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A Review of Cholinesterase Inhibitors: Tacrine, Donepezil and Rivastigmine

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the leading cause of dementia and accounts for more than half of all cases of late-life cognitive dysfunction. Many factors contribute to the pathophysiology of AD and these include degeneration of neurons, neuritic plaque accumulation, and progressive destruction of the cholinergic system.

Acetylcholine (ACh) is the neurotransmitter that propagates cholinergic neurotransmission. Among other functions, ACh can enhance cognition, learning, and memory. The body regulates ACh via cholinesterases that are involved in the synthesis and breakdown of this neurotransmitter. There are two cholinesterases in the brain, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). As AD is characterized by a deficit in the cholinergic system, cholinesterase inhibitors, by curtailing the destruction of ACh, can potentially slow the cognitive degenerative process. Tacrine, donepezil and rivastigmine are three cholinesterase inhibitors that have been used for the treatment of mild and moderate AD. A review of these agents is presented below.

Tacrine

Tacrine (Cognex[®]) was approved in 1993 as the first cholinesterase inhibitor for the treatment of mild to moderate AD. It is a centrally active, non-competitive, reversible inhibitor of both AChE and BChE. This drug undergoes extensive metabolism in the liver by cytochrome P450 1A2 isoenzyme to an active metabolite, 1-hydroxy-tacrine.

In a 30-week double-blind, placebo-controlled study, patients diagnosed with mild to moderate AD received up to 80, 120, or 160 mg/day. Patients in the high dose group improved in both cognition and behavioural symptoms.

Common side effects are nausea, vomiting, diarrhea, sweating, and bradycardia. Headache and myalgia have also been reported. The most important adverse event is the high incidence of hepatotoxicity. Tacrine has a relatively short half-life which necessitates four times daily administration. Due to the need for frequent dosing and the requirement for close monitoring of liver function, it has been replaced by donepezil and rivastigmine.

Donepezil

Donepezil (Aricept[®]) was the second AChE inhibitor, introduced in 1997. It is a highly selective, reversible inhibitor of AChE with less activity against BChE.

In a 24-week study, 473 AD patients were treated with either 5 or 10mg of donepezil or placebo. Improvement in cognitive skills and daily function were observed in those taking donepezil, whereas those taking placebo showed no such improvement. Several efficacy studies have been published with patients treated with donepezil for more than 2 years. The overall results of these studies showed beneficial effects in slowing of cognitive deterioration maintained until the end of the two-year study period.

Like tacrine, cholinergic side effects such as nausea, vomiting and diarrhea are common; unlike tacrine, donepezil does not seem to cause liver enzyme abnormalities.

Donepezil has a long half-life of up to 70 hours, which allows once daily dosing. It is rapidly absorbed from the gastrointestinal tract and is metabolized by the cytochrome P-450 system. Administration at night is recommended to minimize GI side effects.

Rivastigmine

Rivastigmine (Exelon[®]) was licensed in the UK in 1998 and approved for use in North America in year 2000. It is a reversible inhibitor of both AChE and BChE. It is not metabolized by hepatic enzymes, but rather cleared by the renal system.

In a Cochrane review, the evidence available in the clinical trials reveals a modest benefit for high dose rivastigmine on cognition and activities of daily living but not on clinical global impression for patients with mild to moderate AD. On the other hand, low dose rivastigmine showed significant benefit for clinical global impression, but only small benefits on cognition and activities of daily living. The withdrawal rate due to side effects was significantly higher in patients treated with higher doses in comparison to those treated with lower doses of rivastigmine.

Besides the GI side effects as seen with tacrine and donepezil, rivastigmine may also cause weight loss. A warning was issued in January 2001 regarding interrupted treatment with this agent. If treatment is interrupted for longer than several days, it is important to re-start at the lowest daily dose and follow the titration guidelines in order to prevent the possibility of severe vomiting that may induce subsequent esophageal rupture.

Rivastigmine has an average half-life of 10-12 hours, allowing for twice daily dosing. The lowest initial recommended dose is 1.5 mg daily or twice daily and titrating up to a maximum dose of 6 mg twice daily.

Summary

Three cholinesterase inhibitors, tacrine, donepezil and rivastigmine demonstrate efficacy in improving cognition and activities of daily living. They are similar in mechanism of action but differ slightly in the side effect profiles which may be associated with differences in selectivity for AChE and BChE (see Table 1 for comparison). These differences may affect the drug of choice. Due to concerns of hepatotoxicity, tacrine, the pioneering cholinesterase inhibitor, is no longer available in Canada. Donepezil and rivastigmine are the two agents currently available. It remains to be seen whether the selectivity for AChE over BChE represents a favorable attribute. Currently there is no reason to favor rivastigmine over donepezil, or vice versa.

A potential new cholinesterase inhibitor, galantamine (Reminyl[®]), is awaiting approval to be marketed in Canada. Similar to donepezil and rivastigmine, galantamine is selective for AChE over BChE. It is rapidly absorbed after oral dose and has adverse effects similar to that of other cholinesterase inhibitors with respect to gastrointestinal symptoms. Preliminary data indicate beneficial results with the use of galantamine, however, the safety and efficacy of galantamine needs to be determined with long-term use. The continued interest in exploring new agents for treating AD definitely provides more options to doctors and patients in the future.

In summary, cholinesterase inhibitors do not cure AD, but may slow the progression of the disease. They are intended to treat mild to moderate AD, but their effects usually plateau after 6 to 12 months. As such, long term effects of these agents need to be studied. Due to the cholinergic effects of these agents, close monitoring is advised in patients with pre-existing cardiovascular, gastrointestinal, and pulmonary disease processes.

Table 1. Comparison Chart For: Tacrine, Donepezil, Rivastigmine

	TACRINE	DONEPEZIL	RIVASTIGMINE
ENZYMES INHIBITED	BChE >AChE	AChE >>BChE	AChE > BChE
DOSE	Initial dose:10mg q.i.d. ↑by 40mg/d at 6wk intervals as tolerated up to 40mg q.i.d.	Initial dose: 5 mg once daily Max: 10 mg once daily (↑ to 10mg/d after 1-2 months if tolerated)	Initial: 1.5 mg once daily or b.i.d. Minimum 2 weeks between dose increases and base on tolerability. (Max: 6mg b.i.d.)
DOSING	Four times daily	Daily	Twice daily
HALF-LIFE (hrs)	1.5-6	50-70	10 – 12
METABOLISM	Liver	Liver	Kidney
CYTOCHROME P-450	1A2	2D6, 3A4	Minimal
SIDE-EFFECTS	Nausea, vomiting, diarrhea, Hepatotoxicity	Nausea, vomiting, diarrhea	Nausea , vomiting, diarrhea, weight loss
TIME TO EFFECT	Up to 6 months	3-4 weeks	About 4 weeks
GIVEN WITH FOOD	YES	YES	YES
SPECIAL CONSIDERATION			Upon interruption of treatment, reinitiate at the LOWEST daily dose (1.5mg once daily or b.i.d.) and re-titrate to maintenance dose if needed
COST	(No longer available)	\$138 per month	\$140 per month A free three months trial program is currently offered by Novartis

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References are available from Pharmacy Services.