

FOR YOUR INPHARMATION



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Galantamine (Reminyl®)

The current treatment of the cognitive disturbance in Alzheimer's disease (AD) is to increase the declining function of the cholinergic system. The most effective way to do this to date is to decrease the breakdown of acetylcholine (ACh) by inhibiting the enzyme acetylcholinesterase (AChE).^{1,2} The first available agent to stop the breakdown was TACRINE (Cognex®). This agent proved to be unsuccessful primarily due to liver toxicity.³

A review of this agent and the two newer ones, DONEPEZIL (Aricept®) and RIVASTIGMINE (Exelon®) was discussed in the Pharmacy Newsletter, dated April 2001. The important question is whether the latest three drugs have any distinctive features to allow clinicians to choose one agent over another for different Alzheimer patients.

All three cholinesterase inhibitors are similar in that they inhibit AChE, yet they differ in other pharmacological properties.

The Role of AChE Inhibition

AChE is an important inactivator of neuronally released ACh. It is known that inhibiting this enzyme can increase the action of ACh long enough to enhance cognition in Alzheimer patients. Centrally enhanced ACh improves cognition while peripherally enhanced ACh causes the gastrointestinal (GI) side effects characteristic of these drugs, especially at the initiation of dosing, such as nausea and diarrhea.

A second enzyme called butyrylcholinesterase (BuChE) also breaks down ACh. Normally this

enzyme seems to be more important in regulating ACh in peripheral tissues such as the liver, plasma and gut than in the brain. Of the three cholinesterase inhibitors, only rivastigmine inhibits the enzyme BuChE.³ This is thought to be advantageous in the later stages of Alzheimer's disease when less AChE and more BuChE may be present.

Pharmacological Actions of Currently Available Drugs Used to Treat Alzheimer's Disease

Drug	AChE Inhibitor	BuChE Inhibitor	Nicotinic Receptor Modulator
Donepezil	Yes		
Rivastigmine	Yes	Yes	
Galantamine	Yes		Yes

Role of Allosteric Modulation of Nicotinic Receptors

Nicotinic cholinergic receptors may be especially important in regulating cognitive functions, such as attention and in causing the release of more neurotransmitters from cholinergic neurons.¹ Nicotinic receptors can be regulated by both ACh and by allosteric modulators (the term allosteric refers to "other site"). Galantamine binds to a site on nicotinic acetylcholine receptors (nAChR) that is different from the binding site of the natural agonist, ACh. When galantamine and ACh bind simultaneously to nAChR, the response of these receptors to ACh is increased. Nicotinic receptors play an important role in memory and learning and are reduced in patients with AD. Therefore, its dual

effect on the cholinergic system makes galantamine a promising agent for AD. Comparative trials with other acetylcholinesterase inhibitors are lacking.

Efficacy

Galantamine has been evaluated in large (n = 285 to 978), well designed trials of 3 to 6 months' duration in patients with mild to moderate AD, as well as in several small nonblinded studies.

Galantamine 16 or 24 mg/day demonstrated efficacy at 3 to 6 months across all studies, with significant differences from placebo observed for all primary and most secondary efficacy assessment measures.

Galantamine treated patients showed significant improvements in cognition, behavioral symptoms and activities of daily living compared with placebo recipients. Activities of daily living outcomes were significantly better in these galantamine treated patients than placebo recipients.

Long term evaluation indicated that galantamine 24 mg/day maintained cognition and activities of daily living in patients who had received this dose throughout a 12 month study period (6 months' double-blind, then a 6-month extension).⁴

Side Effects

Galantamine was well tolerated in patients with AD. Side effects were those expected from an AchE inhibitor. Overall, 19% (441/2287) of patients treated with galantamine, were discontinued from Phase III controlled clinical trials due to side effects compared to 8% (98/1159) in the placebo group. For patients treated with galantamine, the rate of discontinuation due to side effects was 14% for males and 22% for females. The most common

side effects occurring at least 5% more frequently with galantamine (16 to 24 mg/day) than placebo were nausea, vomiting, diarrhea and anorexia.⁵

Galantamine had no clinically relevant effects on vital signs, hematological or biochemical laboratory parameters and importantly, no hepatotoxicity was observed.

Dosage and Administration

The dosage of galantamine shown to be effective in controlled clinical trials is 16 – 32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16 – 24 mg/day given bid. The dose of 24 mg/day did not provide a statistically significant greater benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg might provide additional benefit in some patients.

The recommended starting dose is 4 mg twice a day. After a minimum of 4 weeks of treatment, if this dose is well tolerated, the dose should be increased to 8 mg twice a day. A further increase to 12 mg twice a day after a minimum of 4 weeks may be considered following appropriate assessment of clinical benefit and tolerability. The drug should be given twice a day with the morning and evening meals. If therapy is interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose to avoid GI side effects such as nausea or diarrhea.⁵

The dose escalation for elderly patients (> 85 years old) with low body weight (especially females) or serious comorbid diseases should be done with caution. In patients with moderately impaired hepatic function, dosing should proceed cautiously and should not exceed 16 mg/day. The drug is not recommended in patients with severe hepatic impairment. Doses

should not exceed 16 mg/day in patients with renal impairment.

Drug Interactions

Succinylcholine: Cholinesterase inhibitors such as galantamine are likely to potentiate the action of succinylcholine on muscle relaxation during anesthesia.

Effect of Other Drugs on the Metabolism of Galantamine

Based on in vitro studies, CYP2D6 and CYP3A4 are the major enzymes involved in the metabolism of galantamine.

Paroxetine: a strong inhibitor of CYP2D6, increased the bioavailability of galantamine 4 mg bid, 8 mg bid and 12 mg bid by 40%, 45% and 48% respectively in individuals receiving paroxetine 20 mg daily.

Cimetidine: Cimetidine at 800 mg daily increased the bioavailability of galantamine by 16% while ranitidine had no effect on the pharmacokinetics of galantamine.

Ketoconazole: a strong inhibitor of CYP3A4 and CYP2D6, when given in a dose of 200 mg bid for 4 days increased the bioavailability of galantamine by 30%.

Erythromycin: a moderate inhibitor of CYP3A4 at a dose of 500 mg qid for 4 days increased the bioavailability of galantamine by 10% when subjects were on a dose of 4 mg bid for 6 days.⁵

Effect of Galantamine on the Metabolism of Other Drugs

Galantamine does not inhibit the metabolic pathways catalyzed by the major forms of cytochrome P450 and thus the inhibitory potential of the drug is very low.⁵

Cost of Treatment

The cost of therapy for all three drugs is approximately the same at \$ 140.00 for one month.

Place in Therapy

The three currently available acetylcholinesterase inhibitors appear to be similar in efficacy. Donepezil can be dosed once daily, while twice daily dosing is needed for rivastigmine and galantamine. The dosage titration period may be longer for rivastigmine than donepezil or galantamine. Long term studies are required to determine the duration of benefit with these agents.⁶

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