



ILOPERIDONE - NEW SECOND GENERATION ANTIPSYCHOTIC: PHARMACOLOGICAL ASPECTS AND SCHIZOPHRENIA CLINICAL MANAGEMENT

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ABSTRACT

Iloperidone is a new atypical antipsychotic drug approved by FDA for the treatment of schizophrenia. In this article, we searched the published randomized controlled trials (RCT) and other literature to review the efficacy and safety of iloperidone using the following database (Science Direct, PubMed) and illustrate its role in the management of schizophrenia. Iloperidone showed efficacy by causing significant improvements in psychiatric scales such as Positive and Negative Syndrome scale (PANSS) and clinical global impressions (CGI). Iloperidone was associated with a number of common side effects such as metabolic and cardiovascular side effects. This review illustrated that iloperidone was well tolerated with significant improvements in disease severity and symptom intensity control in patients suffering with schizophrenia, however, iloperidone was associated with a significantly higher risk of metabolic and cardiovascular side effects with minimal extrapyramidal side effects. These findings would guide psychiatrists and pharmacists in their clinical role for supporting the care of psychiatric patients.

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INTRODUCTION

Schizophrenia is a chronic and debilitating psychiatric disorder with significant morbidity and mortality (1) with a substantial impact on the patients and their carers' psychological, physical and social life (2). Despite the available management options, several patients suffer from treatment-resistant or poor prognosis (3). Schizophrenia prevalence is 0.5%-1% worldwide (4) with the associated management challenges such as frequent antipsychotics switching and poor compliance (5). Atypical antipsychotics are the main group of pharmacological treatments used in the management of schizophrenia due to their favourable side effects (SE) profile compared to the typical antipsychotics (6).

Iloperidone, a new second generation antipsychotics (SGA) with similar structure to risperidone (7), is used for the management of schizophrenia and other psychotic disorders (8). The recommended iloperidone daily dose is 12-24 mg divided as 2 doses (9) with recommended dose titration - starting dosage of 1 mg twice daily to minimize postural hypotension and target dose of 6 mg bid achieved in 4 – 7 days (10,11).

Iloperidone: Pharmacodynamics and pharmacokinetics

Iloperidone has strong affinity for noradrenaline, dopamine, and serotonin receptors. At clinical doses, iloperidone blocks 5-HT_{2A} receptors and reduces dopamine D₂ receptor-mediated neurotransmission (12). Iloperidone also binds to D₃, alpha_{2C}, 5-HT_{1A}, and 5-HT₆ receptors (13). 5-HT_{1A} stimulation and 5-HT₆ antagonism are of primary importance for iloperidone possible beneficial effects on cognition (12). Iloperidone strong 5-HT_{2A} antagonism could stimulate histamine neuron activity with pro-cognitive properties (14). Research using computer models suggested that the clinical effects of iloperidone occur through dopamine receptor coupling in cortical neurons (15).

Iloperidone also affects the noradrenergic system (alpha_{2C} antagonism) resulting in cognitive symptoms changes as iloperidone, when compared with other antipsychotics, has the highest alpha_{2C}/alpha_{2A} ratio (16). Iloperidone also increased dopamine and acetylcholine release in the medial prefrontal cortex via actions on 5-HT_{1A} (17), increased dopa accumulation in response to D₂ receptor antagonism with clozapine-like effects (18) and decreased 5-HT₂ receptors (19).

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Administered orally, iloperidone is well absorbed with 96% bioavailability (20), highly bound to plasma proteins (21). Peak serum concentration is achieved within 2 - 3 hours and eliminated slowly ($t_{1/2}$ 14 hours)(22). Iloperidone was extensively metabolized with CYP1A2, CYP2E1, CYP2D6 and CYP3A4 enzymes(23). When prescribing iloperidone, CYP2D6 extensive and poor metabolizers need to be checked(24) due to different plasma concentrations of iloperidone and its metabolites (25); for example, elimination half-life was 18 h for extensive CYP2D6 metabolizers and around 33 h for poor CYP2D6 metabolizers (26). Iloperidone major metabolite has receptor affinity profile similar to iloperidone and likely to contribute to its clinical effects(27). Iloperidone quality, safety and efficacy could also be affected by acidic, basic hydrolysis and oxidative degradation (8).

Iloperidone efficacy in human studies

Iloperidone showed efficacy in relapse prevention in schizophrenia (relapse rates was just 20% compared to around 63% for placebo) with longer mean time to relapse (139 days versus 71 days)(28). In a big clinical trial with 500 patients on risperidone, olanzapine, or aripiprazole switched to iloperidone, improvement in Clinical Global Impression (CGI) scale was observed(29,30). Iloperidone was also associated with improved Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale-total (PANSS-T) score, and PANSS-positive and PANSS-negative scores (31). Further two trials confirmed iloperidone beneficial decrease of PANSS-T(11,32).

Iloperidone ameliorated excitement/hostility; depression/anxiety; cognition; positive and negative scales(33) and was successful in improving mania and depression scores in mixed mood states, considered difficult to manage in bipolar disorders (34). As iloperidone has the highest affinity to alpha-1 compared to other antipsychotics, it could be helpful in posttraumatic stress disorder management like prazosin (alpha-1 antagonist) with its D2 and 5-HT2 antagonist activities reducing hypervigilance (35).

Iloperidone efficacy in animal studies

Cognitive functions are normally impaired in schizophrenia, while iloperidone showed efficacy in improving choice accuracy (36) and cognitive dysfunction in rat models(37). In experiments using apomorphine and phencyclidine, pre-treatment with iloperidone demonstrated beneficial behavioural actions(38). Iloperidone increased social interaction (39) with its weak D2 and potent alpha-2 antagonism helping to reduce alcohol drinking issues(40).

Safety and tolerability of Iloperidone

Iloperidone most common side effects(SE) were dizziness (5.1%-23.2%), somnolence (4%-13%), dyspepsia (4.8%-7.8%), insomnia (18.1%), anxiety (10.8%) and dry mouth (5.2%-10.4%) with low rates of extrapyramidal disorder (2.5%) or akathisia (3.7 %)(11,28,41). A dose relationship for dizziness, somnolence and dry mouth existed; e.g. number to harm (NNH) for somnolence was 25 for iloperidone 10-16 mg/day and 10 for 20-24 mg/day (42). Nasal congestion, fatigue, sedation and tachycardia occurred especially with higher doses (31). Long-term management with high doses caused SE such as headache (13.9%), weight increase (9.2%), dizziness (6.9%), nausea (6.4%), sedation (6.4%) and insomnia (5.2%) (43). Iloperidone was also associated with a moderate

risk of metabolic syndrome or cardiovascular events (44). Statistically significant changes in serum glucose found with $\geq 7\%$ weight increase (NNH = 11) (45), with young or low baseline body mass index patients most vulnerable (44). Iloperidone prolongs QTc interval to a higher extent compared to quetiapine and co-administration of metabolic inhibitors could further increase risk of QTc changes especially in patients with CYP2D6 polymorphisms (46). Moreover, alpha 2c antagonism could lead to ventricular premature contractions (47) and predispose to cardiac arrhythmias and sudden death; no patient suffered from QT interval of 500 msec or greater (32). Iloperidone has a favourable prolactin profile compared to other antipsychotics, but is associated with disorders of ejaculation such as priapism due to its alpha1- antagonist properties (48-50).

Withdrawal of iloperidone could lead to increased heart rate/palpitations and urinary incontinence (34), hence gradual withdrawal/switching is recommended (29). Discontinuation with iloperidone due to SE was just 4.8% compared to 7.6% for haloperidol and 6.2% for risperidone (51). Caution is needed in elderly patients due to orthostatic SE (9). Iloperidone could increase the incidence of psychotic disorders during the postpartum period (52) with limited safety data for iloperidone in breast feeding (53). Reported rare SE include respiratory depression (54); angioedema (55), neuroleptic malignant syndrome (56) and Tardive Dyskinesia (57). Combinations with other psychiatric medications result in pharmacokinetic and pharmacodynamic interactions such as increase in QTc interval when fluoxetine or paroxetine co-administered with iloperidone(58). Iloperidone co-administered with fluoxetine resulted in significant weight gain (59), while its use while patients taking illicit drugs (e.g. cocaine) led to respiratory failure with mandated respiratory support and prolonged QTc (60).

Pharmacogenomics

Polymorphisms associated with iloperidone efficacy were identified within the neuronal PAS domain protein 3 gene (NPAS3) (61) with more than 75% of iloperidone-treated patients with the optimal genotype combinations showed at least 20% improvement compared with just 37% for patients with other genotypes (62).

DISCUSSION

First generation antipsychotics have facilitated hospital discharge and community psychiatric treatment, while SGA lead to lower risk of extrapyramidal and cognitive SE with better quality of life (63). On the other hand, SGAs have been associated with metabolic SE such as weight gain, lipid/glycaemic imbalance, risk of diabetes mellitus and diabetic ketoacidosis (63).

Iloperidone was shown to be effective like haloperidol, risperidone and ziprasidone in reducing schizophrenia symptoms and preventing relapses(66). Common SE of iloperidone were mild including dizziness, hypotension, dry mouth and orthostatic hypotension (70). Similar to paliperidone, quetiapine and risperidone; iloperidone could cause weight gain and glucose imbalance especially in young, drug-naïve patients with healthy lifestyle counselling recommended (67). Iloperidone could also cause QTc prolongation, with low risk of akathisia, extrapyramidal symptoms compared to haloperidol and risperidone(68). This low risk may be linked to its alpha1 and HT2A antagonism

(69). Patients using other antipsychotic (e.g. risperidone) can easily switch to iloperidone with no serious impact on safety or efficacy(2).

Clinical judgment while taking scientific evidence and patients' preferences in consideration is of primary importance in schizophrenia management(65). Although iloperidone clinical trials were conducted, effectiveness studies as well as safety data in elderly, young and pregnant patients are still lacking(71), especially elderly, who suffer from high comorbidity rates (psychiatric and medical); age-related pharmacokinetics changes and polypharmacy risk(72).

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