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Drug Information Service
Department of Pharmacy
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196
www.cc.nih.gov/phar

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Clinical Specialist, Endocrinology & Women's Health, and Coordinator, Drug Information Service
kcalis@nih.gov

In This Issue

Pramipexole (Mirapex®): A Brief Review

Introduction

Pramipexole, a non-ergot dopamine receptor agonist, is effective in the treatment of both early and advanced Parkinson's disease (PD). Pramipexole and ropinirole, another dopamine receptor agonist, were the first non-ergot derivatives available for the treatment of PD. Ergot-derived dopamine agonists, such as bromocriptine, have been effective in the treatment of this disorder but are associated with many side effects, some potentially irreversible (e.g., pulmonary fibrosis). Use of dopamine agonists in the treatment of Parkinson's disease may delay the introduction of levodopa in the early stages of the disease and perhaps delay the development of levodopa-associated motor fluctuations ("on/off" phenomenon) and dyskinesias related to chronic use of levodopa. In advanced PD, dopamine agonists increase "on time" in patients with levodopa-associated motor fluctuations, thereby allowing for levodopa dose reduction in some patients. The long-term effectiveness of pramipexole in PD has not been evaluated, and it is unknown whether patients will develop tolerance to the dopamine-agonist effects of pramipexole.

Description

Mirapex® (pramipexole dihydrochloride) is marketed by Pharmacia & Upjohn and is available as 0.125-, 0.25-, 0.5-, 1-, and 1.5-mg tablets.

Indications

Pramipexole is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

Pharmacology

Pramipexole dihydrochloride, a benzothiazolamine derivative, is a non-ergot dopamine receptor agonist. *In vitro* studies suggests that pramipexole has intrinsic activity and a high degree of binding specificity at the D2 subfamily of dopamine receptors. Known dopamine receptor subtypes include D2, D3, and D4. The D2 specificity and intrinsic activity of pramipexole is greater than that for the other available ergot-derived dopamine agonists, bromocriptine and pergolide. Pramipexole binds with higher affinity to D3 compared to D2 or D4 receptor subtypes, but the relevance of this specificity is not known. Pramipexole is believed to also stimulate presynaptic dopamine autoreceptors, with resultant inhibition of synthesis and release of dopamine in intact dopaminergic synapses. However, when presynaptic fibers are degenerated and postsynaptic receptors are hypersensitive, pramipexole exerts postsynaptic dopamine agonist activity. Although the precise mechanism of action of pramipexole for the treatment of PD is not known, it is believed to be related to stimulation of postsynaptic dopamine receptors in the striatum. Pramipexole binds with moderate affinity to α2-adrenergic receptors but has little or no affinity for α1, β-adrenergic, acetylcholine, D1, or serotonin receptors.

Pharmacokinetics

Pramipexole is rapidly absorbed, with maximal plasma concentrations achieved in 2 hours. The absolute bioavailability is > 90%, and food does not affect extent of absorption but may increase the time to maximal plasma concentrations by nearly 1 hour. Pramipexole is extensively distributed in body tissues and has a volume of distribution of about 500 L. Approximatly 15% of the drug is bound to plasma proteins. Pramipexole displays linear pharmacokinetics over the entire clinical dose range. Its terminal half-life is 8 hours in young, healthy volunteers and about 12 hours in elderly volunteers.

Urinary excretion of pramipexole is the major route of elimination. About 90% of the dose is recovered in the urine, with the majority as unchanged drug. No metabolites have been identified in either plasma or urine. Tubular secretion contributes to the high rate of renal clearance (about 400 mL/min).

The clearance of pramipexole may be reduced by about 30% in patients with PD compared to healthy elderly volunteers. This difference is thought to reflect reduced renal function in patients with PD, which may be related to an overall poorer health status.

Selected Clinical Trials

Mild to Moderate Parkinson's Disease: Pramipexole vs. Placebo

Methods: Three hundred thirty-five patients with idiopathic PD (Hoehn and Yahr stages I to III) were randomized to pramipexole or placebo in a multicenter, double-blind trial. In addition to usual exclusion criteria, patients were excluded if they had a history of psychosis, prior or current treatment with a direct-acting dopamine agonist, supine systolic BP < 100 mm Hg, or a ≥ 20 mm Hg orthostatic change in systolic blood pressure. Use of selegiline, a monoamine oxidase inhibitor, was allowed during the trial if the dose was stable for 30 days and not greater than 10 mg/day. The groups were stratified according to whether or not they used selegiline. Levodopa use within 60 days of study entry and during the study was not allowed. The pramipexole dose was titrated over 7 weeks from 0.125 mg TID to 1.5 mg TID, followed by a 6-month maintenance phase. Primary endpoints included Unified Parkinson's Disease Rating Scale (UPDRS) parts II (activities of daily living) and III (motor function) between baseline and the end of the maintenance period.

Results: Two hundred three men and 132 women entered the trial. Their mean age was 62.7 years and their mean duration of disease was 1.8 years. Two-thirds of the patients in each group were taking selegiline. No significant differences between groups regarding demographics or disease characteristics were noted. Eighty percent of placebo- and 83% of pramipexole-treated patients completed the study. The mean daily maintenance dose for patients entering this phase was 3.8 mg/day. In the pramipexole group, significant differences in UPDRS II were found when comparing baseline scores (8.2) to end of maintenance scores (6.4). Similar results were obtained for UPDRS III (18.8 vs. 14.1). No decrease in UPDRS II or III scores was noted in the placebo group.

Adverse Events: Adverse events that were reported more frequently in the pramipexole group compared to the placebo group included nausea (39% vs. 21%), insomnia (26% vs. 13%), constipation (18% vs. 6%), somnolence 18% vs. 9%), and visual hallucinations (10% vs. 2%). Orthostatic hypotension occurred in 10% of pramipexole- and 6% of placebo-treated patients. Occurrence of symptomatic orthostatic hypotension did not differ between the groups.

Advanced Parkinson's Disease: Pramipexole or Bromocriptine vs. Placebo

Methods: Two hundred forty-seven patients with idiopathic PD (Hoehn and Yahr stages II to IV during an "on" period) were randomized to pramipexole, bromocriptine, or placebo in a multicenter, double-blind study. All patients were receiving an optimal dose of levodopa (and a decarboxylase inhibitor) and were stable for at least 30 days prior to the study. All subjects experienced motor fluctuations ("wearing off" effects) with levodopa therapy. In addition to usual exclusion criteria, patients were excluded if they had a history of psychosis (other than levodopa- or dopamine agonist-induced), supine systolic BP < 100 mm Hg, or evidence of a symptomatic drop of 20 mm Hg or more after 1 minute of standing. Selegiline, amantadine, and anticholinergic use were allowed, and doses remained fixed throughout the study. The levodopa dose could be decreased to alleviate adverse events, such as dyskinesias, hallucinations, or unspecified psychiatric adverse effects that were presumed to be related to this medication. The pramipexole dose was titrated to 1.5 mg TID and bromocriptine to 10 mg TID. The dose titration was done over 12 weeks and was followed by a 6-month maintenance phase. Primary endpoints included a comparison of UPDRS scores (parts II and III) at baseline and at the end of the maintenance period.

Results: No significant differences were noted between the three groups with regard to gender, age (mean 62.7 years), or duration of PD (mean 7 years). Eighty percent of pramipexole- and bromocriptine-treated patients completed the study, compared to 60% of placebo-treated patients. An average dose of 3.36 mg/day of pramipexole and 22.64 mg/day of bromocriptine was used during the maintenance phase. There were no differences reported in the use of selegiline between the three groups (no data presented). Also, data were not provided regarding differences in the use of amantadine or anticholinergics between the treatment groups. In the pramipexole group, significant differences in UPDRS II (11 vs. 8, $p < 0.0002$) and UPDRS III (25 vs. 16, $p < 0.0006$) scores were found when comparing baseline to end of maintenance. Similarly, in the bromocriptine group, significant differences in UPDRS II (10.25 vs. 9.25, $p < 0.017$) and UPDRS III (23 vs. 17, $p < 0.011$) scores were found when comparing baseline to end of maintenance. Both pramipexole and bromocriptine were significantly more effective than placebo. The investigators did not report whether levodopa dosage was reduced (see adverse events) for any patients.

Adverse Events: The most common adverse events reported with pramipexole, bromocriptine, and placebo, respectively were as follows: dyskinesia (40% vs. 45% vs. 27%), dizziness (33% vs. 27% vs. 21%), headache (20% vs. 13% vs. 10%), insomnia (28% vs. 23% vs. 22%), hallucinations (14% vs. 12% vs. 13%), confusion (14% vs. 7% vs. 7%), postural hypotension (40% vs. 44% vs. 37%), and nausea (36% vs. 37% vs. 25%).

Adverse Effects

Adverse events in studies of early PD comparing pramipexole (388 patients) and placebo (235 patients), respectively were as follows: nausea (28% vs. 18%), somnolence (22% vs. 9%), insomnia (17% vs. 12%), asthenia (14% vs. 12%), constipation (14% vs. 6%), and hallucinations (9% vs. 3%).

Adverse events in trials comparing pramipexole (260 patients) and placebo (264 patients), respectively were as follows: insomnia (27% vs. 22%), asthenia (10% vs. 8%), hallucinations (17% vs. 4%) dyskinesia (47% vs. 31%), and postural hypotension (53% vs. 48%).

Age appears to increase the risk of hallucinations associated with pramipexole. In trials of early PD, hallucinations were 1.9 times more common with pramipexole than placebo in patients < 65 years of age and 6.8 times more common than placebo in patients > 65 years. In trials of advanced PD, risk was 3.5 times greater in patients < 65 years of age and 5.2 times greater in patients > 65 years.

"Sudden sleep onset" associated with pramipexole has been reported in the literature as well as to the FDA (23 patient cases). Reports consist of patients falling asleep during activities of daily living, including the operation of motor vehicles. In many patients this occurred without warning signs of excessive drowsiness. These reports have culminated in a warning letter from the FDA and revision of the product label to reflect this new information.

Although not reported with pramipexole, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot-derived dopamine agonists (e.g., bromocriptine). These adverse effects may not completely resolve after discontinuation of the offending agent.

Degeneration and loss of photoreceptor cells have been observed in the retinas of albino rats, but evaluations in other animal models (albino mice, pigmented rats, monkeys, minipigs) did not reveal similar changes. The potential significance of this effect in humans has not been established.

Drug Interactions

Cytochrome P450 Effects: Since pramipexole is not appreciably metabolized by these isoenzymes, it is unlikely that drugs which inhibit these isoenzymes will alter the elimination of pramipexole. Pramipexole does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1, or CYP3A4 but does inhibit CYP2D6 at concentrations greater than that achieved at the highest recommended dose (4.5 mg/day).

Carbidopa/Levodopa: Carbidopa/levodopa did not alter the pharmacokinetics of pramipexole in 10 healthy volunteers. Pramipexole did not alter the AUC or elimination of carbidopa/levodopa, but did increase the levodopa Cmax by 40% and decrease its Tmax from 2.5 to 0.5 hours. The clinical significance of these alterations in levodopa pharmacokinetics is unknown, but some patients receiving carbidopa/levodopa in conjunction with pramipexole may experience more levodopa-associated adverse effects (e.g., dyskinesia).

Cimetidine: Cimetidine increases pramipexole AUC by 50% and half-life by 40%.

Methylphenidate, Amphetamines, MAOIs: Concomitant administration can possibly result in more dopamine-related adverse effects (these medications were excluded during PD trials).

Drugs Which Decrease Blood Pressure: Antihypertensives and other drugs which are associated with orthostatic hypotension (e.g., antipsychotics, tricyclic antidepressants) may produce additive orthostasis.

Precautions and Contraindications

Geriatric Use: Pramipexole oral clearance is approximately 30% lower in subjects > 65 years of age compared to younger subjects, suggesting differences in renal clearance. Despite this pharmacokinetic difference, clinical trials including large numbers of patients over the age of 65 did not find differences in efficacy or safety (with the exception of increased risk of hallucinations).

Pediatric Use: The safety and efficacy of pramipexole in pediatric patients has not been established.

Pregnancy/Lactation: Pregnancy category C. The teratogenic potential of pramipexole could not be adequately evaluated in animal models due to the high incidence of pregnancy disruption and early embryonic loss (possibly due to dopamine-associated decreases in prolactin). Evidence of adverse effects on embryonic or fetal development was not observed in pregnant rabbits following administration of up to 10 mg/kg/day. Postnatal growth was inhibited in the offspring of rats treated with ≥ 0.5 mg/kg/day during the latter part of pregnancy and throughout lactation. It is not known whether pramipexole is excreted in human milk.

Dosage and Administration

The dose of pramipexole should be increased gradually (starting dose of 0.125 mg TID) to avoid intolerable adverse effects and orthostatic hypotension. The dose should not be increased more frequently than every 5 to 7 days. Pramipexole is effective and well tolerated over a dosage range of 1.5 to 4.5 mg/day (administered in three equally divided doses) with or without concomitant levodopa. It should not be discontinued abruptly, and the dose should be reduced gradually over at least one week.

The starting dose, dosing schedule, and maximal dose of pramipexole should be reduced in patients with renal impairment as follows:

Renal Status	Starting Dose	Maximum Dose
Normal to mild impairment (CrCl > 60 mL/min)	0.125 mg TID	1.5 mg TID
Moderate impairment (CrCl 35 – 59 mL/min)	0.125 mg BID	1.5 mg BID
Severe impairment (CrCl 15 – 34 mL/min)	0.125 mg QD	1.5 mg QD
CrCl < 15 mL/min	Use of pramipexole has not been adequately studied in this group of patients	

Cost

The cost of pramipexole relative to other dopamine agonists is as follows:

Dopamine Agonist	Dose	Cost Per Month*
Pramipexole (Mirapex®)	4.5 mg/day (1.5 mg tab TID)	$99.20
Bromocriptine (generic)	15 mg/day (2 x 2.5 mg tab TID)	$49.98
Pergolide (Permax®)	2-3 mg/day	$90.21 – 135.32
Ropinirole (Requip®)	7.5 mg/day (1 x 0.5 mg tab *and* 1 x 2 mg tab TID)	$95.92

**Federal Supply Schedule*

Conclusions

Pramipexole, a selective D2 agonist, has been shown to be an effective agent as monotherapy (± selegiline) in early PD and as adjunctive therapy to levodopa, amantadine, and anticholinergic agents in patients with advanced PD. In patients with new-onset PD, pramipexole may delay the need for levodopa, a drug which can cause motor fluctuations with long-term use. Addition of pramipexole to adjunctive levodopa in advanced PD is associated with an improvement in motor fluctuations (an increase in "on time") in patients experiencing "on/off" phenomenon associated with levodopa and may decrease the total dose of levodopa required. Pramipexole is associated with significant adverse effects, including nausea, vomiting, insomnia, somnolence, symptomatic or asymptomatic orthostatic hypotension, and hallucinations. Although pramipexole is a more specific dopamine agonist than bromocriptine, it is not known whether these differences impart any additional efficacy in the treatment of PD. The long-term effects (> 6 months) of pramipexole have not been evaluated.

References available upon request.

Drug Information Service

- Patient-specific pharmacotherapy evaluation and management
- Comprehensive information about medications, biologics, and nutrients
- Critical evaluation of drug therapy literature
- Assistance with study design and protocol development
- Clinical trial drug safety monitoring
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FDA Safety Reports

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Argatroban (Acova®), an injectable anticoagulant for prevention or treatment of thrombosis in patients with heparin-induced thrombocytopenia
  Note: Use of this medication requires approval by the Clinical Hematology Service
- Ropinirole (Requip®), an oral non-ergot dopamine receptor agonist for the treatment of idiopathic Parkinson's disease

Editor's Note

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