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Iloperidone

Updated: April 15, 2018.

OVERVIEW

Introduction

Iloperidone is a second generation (atypical) antipsychotic agent that is used for treatment of schizophrenia. Iloperidone is associated with a low rate of serum aminotransferase elevations during therapy, but has not been linked to instances of clinically apparent acute liver injury.

Background

Iloperidone (eye" loe per' i done) is a second generation antipsychotic agent which appears to act as a dopamine type 2 (D2) and serotonin (5-HT)-2A receptor antagonist whose structure and mechanism of action are similar to risperidone. Several randomized controlled trials have shown that iloperidone improves symptoms of schizophrenia with effects comparable to risperidone and ziprasidone. Iloperidone was approved for use in schizophrenia in the United States in 2010 and is available as tablets of 1, 2, 4, 6, 8, 10 and 12 mg under the brand name Fanapt. The typical maintenance dose in adults is 6 to 12 mg twice daily. Common side effects of include dizziness, dry mouth, somnolence, fatigue, nasal congestion, anxiety, restlessness (akathisia) and weight gain. Ilioperidone therapy is also associated with postural hypotension and prolongation of the QTc interval. Rare, but potentially severe adverse reactions (mentioned in most antipsychotic and antidepressant product labels) include tardive dyskinesia, major neurologic events, neuroleptic malignant syndrome, orthostatic hypotension, seizures and neutropenia.

Hepatotoxicity

Liver test abnormalities occur in 1% to 3% of patients on long term therapy with iloperidone, but similar rates are reported with placebo therapy and with comparator agents. The ALT elevations are usually mild, transient and often resolve even without dose modification or drug discontinuation. There have been no published reports of clinically apparent liver injury with symptoms or jaundice attributed to iloperidone therapy.

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

Mechanism of Injury

The mechanism by which iloperidone might cause serum ALT elevations or liver injury is not known. Iloperidone is extensively metabolized by the cytochrome P450 system (CYP 2D6 and 3A4) to its active metabolite and is susceptible to drug-drug interactions with agents that inhibit or induce these microsomal enzymes.

Outcome and Management

The serum aminotransferase elevations that occur on iloperidone therapy are usually self-limited and often do not require dose modification or discontinuation. No instances of acute liver failure, chronic hepatitis or vanishing bile duct syndrome have been attributed to iloperidone. Cross sensitivity to liver related or other hypersensitivity reactions between iloperidone and structurally related antipsychotic agents (such as lurasidone, paliperidone, risperidone and ziprasidone) have not been demonstrated, but may well occur.

Drug Class: Antipsychotic Agents, Atypicals

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Iloperidone – Fanapt®

DRUG CLASS

Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

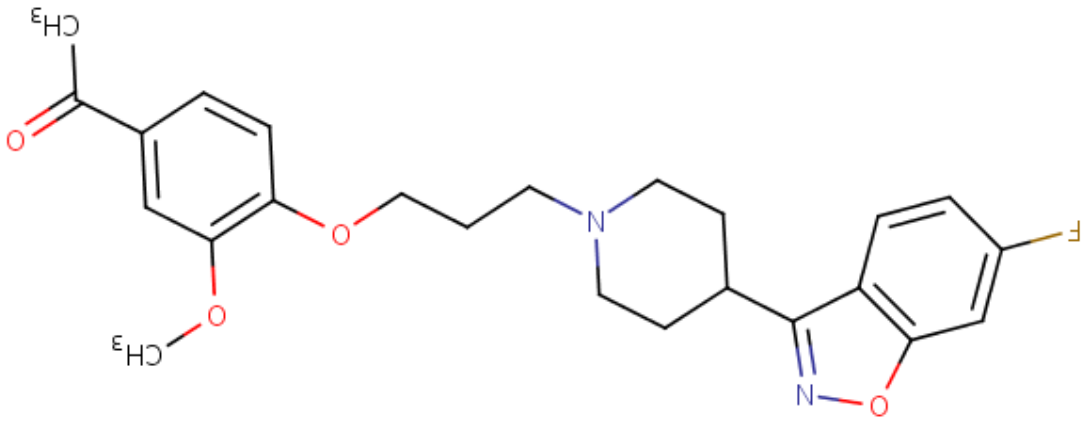
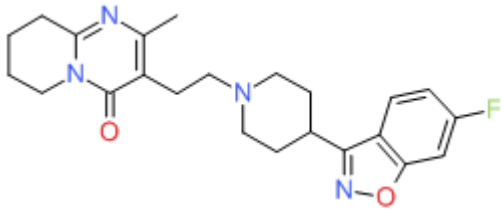
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Iloperidone	133454-47-4	C24-H27-F-N2-O4	

Table continued from previous page.

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Risperidone	106266-06-2	C23-H27-F-N4-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2018

Meyer JM. Pharmacotherapy of psychosis and mania. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 417-56.

(Textbook of pharmacology and therapeutics).

Larry D. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare USA, 2007, pp. 507-26.

(Review of hepatotoxicity of psychiatric agents does not discuss iloperidone).

Kane JM, Lauriello J, Laska E, Di Marino M, Wolfgang CD. Long-term efficacy and safety of iloperidone: results from 3 clinical trials for the treatment of schizophrenia. J Clin Psychopharmacol 2008; 28 (2 Suppl 1): S29-35. PubMed PMID: 18334910.

(Among 371 adults with schizophrenia who were continued on iloperidone for 46 weeks after their participation in a controlled trial, adverse events included insomnia [18%] and anxiety [11%], but "there were no significant effects on liver function tests").

Cutler AJ, Kalali AH, Weiden PJ, Hamilton J, Wolfgang CD. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. J Clin Psychopharmacol 2008; 28(2 Suppl 1): S20-8. PubMed PMID: 18334909.

(Among 593 patients with schizophrenia treated with iloperidone [24 mg daily], ziprasidone [160 mg daily] or placebo for 4 weeks, symptom scores improved in both the active treatment groups and side effects from iloperidone included dizziness, sedation, weight gain, dry mouth, tachycardia and nasal congestion; "mean changes in laboratory values from baseline to end point were similar across treatment groups").

Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD. Safety profile of iloperidone: a pooled analysis of 6-week acute-phase pivotal trials. J Clin Psychopharmacol 2008; 28 (2 Suppl 1): S12-9. PubMed PMID: 18334908.

(Among 1943 adults with schizophrenia treated with various doses of iloperidone, haloperidol, risperidone or placebo for 6 weeks, side effects of iloperidone included dizziness, dry mouth, fatigue, nasal congestion, somnolence and tremor; 1 of 1044 patients on iloperidone, but none of 440 on placebo had a serious adverse event related to serum enzyme elevations; no specific details given).

Potkin SG, Litman RE, Torres R, Wolfgang CD. Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. J Clin Psychopharmacol. 2008 Apr; 28 (2 Suppl 1): S4-11. PubMed PMID: 18334911.

(Among 1943 adults with schizophrenia enrolled in 3 controlled trials of various doses of iloperidone versus haloperidol, risperidone or placebo for 6 weeks, symptom scores improved more with iloperidone than placebo and to a similar extent as with the comparator arms; side effects were not discussed [Weiden 2008]).

Parsons B, Allison DB, Loebel A, Williams K, Giller E, Romano S, Siu C. Weight effects associated with antipsychotics: a comprehensive database analysis. Schizophr Res 2009; 110: 103-10. PubMed PMID: 19321312.

(Analysis of weight gain in 21 placebo controlled trials of antipsychotic agents [~3300 patients]; average monthly weight gain in pounds was +0.1 with placebo, +0.8 olanzapine, 0.6 risperidone, -0.3 ziprasidone; a 5% increase in weight occurred after one year in 13% of placebo, 39% haloperidol, 20% ziprasidone, 45% risperidone and 60% olanzapine treated subjects).

Iloperidone (Fanapt) for schizophrenia. Med Lett Drugs Ther 2010; 52: 13-14. PubMed PMID: 20208474.

(Brief review of efficacy and safety of iloperidone shortly after its approval in the US; common side effects are restlessness, nausea, extrapyramidal symptoms, agitation and somnolence; no mention of liver injury).

Citrome L. Iloperidone: chemistry, pharmacodynamics, pharmacokinetics and metabolism, clinical efficacy, safety and tolerability, regulatory affairs, and an opinion. Expert Opin Drug Metab Toxicol 2010; 6: 1551-64. PubMed PMID: 21034370.

(Review of the chemistry, pharmacology, efficacy and safety of iloperidone mentions that it can prolong the QTc interval, but has not been linked to instances of sudden death; side effects can include weight gain, dizziness, sedation and postural hypotension, but restlessness [akathisia] and extrapyramidal side effects are rare; no mention of ALT elevations or hepatotoxicity).

Dargani NV, Malhotra AK. Safety profile of iloperidone in the treatment of schizophrenia. Expert Opin Drug Saf 2014; 13: 241-6. PubMed PMID: 24206391.

(Systematic review of safety of iloperidone in schizophrenia found 12% rate of significant weight gain, but low rates of akathisia and extrapyramidal symptoms; no mention of ALT elevations or hepatotoxicity).

Muzyk AJ, Cvelich RG, Kincaid BR, Preud'homme XA. Angioedema occurring in patient prescribed iloperidone and haloperidol: a cross-sensitivity reaction to antipsychotics from different chemical classes. J Neuropsychiatry Clin Neurosci 2012; 24: E40-1. PubMed PMID: 22772698.

(24 year old African-American man developed hypersensitivity reaction [angioedema] within 24 hours of starting haloperidol and, after recovery, developed a similar reaction 3 days after starting iloperidone, both episodes responding rapidly to antihistamines and corticosteroids).

Cutler AJ, Kalali AH, Mattingly GW, Kunovac J, Meng X. Long-term safety and tolerability of iloperidone: results from a 25-week, open-label extension trial. CNS Spectr 2013; 18: 43-54. PubMed PMID: 23312567.

(Among 72 patients with schizophrenia who were continued on iloperidone for 25 weeks after participation in a 4 week controlled trial, side effects included headache, weight gain, dizziness, nausea, sedation and insomnia; no mention of ALT elevations or hepatotoxicity).

Drugs for psychiatric disorders. Treat Guidel Med Lett 2013; 11 (130): 53-64; PubMed PMID: 23715100.

(Concise review of safety, efficacy and role of drugs for psychiatric disorders, mentions that iloperidone is a second generation antipsychotic agent whose adverse side effects include orthostatic hypotension, prolongation of the QTc interval, somnolence, dizziness, dry mouth and weight gain, but rarely has extrapyramidal effects; no mention of ALT elevations or hepatotoxicity).

Rado JT, Janicak PG. Long-term efficacy and safety of iloperidone: an update. Neuropsychiatr Dis Treat 2014; 10: 409-15. PubMed PMID: 24600226.

(Review of the efficacy and safety of iloperidone makes no mention of ALT elevations or hepatotoxicity).

Musil R, Obermeier M, Russ P, Hamerle M. Weight gain and antipsychotics: a drug safety review. Expert Opin Drug Saf 2015; 14: 73-96. PubMed PMID: 25400109.

(Extensive systematic review of the literature on the problem of weight gain during therapy with antipsychotic agents, mentions that weight gain of 7% or more occurs in 9-47% of patients on iloperidone, the rates being lower than with olanzapine, but higher than with aripiprazole).

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 seen over a ten year period at 8 US medical centers, one was attributed olanzapine, but none to iloperidone or other antipsychotic medications).

Weiden PJ, Manning R, Wolfgang CD, Ryan JM, Mancione L, Han G, Ahmed S, et al. A randomized trial of iloperidone for prevention of relapse in schizophrenia: the REPRIEVE Study. CNS Drugs 2016; 30: 735-47. PubMed PMID: 27379654.

(Among 303 patients with schizophrenia who were placed on iloperidone and stablized, those continued on iloperidone were less likely to relapse than those switched to placebo [20% vs 64%), while adverse event rates were similar; no mention of ALT elevations or hepatotoxicity).

Drugs for psychotic disorders. Med Lett Drugs Ther 2016; 58 (1510): 160-4. PubMed PMID: 27960194.

(Concise review of drugs used to treat psychotic disorders including iloperidone, mentions adverse events of orthostatic hypotension, QT prolongation, dizziness, somnolence, dry mouth and weight gain, but does not mention ALT elevations or hepatotoxicity).

Solmi M, Murru A, Pacchiarotti I, Undurraga J, Veronese N, Fornaro M, Stubbs B, et al. Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. Ther Clin Risk Manag 2017; 13: 757-77. PubMed PMID: 28721057.

(Extensive review of the safety of antipsychotic medications mentions that significant liver enzyme elevations are rare, but have been reported with olanzapine, quetiapine, and risperidone and that clinically apparent aucte liver injury has been reported with phenothiazines, halothane and clozapine; no mention of hepatotoxicity associated with iloperidone).