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Ropinirole

Updated: July 21, 2017.

OVERVIEW

Introduction

Ropinirole is a selective dopamine receptor agonist used in the therapy of Parkinson disease. Ropinirole therapy is associated with low rate of transient serum enzyme elevations during treatment and has been implicated in rare cases of acute liver injury.

Background

Ropinirole (roe pin' i role") is a synthetic, nonergot derivative dopamine receptor agonist that has selective activity for the D2 class of dopamine receptors and little agonist activity for the D1 class. For this reason, ropinirole may be better tolerated than bromocriptine or pergolide, which act on both classes of dopamine receptors. Ropinirole was approved for use in the United States in 1997 for the therapy of symptomatic Parkinson disease. Indications were later expanded to include restless legs syndrome. Ropinirole is available in tablets of 0.25, 0.50, 1, 2, 3, 4 and 5 mg under the brand name of Requip. Ropinirole is typically initiated in low doses, with adjustment upwards based upon tolerance and clinical effects. In treatment of Parkinson disease, the typical dose of ropinirole is 3 to 6 mg daily in three divided doses, often but not always in combination with levodopa/carbidopa. Ropinirole can be initiated more quickly than bromocriptine or pergolide and does not cause the profound hypotension and nausea that are typical of the ergot derivatives. Rolinirole is also approved for use in restless legs syndrome, typically starting at 0.25 mg daily, 1 to 3 hours before bedtime, and increasing the dose slowly based upon tolerance and effect. Common side effects of ropinirole include somnolence, fatigue, vivid dreams, anxiety, confusion, depression, dizziness, headache and gastrointestinal upset, symptoms that are typical of dopaminergic stimulation.

Hepatotoxicity

Ropinirole has been reported to cause serum aminotransferase or alkaline phosphatase elevations in a small proportion of patients, but these abnormalities are usually mild, asymptomatic and self-limiting even without dose adjustment. Ropinirole has been implicated in a small number of cases of acute liver injury, but the clinical characteristics and typical pattern of enzyme elevations has not been characterized. In one case report, the time to onset was 2 months and the pattern of liver enzyme elevations was mixed and associated with marked jaundice. Immunoallergic and autoimmune features were not present. The injury resolved within 2 months of stopping. Thus, ropinirole can cause acute, clinically apparent liver injury with jaundice, but it is rare.

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

Mechanism of Injury

Ropinirole is extensively metabolized in the liver, largely by the cytochrome P450 system (CYP 1A2) to inactive metabolites. Liver injury may be caused by production of a toxic or immunogenic intermediate of its metabolism.

Outcome and Management

Instances of liver injury attributed to ropinirole have been mild to moderate and self-limiting. No instances of acute liver failure or chronic injury have been reported.

Drug Class: Antiparkinson Agents

Other Drugs in the Subclass, Dopamine Receptor Agonists: Apomorphine, Bromocriptine, Pergolide, Pramipexole, Rotigotine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ropinirole – Generic, Requip®

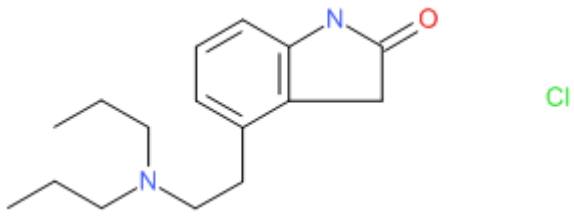
DRUG CLASS

Antiparkinson Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Ropinirole	91374-20-8	C16-H24-N2-O.Cl-H	

REFERENCES

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 ropinirole).

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).

Sethi KD, O'Brien CF, Hammerstad JP, Adler CH, Davis TL, Taylor RL, Sanchez-Ramos J, et al. Ropinirole for the treatment of early Parkinson disease: a 12-month experience. Ropinirole Study Group. Arch Neurol 1998; 55: 1211-6. PubMed PMID: 9740115.

(147 patients with early Parkinson disease [not on levodopa] were randomized to receive ropinirole or placebo; no mention of ALT elevations or hepatic adverse events).

Hauser RA, Molho E, Shale H, Pedder S, Dorflinger EE. A pilot evaluation of the tolerability, safety, and efficacy of tolcapone alone and in combination with oral selegiline in untreated Parkinson's disease patients. Tolcapone De Novo Study Group. Mov Disord 1998; 13: 643-7. PubMed PMID: 9686768.

(Among 83 patients with Parkinson disease treated with tolcapone with or without selegiline for 8 weeks, ALT elevations occurred in 1 patient [2%] on tolcapone alone).

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).

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).

Hening WA, Allen RP, Ondo WG, Walters AS, Winkelman JW, Becker P, Bogan R, et al; SP792 Study Group. Rotigotine improves restless legs syndrome: a 6-month randomized, double-blind, placebo-controlled trial in the United States. Mov Disord 2010; 25: 1675-83. PubMed PMID: 20629075.

(Among 505 patients with restless leg syndrome treated with one of 4 doses of transdermal rotigotine or placebo for 6 months, symptom scores improved with higher doses [2 or 3 mg/24 hours] and side effects included application site reactions, nausea, somnolence, headache and insomnia, but there were no liver related serious adverse events).

Navacerrada F, González-Alonso MR, Alonso-Navarro H, Pilo-de-la-Fuente B, Plaza-Nieto JF, Jiménez-Jiménez FJ. Liver toxicity possibly related with ropinirole use in the treatment of restless legs syndrome. Eur J Neurol 2011; 18: e65. PubMed PMID: 21199184.

(68 year old woman developed jaundice 3 months after starting ropinirole for restless leg syndrome [bilirubin 11.1 mg/dL, ALT 2399 U/L, Alk P 2020 U/L], resolving within 2 months of stopping and no other cause was found).

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).