Use of cholinesterase inhibitors for treatment of Alzheimer disease

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ABSTRACT

The four cholinesterase inhibitors now available for treatment of Alzheimer disease (AD) may be most beneficial, especially in the long run, if started early in the course of the disease. This paper reviews the efficacy, pharmacokinetics, metabolism, side effects, dosage, and precautions for the use of these agents, which may produce modest improvements in cognition, behavior, and the ability to perform activities of daily living.

Four drugs are approved for treating Alzheimer disease

GALANTAMINE (Reminyl) recently became the fourth drug of its type approved for the purpose of improving cognition, behavior, and the ability to perform activities of daily living in patients with mild to moderate Alzheimer disease (AD). All four drugs—tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), and galantamine—are cholinesterase inhibitors, which means they work by increasing levels of acetylcholine by inhibiting its breakdown.

The effects of these drugs are modest; they may slow but do not halt disease progression. This paper reviews their efficacy, pharmacokinetics and metabolism, side effects, dosage, and precautions.

We also touch on the current focus of research: prevention and treatment of underlying pathogenic mechanisms.

*The author has indicated she is on the speakers bureau of the Novartis, Pfizer, Eisai, and Janssen corporations. This paper discusses therapies that are not yet approved by the US Food and Drug Administration for the use under discussion.

CHOLINESTERASE INHIBITORS

In the 1970s, researchers discovered that a decline in cholinergic function in the basal forebrain nuclei, entorhinal cortex, and hippocampus of the brain is associated with cognitive decline in AD. This finding led to efforts to improve cognitive function by reversing the cholinergic deficit, which ultimately resulted in the development of cholinesterase inhibitors.

Two enzymes break down acetylcholine: acetylcholinesterase and butylcholinesterase. Cholinesterase inhibitors increase levels of acetylcholine by slowing its degradation by these two enzymes.

Evaluating efficacy

The efficacy of cholinesterase inhibitors can be measured with a number of tools, including the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog).[1] The ADAS-Cog measures memory, orientation, reasoning, language, and other areas of cognition (TABLE 1). Scores range from 0 to 70; the higher the score, the greater the cognitive impairment. In general, a 3-point to 4-point improvement is needed to see a clinical difference in symptoms.

TACRINE

Tacrine (Cognex), the first cholinesterase inhibitor, was approved by the US Food and Drug Administration (FDA) for the treatment of AD in 1993. It reversibly inhibits both acetylcholinesterase and butylcholinesterase.

Efficacy

Knapp et al,[2] in a randomized, double-blind, placebo-controlled trial in 663 patients, found

that patients who received tacrine 160 mg/day for 30 weeks had a mean ADAS-Cog score more than 3 points lower (ie, better) than those who received placebo ($P < .001$).

Knopman et al[3] conducted a 2-year follow-up study of these same 663 patients and found that those who took the highest doses of tacrine (120 to 160 mg/day) were statistically significantly less likely to be placed in a nursing home than those taking 80 mg/day or less (odds ratio 2.8). Patients who took more than 120 mg/day also were less likely to have died than those taking lower doses, although this trend was not statistically significant.

Pharmacokinetics and metabolism

Peak plasma concentrations occur in 1 to 2 hours. Tacrine has a terminal elimination half-life of 2 to 3 hours and is metabolized in the liver by the cytochrome P450 system.

Side effects

The most common side effects are gastrointestinal symptoms such as nausea, vomiting, anorexia, and diarrhea. Hepatotoxicity also occurs in a high percentage of patients, necessitating frequent monitoring of liver transaminase levels.

Dosage

Optimal responses occur with a dose between 120 to 160 mg/day. In view of tacrine's short half-life and high incidence of side effects, the dosage is started low and titrated upward in four steps. The starting dosage is 10 mg four times a day. As long as patients tolerate the drug well and their liver enzyme levels stay within acceptable limits, the dose should be increased by 10 mg every 4 weeks to a maximum of 40 mg four times a day.

If the drug must be stopped because of elevated liver enzymes, it can be restarted as soon as the enzyme levels return to normal.

Cautions

Because of the risk of hepatotoxicity, serum transaminase levels should be monitored every other week from the fourth through the 16th week of therapy, after which they should be monitored every 3 months.

Drug interactions with theophylline are possible. Anticholinergic agents (eg, amitriptyline and tricyclic antidepressants) may counteract the effects of tacrine.

DONEPEZIL

Cholinesterase inhibitors only slow the disease

Donepezil (Aricept), like tacrine, is a reversible cholinesterase inhibitor. Approved in 1997, it is not hepatotoxic, so there is no need to monitor liver enzyme levels. Also, it has a much longer half-life, which permits once-daily dosing.

Efficacy

A 24-week double-blind, placebo-controlled trial[4] showed that patients who took donepezil did better than placebo recipients by a mean of nearly 3 points on the ADAS-Cog subscale ($P \leq .05$). The group that received 10 mg of donepezil daily had a slightly better response than those who received 5 mg, but the difference was not statistically significant. However, a later trial did show a statistically significant difference between the two doses.[5]

Pharmacokinetics and metabolism

Peak serum concentrations occur in 3 to 4 hours. The terminal elimination half-life is 70 hours. Donepezil is metabolized by the cytochrome P450 system.

Side effects

The most common side effects of donepezil are diarrhea, anorexia, nausea, vomiting, muscle cramps, and fatigue.

Dosage

The recommended starting dose of donepezil is 5 mg at bedtime for 4 to 6 weeks. If the patient tolerates the drug well, the dose should be increased to a maximum of 10 mg a day.

RIVASTIGMINE

Rivastigmine (Exelon), approved in 2000, inhibits both acetylcholinesterase and butylcholinesterase.

Efficacy

In a double-blind, placebo-controlled trial in 725 patients, Rösler et al[6] found a mean difference of 4 points on the ADAS-Cog subscale between the patients who took the highest dose of rivastigmine (6 to 12 mg/day) and those taking placebo.

Pharmacokinetics and metabolism

The peak plasma concentration of rivastigmine is reached in 1 hour. The elimination half-life is 1.5 hours. Unlike tacrine and donepezil, rivastigmine is a pseudo-irreversible inhibitor, meaning that it is inactivated by enzymatic cleavage at the active site of the cholinesterase rather than by metabolism. It therefore has no interactions with the cytochrome P450 system.

Dosage

The starting dose is 1.5 mg twice a day. The dose should be increased by 3 mg (1.5 mg twice a day) every 2 to 4 weeks, or slower if necessary, to a maximum dose of 12 mg (6 mg twice a day).

Side effects

The main side effects of rivastigmine are nausea, vomiting, and diarrhea.

GALANTAMINE

Galantamine (Reminyl) is the newest reversible cholinesterase inhibitor, approved by the FDA in February 2001. It is specific for acetylcholinesterase.

Unlike the other three drugs of its type, galantamine also binds to nicotinic receptors in presynaptic neurons, stimulating greater release of acetylcholine. Nicotinic receptor stimulation may improve memory, concentration, and attention.

Efficacy

Tariot et al[7] conducted a 5-week, randomized, placebo-controlled, double-blind study in which 978 patients were randomized to receive one of four treatments: galantamine 8, 16, or 24 mg/day or placebo. Patients who took 16 mg/day and 24 mg/day had a mean change in the ADAS-Cog score from baseline that was at least 3.3 points better than those taking placebo ($P < .001$). Furthermore, patients in these two groups were still above baseline at the end of the study. Compared with the placebo group, the 16-mg/day and 24-mg/day groups were able to perform activities of daily living for a longer period of time and developed fewer behavioral problems.

Pharmacokinetics and metabolism

Peak plasma concentration occurs in about 1 hour. Galantamine has a terminal elimination half-life of 7 hours and is metabolized in the liver by the cytochrome P450 system.

Side effects

The most common side effects are nausea, vomiting, anorexia, diarrhea, and weight loss.

Dosage

The recommended starting dosage is 4 mg twice a day for 4 weeks. If the patient tolerates the drug well, the dosage should be increased to 8 mg twice a day for another 4 weeks. As long as the patient continues to do well, the dose should be increased to a maximum of 12 mg twice a day.

WHAT TO EXPECT WITH CHOLINESTERASE INHIBITOR THERAPY

Each patient responds to cholinesterase inhibitors differently. At best, the drugs temporarily delay the onset of behavioral problems, improve memory and cognition, and allow patients to continue with their activities of daily living. Their main benefits: they

Give patients the highest dose they can tolerate

give patients an opportunity to get their affairs in order, and they reduce the economic and physical burden on the caregiver. They may conceivably also buy time until newer treatments become available that prevent and treat the underlying pathogenic mechanisms.

All of the cholinesterase inhibitors have a definite dose-related response, so it is important to give patients the highest dose they can tolerate. To enhance tolerability, the drugs may be given with food, the doses split, and the titration slowed.

How early should therapy be started?

All four cholinesterase inhibitors have been approved to treat mild-to-moderate AD, which translates into a score between 10 and 26 on the Mini-Mental State exam (MMSE). However, it is still not known how early in the course of the disease treatment should be started.

Several studies, including open-label extensions of the pivotal trials, shed some light on this question. In the donepezil and rivastigmine studies, for example, patients who had been taking placebo during the double-blind phase improved when they were started on the open-label drug. However, as a group, they never caught up to the group that had been receiving the active drug all along. The implication is that the placebo groups "lost ground" that could not be regained. This suggests that starting cholinesterase inhibitors earlier may be more beneficial, especially in the long run.

The drugs may reduce the burden on the caregiver

How long should patients remain on therapy?

Treatment should continue as long as patients are able to participate meaningfully in their daily lives. In practical terms, this means that even if a patient is in a nursing home and requires a lot of assistance with activities of daily living, it most likely is worth keeping him or her on a cholinesterase inhibitor if he or she can still recognize and communicate with family members. Even an individual with a very low MMSE score may benefit because of improvements in behavior. If a patient is curled up in a fetal position and is not communicating, continuing drug therapy probably will not help.

AREAS OF CURRENT RESEARCH

The current focus of AD research is on prevention and treatment of underlying pathogenic mechanisms. A number of promising treatments have been investigated, but their effects in humans remain unclear.

Nicotine

An earlier, unconfirmed observation suggested that smoking may reduce the risk of AD. Researchers believe that continuous tonic stimulation of nicotinic receptors may actually slow the degeneration of nerve cells and delay the onset or prevent the appearance of some of these neural degenerative disorders. The problem with nicotine is that patients become quickly habituated to it. In addition, nicotine poses a cardiovascular risk.

Bottom line: At present, no reliable data support the use of nicotine in patients with AD.

Estrogen

In three studies, estrogen replacement therapy after menopause seemed to reduce the risk of AD by about half.[8–10] This observation led to two large studies of estrogen therapy in patients with AD.[11,12] Unfortunately, both studies showed disappointing results.

Bottom line: Estrogen is not currently used to treat AD.

Nonsteroidal anti-inflammatory drugs

Observational evidence suggested that people with rheumatoid arthritis do not get AD. That led some researchers to wonder if the disease was related in some way to inflammation. The Baltimore Longitudinal Study compared patients who had been taking nonsteroidal anti-inflammatory drugs (NSAIDs) with those who had not.[13] The incidence of AD was only about half as high in persons taking NSAIDs, and only about 40% as high among persons who had been taking NSAIDs for more than 2 years. Even those who had been taking an NSAID for less than 2 years had a reduced risk. However, people who take NSAIDs have a higher risk of renal dysfunction and gastric ulcers.

Researchers have also studied the effects of anti-inflammatory agents in people with AD. Again, these results have been disappointing.

Bottom line: Although the results of these studies are interesting and probably warrant further investigation, NSAIDs are not currently recommended for preventing or treating AD.

Antioxidants

Direct and indirect evidence suggests that oxidative stress is involved in the pathogenesis of AD. In a study by Sano et al,[14] patients with AD received vitamin E, selegiline, both vitamin E and selegiline, or placebo for 2 years. Patients in all three active-treatment groups experienced a slight delay in the progression of AD and the need for institutionalization, although there was no appreciable effect on cognition.

Bottom line: Based on these modest effects, it may be prudent to treat newly diagnosed patients with 2,000 IU of vitamin E per day (or, in patients taking warfarin or with bleeding abnormalities, a maximum of 1,000 IU daily).

Alzheimer vaccine

Researchers are working on a vaccine to block the formation of the amyloid plaques of AD. In one study,[15] mice that were genetically engineered with a mutation in the amyloid precursor protein gene developed cerebral amyloid plaques and evidence of cognitive dysfunction on maze tests. When these mice were vaccinated at birth with a synthetic beta-amyloid protein, they did not develop plaques or cognitive deficits. Mice treated later in life showed evidence of regression of plaques that had previously formed.

Limited preliminary human safety studies have been performed, with no adverse effects so far. More extensive testing is planned in the near future. An intranasal form of the vaccine is also being investigated.

Bottom line: Although promising, the vaccine requires several more years of testing in humans.

Stem cell transplants

Cell transplant technology, such as the implantation of fibroblasts engineered to produce nerve growth factor, or the transplantation of stem cells, is another active area of research that is still in its very early stages.

Each patient responds differently to drug therapy

CONCLUSIONS

At present, cholinesterase inhibitors are the mainstay of treatment for AD. These drugs produce modest improvement in cognition in patients with mild to moderate AD; recent research suggests that earlier treatment provides greater benefit in the long run, and that patients continue to benefit from cholinesterase inhibitor therapy well into the severe stages of the disease. Current research is focused on therapies that will target the underlying pathologic mechanisms of AD.

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