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Rasagiline

Updated: July 21, 2017.

OVERVIEW

Introduction

Rasagiline is an inhibitor of monamine oxidase used as adjunctive therapy in combination with levodopa and carbidopa in the management of Parkinson's disease. Rasagiline has been associated with a low rate of serum enzyme elevations during treatment, but has not been linked to instances of clinically apparent acute liver injury.

Background

Rasagiline (ra sa' ji leen) is a specific inhibitor of monamine oxidase (MAO) type B which is a major enzyme in the pathway of dopamine and levodopa metabolism. As a result, rasagiline results in an increase in the bioavailability of levodopa enhancing and increasing the duration of its effects in Parkinson disease. Rasagiline was approved for use in the United States in 2007, the second MAO-B inhibitor approved for use in the therapy of Parkinson disease, and is currently approved for use monotherapy or as an adjunct to levodopa therapy. Rasagiline is available in tablets of 0.5 and 1 mg under the brand name of Azilect. Rasagiline is typically given in oral doses of 0.5 to 1 mg once daily alone or in combination with levodopa/carbidopa. Common side effects include headache, nausea, dizziness, agitation, delusions, insomnia, orthostatic hypotension, dry mouth, headache and gastrointestinal upset – most of which are attributable to enhanced dopaminergic effects.

Hepatotoxicity

Rasagiline has been reported to cause serum enzyme elevations in a small proportion of patients treated long term, although the abnormalities were usually mild and self-limiting. Rasagiline has not been implicated in cases of acute liver injury, but such instances have been reported with other less specific MAO inhibitors.

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

Mechanism of Injury

Rasagiline is extensively metabolized by the hepatic cytochrome P450 system (CYP 1A2) to inactive metabolites.

Outcome and Management

Instances of hepatotoxicity attributed to rasagiline have been mild and self-limiting elevations in serum enzymes. No instances of severe liver injury, acute liver failure, chronic hepatitis or vanishing bile duct syndrome have been linked to rasagiline use.

Drug Class: Antiparkinson Agents

Other Drugs in the Subclass, Selective MAO-B Inhibitors: Safinamide, Selegiline

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Rasagiline – Generic, Azilect®

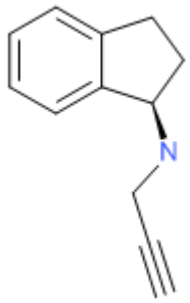
DRUG CLASS

Antiparkinson Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Rasagiline	136236-51-6	C12-H13-N	

ANNOTATED BIBLIOGRAPHY

References updated: 21 July 2017

Zimmerman HJ. Antiparkinsonism drugs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 715-7.

(Expert review of hepatotoxicity published in 1999; among anticholinergic agents, "only trihexyphenidyl has been incriminated in hepatic injury"; other antiparkinsonism drugs discussed include levodopa, lergotrile [no longer available], pergolide and bromocriptine, but not rasagiline).

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 Inc, 2013, pp. 443-62.

(Review of hepatotoxicity of agents acting on the central nervous system).

Standaert DG, Roberson ED. Treatment of central nervous system degenerative disorders. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 609-28.

(Textbook of pharmacology and therapeutics).

Lambert D, Waters CH. Comparative tolerability of the newer generation antiparkinsonian agents. Drugs Aging 2000; 16: 55-65. PubMed PMID: 10733264.

(Review of mechanism of action, tolerability and safety of selegiline, pramipexole, ropinirole, tolcapone and entacapone in Parkinson disease).

Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch Neurol 2005; 62: 241-8. PubMed PMID: 15710852.

(Controlled trial of 26 weeks of rasagiline vs placebo in 472 patients with Parkinson disease on levodopa with motor fluctuations; side effects that were more common with rasagiline were anorexia, weight loss, vomiting and balance difficulty, "there were no significant group differences in laboratory values during treatment").

Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe W, Stocchi F, Tolosa E; LARGO study group. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet 2005; 365: 947-54. PubMed PMID: 15766996.

(Randomized controlled trial of rasagiline vs entacapone vs placebo for 18 weeks in patients with Parkinson disease on levodopa/carbidopa found little difference in side effects; no mention of ALT elevations or 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. PubMed PMID: 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 agents used for Parkinson disease).

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: 1419-25,1425. PubMed PMID: 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 96 were attributed to an agent used to treat Parkinson disease).

Drugs for Parkinson's disease. Treat Guidel Med Lett 2013; 11 (135): 101-6. PubMed PMID: 24165688.

(Concise review of recommendations for therapy of Parkinson disease with description of mechanisms of action, efficacy and adverse events).

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. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to an agent to treat Parkinson 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. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury from the US enrolled in a prospective database between 2004 and 2012, none were attributed to an agent used to treat Parkinson disease).