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SAFETY/TOLERABILITY TRIAL OF SDZ ENA 713 IN PATIENTS WITH PROBABLE ALZHEIMER'S DISEASE

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Summary

SDZ ENA 713 (ENA 713) is an acetylcholinesterase inhibitor being developed as a potential treatment for Alzheimer's disease (AD). A prior Phase II safety and efficacy study used an upper dose limit of 6 mg/day ENA 713. The present study was designed to assess the safety and tolerability of higher doses of ENA 713 in probable AD patients. Fifty AD patients (22M; 28F, mean age 68 yrs, range 45-90) were assigned to a fixed, nine-week dose escalation schedule in which they were randomized to receive up to 12 mg/day of ENA 713 bid (n=20) or tid (n=20), or placebo (n=10) followed by a one-week washout. Mg/day dose escalation for the bid and tid ENA 713 groups was identical, beginning with 2 mg/day on Days 1 to 3 and escalating to 12 mg/day in Weeks 8 and 9. Doses through 12 mg/day were well tolerated. Most adverse events were mild to moderate in severity and of limited duration, most commonly headache, nausea, dizziness, and diarrhea. Three of forty patients on ENA 713 discontinued, all due to adverse events. Two experienced nausea and vomiting; the third experienced an unrelated mild atrial fibrillation.

Key Words: SDZ ENA 713, Alzheimer's disease, bridging study, Phase I trials

Although multiple neurotransmitter deficits have been documented in the brains of patients with Alzheimer's disease (AD) (for a review see Bowen et al 1995 [1]), the most prominent deficits described to date have been in presynaptic cholinergic markers (2,3) and the loss of cholinergic cell bodies (4). This has led to the hypothesis that cholinergic substitution therapy may be beneficial in AD (1).

SDZ ENA 713 {ENA 713 or (+)(S)-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methyl-phenylcarbamate hydrogentartrate} is a brain-selective carbamate acetylcholinesterase (AChE) inhibitor which prevents the degradation of acetylcholine in the synaptic cleft, thereby facilitating cholinergic transmission. It inhibits AChE more potently in the cortex and

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hippocampus, both main targets for symptomatic treatment of AD, than in other brain regions (5). ENA 713 represents a potential improvement over the AChE inhibitor tacrine for several reasons. As a carbamate, ENA 713 has a different mechanism of enzyme inhibition than tacrine, resulting in a longer duration of cholinesterase activity blockade: up to ten hours in animals after a single dose (data on file, Sandoz Pharmaceuticals). ENA 713 has also been shown to potentiate central cholinergic transmission at doses not associated with peripheral cholinergic effects, which could permit greater tolerance at effective doses than that seen with tacrine. Furthermore, ENA 713 appears to have little potential for organ toxicity, as the major drug metabolite seen in both animals and man is a phenolic cleavage product, and there is no further metabolism through classical metabolic pathways.

Studies in healthy volunteers showed that multiple doses of ENA 713 up to 3 mg/day were well tolerated. In early safety/tolerability studies in Alzheimer's patients, doses up to 3 mg bid were also well tolerated. Adverse events, including headache, dizziness, nausea, and diarrhea, were generally mild and short-lived and did not result in dose reduction or discontinuation. A placebo-controlled efficacy and tolerability trial was performed at doses of 2 and 3 mg bid in 402 AD patients, but primary efficacy variables showed no evidence of a statistically significant effect after 13 weeks, though two of six secondary efficacy variables showed greater improvement in patients receiving ENA 713 than in placebo patients (data on file, Sandoz Pharmaceuticals Corporation). Thus, the present study was designed to determine the maximum tolerated dose (MTD) of ENA 713 in Alzheimer's patients, in order to maximize the potential for demonstrating efficacy in subsequent extended clinical trials.

Methods

Outpatients with probable AD were selected to participate in this double-blind, prospective, randomized, parallel-group safety/tolerability study. Patients must have met NINCDS-ADRDA criteria for probable AD (6), have had a Mini-Mental Status Examination (7) score between 10 and 26 inclusive, and not have had medical, neurological or psychiatric disorders (other than AD) which might confound assessment of the dementia. Patients were excluded if they had severe cardiovascular or pulmonary disease, unstable diabetes, peptic ulceration within five years, evidence of alcohol or substance abuse, or disease of any organ system which could affect study results or place patients at risk. Patients were also excluded if they had taken any other investigational drug within four weeks, any drug known to cause toxicity in a major organ system (including tacrine) within three months, tranquilizers within the past two weeks, antidepressants in the past month, or neuroleptics in the past two months, or if the patients would require concomitant medication with potential for interaction with ENA 713. All patients and their caregivers gave written and oral informed consent before participating, and the protocol was approved by a local investigational review board.

Patients were randomized to receive ENA 713 bid, ENA 713 tid, or placebo for nine weeks of fixed dose escalation followed by a one-week washout period. All patients received three doses of study medication per day, with patients in the ENA 713 bid group receiving placebo at the midday dose. The schedule of dose escalation was identical in the two ENA 713 treatment groups: 2 mg/day on Days 1-3, 3 mg/day on Days 4-7, 4 mg/day in Week 2, 5 mg/day in Week 3, 6 mg/day in Week 4, 7.25 mg/day in Week 5, 8.5 mg/day in Week 6, 10 mg/day in Week 7, and 12 mg/day in Weeks 8 and 9. In the event of poor dose toleration, patients were permitted to skip up to six doses at each dose level, but no more than three in sequence. The treatment-free washout period occurred in Week 10.

Patients were evaluated during screening, at baseline, and weekly through Week 4 (6 mg/day) as outpatients. Since doses above 6 mg/day had not previously been tested in AD patients, patients were hospitalized for the first nine doses (minimum three days) of each dose escalation in weeks 5-8 and were evaluated prior to each discharge. In Weeks 9 and 10, patients returned for evaluations as outpatients.

Safety assessments included a physical examination at screening, baseline, and follow-up; vital signs, electrocardiogram (ECG), clinical laboratory evaluations, and volunteered and observed adverse event reports at screening, baseline, and weekly thereafter; and a diary of adverse events maintained by patients or their caregivers. Other data obtained at screening to support the patient's health status and diagnosis included medical and treatment histories, a modified Hachinski ischemic score (8), drug and hepatitis screens, a chest X-ray, computerized tomography or magnetic resonance imaging, and an electroencephalogram.

Chi-square tests and Fisher's Exact tests were used to test homogeneity of treatment groups at baseline. Significance of treatment group differences in adverse event profiles and the proportions of abnormal ECG, clinical laboratory, and vital sign measurements were assessed by Fisher's Exact test. At each post-baseline time point, one-way ANOVA and pairwise t-tests were used to assess between-treatment differences in ECG, clinical laboratory, and vital sign changes from baseline.

Results

Fifty probable AD patients (22M; 28F, mean age 68 yrs, range 45-90) were randomized to receive ENA 713 bid (n=20), ENA 713 tid (n=20), or placebo (n=10). Two patients on placebo discontinued the study: one was called out of town; one misdosed himself and elected to discontinue. Three patients on ENA 713 discontinued, all due to adverse events. One was an 82-year old female who discontinued at 4mg/day (tid regimen) after experiencing mild atrial fibrillation. This patient was later found to have had a history of atrial arrhythmias, including atrial tachycardia, and the event was judged unrelated to study medication. The second was a 57-year old female on the bid regimen who, after experiencing intermittent mild to moderate nausea and vomiting beginning at 5 mg/day, discontinued at 8.5 mg/day. The third was a 47-year old female on the tid regimen who discontinued after experiencing nausea and severe vomiting at 12 mg/day.

Adverse events that occurred in at least 15% of patients on either ENA 713 regimen are listed in Table 1. The most common adverse events experienced by patients on ENA 713 were headache (65%), nausea (48%), dizziness (40%), diarrhea (38%), vomiting (28%), and fatigue (28%). Nausea appeared sporadically at all dose levels, occurring at a greater incidence ($p<0.05$) in the ENA 713 tid group than in the placebo group. There were trends for patients treated with ENA 713 to show greater incidences of agitation (bid regimen) and fatigue (tid regimen) than patients on placebo ($0.05<p<0.10$). Except for the three patients who discontinued, adverse events associated with ENA 713 were generally short-lived and were easily managed by withholding up to three doses before resuming treatment. Once an adverse event had been tolerated, it did not reappear at a higher dose level. There was no apparent pattern for emergence of adverse events over the dose escalation period. Overall, there was no difference in treatment tolerability between patients on bid and tid regimens of ENA 713.

There were no clinically significant changes in laboratory values, ECGs, or vital signs during the study.

Table 1. Number and percentage of patients having adverse events occurring in >15% of either ENA 713 group.

Adverse event	ENA 713 BID n=20	ENA 713 TID n=20	Placebo n=10
ANY EVENT	20 (100)	18 (90)	10 (100)
headache	13 (65)	13 (65)	7 (70)
nausea	8 (40)	11 (55)*	1 (10)
dizziness	8 (40)	8 (40)	3 (30)
diarrhea	8 (40)	7 (35)	3 (30)
vomiting‡	6 (30)	5 (25)	2 (20)
flatulence	6 (30)	3 (15)	1 (10)
agitation	6 (30)†	0	0
fatigue	5 (25)	6 (30)†	0
abdominal pain	5 (25)	5 (25)	4 (40)
rhinitis	4 (20)	5 (25)	4 (40)
coughing	4 (20)	3 (15)	3 (30)
myalgia	4 (20)	1 (5)	0
urinary incontinence	4 (20)	0	0
dyspepsia	3 (15)	5 (25)	3 (30)
sweating	2 (10)	5 (25)	0
asthenia	2 (10)	5 (25)	0
hot flushes	0	4 (20)	0
ADVERSE EVENTS BY BODY SYSTEM			
gastrointestinal system disorders	17 (85)	13 (65)	9 (90)
central & peripheral nervous syst.	15 (75)	14 (70)	7 (70)
psychiatric disorders	13 (65)	8 (40)	3 (30)
musculoskeletal system disorders	11 (55)	7 (35)	6 (60)
body as a whole - general	10 (50)	13 (65)	4 (40)
respiratory system disorders	8 (40)	9 (45)	6 (60)
urinary system disorders	7 (35)†	2 (10)	0
autonomic nervous system dis.	4 (20)	7 (35)	1 (10)
skin & appendages disorders	4 (20)	5 (25)	4 (40)
vision disorders	3 (15)	4 (20)	0

*$p<0.05$ compared to placebo according to Fisher's Exact Test, two-tailed
†$p<0.10$ compared to placebo
‡Of 11 ENA 713 patients who vomited, all experienced nausea, whereas neither of the 2 placebo patients who vomited experienced nausea.

Discussion

In this study, administration of ENA 713 to patients with probable AD appeared to be safe and well tolerated at doses up to 12 mg/day. Mild to moderate adverse events experienced by at least 30% of patients in either of the two ENA 713 treatment groups included headache

nausea, dizziness, diarrhea, vomiting, flatulence, agitation, and fatigue. These adverse events were predicted by earlier studies of the compound and suggest that the potential liabilities of ENA 713 are primarily mechanism-related side effects associated with excessive cholinergic stimulation. The dose titration used in this and previous ENA 713 studies was relatively slow, in order to allow for development of tolerance to cholinergic symptoms, particularly nausea and vomiting; however, adverse events were similar (in type and frequency) in this study to those which appeared in an earlier titration study which used doses up to 3 mg bid in probable AD patients. Both bid and tid regimens of ENA 713 were equally well tolerated, suggesting that future efficacy studies can employ the less frequent dosing regimen to improve patient compliance with taking study medication.

No maximum tolerated dose (MTD) was reached in this study, nor was an MTD sought in any of the preliminary studies of ENA 713 performed in healthy elderly subjects or probable AD patients, though 3 mg was the highest well tolerated single dose in healthy young volunteers. Operationally, the MTD is defined as the dose immediately below the minimal intolerated dose (MID), based on multiple-dose administration of study drug to panels of at least six patients, with each panel receiving progressively higher doses. Our experience with MTD-determining studies suggests that patients with probable AD frequently tolerate higher doses of cholinergic compounds than do normal subjects (higher than young normals: refs 9-12; higher than elderly normals: refs 13-15). Further evidence for differences in tolerability of cholinergic agents between AD and normal patients comes from recent reports that AD patients are hypersensitive to dilute amounts of the cholinergic antagonist tropicamide dropped into the eye (16). These differences suggest that traditional dose defining methods, which base clinical dosage constraints on the maximum well tolerated dose in healthy volunteers, may not predict dosages which will be useful for patients.

In this study, the highest dose permitted was 12 mg/day, based on 50% of the no-toxic-effect level (NTEL) determined in animals. Dose levels above the NTEL produced cholinergic effects in animals (e.g. emesis, hypersalivation, diarrhea) but no permanent damage such as organ toxicity or changes in hematology or blood chemistry. In retrospect, establishing the upper human dosage based on the NTEL in animals was a handicap, since it did not allow us to determine the MTD for this compound in target patients. While animal studies should explore dosages well above any anticipated for use in humans in order to permit adequate characterization of the compound's toxicology, it is unclear how the NTEL can best be used to derive dose limits which may be useful in the development of cholinergic treatments for AD, since this patient population frequently tolerates doses well above those predicted.

Tolerability differences between patients and healthy volunteers are an important reason to conduct phase I safety/tolerability studies ("bridging" studies) such as this one before initiating phase II efficacy trials (17). If healthy volunteers do not tolerate a compound as well as patients, and only the doses well tolerated in normals are used in Phase II, potentially useful agents may appear ineffective. A bridging study determines the MTD in the patient population *before* efficacy trials begin, thus permitting dose designs which maximize the potential to detect efficacy and save development time.

Recent work with tacrine and xanomeline tartrate, showing that improvement with cholinergic agents is dose-proportional, further demonstrates the value of determining a patient MTD early in development. Large-scale trials of tacrine were conducted using low (80 mg/day) doses (18,19), despite earlier evidence that 160 mg/day showed some benefit (20). Overall efficacy results in these two large trials were inconclusive, and a later study using doses up to 160

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