Donepezil Made a Difference in Severe Alzheimer's

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Patients with severe Alzheimer's disease showed improved cognition and function when treated with donepezil in a 24-week, placebo-controlled trial, Dr. Sandra Black and her associates reported in a poster at the annual meeting of the American Geriatrics Society.

The results are consistent with a Swedish nursing home study in a similarly severe, institutionalized population (Lancet 2006;367:1262-70), suggesting that even patients with severe disease can benefit from treatment with donepezil.

"The two studies taken together suggest that this stage of disease can show measurable benefits of treatment with donepezil," Dr. Black, professor of medicine and head of neurology at Sunnybrook Health Sciences Centre, University of Toronto, said in an interview. "They give a new evidence-based option for treatment, which gives hope for a better quality of life in the final phase of this devastating disease."

Currently, donepezil (Aricept) is approved for mild to moderate Alzheimer's disease. In February 2006, the U.S. Food and Drug Administration accepted a supplemental new drug application for donepezil in severe Alzheimer's disease.

Doses of 5 mg and 10 mg of donepezil are typically administered once daily, although the higher 10-mg dose did not provide significantly greater clinical benefit in previous clinical trials.

Data from the two studies taken together show that donepezil has a measurable benefit in patients with severe Alzheimer's disease.

Dr. Black and her colleagues' study randomized 343 patients with severe Alzheimer's disease to an initial dose of donepezil 5 mg/day for 6 weeks and then 10 mg/day donepezil (176 patients) or placebo (167 patients) for 24 weeks. Patients resided in the community or in assisted-living facilities. Baseline characteristics were similar in both groups. Their mean age was 78 years, their mean Mini-Mental State Exam score was 7.5, and the majority (86.3%) had Functional Assessment Staging scores of 6.a-6.e.

Overall, 117 of the 176 donepezil-treated patients and 127 of the 167 placebo patients completed the study, which was supported by Eisai Inc. and Pfizer Inc. Dr. Black holds no financial interest in either firm, but has been a study investigator for both. She is an ad hoc consultant and speaker, and has received honoraria from Pfizer.

Primary end points were change from baseline in Severe Impairment Battery (SIB) total score and Clinician's Interview-Based Impression of Change with Caregiver Input (CIBIC-plus) at 24 weeks.

The primary analysis was based on the intent-to-treat population using a last observation carried forward analysis at 24 weeks. The intent-to-treat population consisted of all patients who were randomized, received at least one dose of either donepezil or placebo, and had a baseline and at least one postbaseline efficacy value.

Categories in the CIBIC-plus analysis were collapsed (1-3 equals improved, 4 equals no change, and 5-7 equals worsened) because the distribution of values was sparse in categories 1, 2, and 7.

Donepezil was significantly superior to placebo on the SIB score at week 24 in the intent-to-treat population (mean difference 5.3), and at weeks 8, 16, and 24 in patients who completed the study, she said.

The collapsed category CIBIC-plus analysis significantly favored donepezil at week 24 in the intent-to-treat population and in patients who completed the study. Among donepezil-treated patients, 28% improved, 38% had no change, and 34% worsened, compared with 23%, 29%, and 48% of placebo patients, respectively.

Most reported adverse events were mild to moderate (74%), the most common of which were diarrhea, nausea, and insomnia. Placebo patients reported more serious and severe adverse events than donepezil-treated patients. However, more patients discontinued treatment because of adverse events in the donepezil group than in the placebo group (18.3% vs. 10.8%, respectively), Dr. Black reported. ■

History of Infection, Bleeding Found In Hydrocephalus, Not Dementia

BY PATRICIA L. KIRK
Contributing Writer

GRAPEVINE, TEX. — At least 6% of patients diagnosed with dementia are actually suffering from normal-pressure hydrocephalus, which often can be treated, Dr. Mark S. Maxwell said at the annual meeting of the American College of Osteopathic Family Physicians.

Normal-pressure hydrocephalus (NPH) usually occurs in people with a history of arachnoid insult in which infection or bleeding affects the ability to absorb spinal fluid. And the prevalence of NPH is rising because of improved detection.

However, there are still populations in whom NPH goes unidentified. NPH can be seen on encephalography, but physicians frequently fail to order this test in elderly patients because cognitive symptoms resemble subcortical dementia, and the symptoms can take years to manifest, explained Dr. Maxwell, chair of neurology and neurosurgery at Hendrick Medical Center in Abilene, Tex.

Unlike hydrocephalus in children, which has a rapid onset, NPH in older populations involves a gradual process of ventricular enlargement that takes years to encroach on surrounding tissue and vessels and affect cognitive function. The sphere of distended ventricles grows larger over time, causing a triad of symptoms, including gait unsteadiness, psychomotor retardation, and urinary incontinence, commonly referred to as wet, wobbly, and wacky.

About 80% of NPH patients exhibit cognitive impairment that is characterized by being inattentive and easily sidetracked, and having memory loss and slow but accurate recall. These patients also lack spontaneity, and have trouble forming words, interpreting stimuli, and carrying out simple sequential tasks——all of which may be mistaken for subcortical dementia symptoms.

About 90% of NPH patients are wobbly. These patients have a hard time initiating gait, and often fall down, he said. They also walk slowly, take shorter strides, shuffle their feet, and tend to lean forward and push on walls or whatever is handy to steady themselves.

After the onset of gait changes, up to 90% of NPH patients develop early symptoms of incontinence, in which there is a sudden sense of urgency to urinate, Dr. Maxwell said. The urologic symptoms stem from poor detrusor contraction. He pointed out that this symptom differs from overflow incontinence in that the need to void is a surprise.

In diagnosing NPH, Dr. Maxwell provided a checklist: history of wet, wobbly, and wacky; enlarged ventricles on CT or MRI; a gradual progressive course of symptoms; and a history of falls.

Tests should be performed to rule out Alzheimer's disease and dementia. Testing might involve cisternography with a high-volume tap of 50 cc of cerebrospinal fluid. Gait tests should be performed before and after a lumbar drain of 50-100 cc per day for 3 days in hard-to-diagnose cases to see if the patient improves, he says, noting that lumbar drain is the standard test.

In the case of NPH from an excess of fluid, a shunt with a valve is implanted to keep fluid from backing up, said Dr. Maxwell. A needle can be inserted so that spinal samples can be routinely checked to see if the shunt is still working. One-third of patients undergoing this procedure experience significant improvement, one-third stabilize or experience minor change, and the other third continue to decline. Patients who perform better following a simple tap test are most likely to improve following this strategy.

Ten percent of patients undergoing this procedure have complications, but those complications are generally are not serious. Mortality due to hydrocephalus is unknown."But with early detection there is definitely a better chance for a good outcome," he said. ■

Methylphenidate Eased Apathy Due to Dementia

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Methylphenidate may be effective in the treatment of apathy associated with dementia of the Alzheimer's type, Dr. Prasad Padala and associates reported in a poster at the annual meeting of the American Geriatrics Society.

Results from an open-label study in 13 patients suggest that methylphenidate (Ritalin) has a substantial effect on apathy, with smaller but significant positive effects on mood, cognition, and independent activities of daily living.

The findings warrant further testing with a double-blind, placebo-controlled trial, he noted.

Apathy is the most common behavior problem reported in persons with Alzheimer's disease, affecting about 70%-90% of patients.

All patients in the study had dementia of the Alzheimer's type, Mini-Mental State Examination (MMSE) scores greater than 18, and Apathy Evaluation Scale (AES) scores greater than 30. Their mean age was 69 years.

All patients were started on methylphenidate 5 mg twice daily; the dose was titrated to 10 mg twice daily over a 2-week period. Follow-up visits were scheduled at 4, 8, and 12 weeks. Significant improvement in apathy (AES 52.6 vs. 31.6) was reported from baseline over 12 weeks, reported Dr. Padala, of the department of psychiatry at the University of Nebraska, Omaha, and a psychiatrist at the Omaha division of the Veterans Affairs Nebraska Western Iowa Health Care System.

Less robust but significant improvement was noted at 12 weeks in Geriatric Depression Scale scores (93 vs. 63), MMSE scores (24.2 vs. 25.5), and Independent Activities of Daily Living criteria (13.7 vs. 16).

Subjective improvement was noted by caregivers, who reported increased energy, ambition, spontaneity, and motivation in the patients. One caregiver reported that the patient was monitoring his medications better and started taking care of his finances again after a long hiatus.

None of the patients discontinued medication because of adverse events. In one patient, the dose of methylphenidate was reduced because of appetite loss possibly related to treatment, Dr. Padala reported.

The study was funded by the Nancy and Ronald Reagan Alzheimer's Scholarship Fund, established at the University of Nebraska to support Alzheimer's disease research. ■