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Galantamine

Updated: January 15, 2020.

OVERVIEW

Introduction

Galantamine is an oral acetylcholinesterase inhibitor used for therapy of Alzheimer disease. Galantamine is associated with a minimal rate of serum enzyme elevations during therapy and has not been implicated as a cause of clinically apparent liver injury.

Background

Galantamine (ga lan' ta meen) is a selective acetylcholinesterase inhibitor which acts by inhibition of the metabolism of acetylcholine in the postsynaptic clefts, thus enhancing cholinergic neurotransmission. Alzheimer disease is associated with a cholinergic deficiency in the cerebral cortex, and the increase in concentration of acetylcholine with acetylcholinesterase inhibition is associated with improvement in cognitive function in affected patients. Galantamine has selective activity for acetylcholinesterase in the central nervous system with little effect on the enzyme in peripheral tissue. Galantamine was approved for use in the United States in 2001, and current indications include mild-to-moderate dementia of the Alzheimer disease type. Galantamine is available generically and under the brand name of Razadyne in tablets of 4, 8 and 12 mg and as extended release capsules of 8, 16 and 24 mg. It is also available as an oral solution (4 mg/mL). The usual maintenance dose is 16 to 24 mg daily in two divided doses or once daily using the extended release forms. Common side effects include nausea, vomiting, diarrhea, abdominal pain, dizziness, fatigue, insomnia, vivid dreams, anxiety, restlessness, blurred vision, dry mouth and pruritus, symptoms common to cholinergic stimulation. Uncommon but potentially severe adverse events include bradycardia and atrioventricular block, urinary retention, gastrointestinal bleeding and hypersensitivity reactions.

Hepatotoxicity

In several large placebo controlled clinical trials, there was no increase in the rate of serum enzyme elevations in patients treated with galantamine compared to those on placebo and no reports of hepatotoxicity. No individual case reports of clinically apparent hepatotoxicity have been published, although cases of liver enzyme elevations and hepatitis attributed to galantamine have been reported to the sponsor. With the exception of tacrine, the acetylcholinesterase inhibitors used for Alzheimer disease have only rarely been linked to instances of clinically apparent, acute liver injury.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Galantamine is extensively metabolized by the hepatic cytochrome P450 system (CYP 2D6 and 3A4) followed by glucuronidation. Hepatotoxicity might occur as a result of its idiosyncratic metabolism to a toxic or immunogenic intermediate.

Outcome and Management

Galantamine has not been associated with published cases of clinically apparent hepatotoxicity, acute liver failure, chronic hepatitis or vanishing bile duct syndrome. There is no information on the possible cross sensitivity to liver injury among the various acetylcholinesterase inhibitors.

References regarding the safety and potential hepatotoxicity of the drugs used for Alzheimer disease are provided below for galantamine and again for all agents after the overview section of Alzheimer Disease Agents.

Drug Class: Alzheimer Disease Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Galantamine – Generic, Razadyne®

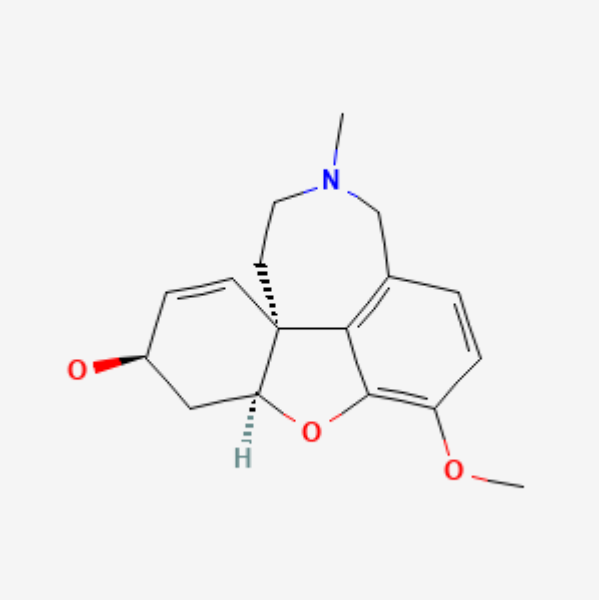
DRUG CLASS

Alzheimer Disease Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Galantamine	357-70-0	C17-H21-N-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 15 January 2020

Zimmerman HJ. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 709-42.

(Expert review of hepatotoxicity published in 1999; tacrine, the first cholinesterase inhibitor approved for use in Alzheimer disease, was associated with a very high rate of serum ALT elevations [~50%], but rarely caused clinically apparent liver injury; the other Alzheimer disease agents are not discussed).

Larrey D, Ripault MP. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 518.

(Review of hepatotoxicity of psychotropic agents; drugs for Alzheimer disease are not specifically discussed).

Roberson ED. Alzheimer's disease. Treatment of central nervous system degenerative disorders. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 333-5.

(Textbook of pharmacology and therapeutics).

Fulton B, Benfield P. Galanthamine. Drugs Aging 1996; 9: 60-5. 8818586

(Review of pharmacology, efficacy and safety of galantamine in Alzheimer disease; most side effects were due to its cholinergic properties, including nausea, vomiting, abdominal pain, diarrhea, anxiety and dizziness; "to date, elevations in liver enzymes or other signs of liver toxicity have not been reported with galanthamine").

Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomized controlled trial. Galantamine International-1 Study Group. BMJ 2000; 321: 1445-9. 11110737

(Controlled trial of 6 months of two doses of galantamine vs placebo in 653 patients with Alzheimer disease; side effects included nausea, diarrhea, headache, anorexia and weight loss, but there were "no consistent trends or clinically important differences" in blood chemistry results).

Pirttilä T, Wilcock G, Truyen L, Damaraju CV. Long-term efficacy and safety of galantamine in patients with mild-to-moderate Alzheimer's disease: multicenter trial. Eur J Neurol 2004; 11: 734-41. 15525294

(Results of continuing galantamine for 24 months in 491 patients with Alzheimer disease; reported no instances of liver toxicity and "no clinically relevant trends" in "clinical laboratory parameters").

Farlow MR, Cummings JL. Effective pharmacologic management of Alzheimer's disease. Am J Med 2007; 120: 388-97. 17466645

(Review of safety and efficacy of medications for Alzheimer disease; no discussion of hepatotoxicity).

Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin Interv Aging 2008; 3: 211-25. 18686744

(Systematic review of 3 cholinesterase inhibitors in Alzheimer disease; most common adverse events were nausea [19%], vomiting [13%], diarrhea [11%] and weight loss [9%] and withdrawal for adverse events in 11-21%; no mention of ALT elevations or hepatotoxicity).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. 18955056

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008; none were attributed to a drug used to treat Alzheimer disease).

Mayeux R. Early Alzheimer's disease. N Engl J Med 2010; 362: 2194-201. 20558370

(Case discussion and review of current understanding of Alzheimer disease including role of therapy; common side effects of cholinesterase inhibitors include nausea, vomiting, anorexia, diarrhea, dizziness, muscle cramps, insomnia and vivid dreams; memantine can cause constipation, dizziness, headache and body pains; no mention of hepatotoxicity).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. 20949552

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to drugs used to treat Alzheimer disease).

Tan CC, Yu JT, Wang HF, Tan MS, Meng XF, Wang C, Jiang T, et al. Efficacy and Safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 2014; 41: 615-31. 24662102

(Systematic review of safety and efficacy of 4 Alzheimer drugs does not mention ALT elevations or hepatotoxicity).

Tricco AC, Soobiah C, Berliner S, Ho JM, Ng CH, Ashoor HM, Chen MH, Hemmelgarn B, Straus SE. Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review and meta-analysis. CMAJ. 2013 Nov 5; 185 (16): 1393-401. 24043661

(Systematic review of 8 clinical trials and 3 reports on the safety and efficacy of Alzheimer drugs mentions that side effects of nausea, diarrhea, vomiting and headaches were usually more frequent with the active drugs compared to placebo; no mention of ALT elevations or clinically apparent liver injury).

Hager K, Baseman AS, Nye JS, Brashear HR, Han J, Sano M, Davis B, Richards HM. Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer's disease. Neuropsychiatr Dis Treat 2014; 10: 391-401. 24591834

(Among 2045 patients with Alzheimer disease treated with galantamine or placebo for up to 2 years, symptoms of nausea, vomiting, and fatigue were slightly more frequent with galantamine than placebo, but serious adverse events were similar in the two groups and "No clinically meaningful changes were observed in... laboratory tests").

Wang HF, Yu JT, Tang SW, Jiang T, Tan CC, Meng XF, Wang C, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. J Neurol Neurosurg Psychiatry 2015; 86: 135-43. 24828899

(Systematic review of 10 trials of Alzheimer disease drugs in Parkinson disease and other forms of dementia reported that the common adverse events were cholinergic in nature [anorexia, nausea, diarrhea] and were generally mild-to-moderate in severity; serious adverse events were similar to rates with placebo; no mention of ALT elevations or hepatotoxicity).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. 23419359

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none of the cases were attributed to a drug used to treat Alzheimer disease).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol 2014; 13: 231-9. 24552865

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to a drug for Alzheimer disease).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. 25754159

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were due to a drug for Alzheimer disease).

Kröger E, Mouls M, Wilchesky M, Berkers M, Carmichael PH, van Marum R, Souverein P, et al. Adverse drug reactions reported with cholinesterase inhibitors: an analysis of 16 years of individual case safety reports from VigiBase. Ann Pharmacother 2015; 49: 1197-206. 26324356

(Analysis of spontaneous adverse event reports made between 2006 and 2013 to a WHO drug monitoring database identified 16,995 serious adverse events in patients receiving cholinesterase inhibitors, 121 of which were hepatobiliary, including 47 for donepezil, 53 rivastigmine and 21 galantamine; no details provided).

Mohammad D, Chan P, Bradley J, Lanctôt K, Herrmann N. Acetylcholinesterase inhibitors for treating dementia symptoms - a safety evaluation. Expert Opin Drug Saf 2017; 16: 1009-19. 28678552

(Review of safety of donepezil, galantamine and rivastigmine in Alzheimer disease concludes that adverse events are "generally mild", mostly gastrointestinal, comparable among the different agents, but usually greater with higher doses and less with transdermal formulations).

Dou KX, Tan MS, Tan CC, Cao XP, Hou XH, Guo QH, Tan L, et al. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. Alzheimers Res Ther 2018; 10: 126. 30591071

(Meta-analysis of 41 published randomized controlled trials of drugs for Alzheimer disease concluded that all had beneficial effects on cognition and function but not on neuropsychiatric symptoms, and all had adverse effects but memantine showed "the best profile of acceptability"; no mention of ALT elevations or hepatotoxicity).

Khoury R, Rajamanickam J, Grossberg GT. An update on the safety of current therapies for Alzheimer's disease: focus on rivastigmine. Ther Adv Drug Saf 2018; 9: 171-8. 29492246

(Review of the safety of Alzheimer disease agents discusses gastrointestinal adverse events, cardiac side effects, skin reactions [to transdermal formulations] and neuropsychiatric effects, but not hepatic adverse events).

Bhattacharjee S, Patanwala AE, Lo-Ciganic WH, Malone DC, Lee JK, Knapp SM, Warholak T, Burke WJ. Alzheimer's disease medication and risk of all-cause mortality and all-cause hospitalization: A retrospective cohort study. Alzheimers Dement (N Y) 2019; 5: 294-302. 31338414

(Among more than 20,000 Medicare beneficiaries receiving Alzheimer disease drugs, overall survival was better for those on donepezil than memantine or rivastigmine; no mention of serious hepatic adverse events or liver related deaths).

Carney G, Bassett K, Wright JM, Maclure M, McGuire N, Dormuth CR. Comparison of cholinesterase inhibitor safety in real-world practice. Alzheimers Dement (NY) 2019; 5: 732-9. 31921965

(Among 29,047 Canadian patients with Alzheimer disease who initiated anticholinesterase therapy between 2007 and 2016, all-cause mortality and serious cardiovascular event rates were lower in those receiving galantamine than those on donepezil; no mention of hepatic adverse events or liver related deaths).

Matsunaga S, Fujishiro H, Takechi H. Efficacy and safety of cholinesterase inhibitors for mild cognitive impairment: a systematic review and meta-analysis. J Alzheimers Dis 2019; 71: 513-23. 31424411

(Systematic review of 14 randomized controlled trials of anticholinesterase drugs in Alzheimer disease concluded that the agents had slight efficacy in ameliorating symptoms but a moderate rate of discontinuation because of adverse events such as abnormal dreams, dizziness, headache, insomnia, diarrhea, muscle cramps, nausea and weight loss; no mention of discontinuations because of ALT elevations or hepatotoxicity).

Li DD, Zhang YH, Zhang W, Zhao P. Meta-analysis of randomized controlled trials on the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease. Front Neurosci 2019; 13: 472. 31156366

(Meta-analysis of 36 controlled trials of drugs for Alzheimer disease focusing upon relative efficacy and rates of discontinuation in comparison to placebo).