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Editorial

Galantamine as benzofuro-benzazepine alkaloid used in cognition and dementia

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ABSTRACT

Galantamine is used to treat the symptoms of Alzheimer's disease (AD; a brain disease that slowly destroys the memory and the ability to think, learn, communicate and handle daily activities). Galantamine is in a class of medications called acetyl cholinesterase inhibitors. It works by increasing the amount of a certain natural substance in the brain that is needed for memory and thought. Galantamine may improve the ability to think and remember or slow the loss of these abilities in people who have AD. However, galantamine will not cure AD or prevent the loss of mental abilities at some time in the future.

Keywords: Benzazepine, Cognition, Dementia, Acetyl cholinesterase

INTRODUCTION

Inventor: **Dimitar Paskov**, Invented Year: 1959, Country: Bulgaria, Invention Field: Medicine & Healthcare. Galantamine (Nivalin, Razadyne, Razadyne ER, Reminyl, Lycoremine) is used for the treatment of mild to moderate Alzheimer's disease and various other memory impairments, in particular those of vascular dementia. It is an alkaloid that is obtained synthetically or from the bulbs and flowers of *Galanthus caucasicus* (Caucasian snowdrop), *Galanthus woronowii* (Voronov's snowdrop) and some other members of the family Amaryllidaceae such as Narcissus (daffodil), *Leucojum aestivum* (snowflake) and Lycoris including *Lycoris radiata* (red spider lily). It has acetyl cholinesterase (AChE)-inhibiting properties. It is available in both a prescription form and as an over the counter (OTC) supplement in twice-a-day tablets, in once-a-day extended-release capsules and in oral solution.[1]

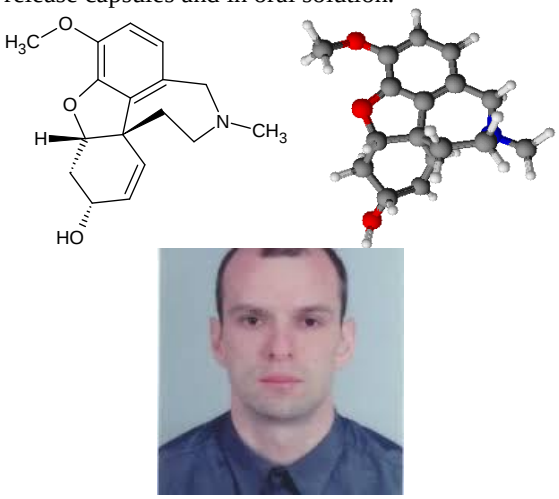


Figure-1: Galantamine and Inventor Dimitar Paskov

Description: It is a benzazepine alkaloid derived from norbelladine. It is found in galanthus and other amaryllidaceae. Galantamine is a cholinesterase inhibitor that has been used to reverse the muscular effects of gallamine triethiodide and tubocurarine and has been studied as a treatment for Alzheimer's disease and other central nervous system disorders.[2]

Chemical Formula: (CAS registry number: 357-70-0) $C_{17}H_{21}NO_3$. IUPAC Name: (4aS,6R,8aS)-5,6,9,10,11,12-hexahydro-3-methoxy-11-methyl-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin-6-ol. It has three chiral centres (4aS,6R,8aS) in which 4aS and 8aS are S-enantiomers (dotted lines) and 6R is R-enantiomer (bold line) and (–) enantiomer is biologically active out of 2^3=8 isomers.

Indication: It is used for the treatment of mild to moderate dementia of the Alzheimer's type which has also been investigated in patients with mild cognitive impairment who did not meet the diagnostic criteria for Alzheimer's disease. Galantamine's side effect profile is very similar to that of other cholinesterase inhibitors, with gastrointestinal symptoms being the most notable and most commonly observed. In practice, some other cholinesterase inhibitors might be better tolerated; however, a careful and gradual titration over more than three months may lead to equivalent long-term tolerability. Galantamine preparations (liquid, regular tablets and extended release tablets) warning of the risk of bradycardia (slow resting heart rate) and sometimes atrioventricular block, especially in predisposed persons. At the same time, the risk of syncope (fainting) seems to be increased relative to placebo. Main side effects are: nausea, vomiting, diarrhea, loss of appetite, stomach pain, heartburn, weight loss, extreme tiredness, dizziness, pale skin, headache, shaking of a part of your body that you cannot control, depression, difficulty falling asleep or staying asleep and runny nose.

Some side effects can be serious. The following symptoms are uncommon, but if you experience any of them, call your doctor immediately: difficulty in urinating, blood in the urine, pain or burning while urinating, seizures, slowed heartbeat, fainting, shortness of breath, black and tarry stools, red blood in the stools, bloody vomit and vomit that looks like coffee grounds.[3]

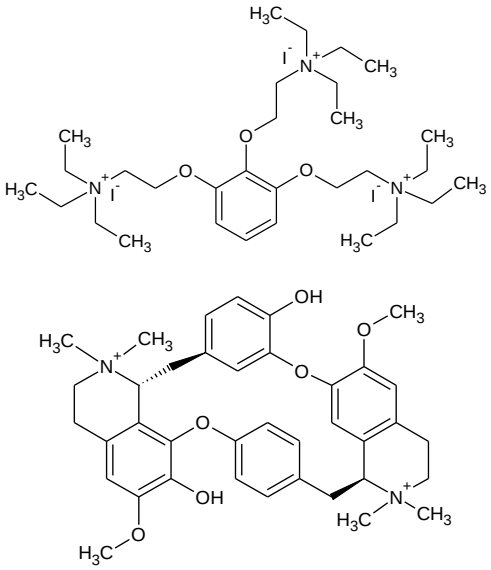
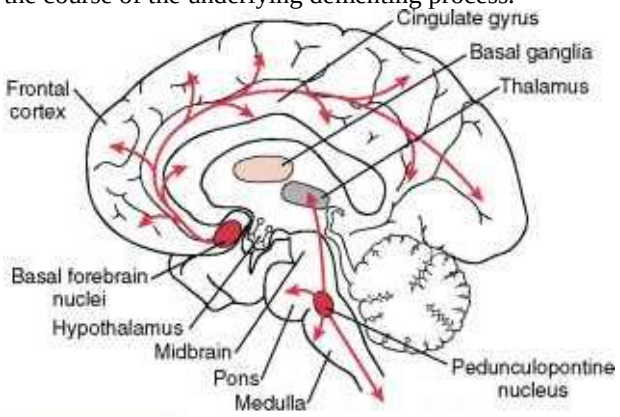


Figure-2: Gallamine triethiodide and Tubocurarine

Pharmacodynamics: Galantamine is a parasympathomimetic, specifically, a reversible cholinesterase inhibitor. It is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. An early patho-physiological feature of Alzheimer's disease that is associated with memory loss and cognitive deficits is a deficiency of acetylcholine as a result of selective loss of cholinergic neurons in the cerebral cortex, nucleus basalis and hippocampus. Galantamine is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetyl cholinesterase. If this proposed mechanism of action is correct, Galantamine's effect may lessen as the disease progresses and fewer cholinergic neurons remain functionally intact. There is no evidence that Galantamine alters the course of the underlying dementing process.[4]



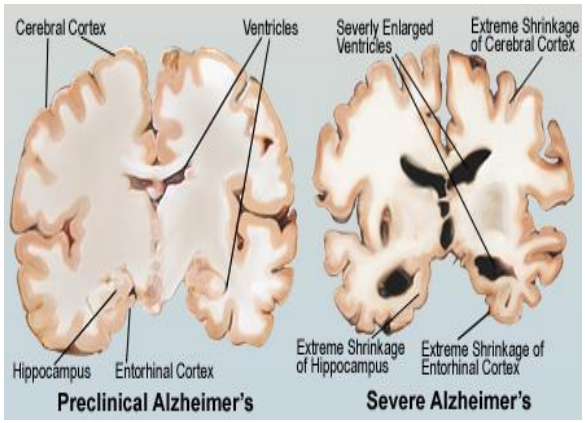
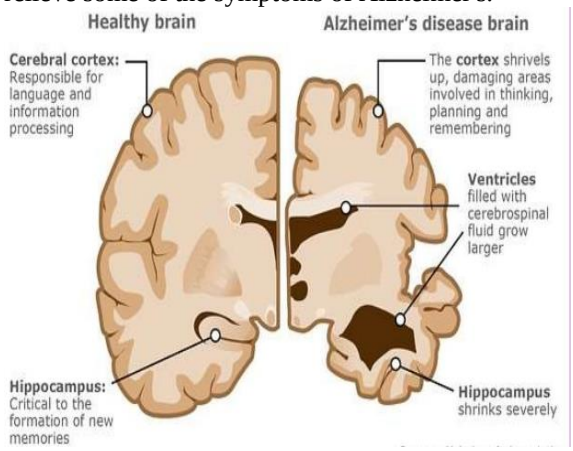


Figure-3: Alzheimer's disease

Pharmacokinetics: Absorption of galantamine is rapid and complete and shows linear pharmacokinetics. It is well absorbed with absolute oral bioavailability between 80 and 100%. It has a half-life of seven hours. Peak effect of inhibiting acetyl cholinesterase was achieved about one hour after a single oral dose of 8 mg in some healthy volunteers. Applies to the following strength(s): 4mg; 8mg; 12mg; 4mg/mL; 16mg; 24mg.[5]

Pharmacology: Galantamine is a potent allosteric potentiating ligand of human nicotinic acetylcholine receptors (nAChRs) α4β2, α7/5-HT3, α3β4, and α6β4 in certain areas of the brain, as well as a weak competitive and reversible cholinesterase inhibitor in all areas of the body. It increases the concentration and thereby action of acetylcholine in certain parts of the brain. It has shown activity in modulating the nicotinic cholinergic receptors on cholinergic neurons to increase acetylcholine release. It is hypothesized that this action might relieve some of the symptoms of Alzheimer's.



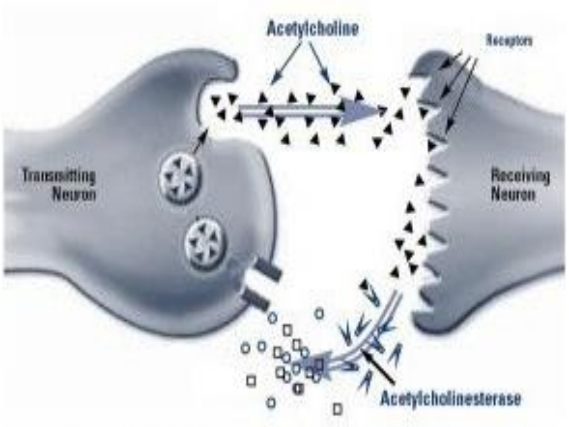


Figure-4: Healthy brain and Alzheimer's brain with Acetyl cholinesterase action

Galantamine in its pure form is a white powder. The atomic resolution 3D structure of the complex of galantamine and its target, acetyl cholinesterase, was determined by X-ray crystallography in 1999. There is no evidence that galantamine alters the course of the underlying dementing process. Plasma protein binding of galantamine is about 18%, which is relatively low. Before using this medication, tell your doctor or pharmacist of all prescription and nonprescription/herbal products you may use, especially of: anticholinergic drugs (e.g., atropine, benztropine, diphenhydramine, scopolamine, tolterodine), aspirin (high doses used for arthritis), cholinergic drugs (e.g., bethanechol), cholinesterase inhibitors (e.g., neostigmine), long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs such as ibuprofen, naproxen), drugs affecting liver enzymes that remove galantamine from your body (such as azole antifungals including ketoconazole, amitriptyline, SSRI antidepressants including paroxetine, quinidine). Also report the use of heart drugs (those that decrease heart rate or block AV impulse conduction) such as: beta-blockers (e.g., metoprolol, propranolol), calcium channel blockers (e.g., diltiazem, verapamil), digoxin. Check all prescription and nonprescription medicine labels carefully since many medications contain pain relievers/fever reducers (NSAIDs such as aspirin, ibuprofen, or naproxen) which, if taken together with galantamine, may increase your risk for stomach/intestinal bleeding. Low-dose aspirin, as prescribed by your doctor for specific medical reasons such as heart attack or stroke prevention (usually at dosages of 81-325milligrams per day), should be continued. Consult your doctor or pharmacist for more details.[6]

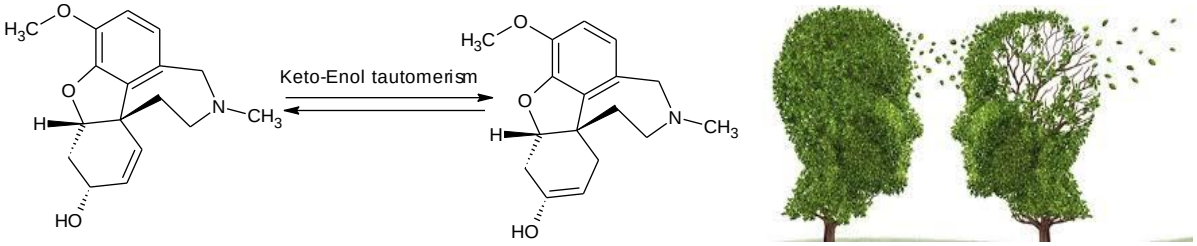


Figure-5: Lipid soluble, Acidic and Basic property of galantamine

Mechanism of action: Galantamine is a benzazepine alkaloid and a reversible, competitive acetyl cholinesterase inhibitor. It is not structurally related to other acetyl cholinesterase inhibitors. Galantamine's proposed mechanism of action involves the reversible inhibition of acetyl cholinesterase, which prevents the hydrolysis of acetylcholine, leading to an increased concentration of acetylcholine at cholinergic synapses. Galantamine also binds allosterically with nicotinic acetylcholine receptors and may possibly potentiate the action of agonists (such as acetylcholine) at these receptors. Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated and excreted unchanged in the urine. Volume of distribution: 175L, Protein binding: 18%, Route of elimination: Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated and excreted unchanged in the urine, Half life: 7hours, Clearance: 300mL/min [After IV or oral administration], Toxicity: LD_{50}=75mg/kg (rat).[7] Melting point: 269-270°C (HBr salt), Water solubility: 10mg/mL (HBr salt), logP: 1.8 (lipid soluble), pKa (Strongest Acidic): 14.81 (enolic –OH), pKa (Strongest Basic): 8.91 (tertiary amino group). Specific optical rotation = –118.7° at 20°C (c=1.378g/100 ml in benzene)

Metabolism: Approximately 75% of a dose of galantamine is metabolized in the liver. In vitro studies have shown that Hepatic CYP2D6 and CYP3A4 are involved in galantamine metabolism. For Razadyne ER, the once-a-day formulation, CYP2D6 poor metabolizers had drug exposures that were approximately 50% higher than for extensive metabolizers. About 7% of the population has this genetic mutation; however, because the drug is individually titrated to tolerability, no specific dosage adjustment is necessary for this population.[8]

Conclusion: Galantamine is a parasympathomimetic, specifically, a reversible cholinesterase inhibitor. It is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. It is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetyl cholinesterase. If this proposed mechanism of action is correct, Galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that Galantamine alters the course of the underlying dementing process. Galantamine's proposed mechanism of action involves the increase of the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetyl cholinesterase. It is approved by USFDA as cholinesterase inhibitors, nootropic agents and parasympathomimetics. It is used for the treatment of mild to moderate Alzheimer's disease and various other memory impairments, in particular those of vascular origin.

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