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THE ROLE OF GALANTAMINE IN ALZHEIMER'S DISEASE: A COMPREHENSIVE REVIEW

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ABSTRACT:

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by cognitive decline, memory loss, and behavioral disturbances. Despite extensive research, a definitive treatment for AD remains elusive. Galantamine, a reversible acetylcholinesterase inhibitor and allosteric modulator of nicotinic acetylcholine receptors, has emerged as a promising therapeutic option for the treatment of cognitive symptoms of AD. This review article provides a comprehensive analysis of the mechanism of action, clinical efficacy, safety profile and future perspectives of galantamine in the treatment of AD.

Keywords: Alzheimer's Disease, Neurodegenerative Disorder, Reversible Acetylcholinesterase Inhibitor, Clinical Efficacy.

INTRODUCTION :

Galantamine is a tertiary alkaloid and a reversible, competitive inhibitor of the enzyme acetylcholinesterase (AChE), a widely studied therapeutic target used in the treatment of Alzheimer's disease.[1] First characterized in the early 1950s, galantamine is a tertiary alkaloid extracted from botanical sources such as Galanthus nivalis.[2] Galantamine was first studied for paralytic and neuropathic conditions such as myopathies and post-polio paralytic conditions and to reverse neuromuscular blockade.[2,3] After the discovery of its AChE inhibitory properties, the cognitive effects of galantamine have been widely studied. various psychiatric disorders such as mild cognitive impairment, cognitive impairment in schizophrenia and bipolar disorder, and autism. However, renewal of the Alzheimer's drug did not begin until the early 1990s due to extraction and synthesis difficulties.[2] Galantamine prevents the breakdown of acetylcholine in the synaptic cleft, which increases acetylcholine neurotransmission. It also acts as an allosteric modulator of the nicotinic receptor, giving its dual mechanism of action clinical significance.[3] The drug was approved by the FDA in 2001 to treat mild to moderate dementia of the Alzheimer's type. Because Alzheimer's disease is a progressive neurodegenerative disease, Galantamine cannot alter the course of the dementia process. Galantamine inhibits the enzyme responsible for breaking down acetylcholine in the synaptic cleft, increasing the activity and signal transmission of cholinergic neurons. According to this hypothesized mechanism of action, the therapeutic effect of galantamine may decrease as the disease progresses and fewer cholinergic neurons remain functionally intact.[5] Therefore, it is not considered a disease-modifying

drug.[4] Galantamine is marketed under the brand name Razadyne and is available as immediate and long acting oral tablets,capsules and as a solutions.[5]

Mechanism of action :

Galantamine, a unique drug, is an allosteric potentiator of α4β2 and presynaptic α-7 nicotinic acetylcholine receptors.[6] This action facilitates the release of acetylcholine from presynaptic neurons, giving its dual mode of action clinical significance. Nicotinic acetylcholine receptors (nAChRs) in the central nervous system are mainly expressed on the membranes of presynaptic neurons and regulate the release of several neurotransmitters, such as ACh, GABA, glutamate, norepinephrine, dopamine and serotonin, which are involved in memory and thinking and learning. nAChR agonists improve cognitive functions, while nAChR antagonists cause cognitive impairment.

Some studies have shown a decrease in both the expression and activity of nAChR in patients with Alzheimer's disease, which may explain the impairment of central cholinergic neurotransmission in these patients. Galantamine is a cholinomimetic agent which binds to nAChRs at an allosteric site, triggering a receptor conformational change that increases ACh release and enhances the activity of adjacent serotonergic and glutaminergic neurons. This modulation of nAChRs facilitates cholinergic transmission, both excitatory and inhibitory, in brain tissue and also increases receptor sensitivity. Galantamine-induced modulated release of other neurotransmitters may also contribute to nAChR regulation and improvement of behavioral symptoms in AD.[7–9]

Clinical Efficacy:

Galantamine has been evaluated in large (n = 285 to 978), well-designed 3- to 6-month trials in patients with mild to moderate AD, as well as several small, open-label studies. Galantamine at 16 or 24 mg/day was effective for 3 to 6 months in all studies, and significant differences from placebo were observed for all primary and secondary efficacy endpoints when a final intention-to-treat transfer (LOCF) analysis was performed. at the end of the double-blind study period. Galantamine-treated patients showed significant improvements in cognition, behavioral symptoms, and daily activities compared to placebo-treated patients. These beneficial effects of galantamine treatment on cognition and activities of daily living were achieved independently by the number of apolipoprotein E ε4 alleles count [assessed by the Cognitive (11-item) and Disability Assessment of Alzheimer's Disease Assessment Scale (ADAS-cog/11).The mean decrease (improvement) in ADAS-cog/11 points from baseline in these patients was 0.6 to 1.9 points, compared with an increase (worsening) of 0.6 to 2.2 points in the placebo group. Overall, clinician-interviewed impressions of change with caregiver input (CIBIC-plus) were significantly better (p andlt; 0.05 all comparisons) with galantamine than with placebo. A clinically significant improvement of ≥4 points in ADAS-cog/11 scores was observed in two patients receiving galantamine (16-32 mg/day) more (33.3-37% of patients) than in patients receiving placebo (16.6 and 19.6%) and in 11 points. 6-month studies ($p < 0.01$ for all comparisons within each study). These galantamine-treated patients also had significantly better performance of daily life outcomes than placebo-treated patients, benefiting both the baseline and instrumental DAD group. In addition, galantamine recipients showed significantly better outcomes in terms of behavioral symptoms than placebo recipients based on neuropsychiatric analysis, and galantamine treatment slowed the onset of behavioral and psychiatric symptoms. A long-term evaluation showed that galantamine at a dose of 24 mg/day preserved cognition and activities of daily living in patients who received this dose during a 12-month study period (6 months of a double-blind study followed by 6 months of follow-up. -up where the researchers remained). blinded). for treatment in the double-blind phase). ADAS-cog/11 and DAD scores were maintained compared to baseline in these patients treated with galantamine. Patients in other double-blind groups (galantamine 32 mg/day or placebo) who received galantamine 24 mg/day during the follow-up phase had a reduction in these scores. During the 6-month follow-up phase, a similar proportion of patients (54–61%) in each of the previous double-blind treatment groups remained stable or improved according to the CIBIC-plus score. Galantamine reduced the need for caregiver input compared with placebo. In the six-month study, patients receiving galantamine 24 or 32

mg/day did not show a significant change in need for caregiver supervision from baseline compared with placebo recipients who required 2 hours of additional supervision at 6 months (p andlt; 0.001 vs. baseline). There was also a reduction in the amount of time caregivers spent assisting galantamine recipients with activities of daily living (≤38 minutes per day), compared to a significant increase of 23 minutes from baseline in the placebo group. A time-to-treatment analysis shows that galantamine treatment reduces anxiety caused by the patient's behavioral symptoms.[10-14]

Safety and tolerability :

The safety and tolerability profile was analyzed based on gender, age, body weight, Thai Mental Status Examination (TMSE) score, cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), and Alzheimer's Disease Co-Exam/Activities of Daily Living Life. (ADCS). . /ADL) score. The most common side effects were nausea, dizziness and weight loss, which occurred more frequently during the dose escalation phase. Average weight loss at week 24 was 0.9 kg. Gender, age, body weight and ADAS-cog score did not influence the incidence of adverse events. Dizziness was more likely to occur in patients with low TMSE and high ADCS/ADL scores ($p = 0.02$ and $p = 0.050$). Patients with a TMSE score of at least 23 experienced more muscle cramps and fatigue than those with a TMSE score of less than 23 ($p < 0.05$). However, flexible titration of galantamine based on a 4-week schedule was safe and well tolerated in Thai AD patients.[15–17]

Disease Modification and Neuroprotection:

Recent studies indicate that galantamine may have disease-modifying potential beyond symptomatic relief. Preclinical studies show that it can prevent the formation of beta-amyloid plaques, prevent neuroinflammation and promote the survival of nerve cells. However, further studies are needed to clarify their potential neuroprotective effects.[18-20]

Challenges and Future Directions:

Although galantamine offers promising treatment options, problems remain. Patient response variability, dose optimization and potential drug interactions require careful consideration. Future studies could investigate combination treatments, longer-term treatment effects and potential benefit in the prodromal or mild cognitive decline phase of AD.[21–22]

Conclusion:

The dual mechanism of action of galantamine as a cholinesterase inhibitor and nicotinic receptor modulator makes it an important tool in the treatment of Alzheimer's disease. Its effects on cognitive function, relatively manageable side effects, and potential disease-modifying properties make it a valuable choice in a comprehensive AD treatment strategy. However, continued research and clinical trials are needed to fully understand its mechanisms, optimize its use, and maximize its benefits for AD patients.

In summary the multifaceted role of galantamine in enhancing cholinergic transmission, improving cognitive function, and potentially influencing disease progression underscores its importance as an important therapeutic agent for Alzheimer's disease.

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