New Drug

Iloperidone for the Management of Adults with Schizophrenia

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ABSTRACT

Background: Iloperidone is a second-generation antipsychotic drug approved in May 2009 by the US Food and Drug Administration (FDA) for the acute treatment of schizophrenia in adults. It is a piperidinyl-benzisoxazole derivative with mixed serotonin (5HT2A) and D2 dopamine antagonist properties.

Objective: The purpose of this article was to review the pharmacology, pharmacokinetics, efficacy, safety, and role in treatment for iloperidone in schizophrenia.

Methods: Scientific and clinical data were collected through searches of PubMed, ClinicalTrials.gov, International Pharmaceutical Abstracts, and the FDA, using the search term *iloperidone*, and limited to English-language articles. Reference lists were reviewed for additional publications. Dates included the beginning of the database through 2010. No limits were placed on study design.

Results: In a 4-week Phase III trial, iloperidone 12 mg twice daily lowered the Positive and Negative Syndrome Scale (PANSS) total scores to a significantly greater extent than did placebo (−12 vs −7.1; $P < 0.01$). The ziprasidone active control also separated from placebo (−12.3 vs −7.1; $P < 0.05$). A pooled analysis of 3 Phase III trials compared iloperidone in divided doses to placebo. The primary outcome was reduction in PANSS scores. Study 1 included iloperidone 4, 8, or 12 mg/d, haloperidol as an active control, and placebo. The PANSS reduction in the 12 mg/d group was significantly greater at end point versus baseline when compared with placebo (−9.9 vs −4.6; $P = 0.047$). Study 2 included iloperidone 4 to 8 mg/d or 10 to 16 mg/d, risperidone 4 to 8 mg/d, or placebo. The primary efficacy measure was change from baseline to end point in the Brief Psychiatric Rating Scale (BPRS). Improvement from baseline on all iloperidone doses was significantly greater than with placebo (4–8 mg/d group: −6.2, $P = 0.012$; 10–16 mg/d group: −7.2, $P = 0.001$; placebo, −2.5). Study 3 included iloperidone 12 to 16 mg/d, risperidone 6 to 8 mg/d, and placebo. The results on the primary efficacy variable, reduction in the BPRS score, was not significant for the 12 to 16 mg/d group versus placebo (−7.1 vs −5.0; $P = 0.09$), but was significant for the 20 to 24 mg/d iloperidone group (−8.6 vs −5.0; $P = 0.01$) and for the risperidone group (−11.5 vs 5.0; $P < 0.001$). A 52-week maintenance trial included iloperidone versus haloperidol as an active control. The primary efficacy variable was time to relapse. Comparison of mean time to relapse of the 2 arms showed no significant difference. The most common adverse events (AEs) associated with iloperidone were dizziness (5.1%–23.2%), dry mouth (5.2%–10.4%), somnolence (4%–13%), and dyspepsia (4.8%–7.8%). AEs appeared dose related. Prescribing information recommends a starting dosage of 1 mg twice daily and then titrated over 7 days to reach a target dosage of 12 to 24 mg/d. The titration is necessary to reduce the risk of orthostatic hypotension-related dizziness.

Conclusions: Data support that when titrated slowly to a therapeutic dosage, iloperidone is generally well tolerated, has a favorable safety profile, and is an effective treatment option in patients with schizophrenia. Its place in therapy and performance in a typical patient population remain to be established. Slow initial titration and twice-daily dosing are potential disadvantages. (*Clin Ther.* 2011;33:330–345)

Key words: antipsychotic drugs, iloperidone, schizophrenia, second-generation antipsychotics.

INTRODUCTION

Schizophrenia is a debilitating psychiatric illness. It has a chronic, degenerative relapsing course associated

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with hospitalizations, disability, compromised quality of life, comorbid illness, and a large burden on health system and caregiver resources. In addition to morbidity, the disease is associated with significant mortality. Suicide is common, with 20% to 40% of affected individuals attempting suicide at some point, and up to 13% of them completing the attempt.[1]

Schizophrenia has an incidence of approximately 1% worldwide. Various genetic, biochemical, and environmental factors have been implicated in its pathogenesis. Symptoms include not only the cardinal positive psychotic features such as hallucinations, delusions, and disorganized speech and behavior but also negative features such as withdrawal, apathy, and affective blunting; cognitive symptoms such as impairment of executive function; and mood symptoms such as irritability, depression, and dysphoria.[2]

Schizophrenia accounts for approximately 2.5% of the total health care budget in the United States.[3] Goals of treatment are to both reduce symptoms and improve function of individuals with this illness.

The etiology and pathophysiology of the disorder is not fully understood, but an overactivity of the central nervous system dopaminergic pathways is thought to account in part for the constellation of symptoms seen in schizophrenia. Also implicated in its pathogenesis are other neural pathways, including those of serotonin and glutamate. Neurodevelopmental and neuroanatomic models have also been hypothesized.[4]

Antipsychotic drugs are the mainstay of the treatment of schizophrenia. Atypical or second-generation antipsychotic (SGA) drugs (eg, risperidone, olanzapine, quetiapine) are as effective as conventional or first-generation antipsychotic (FGA) drugs (eg, haloperidol, chlorpromazine, perphenazine), but comparative outcomes research does not show consistent superiority of SGA drugs over FGA drugs.[5,6] The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that 75% of patients who received risperidone, olanzapine, quetiapine, ziprasidone, or perphenazine had discontinued treatment within 18 months.[5] The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS) showed no quality of life advantage for patients switched from an FGA drug to an SGA drug, compared with continued treatment with an FGA drug.[6] Many patients fail to respond adequately to treatment or have difficulty with intolerable side effects, illustrating the continued need for research into novel agents for treatment.

Iloperidone is an SGA drug that was approved in May 2009 by the US Food and Drug Administration (FDA) for the treatment of schizophrenia. The purpose of this article is to review its preclinical and clinical pharmacology, pharmacokinetics, efficacy, safety, and place in the treatment of schizophrenia.

METHODS

Scientific and clinical data were collected through online searches of PubMed (http://www.ncbi.nlm.nih.gov/pubmed), International Pharmaceutical Abstracts (IPA), ClinicalTrials.gov (http://www.clinicaltrials.gov), and the FDA (http://www.fda.gov), using the search term *iloperidone*. Dates included the beginning of each database through 2010. No limits were placed on study design, but the search was limited to English-language publications. Reference lists of articles were reviewed for additional pertinent publications. The search was updated August 5, 2010.

RESULTS

Search of PubMed yielded 60 citations, all English language. Fifteen citations were identified at IPA, 4 of which were not also included in the PubMed search. Four references describe the results of Phase III pivotal efficacy trials. Preclinical receptor pharmacology, pharmacodynamics, and pharmacokinetics are described in 19 references. Four articles describe genetic predictors of response or adverse effects. The remaining citations are reviews. A single study was identified at ClinicalTrials.gov, which included data subsequently published and found in the PubMed search. No additional studies were accessed at the FDA site.

Pharmacologic Mechanisms and Pharmacodynamics

Receptor Pharmacology

Receptor affinity of iloperidone and selected antipsychotic agents at various receptor systems is summarized in **Table I**. Iloperidone is a piperidinyl-benzisoxazole derivative originally developed by Hoechst Marion Roussel Inc and known by its research code, HP-873, before its generic name was assigned. Phase I clinical trials began in 1995. Schizophrenia was identified as a target for the compound based on its effects on serotonin (5-HT) and dopamine receptors.[7-10]

Iloperidone is a mixed antagonist of 5-HT2A serotonin receptors and D2 dopamine receptors. Such a receptor pharmacology profile is similar to agents classified as atypical or SGA drugs.[8,11,12] Although antagonism of