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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Iloperidone. [Updated 2023 Jun 5].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Iloperidone

Updated: June 5, 2023.

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 and 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 adults with schizophrenia in the United States in 2009 and is available as tablets of 1, 2, 4, 6, 8, 10 and 12 mg generically and under the brand name Fanapt. The recommended dose regimen is a slow escalation to a 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), peripheral edema, sexual dysfunction, weight gain and changes in glucose and lipid levels. Iloperidone 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 increased mortality in elderly patients with dementia-related psychosis and suicidal thoughts and behaviors. Other rate adverse reactions are tardive dyskinesia, major neurologic events, neuroleptic malignant syndrome, priapism, orthostatic hypotension, seizures, suicidal thoughts and behaviors, 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 usually 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 usually 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 – Generic, Fanapt®

DRUG CLASS

Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

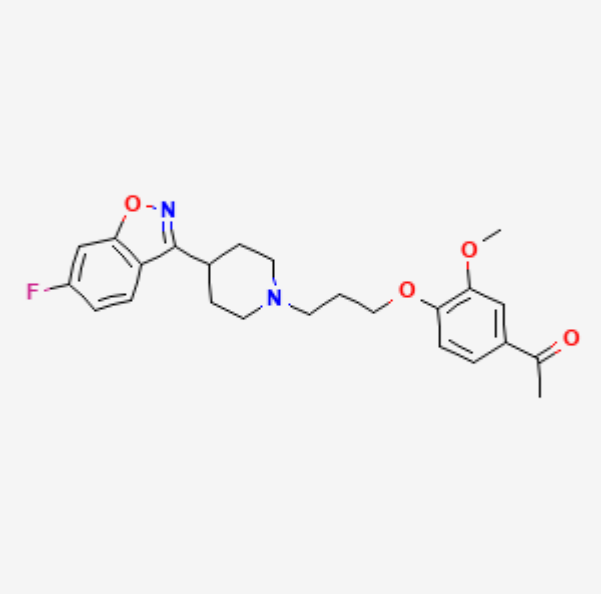
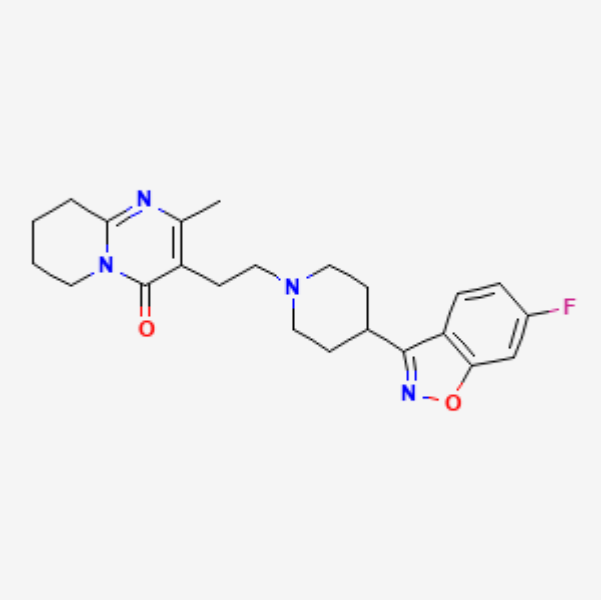
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Iloperidone	133454-47-4	C24-H27-F-N2-O4	

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: 06 June 2023

Meyer JM. Pharmacotherapy of psychosis and mania. 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. 279-302.

(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)--another second-generation antipsychotic. 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.

(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.e7. 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 stabilized, 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 medications available in the US for therapy of psychotic disorders; mentions that olanzapine can cause aminotransferase elevations, and that olanzapine and ziprasidone can cause DRESS syndrome, but does not mention ALT elevations or hepatotoxicity for any of agents discussed, including aripiprazole, brexpiprazole, cariprazine, clozapine, quetiapine, risperidone, asenapine, iloperidone, paliperidone and lurasidone).

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 acute liver injury has been reported with phenothiazines, halothane and clozapine; no mention of hepatotoxicity associated with iloperidone).

Subeesh V, Maheswari E, Singh H, Beulah TE, Swaroop AM. Novel adverse events of iloperidone: A disproportionality analysis in US Food and Drug Administration Adverse Event Reporting System (FAERS) database. Curr Drug Saf. 2019;14:21–26. PubMed PMID: 30362421.

(Data mining of the FDA's Adverse Event Reporting System for adverse events associated with iloperidone, identified signals for akathisia, dyskinesia, peripheral edema, priapism and sexual disfunction, but not for ALT elevations or clinically apparent liver injury).

Nair A, Salem A, Asamoah AL, Gosal R, Grossberg GT. An update on the efficacy and safety of iloperidone as a schizophrenia therapy. Expert Opin Pharmacother. 2020;21:1793–1798. PubMed PMID: 32735148.

(Comprehensive review of the chemical structure, mechanism of action, clinical efficacy, adverse events, and relative efficacy and safety of iloperidone in comparison to other second-generation antipsychotic agents, mentions that it has a low likelihood of causing liver injury).

Druschky K, Toto S, Bleich S, Baumgärtner J, Engel RR, Grohmann R, Maier HB, et al. Severe drug-induced liver injury in patients under treatment with antipsychotic drugs: data from the AMSP study. World J Biol Psychiatry. 2021;22:373–386. PubMed PMID: 32892689.

(Among 246 cases of severe liver injury due to antipsychotic medications identified in a prospective registry of German psychiatric hospitals between 1993 and 2016, 46 arose in 38,349 patients [0.12%] who received clozapine [34 as a single antipsychotic agent]; other commonly implicated agents being olanzapine [n=90 of 54,822: 0.16%], quetiapine [34 of 66,209: 0.05%] and risperidone [27 of 51,683: 0.05%]; two fatal cases occurred in olanzapine-treated patients; low rates were found for ziprasidone [no cases among 3568 patients treated] and aripiprazole [6 cases of 15,988 patients treated: 0.01%]; iloperidone not listed).