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Rivastigmine

Updated: January 15, 2020.

OVERVIEW

Introduction

Rivastigmine is an oral acetylcholinesterase inhibitor used for therapy of Alzheimer disease. Rivastigmine is associated with a minimal rate of serum enzyme elevations during therapy and is a rare cause of clinically apparent liver injury.

Background

Rivastigmine (riv" a stig' meen) is a selective acetylcholinesterase inhibitor which acts by inhibition of the metabolism of acetylcholine in the postsynaptic clefts, thus enhancing cholinergic neurotransmission. Rivastigmine has selective activity for acetylcholinesterase in the central nervous system with little effect on the enzyme in peripheral tissue. The increase in concentration of acetylcholine is associated with improvement in cognitive function in patients with Alzheimer disease who typically have relative cholinergic deficiency in the cerebral cortex. Rivastigmine was approved for use in the United States in 2007 for treatment of mild-to-moderate dementia in Alzheimer and Parkinson disease. Rivastigmine is available generically and under the brand name Exelon in capsules of 1.5, 3, 4.5 and 6 mg, as an oral solution of 2 mg/mL, and a transdermal patch of 14.6 and 9.5 mg applied every 24 hours. The usual maintenance dose is 3 to 6 mg twice daily. Common side effects include diarrhea, nausea, vomiting, 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 seizures, nightmares, hypersensitivity reactions, urticaria and Stevens-Johnson Syndrome.

Hepatotoxicity

In large placebo controlled trials, rivastigmine therapy was not associated with an increased rate of serum enzyme elevations compared to placebo treatment and no instances of clinically apparent liver injury with jaundice were reported. Nevertheless, since its introduction into clinical use, rivastigmine (administered by transdermal patch) has been implicated in at least one report of clinically apparent hepatotoxicity with mild jaundice. The time to onset was 2 months and the serum enzyme elevations had a mildly hepatocellular pattern. Mild rash and eosinophilia were also present, but autoimmune features were not. Recovery was complete within 5 weeks of drug discontinuation.

Likelihood score: D (possible, rare cause of clinically apparent drug-induced liver injury).

Mechanism of Injury

Rivastigmine differs from the other acetylcholinesterase inhibitors in not having major hepatic metabolism. The mechanism of potential hepatotoxicity of rivastigmine is not known, but is likely to be immunological idiosyncrasy.

Outcome and Management

Cases of hepatotoxicity from rivastigmine have been too few to characterize clinically. There have been no published reports of acute liver failure, chronic hepatitis or vanishing bile duct syndrome attributed to rivastigmine. 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 rivastigmine and again for all agents after the overview section of Alzheimer Disease Agents.

Drug Class: Alzheimer Disease Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Rivastigmine – Generic, Exelon®

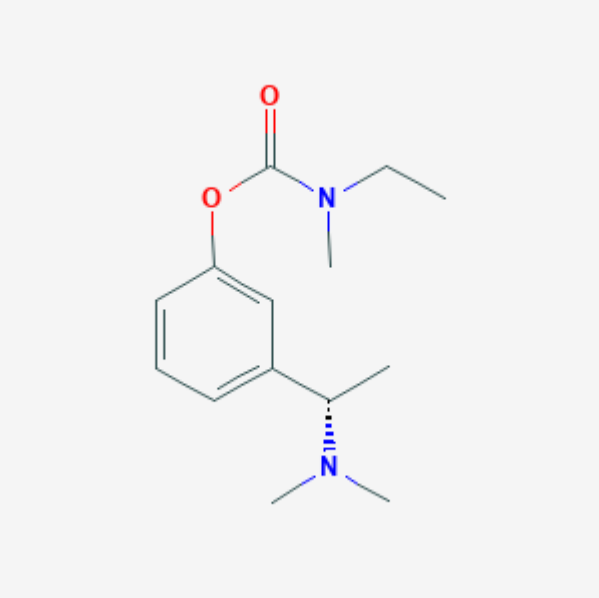
DRUG CLASS

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
Rivastigmine	123441-03-2	C14-H22-N2-O2	

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).

Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, Stälin HB, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999; 318: 633-8. 10066203

(Controlled trial of two doses of rivastigmine vs placebo for 26 weeks in 725 patients with Alzheimer disease, no differences in ALT elevations between treatment and placebo arms; side effects included nausea, dizziness, headache, anorexia, fatigue and abdominal pain).

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).

Mumoli N, Carmignani G, Luschi R, Cei M, Chiavistelli P. Hepatitis with cholestasis caused by rivastigmine transdermal patch. Am J Gastroenterol 2009; 104: 2859-60. 19888250

(84 year old woman developed jaundice and rash 2 months after starting transdermal rivastigmine for Alzheimer disease [bilirubin 3.0 mg/dL, ALT 857 U/L, Alk P 344 U/L, eosinophils 8%], resolving within 5 weeks of stopping).

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; 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).

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).

Emre M, Poewe W, De Deyn PP, Barone P, Kulisevsky J, Pourcher E, van Laar T, et al. Long-term safety of rivastigmine in parkinson disease dementia: an open-label, randomized study. Clin Neuropharmacol 2014; 37 (1): 9-16. 24434526

(Among 583 patients with Parkinson disease dementia treated with either rivastigmine capsules or patch, adverse events were more frequent with capsules, particularly tremor, nausea, vomiting, diarrhea and syncope; no mention of ALT elevations or hepatotoxicity).

Gauthier S, Robillard A, Cohen S, Black S, Sampalis J, Colizza D, de Takacsy F, et al.; EMBRACE investigators. Real-life effectiveness and tolerability of the rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease: the EMBRACE study. Curr Med Res Opin 2013; 29: 989-1000. 23647369

(Among 969 Canadian patients with Alzheimer disease treated with rivastigmine patch for 18 months, 18% stopped treatment because of adverse events, usually skin reactions or nausea/vomiting; no mention of ALT elevations or clinically apparent liver injury).

Mäurer M, Ortler S, Baier M, Meergans M, Scherer P, Hofmann W, Tracik F. Randomised multicentre trial on safety and efficacy of rivastigmine in cognitively impaired multiple sclerosis patients. Mult Scler 2013; 19: 631-8. 23069874

(Among 86 patients with multiple sclerosis and cognitive decline treated with rivastigmine or placebo patches for 16 weeks, side effects were similar in the two groups; 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).

Chang CC, Peng GS, Lai TJ, Li CH, Liu CK. A 48-week, multicenter, open-label, observational study evaluating oral rivastigmine in patients with mild-to-moderate Alzheimer's disease in Taiwan. Adv Ther 2019; 36: 1455-64. 30953330

(Among 151 Taiwanese patients with Alzheimer disease treated with rivastigmine, common side effects were dizziness [13%] and nausea [9%], and there were "no new or unexpected" adverse events and no mention of ALT elevations or hepatotoxicity).

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).