Drug Review

Iloperidone – a Novel Drug for Treatment of Schizophrenia

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Introduction

Iloperidone has been studied for nearly 20 years.[1] In May 2009, the Food and Drug Administration approved the marketing of iloperidone for the acute treatment of schizophrenia in adults.[2] This article reviews the clinical pharmacology, pharmacokinetics, pharmacogenomics, efficacy, and tolerability of iloperidone.

Chemistry

Iloperidone is a piperidinylbenzisoxazole derivative, a tertiary amine, and an antagonist of adrenergic, serotonergic, and dopaminergic receptors.[3-5]

Chemically, iloperidone is referred to as 1-[4-[3-[4-(6-fluoro-1,2- benzisoxazol-3-yl)-1-piperidinyl]- propoxy]-3-methoxyphenyl]ethanone, with a molecular formula of $C_{24}H_{27}FN_2O_4$ and a molecular weight of 426.8.[6]

Pharmacodynamics

Iloperidone is a pure antagonist and has no agonist activity at any receptor.[7]

Kalkman et al.[5] determined, through radioligand affinities, that iloperidone has the most affinity for dopamine D3 receptors, followed by norepinephrine α-2c, serotonin 5-hydroxytryptamine (5-HT)1A, dopamine D2A, and 5-HT6 receptors in decreasing affinities. Iloperidone has a low affinity for histaminergic receptors and therefore is expected to have a low risk of sedation or weight gain.[8] Iloperidone is highly noradrenergic, similar to clozapine, with respect to its norepinephrine α-2c-receptor:dopamine D2-receptor ratio.[8]

Pharmacokinetics

Pharmacokinetic studies have determined that iloperidone is well absorbed orally, with a bioavailability of 96%.[4, 9,10] Peak serum iloperidone values were seen within 2–4 hours of administration. Iloperidone has a half-life of 13.5–14 hours.[4] Iloperidone reaches a steady-state concentration within three to four days of initial administration.[10]

Iloperidone is extensively metabolized by O-dealkylation (mediated by cytochrome P-450 [CYP] isoenzyme 3A4), hydroxylation (mediated by CYP2D6), decarboxylation/oxidation, and reduction.[4,10] Iloperidone is partly metabolized via CYP1A2, CYP2E1, and CYP3A4.

Pharmacogenomics

Iloperidone is the first antipsychotic drug with specific genetic markers to help clinicians determine efficacy. Six single-nucleotide polymorphisms (SNPs) that correlate with iloperidone response have been identified.[11]For some clinicians, the ability to test for patient response by identifying specific genes is the biggest benefit of iloperidone.[4]

Clinical Efficacy

The clinical efficacy of iloperidone has been studied in various phase-II and phase-III clinical trials.[11] A brief account of some important studies is given below:

Safety And Tolerability

Safety and tolerability data obtained from pooled four week and six-week, fixed-dose or flexible-dose Phase II and III studies,[12-14] has exhibited that discontinuation rates due to treat-

Table 1.
Summary of Outcome Measures of Randomized, Placebo-Controlled Phase III Clinical Trials With Iloperidone[a]

Study and Treatment	Change in PANSS Total Score[b]	p^c	Change in CGI-S Score[b]	p^c	Change in BPRS Score[b]	p^c
Potkin et al.[12] (study 1)						
Placebo (n = 127)	−4.9	NA	NR	NA	−3.6	NA
Iloperidone 4 mg/day (n = 121)	−9.0	0.097	NR	NA	−6.4	0.070
Iloperidone 8 mg/day (n = 125)	−7.8	0.227	NR	NA	−6.2	0.095
Iloperidone 12 mg/day (n = 124)	−9.9	0.047	NR	NA	−6.8	0.042
Haloperidol 15 mg/day (n = 124)	−13.9	<0.001	NR	NA	−9.0	<0.001
Potkin et al.[12] (study 2)						
Placebo (n = 156)	−3.5	NA	−0.2	NA	−2.5	NA
Iloperidone 4–8 mg/day (n = 153)	−9.5	0.017	−0.6	0.003	−6.2	0.012
Iloperidone 10–16 mg/day (n = 154)	−11.1	0.002	−0.5	0.006	−7.2	0.001
Risperidone 4–8 mg/day (n = 153)	−16.6	<0.001	−0.8	<0.001	−10.3	<0.001
Potkin et al.[12] (study 3)						
Placebo (n = 160)	−7.6	NA	−0.4	NA	−5.0	NA
Iloperidone 12–16 mg/day (n = 244)	−11.0	0.101	−0.6	0.028	−7.1	0.900
Iloperidone 20–24 mg/day (n = 145)	−14.0	0.005	−0.6	0.037	−8.6	0.010
Risperidone 6–8 mg/day (n = 157)	−18.8	0.001	−0.9	<0.001	−11.5	<0.001
Cutler et al.[13]						
Placebo (n = 149)	−7.08	NA	NR	NA	−4.6	NA
Iloperidone 24 mg/day (n = 295)	−12.01	0.006	NR	NA	−7.4	0.013
Ziprasidone 160 mg/day (n = 149)	−12.27	0.012	NR	NA	−7.2	0.420

[a]PANSS = Positive and Negative Symptom Scale, CGI-S = Clinical Global Impression of Severity, BPRS = Brief Psychiatric Rating Scale, NA = not applicable, NR = not reported.
[b]Negative values indicate improvement.
[c]Compared with placebo.

ment-related adverse effects in the iloperidone-treated groups were similar to those seen with placebo (3.9% to 5.6%).

The most common adverse effects (occurring in at least 5% of patients or with a twofold greater frequency than with placebo) were dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight gain.

Dizziness, tachycardia, and weight gain were at least twice as common with higher doses (20–24 mg daily) than with lower doses (10–16 mg daily).[10] Insomnia and anxiety were the most common adverse events in three long-term studies comparing iloperidone and haloperidol, though the rate of drug discontinuation due to these adverse events was lower in iloperidone-treated patients (6.7% versus 9.4% with haloperidol).[15]

Contraindications[10,16-19]

Hypersensitivity to iloperidone or any component of its formulation.

Black Box Warning(S)[10,16-19]

Atypical antipsychotics may increase the risk of death when used in elderly patients with dementia-related psychoses. Iloperidone is thus not approved for the treatment of patients with dementia-related psychosis.

Precautions[10,16-19]

- Abrupt discontinuation is not advised
- Cognitive and motor impairment risk
- Concomitant use with drugs that prolong the QT interval should be avoided
- Diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia
- Dysphagia risk (risk of aspiration)
- Exposure to extreme temperatures (hypothermia)
- Elderly patients, particularly elderly women, are at increased risk of tardive dyskinesia
- Hematological disease (neutropenia, agranulocytosis, etc)
- Hepatic disease
- Hypotensive medication use, low BP
- Increased duration of therapy and/or higher

cumulative doses
- Seizure disorder, history, or conditions which lower seizure threshold
- Substance abuse history
- Risk of suicide
- Tardive dyskinesia, potentially irreversible

Drug Interactions[10,16-19]

- Agents causing QT prolongation – additive effect could induce torsade de pointes.
- Antihypertensive agents – additive hypotensive effects.
- CYP2D6 inhibitors – may increase the therapeutic effect and AUC of iloperidone to possibly toxic levels.
- CYP3A4 inhibitors – may increase the therapeutic effect and AUC of iloperidone to possibly toxic levels.
- Central dopamine agonists (Antiparkin-sonian) – iloperidone antagonizes central DA receptors and may cause negating effect.
- CNS depressants – additive depressant effects.
- Ethanol – may increase intensity of drowsiness, dizziness, and/or sedation.
- Lithium – possible neurotoxicity when used concurrently with antipsychotics.
- Antidiabetics – iloperidone may worsen glycemic control.
- Medications that lower the seizure threshold – additive effects.
- Metoclopramide – combination of synergistic dopamine antagonization may increase the risk of extrapyramidal effects.

Dosing/Administration[10,12,13,15,16-19]

Schizophrenia

- *Adults:* initially, 1 mg orally twice daily on day 1.
- *Adult titration:* 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg orally twice daily on days 2, 3, 4, 5, 6, and 7 respectively, or until a target maintenance dose of 6 to 12 mg orally twice daily has been reached.
- *Maximum adult dose:* 12 mg orally twice daily (24 mg per 24 hours).
- Iloperidone dose should be reduced by 50% when used with CYP2D6 inhibitors.
- Iloperidone dose should be reduced by 50% when used with CYP3A4 inhibitors.
- The daily dose of tetrabenazine should be halved in patients receiving strong CYP2D6 inhibitors such as fluoxetine, paroxetine, or quinidine.
- If iloperidone therapy is interrupted for 3 days or longer, the initial dose titration should be repeated properly to re-initiate therapy.
- Dose adjustments for the geriatric patient population are not required.
- Safety and efficacy have not been established in adolescents and children.
- Iloperidone should not be used in patients with hepatic insufficiency.
- Dose adjustments in renally impaired patients are not required.

Use In Special Circumstances[10,16-20]

Pregnancy

FDA pregnancy risk category C

Safe use of iloperidone during pregnancy has not been established.

The effects of iloperidone during labor and delivery are unknown.

Lactation

Iloperidone should not be used while breast feeding.

Conclusions

Iloperidone may be considered as a novel drug for the treatment of schizophrenia, as it has a low risk of causing extrapyramidal symptoms and adverse metabolic effects. However, iloperidone has many disadvantages- requires dosage adjustment due to orthostatic hypotension risks, must be taken twice daily and lastly, there is a risk of Q-Tc interval prolon-gation.

To conclude, Iloperidone may be a useful and safe option for the treatment of schizophrenia but it does not possess any distinct advantage over other antipsychotic agents.

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