agitation, hallucinations, wandering, fearfulness, compulsiveness, tearfulness, mood swings, violent behavior, threatening behavior, unsafe use of appliances, dangerous driving, careless smoking, sleep altered/increased/decreased, and appetite increased/decreased. Each item is scored from 0 (absent) to 3 (severe). This test was administered at each clinic and home visit (1 through 36). The Nurses' Observational Scale for Geriatric Patients, NOSGER (Spiegel et al., 1991) is a 30-item instrument that incorporates assessment of both behavior and activities of daily living. NOSGER comprises six different domains including memory, instrumental activities of daily living, self-care, mood, social behavior, and disturbing behavior. The NOSGER total score ranges from 30 to 150; lower scores are indicative of less severe AD. NOSGER data included in the analyses were collected at baseline and weeks 4, 8, and 12, and at early termination.

Statistical Analysis

Three types of analyses were performed: (a) end-point analyses, also referred to as last visit carried forward, used the last collected measurement during double-blind study drug administration; (b) completer analyses used only patients who completed the 6-month trial; and (c) Treatment-Emergent Signs and Symptoms (TESS) analysis of the Alzheimer's Disease Symptomatology Scale (ADSS) compared treatment groups with respect to the number and percentage of patients who experienced a given symptom during the double-blind part of the study (visits 5 through 33) at a severity worse than during the baseline visits (1 through 4).

Baseline Patient Characteristics

Despite randomization, MMSE scores were imbalanced across the treatment arms at baseline. The average score for the low-dose xanomeline (25 mg t.i.d.) group was 18.6, and the other three groups ranged from 19.6 to 20.0 ($p = 0.021$). No other treatment group imbalances were noted. Of the 343 patients randomized, 57% were female, 92% were caucasian, mean age was 75 years (60–90 years), average weight was 68 kg, and 54% had up to 12 years of formal education.

RESULTS

Cognition

In patients who completed the study, analysis of ADAS-Cog suggests a significant benefit to cognition (dose–response $p = 0.033$ and 75 mg t.i.d. vs. placebo $p = 0.045$). Simple reaction time, an objective measure of arousal, was significantly faster for the 75 mg t.i.d. treatment arm relative to placebo ($p = 0.044$). Maximal response for this parameter was achieved after 8 weeks of treatment and occurred simultaneously with the maximal cognitive response (measured by the ADAS-Cog). However, an end-point analysis of cognitive improvement using the ADAS-Cog did not show a significant treatment difference ($p = 0.32$). Of the 78 patients in the high-dose (75 mg t.i.d.) group, 28 discontinued due to side effects at 4 weeks or less. Examination of the time–response relationship suggests that xanomeline exerts a maximal effect on cognition only after 8 weeks of therapy. To minimize the effects of early discontinuation, a second ADAS-Cog end-point analysis was performed in which only patients who completed at least 1 month of therapy (visit 13) were considered. In this end-point analysis, the dose–response relationship approached significance ($p = 0.073$). A completer analysis of the ADAS-Cog was also performed in a subset of patients with disease severity defined as baseline ADAS-Cog greater than or equal to 21. In this subanalysis, the therapeutic effect was 5.2 ADAS-Cog units (the difference between the 75 mg t.i.d. and placebo arms in the mean arithmetic change from baseline) and, using adjusted end-point means, the difference was 5.7 units.

Global Assessment

Completer analysis of the clinician's/caregiver's global assessment measured by the CIBIC+ revealed a significant ($p = 0.005$) dose response. Pairwise comparisons of the 75 mg t.i.d. ($p = 0.022$) and 50 mg t.i.d. ($p = 0.036$) treatment arms to placebo were also indicative of a favorable drug effect. End-point analysis of the

CIBIC+ revealed a significant ($p = 0.014$) dose response. Similarly, pairwise end-point comparisons of the 75 mg t.i.d. ($p = 0.057$) and 50 mg t.i.d. ($p = 0.017$) treatment arms to placebo were suggestive of a favorable drug effect.

Behavior

TESS analysis of the ADSS revealed a significant dose-dependent reduction in vocal outbursts, suspiciousness, delusions, agitation, hallucinations, wandering, fearfulness, compulsiveness, tearfulness, mood swings, and threatening behavior. Of these, the most pronounced effects ($p \leq 0.002$) were evident for vocal outbursts, suspiciousness, delusions, agitation, and hallucinations. Drug effects on careless smoking, sleep, or appetite were not apparent.

With increasing xanomeline dose, delusions ($p = 0.001$), suspiciousness ($p = 0.003$), wandering ($p < 0.001$), vocal outbursts ($p = 0.002$), hallucinations ($p = 0.012$), dangerous driving ($p = 0.050$), fearfulness ($p = 0.004$), agitation ($p = 0.019$), and threatening behavior ($p = 0.022$), when they were absent at baseline, were prevented during the 6-month double-blind phase of the study. With increasing xanomeline dose, hallucinations ($p = 0.008$), unsafe use of appliances ($p = 0.015$), vocal outbursts ($p = 0.017$), compulsiveness ($p = 0.005$), delusions ($p = 0.021$), and suspiciousness ($p = 0.028$), which were present at baseline, remitted during the double-blind phase of the study.

A dose–response relationship was observed at end point ($p = 0.018$) in the assessment of effects on behavior and functionality using the NOSGER-Total. Significant improvements were also observed in the high-dose (75 mg t.i.d.) group relative to placebo ($p = 0.032$). Pairwise analyses (75 mg t.i.d. vs. placebo) of NOSGER subcomponents showed significant beneficial effects for NOSGER-Social Behavior ($p = 0.039$), NOSGER-Disturbing Behavior ($p = 0.051$), and NOSGER-Instrumental Activities-of-Daily-Living ($p = 0.026$). NOSGER scales that did not show a statistically significant treatment effect were NOSGER-Memory, NOSGER-Self-care, and NOSGER-Mood.

Adverse Events and Safety

Approximately 59% of patients who were in the high-dose (75 mg t.i.d.) xanomeline arm discontinued treatment during the double-blind phase of the study. In comparison, 35% in the placebo arm discontinued, as did 19% of patients in the 25 mg t.i.d. and 48% in the 50 mg t.i.d. dosage arms. In the high-dose arm, 88% of discontinuations were attributable to adverse events; the rest were attributable to patient, physician, or sponsor decision.

In the course of this study of the oral formulation, dose-dependent adverse events were primarily gastrointestinal in nature, and included vomiting, nausea, dyspepsia, hypersalivation, fecal incontinence, nausea with vomiting, and dysphagia. Syncope, defined as a transient loss of consciousness and muscle tone, occurred in 12.6% of patients in the high-dose (75 mg t.i.d.) group, 13.3% of those in the intermediate-dose (50 mg t.i.d.) group, 3.5% of those in the low-dose (25 mg t.i.d.) group, and 4.6% of those in the placebo group. After the reported syncopal episodes, patients recovered rapidly, without sequelae or the need for extraordinary medical attention. A recently completed study, undertaken to elucidate the mechanisms underlying these syncopal episodes, suggests that these episodes are not attributable to arrhythmogenic cardiac events. Rather, they appear to result from a decrease in blood pressure, possibly preload reduction, coupled with a blunting of the baroreceptor reflex.

DISCUSSION

The data demonstrate that the highest dose of xanomeline (75 mg t.i.d.) is associated with improvement in cognitive performance and clinical global impression in patients completing the study. Unexpectedly, we observed a substantial dose-related reduction in a number of disturbing behaviors, including vocal outbursts, suspiciousness, delusions, agitation, hallucinations, wandering, fearfulness, compulsiveness, tearfulness, mood swings, violent behavior, and threatening behavior. Finally, activities of daily living, as measured by the NOSGER, improved relative to placebo in the high-dose (75 mg t.i.d.) arm. Adverse events, particularly gastrointestinal side effects, associated with the oral formulation are prominent and, for that reason, development of a transdermal formulation has been undertaken.

Effects on Cognition and Behavior

The overall effects of xanomeline on cognition in this study can be compared, at least approximately, to those achieved with the cholinesterase inhibitor tacrine (Farlow et al., 1992). To compare meaningfully the magnitude of response, a completer analysis of the ADAS-Cog was performed using the subset of patients with disease severity (defined as baseline ADAS-Cog ≥ 21) approximating to that of the patient population in the tacrine study. In this analysis, the therapeutic effect was 5.2 ADAS-Cog units (the difference between the 75 mg t.i.d.

and placebo arms in the mean arithmetic change from baseline). Using adjusted end-point means, the difference was 5.7 units. By comparison, in the tacrine study of Farlow et al. (1992), the difference in arithmetic means between the high-dose tacrine arm and the placebo arm was 4.1 units, and the difference in adjusted means was 5.3 units. Therefore, the magnitude of the cognitive effects achieved in the xanomeline and tacrine studies is approximately equivalent. Moreover, it is interesting to note that the set of cognitive subcomponents affected by xanomeline may differ from that affected by tacrine. A direct comparison in the same study will be required to compare and contrast adequately the effects of a cholinesterase inhibitor, such as tacrine, and a direct-acting cholinomimetic, such as xanomeline, on AD symptomatology. It is also conceivable that these mechanisms of action are complementary and that a cholinesterase inhibitor and a muscarinic agonist administered concomitantly would be better than either alone.

Although there are differences in the subtleties of cognitive improvement reported for cholinesterase inhibitors and observed for xanomeline in the present study, effects on cognition for the group of AD patients are, on the whole, modest. In the present study it is somewhat surprising that a modest effect on cognition is accompanied by a robust effect on the clinical global impression (CIBIC+). Conceivably, these global measures reflect an amalgam of both the cognitive and behavioral improvement observed after treatment with xanomeline. Using the 20-item ADSS, we observed a dose-dependent reduction, over the course of the 6-month trial, in the incidence of various behavioral symptoms, including vocal outbursts, suspiciousness, delusions, agitation, hallucinations, wandering, fearfulness, compulsiveness, tearfulness, mood swings, violent behavior, and threatening behavior. These behavioral symptoms appear to be both prevented and reduced by xanomeline treatment. To put this finding in perspective, Rosen and Zubenko (1991), in a longitudinal study of AD symptomatology, have reported that spontaneous remission of psychotic symptoms occurred in only 2 of 15 AD patients before death. In the present study, 1 of 17 patients in the placebo group experienced a spontaneous remission of hallucinations, and 9 of 17 experienced remission in the high-dose xanomeline arm.

Although the ADSS measures a wide range of social and disturbing behaviors characteristic of AD, it has not been validated in previous large-scale studies. [The Neuropsychiatric Inventory (Cummings et al., 1994) was introduced and validated after the initiation of this study.] A second instrument employed in the study, NOSGER, has been designed to measure behaviors and function in the elderly (not specifically in AD), and has demonstrated high inter-rater and test–retest reliability, as well as high correlation with a variety of established instruments (Spiegel et al., 1991). Statistical significance in favor of xanomeline for NOSGER-Total, NOSGER-Social Behavior, and NOSGER-Disturbing Behavior scores was achieved for the 6-month end-point dose–response analysis.

It is unlikely that the rather robust improvement in disturbing behaviors observed after treatment with xanomeline is attributable to a sedative effect of the drug, because sedation per se was not reported as an adverse event. Moreover, whereas haloperidol and other conventional neuroleptics have been shown to impair simple response time, xanomeline appears to improve performance on this parameter. Sleep patterns did not change significantly on xanomeline. [TESS analysis revealed no change in sleep increase ($p > 0.20$, 75 mg t.i.d. vs. placebo, one-sided), sleep decrease ($p > 0.20$), or sleep alteration ($p > 0.20$).]

Independent Mechanisms May Underlie Behavioral and Cognitive Decline

The cognitive and behavioral responses to xanomeline appear to have distinct time courses. We observe a maximal effect of xanomeline on cognition after approximately 12 weeks of treatment, whereas the effects on behavior manifest within the first 4 weeks of treatment. Moreover, on drug discontinuation, significant worsening of behavioral symptoms is apparent within 1 week. By contrast, little or no worsening of cognitive function, relative to placebo, is observed in the 4 weeks after discontinuation. These differences in the patterns of symptom response and relapse suggest that xanomeline may be affecting behavior and cognition through separate mechanisms. Longitudinal studies of the natural history of AD also suggest that the behavioral and cognitive deficits of AD may be attributable to distinct mechanisms. Wagner et al. (1995) concluded that levels of cognitive performance were largely unrelated to behavioral symptoms. Furthermore, Gilley et al. (1991) suggested that behavioral demise, cognitive deficits, and functional disturbances are relatively independent, with separate genesis, progression, and neuropathology. Mortimer et al. (1992) suggest that rates of cognitive and functional decline are predicted by different risk factors and are representative of parallel but distinct processes.

COMMENTS

To our knowledge, our study is the first large-scale effort to determine the therapeutic effects of a selective

muscarinic agonist in patients with AD. The data suggest that xanomeline (75 mg t.i.d.) is associated with modest cognitive improvement relative to placebo, an improvement of approximately the same order of magnitude as that previously reported for the cholinesterase inhibitor tacrine. We also observed a relatively robust improvement in disturbing behavioral symptoms associated with AD. We believe, on balance, that both the cognitive and behavioral effects of xanomeline are clinically significant.

However, xanomeline treatment is also associated with a number of adverse events, which may limit the therapeutic utility of the oral formulation of this compound. Moreover, the relatively short elimination half-life and extensive first-pass metabolism of the oral formulation of xanomeline may also limit its clinical use. Consequently, we are developing a transdermal formulation, which in preliminary studies is better tolerated than the oral formulation. Administration of xanomeline by the transdermal route eliminates high concentrations of xanomeline in the gastrointestinal tract, reduces presystemic hepatic metabolism, and eliminates spiking plasma levels of parent and metabolites observed with the oral formulation (data on file; Eli Lilly and Company). Early clinical studies of the transdermal formulation suggest that gastrointestinal events are reduced to placebo levels. The transdermal formulation is now under evaluation in a large-scale study of safety and efficacy.

An improvement in psychotic behavior in patients with AD can have meaningful impact on functionality and quality of life (Ferris et al., 1985; Wragg and Jeste, 1989), and traditional antipsychotic drugs have proved of some value in this regard (Teri et al., 1992). However, the utility of these drugs is limited by adverse effects on arousal and cognition and their propensity to cause extrapyramidal side effects and late-onset tardive dyskinesia. In contrast to neuroleptic agents, xanomeline causes no catalepsy when administered in relatively high doses to rats, and therefore may not be associated with extrapyramidal side effects. Among drugs with demonstrated effects on psychosis and agitation in patients with AD, xanomeline may be unique in that it also has a beneficial effect on cognition. Therefore, the transdermal formulation of xanomeline may be especially useful for treating (and preventing) psychotic symptoms and agitation associated with AD.

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