National PBM Drug Monograph

Ropinirole (Requip®)

VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel

INTRODUCTION

Parkinson's Disease is a degenerative brain disorder that affects approximately 500,000 to 1 million people in the United States. The average age of onset is 58 years, however the disease follows no age limits. Development of symptoms has occurred in patients as young as twenty and as old as ninety years. Symptoms of this disease include resting tremor, muscle rigidity, bradykinesia, and postural instability. The underlying etiology of Parkinson's Disease (PD) involves the progressive loss of dopamine producing cells in the substantia nigra, which results in a decrease in dopamine in the corpus striatum. A reduction in quality of life occurs as the disease progresses. Perhaps more meaningful, mortality is estimated to be 2 to 5 times greater in patients with Parkinson's Disease than in age-matched controls. The goal of therapy is to replace the lack of dopamine within the substantia nigra. This can be accomplished through the use of dopamine agonists and/or levodopa. Additionally, the concept of neuroprotective agents is also being investigated. The major disadvantage for levodopa is that the effectiveness of this medication deteriorates over time. Most patients witness a decreased response to levodopa therapy within 5 years after initiation of therapy. The role of dopamine agonists has increased in the early therapy of Parkinson's disease. These agents are no longer viewed as solely levodopa sparing but are now used early in the course of PD for their neuroprotective effects and to delay the initiation of levodopa therapy.

CLINICAL PHARMACOLOGY[1,2]

Ropinirole is a selective non-ergoline dopamine agonist. It binds to both central and peripheral dopamine receptors. When ropinirole binds to the central postsynaptic dopamine D_2 receptors, it acts as a dopamine replacement. The neuroprotective action of ropinirole may be linked with the ability of the agent to reduce the turnover and release of toxic metabolites, and therefore decrease oxidative stress. The peripheral actions of ropinirole result in increased sympathetic tone. This may result in hypotension and nausea, but these effects may be reduced with slow titration of ropinirole dose. Additionally, ropinirole has been used in the therapy of restless legs syndrome. The exact mechanism for this effect is unknown and therapy is aimed at symptomatic relief. In addition, there are no clinical trials available to support the use of ropinirole over other agents such as levodopa, pergolide, pramipexole, benzodiazepines or antiepileptic agents.

PHARMACOKINETICS[1]

Due to the action of this agent as a dopamine agonist, the majority of studies have been conducted in patients with PD as a healthy, normal volunteer population will develop adverse effects with even small doses.

There is significant interpatient variability with all pharmacokinetic parameters and patient specific titration of dose is recommended to minimize this variability. Ropinirole displays linear pharmacokinetics with both single dose and steady state dosing. The agent is rapidly and almost totally absorbed with a mean bioavailability of the oral formulation near 50%. Dosing in conjunction with food intake may decrease the rate of absorption but minimally affects the total amount absorbed. Ropinirole displays low protein binding, independent of plasma concentration. The majority of an absorbed dose of ropinirole is metabolized by the liver with only 10% excreted unchanged in the urine. The major metabolites of ropinirole include an N-despropyl, glucuronide and carboxylic acid forms. Only one metabolite displays weak activity, however this form is rapidly glucuronidated and account for a negligible portion of the parent compounds activity. The major microsomal enzyme involved in ropinirole metabolism is CYP1A2.

There is a negligible effect of gender, age, renal function, concurrent disease states, stage of PD and concomitant medications on the pharmacokinetics of ropinirole. While a slower clearance of the drug may be observed with advancing age, there is no clinically significant effect on the pharmacokinetics of the drug.

CLINICAL TRIALS

Ropinirole has been investigated in several therapeutic areas; monotherapy[15-17] prior to levodopa initiation, adjunct therapy with levodopa[18,19] and as a therapy for restless leg syndrome[8,9]. In the areas of adjunct therapy with levodopa, ropinirole has been compared with placebo and other commonly employed dopamine agonists such as bromocriptine and pramipexole. The most useful outcome measures in the PD trials involve the motor scores as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) and activities of daily living (ADL) scores.

Ropinirole has been investigated as monotherapy in patients with early stage PD (Hoehn and Yahr stages I to III). Three trials have compared ropinirole to placebo in a muticenter, randomized, double-blind fashion.[15-17] One of the trials was a six-month extension of another trial; therefore efficacy data could be extrapolated to one year. In the largest trial (N=241) a significant improvement from baseline UPDRS score was seen ($p<0.001$).[15] Additionally, 47% of patients were classified as responders in the ropinirole group versus 20% in the placebo arm. Responder was defined as patients with $\geq$30% reduction in baseline UPDRS scores. After 12 months of ropinirole therapy 19.8% of patients were responders versus 48% classified as nonresponders ($p<0.001$).[17]

In a three-year evaluation of 335 patients, a comparison of dopamine agonist therapy was evaluated.[14] The mean doses employed for the trial were 12 mg/day and 24 mg/day for ropinirole and bromocriptine respectively. There was no significant difference in the incidence of dyskenisias during treatment between the groups. The percent of patients able to complete the trial without levodopa therapy was 36% and 35% for ropinirole and bromocriptine, respectively. The improvements seen in UPDRS scores were significantly better with ropinirole therapy than bromocriptine. Additionally, ropinirole showed a greater improvement from baseline in the motor score portion of the UPDRS.

A five-year trial of 268 patients evaluated ropinirole versus levodopa therapy. There was no significant difference in ADL scores between the groups. However, motor scores were significantly improved with levodopa therapy in contrast to ropinirole. The incidence of dyskenesia was significantly higher in the levodopa treated group, 20% vs. 45%, ropinirole to levodopa respectively ($p<0.0001$).[13]

The safety and efficacy of substituting dopamine agonist therapy to ropinirole was investigated in 78 patients with PD. Patients could be receiving dopamine agonist therapy alone or in combination with levodopa. In patients receiving pergolide, conversion to ropinirole occurred with 1:6 dose equivalence (pergolide:ropinirole) and in patients on bromocriptine 10:6. There were no significant changes in UPDRS scores after conversion.

Ropinirole has been evaluated as an adjunct therapy to levodopa in advanced PD. Patients with PD for 8-9 years and on a stable levodopa dose for the last 2 weeks had ropinirole therapy added. A decrease in levodopa dosage and an improvement in UPDRS motor scores were seen.[18,19]

ADVERSE REACTIONS

The most concerning adverse event to be described with ropinirole therapy is the development of somnolence, often without warning. This occurs during activities of daily living (ADL) and has been reported to occur during operation of a motor vehicle, reading and eating. It is possible this effect can be seen with any dopamine agonist. A meta analysis conducted by Etminan et al [20] concluded that patients receiving ropinirole or pramipexole were at a five times higher risk to develop somnolence than those taking placebo or nearly double the risk of those taking levodopa alone. Further investigation is required to determine the mechanism for this reaction.

The majority of safety data for this agent was established in patients with either early or advanced PD. Since these two populations may have a different likelihood for development of adverse effects due to coadministration with levodopa, they will be reviewed separately. Table I reviews the adverse events associated with the highest discontinuation rates during randomized, controlled clinical trials with ropinirole.

Table I: Treatment Associated Adverse Events

Adverse event	Without levodopa (%)		With levodopa (%)	
	Ropinirole (N=157)	Placebo (N=147)	Ropinirole (N=208)	Placebo (N=120)
Nausea	60	22	30	18
Dizziness	40	22	26	16
Hallucinations	5	1	10	4
Somnolence	40	6	20	8
Vomiting	12	7	7	4
syncope	12	1	3	2
Dyskinesia	2	1	34	13
Confusion	5	1	9	2
Increased sweating	6	4	7	2

DRUG INTERACTIONS

The major hepatic enzyme responsible for ropinirole metabolism has been shown to be CYP1A2. Therefore, concurrent therapy with a drug known to affect the same isoenzyme may require an alteration of ropinirole dose. Theophylline a substrate of CYP1A2 has not been shown to affect the steady state pharmacokinetics of ropinirole. Additionally, ropinirole did not affect theophylline metabolism. [10] Ciprofloxacin, an inhibitor of CYP1A2, has been shown to increase the AUC and Cmax of ropinirole.

Since ropinirole is a dopamine agonist it is possible that dopamine antagonists such as phenothiazines or metoclopramide would decrease the efficacy of ropinirole. The possible benefits of combination therapy would need to be evaluated for individual patients.[12]

Ropinirole has not been shown to affect other commonly used agents for PD such as selegiline, amantadine, anticholinergics and levodopa. In addition, these agents do not affect the oral clearance of ropinirole.

CONTRAINDICATIONS

Ropinirole is contraindicated in patients who have experienced a hypersensitivity to the product.

DOSAGE AND ADMINISTRATION

Ropinirole should be given three times daily. It can be taken with or without food.[11] Administration with food will lower the maximum concentration of ropinirole, however since the dose is carefully titrated in each patient, this should not prove clinically significant. In some patients this effect may alleviate some of the nausea caused by the medication.

Ropinirole should be titrated based on individual patient response. The manufacturer recommends initiation of therapy with 0.25mg three times daily, increasing by 0.25 mg per dose on a weekly basis. Dosages above 24 mg/day have not been tested in clinical trials. Therapy should not be abruptly discontinued. The dose of ropinirole should be gradually decreased over a 7day period.

DRUG COST

Ropinirole is available from Glaxo Smith Kline in 0.25, 0.5, 1, 2, 3, 4and 5 mg tablets

Drug	Usual Dose per Day	Cost per Day	Cost per Month
Ropinirole (Requip®) 0.25, 0.5, 1, 2, 3, 4, 5 mg	0.75- 24 mg	$1.12- 7.06	$33.60-211.80
Bromocriptine -Geneva 2.5, 5 mg	10- 40 mg	$1.62-6.51	$48.60-195.30
Pramipexole (Mirapex®) 0.125, 0.25, 0.5, 1, 1.5 mg	1.5- 4.5 mg	$1.15- 3.46	$34.50-103.80
Entacapone (Comtan®) 200 mg	600 –1200 mg	$3.132- 6.26	$93.96-187.80
Carbidopa/Levodopa 10/100, 25/100. 25/250 (Endo) Sinemet CR® 25/100, 50/200 (DuPont)	3-5 Tablets 2-3 CR Tablets	$0.15-0.25 $0.52-1.58	$9.00- 15.00 $15.60-47.40
Pergolide (Permax®) 0.05,0.25,1 mg	3 mg	$4.86	$145.82
Selegiline (Par) 5 mg	5- 10 mg	$0.10-0.20	$3.00-6.00

REFERENCES

1. Kaye CM, Nicholls B.Clinical pharmacokinetics of ropinirole. Clin Pharmacokinet. 2000 Oct;39(4):243-54.
2. Matheson AJ, Spencer CM.Ropinirole: a review of its use in the management of Parkinson's disease. Drugs. 2000 Jul;60(1):115-37.
3. Clarke CE, Deane KH. Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Cochrane Database Syst Rev. 2000;(3):CD001517.
4. Clarke CE, Deane KH. Ropinirole for levodopa-induced complications in Parkinson's disease. Cochrane Database Syst Rev. 2000;(3):CD001516.
5. LeWitt PA. New drugs for the treatment of Parkinson's disease. Pharmacotherapy. 2000 Jan;20(1 Pt 2):26S-32S.
6. Hobson De, Pourcher E, Martin WR. Ropinirole and pramipexole, the new agonists. Can J Neurol Sci. 1999 Aug;26 Suppl 2:S27-33.
7. Kurzel MD. Ropinirole: a dopamine agonist for the treatment of Parkinson's disease. Am J Health Syst Pharm. 1999 Feb 1;56(3):217-24.
8. Ondo W. Ropinirole for restless legs syndrome. Mov Disord 1999 Jan; 14: 138-40
9. Freeman A, Rye D, Bliwise D, et al. Ropinirole for restless legs syndrome (RLS) [abstract]. Neurology 2000; 54 Suppl. 3: A19
10. Thalamas C, Taylor A, Brefel-Courbon C, et al. Lack of pharmacokinetic interaction between ropinirole and theophylline in patients with Parkinson's disease. Eur J Clin Pharmacol 1999 Jun 4; 55: 299-303
11. Brefel C, Thalamas C, Rayet S, et al. Effect of food on the pharmacokinetics of ropinirole in parkinsonian patients. Br J Clin Pharmacol 1998 Apr; 45: 412-5
12. Taylor AC, Beerahee A, Citerone DR, et al. Lack of a pharmacokinetic interaction at steady state between ropinirole and L-dopa in patients with Parkinson's disease. Pharmacotherapy 1999 Feb; 19: 150-6
13. Rascol O, Brooks DJ, Korczyn AD, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med 2000; 342 (20): 1484-91
14. Korczyn AD, Brunt ER, Larsen JP, et al. A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease [erratum published in Neurology 1999; 53: 1162]. Neurology 1999; 53 (2): 364-70
15. Adler CH, Sethi KD, Hauser RA, et al. Ropinirole for the treatment of early Parkinson's disease. Neurology 1997 Aug; 49: 393-9
16. Brooks DJ, Abbott RJ, Lees AJ, et al. A placebo-controlled evaluation of ropinirole, a novel D_2 agonist, as sole dopaminergic therapy in Parkinson's disease. Clin Neuropharmacol 1998 Mar-Apr; 21: 101-7
17. Sethi KD, O'Brien CF, Hammerstad JP, et al. Ropinirole for the treatment of early Parkinson disease: a 12-month experience. Arch Neurol 1998 Sep; 55: 1211-6
18. Rascol O, Lees AJ, Senard JM, et al. Ropinirole in the treatment of levodopa-induced motor fluctuations in patients with Parkinson's disease. Clin Neuropharmacol 1996 Jun; 19: 234-45
19. Lieberman A, Olanow CW, Sethi K, et al. A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. Neurology 1998 Oct; 51: 1057-62
20. Etminan M, Samii A, Takkouche B, Rochon PA. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease. A meta-analysis of randomized controlled trials. Drug Safety 2001;24(11):863-868

Prepared by: Kathryn Tortorice, Pharm D, BCPS