Ropinirole and Pramipexole, the New Agonists

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ABSTRACT: Ropinirole and pramipexole are non-ergoline dopamine agonists which are relatively specific for the D2 family of dopamine receptors. They have side-effect profiles linked to peripheral and central dopaminergic stimulation, amenable to tolerance through a slow titration or the addition of domperidone in sensitive patients. They do not have the uncommon but problematic ergot-related side effects of bromocriptine and pergolide. Ropinirole and pramipexole have both been shown to be efficacious when used as monotherapy in early Parkinson's disease (PD), and have been suggested as being less likely than levodopa to lead to the early development of motor fluctuations and dyskinesias in this clinical setting. They have also been shown to be useful as adjunctive therapy to levodopa in advanced PD and to have a levodopa-sparing effect in these patients. Dose equivalents amongst the available dopamine agonists is difficult to know with certainty but has been estimated as follows: 30 mg of bromocriptine, 15 mg of ropinirole, 4.5 mg of pramipexole, and 3.0 mg of pergolide

R SUM : Le ropinirole et le pramipexole, deux nouveaux agonistes dopaminergiques. Le ropinirole et le pramipexole sont des agonistes dopaminergiques non dérivés de l'ergot, qui sont relativement spécifiques pour les récepteurs dopaminergiques de la famille D2. Ils ont des profils d'effets secondaires reliés à la stimulation dopaminergique périphérique et centrale, et une augmentation progressive de la posologie ou l'addition de dompéridone chez les patients sensibles favorise la tolérance. Ils n'ont pas les effets secondaires rares et problématiques, reliés à l'ergot, de la bromocriptine et du pergolide. Il a été démontré que le ropinirole et le pramipexole sont tous deux efficaces en monothérapie dans la maladie de Parkinson (MP) au début, et il semble qu'ils aient moins tendance que la lévodopa à provoquer l'apparition précoce de fluctuations motrices et de dyskinésies dans ce contexte clinique. On a également démontré qu'ils sont utiles comme traitement adjuvant à la lévodopa dans la MP en phase avancée et qu'ils ont un effet d'épargne de la lévodopa chez ces patients. Il est difficile de déterminer avec certitude les doses équivalentes des agonistes dopaminergiques disponibles, mais elles ont été estimées comme suit: bromocriptine 30 mg, ropinirole 15 mg, pramipexole 4.5 mg et pergolide 3.0 mg.

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Dopamine deficiency as the neurochemical basis for Parkinson's disease (PD) was clearly demonstrated in 1960.[1] Shortly thereafter, the dramatic benefit associated with the therapeutic use of levodopa was established.[2,3] Nearly three decades later, however, it is apparent that simply replacing dopamine by oral levodopa is not the ideal solution to the long term problems associated with this neurodegenerative disease.

Levodopa may improve longevity in PD[4] but does not halt disease progression. Wearing off, dyskinesia, and motor fluctuations become problematic with continued levodopa treatment.[5] These issues relate to a shortened duration of action, and to pharmacodynamic changes affecting striatal dopaminergic receptors over time. Increased frequency of dosing and the resultant fluctuating dopamine levels, resulting in "pulsatile" stimulation of dopamine receptors, may also be implicated in the genesis of these complications.[6] Particularly frustrating is the tendency for younger patients to develop these problems early in the course of their illness.[7] There is considerable debate over the concern that levodopa may be toxic.[8,9] Although wide-ranging experimental evidence supports this theory[10,11] the toxicity of levodopa in humans remains unproven.[12]

The older agonists (bromocriptine and pergolide), at commonly recommended doses, have not demonstrated the same efficacy as levodopa.[13,14] Their titration to effective doses is slow and they share the significant adverse effects of postural hypotension and a variety of gastrointestinal symptoms.[15] Although tolerance develops in many patients to these peripheral side effects, these agonists also have activity at adrenergic and serotonergic receptors creating other side-effects, especially in the urogenital sphere. They can produce erythromelalgia[16] and rarely pleuropulmonary and retroperitoneal fibrosis[17,18] as a result of their common ergot chemical structure.

By the end of the 1980s, there was sufficient knowledge about

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the chemical configuration of dopamine receptors that it became possible to engineer non-ergot dopamine agonists with the potential of achieving higher affinities, more specificity, and fewer side effects. Two new agonists, ropinirole and pramipexole, now provide new options for managing Parkinson's disease.

Receptor Affinities

Ropinirole

Ropinirole {4-[2-(dipropylamino)ethyl]-2-indolinone monohydro-chloride} is a dopamine agonist which is relatively specific for D2 receptors. Relative agonist competitive binding analysis demonstrates very low affinities to acetylcholine, alpha-adrenergic, β-adrenergic, and 5-hydroxytryptophan receptors.[19] Within the D2 family of dopamine receptors the affinity is greater for the D3 than the D2 subtype.[20] Ropinirole has low affinity for the D1 family and for the D4 subtype of the D2 family. In contrast, both pergolide and bromocriptine have greater activity at D2 than D3 receptors as well as significant D1 activity (agonistic and antagonistic respectively).[21,22]

Pramipexole

Pramipexole {(S)-4,5,6,7-tetrahydro-*N*-6-propyl-2,6-benzothiazidole -diamine dihydrochloride monohydrate} has agonist activity at presynaptic and postsynaptic dopamine receptors of the D2 family.[23,24] Within the D2 family, pramipexole has a 5 to 7 fold higher affinity to the D3 than either D2 or D4 subtypes. Pramipexole has a low affinity for the D1 family as well as acetylcholine, β-adrenergic, and 5-hydroxytryptophan receptors, and moderate affinity at alpha-adrenergic receptors.

Summary

Ropinirole and pramipexole are both nonergoline dopamine agonists, selective for the D2 receptor family with slight differences in specificity within this family. Both compounds prefer the D3 sub-type and have little activity at the D4 subtype (D3>D2>D4). The clinical significance of the D3 preference in humans is unknown at this time. A potential effect on motivation and mood may be hypothesized from the preferential location of the D3 sub-type in the "limbic striatum".[25] Although hypothesized "optimal" combinations of receptor stimulation exist,[26] the ideal combination of receptor subtype stimulation in Parkinson's disease remains unknown.

Pharmacokinetics

Ropinirole

This compound is rapidly absorbed, reaching peak plasma concentrations at 1.5 hours.[27] It has an absolute bioavailability of approximately 50 percent. Food modulates the rate of absorption of ropinirole, decreasing C_{max} by about 25% and delaying the median T_{max}, but has no effect on the extent of absorption.[28] Its elimination half-life is about 6 hours. Ropinirole undergoes 90% of its metabolism through hepatic N-depropylation and hydroxylation via the cytochrome P450 system and is then excreted in the urine. Drug interactions can occur at this step with ciprofloxacin which inhibits ropinirole's metabolism and results in increased plasma concentration. Ropinirole is mainly metabolized through the CYP 1A2 sub-system. The CYP 3A system contributes particularly at higher concentrations.[29] It must be used with caution in hepatic or renal failure. Ropinirole does not affect levodopa drug levels.

Pramipexole

Pramipexole is also rapidly absorbed, reaching peak concentrations at 1.75 hrs.[30] Bioavailability is 90% and follows linear kinetics. Food does not interfere with its absorption.[31] Pramipexole does not alter the extent of absorption of levodopa or its elimination, but it does result in a quicker rise to, and an increase in the maximal plasma concentration of levodopa, increasing its C_{max} by 40%.[32] Adjustments in the levodopa dose may therefore be required. Because this agonist is eliminated via a renal cationic transport mechanism, drugs that compete for cationic transport (cimetidine, ranitidine, calcium channel blockers and quinidine) will increase its concentration. Pramipexole is contraindicated in renal failure.

In a monkey model of PD, Bedard et. al.[33] demonstrated that the longer the half life of an agonist, the lower the tendency toward dyskinesias. The "terminal phase elimination half life" for current agonists is as follows: pergolide 12-24 hrs,[34] pramipexole 9 hrs with a range of 8 – 22 hrs,[30] ropinirole 6 hrs,[27] and bromocriptine 5 hrs.[34]

Preclinical data

Both ropinirole and pramipexole affect the turn-over and whole brain content of dopamine and its metabolite HVA in mice without interacting with 5HT or norepinephrine metabolism. They both inhibit the firing rate of dopaminergic neurons in the substantia nigra pars compacta by stimulating presynaptic D2 receptors.[35] This regulation of presynaptic dopamine release is hypothesized to be a possible neuroprotective factor, via the subsequent reduction in the amount of hydrogen peroxide generated through dopamine metabolism.[36] Both molecules are effective in animal models of PD including rats with unilateral 6-hydroxydopamine lesions and MPTP lesioned primates. In the drug naive MPTP marmoset, a one-month study with ropinirole strongly suggests that ropinirole has a much lower ability to produce dyskinesia than levodopa, and therefore may be of clinical value in the treatment of early PD.[37]

Clinical Trials in Parkinson's Disease

The role of bromocriptine and pergolide in PD has been based on the fact that dopamine receptors remain responsive regardless of the status of denervation of the striatum. They have been used mainly as adjunctive treatment to levodopa. Other advantages of these older agonists include the absence of competition with dietary amino acids for gastrointestinal uptake and blood brain barrier transfer resulting in an increased reliability of the effect of individual doses. These advantages are desirable in advanced PD with fluctuations of performance. The development of high affinity drugs with an improved side effect profile has broadened the potential role of agonists to include the control of early PD. Trials have thus been performed in both early and late stages of the disease with these new agonists.

Early Parkinson's Disease

Ropinirole

Ropinirole has been compared to placebo, levodopa, and

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bromocriptine in separate trials in early Parkinson's disease patients. It has been shown to provide significant improvement vs. placebo on motor function in a 12 week study involving 62 patients.[38] This was a prospective, randomized, double blind, parallel group trial in patients with limited or no prior dopaminergic therapy. The dose ranged from 0.5 mg to 5 mg bid. Significantly more ropinirole-treated patients (71% vs. 41% of placebo-treated patients) achieved at least 30% improvement in the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS).[39] The occurrence of adverse events was not different in the two groups with nausea, dizziness, and somnolence being the most frequently reported.

An extension of a 6-month, double blind trial by Krieder[40] studied the efficacy of ropinirole as monotherapy at 1 year in 147 patients with early PD. The percent of patients with an insufficient therapeutic response (defined as the need for additional levodopa) was smaller with ropinirole than placebo (20% vs. 48%; $p < 0.001$). About 44% of patients remained on ropinirole alone for 12 months without requiring additional symptomatic therapy with levodopa compared to 22% on placebo ($p < 0.001$).

Adler et al. published a much larger controlled study comparing ropinirole with placebo in early PD.[41] This was a 6-month, prospective, randomized, double blind, parallel group trial on 241 patients with limited or no prior dopaminergic therapy. The starting dose of ropinirole was 0.25 mg tid with titration to at least 1.5 mg tid (maximum 8mg tid). The primary endpoint (percent improvement in the UPDRS motor score) showed a greater change with ropinirole than placebo (+24% vs. 3%; $p > 0.0001$). The number of responders (patients whose baseline UPDRS motor score improved by more than 30%) was greater with ropinirole than placebo (47% vs. 20%). In this analysis, stratification according to the presence or absence of selegiline revealed a significantly greater treatment effect in favor of ropinirole in the patients receiving selegiline (56% vs. 14%; $p = 0.008$). In those not receiving selegiline, a similar treatment effect was observed, although this was not statistically significant (38% vs. 25%). At endpoint, 33% of ropinirole-treated patients were considered to be "very much improved" from baseline on a clinical global improvement scale compared with 12% in the placebo group. By the end of the 6 month treatment period, 29% of placebo-treated patients required levodopa rescue compared to 11% of ropinirole-treated patients.

Adverse events in this study[41] were frequent but usually well tolerated and of the type commonly linked to peripheral dopaminergic stimulation. About 52% of patients receiving ropinirole experienced nausea, 32% dizziness, and 36% somnolence (compared to 21%, 18%, and 4% respectively on placebo). Nausea severe enough to cause withdrawal occurred in 6.9% of ropinirole patients. Nausea was most frequently seen during the first 4 weeks of treatment and declined to a level equivalent to placebo by week 12. Dizziness was the second most frequent side effect leading to withdrawal, occurring in 4.3%, and peaking at 4 to 8 weeks of treatment. About 17% of ropinirole-treated patients withdrew from the study because of side effects compared to 11% of placebo-treated patients. About 16% of patients in the ropinirole group developed neuropsychiatric problems. These were severe enough for patients to withdraw from the study in 3 of 19 patients. In summary, ropinirole provided effective symptomatic reduction in early Parkinson's disease with a profile of side effects similar to the older agonists.

In a 6-month interim analysis of a 5 year, randomized, double blind study of ropinirole vs. levodopa in early Parkinson's patients, Rascol et al.[42] demonstrated ropinirole to be as effective as levodopa in mildly disabled patients. This was based on the lack of difference in a clinical global impression score for patients with Hoehn and Yahr stages I-II disease. For more severely affected early patients (stage II.5-III), however, levodopa (mean dose 464 mg/day) was superior to ropinirole (mean dose 9.7 mg /day). It should be noted that the above observations are based on a subgroup analysis and that the principal assessment of efficacy in this study (percentage improvement in UPDRS motor scores) showed a significantly greater improvement with levodopa in the entire Hoehn and Yahr I-III group. There was no significant interaction between treatment and selegiline strata in this study. Few patients required rescue with supplementary open-label levodopa (4% for ropinirole vs. 1% for levodopa). Adverse events occurred in 84% of patients in both treatment groups, the principal ones being nausea, dizziness, and somnolence. Other side effects included edema, vomiting, and syncope. Adverse events leading to withdrawal from the study were uncommon in both groups (8% for ropinirole, 13% for levodopa).

Korcyn et al.[43] has published the only ropinirole vs. bromocriptine comparison trial in early Parkinson's disease, reporting an interim (6-month) analysis of 335 patients in a three-year, double blind, multi-center study. At endpoint, the ropinirole group had a mean dose of 8.3 mg per day compared to 16.8 mg per day of bromocriptine. In patients not receiving selegiline, the treatment response significantly favored ropinirole (34% improvement in UPDRS motor score for ropinirole-treated vs. 20% for bromocriptine-treated patients) as well as for the number of responders (55% vs. 33%). In patients receiving selegiline, improvements were similar in the two groups (34% for ropinirole vs. 37% for bromocriptine), with 63% responders in both groups. Few patients required rescue with levodopa during this 6 month period in either group (7% of ropinirole-treated patients vs. 11% of those receiving bromocriptine). Adverse effects occurred in 80% of patients in both groups. The most common side effects were nausea (35% of ropinirole-treated patients vs. 20% with bromocriptine), dizziness (16% of both groups), vomiting (9% with ropinirole vs. 4% with bromocriptine), headache (8% vs. 13%), and insomnia (7% vs. 6%). Adverse events caused premature withdrawal in 5% of ropinirole patients compared to 10% of bromocriptine patients.

In summary, these studies have demonstrated that ropinirole is efficacious as monotherapy in early PD. It appears to be more effective than bromocriptine, and in early stages (Hoehn and Yahr stage I-II) can equal that of levodopa. The results suggest a 1-year levodopa delaying potential in approximately 50% of patients.

Pramipexole

An early, ascending dose, tolerance and efficacy trial[44] involving 55 patients was published in 1995. This was a multicenter, single blind, placebo controlled, parallel group, 9-week study of patients who had not been treated with agonists and did not yet require levodopa. The dose was titrated to the highest dose tolerated (a maximum of 4.5 mg/day). There was a 140% improvement ($p = 0.002$) in the mean UPDRS activities of daily living (ADL) score, and a 44% improvement ($p = 0.1$) in the mean UPDRS motor score in the pramipexole group compared to

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placebo. The adverse effect profile was similar to other dopamine agonist trials. Symptomatic orthostatic hypotension was no more common with pramipexole than placebo. When hypotension occurred it was mild, not dose limiting and didn't require ancillary therapy. Overall, 8 of 28 (29%) of the pramipexole patients experienced dose limiting toxicity, 3 due to visual hallucinations.

The Parkinson's Study Group[45] reported a 10-week, multicenter, randomized, double blind, parallel-group trial, on 264 patients with early Parkinson's disease not on other therapy. Placebo was compared to four doses of pramipexole (1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg/d). The primary outcome measure, the total UPDRS, improved by approximately 20% over the course of the study at all pramipexole doses. The 4.5 mg/d dose provided the best benefit vs. side effect ratio. The 6 mg dose was poorly tolerated due to somnolence (31%), constipation (18%), and hallucinations (9%). Hypotension was no more common in the active treatment groups than with placebo. The authors concluded that pramipexole was safe and effective short-term with an effective dose ranging from 1.5 to 4.5 mg/d. Patients were followed through a 15 month extension at the end of which 70% of patients remained well controlled on pramipexole alone.

A longer eight-month trial[46] on 333 patients with early Parkinson's disease and not previously on levodopa compared placebo vs. pramipexole titrated to optimal doses (up to 4.5 mg/d) over seven weeks and then maintained for six months. Primary outcome measures included the mean UPDRS ADL score and motor score. The mean daily maintenance dose of pramipexole was 3.8 mg/d. The ADL score, as percent improvement from baseline, showed a significant difference at two weeks and a 28% improvement in favor of pramipexole over the 31 weeks ($P < 0.0001$). The motor score demonstrated significant efficacy at three weeks with 31% more improvement at the end of eight months compared to placebo ($P < 0.0001$). An extension of this trial has demonstrated ongoing benefit for 16 months. 73% of patients were still maintained on monotherapy at two years. The adverse effects were similar to the previous trial with somnolence, nausea, dizziness, insomnia, constipation, and visual hallucinations being the most prominent. Hypotension occurred with equal frequency (10%) in pramipexole and placebo patients.

Advanced Parkinson's Disease

Ropinirole

Several studies have compared placebo with ropinirole in patients with advanced PD. Brooks et al.[38] summarized two double blind, placebo controlled pilot studies of twelve weeks duration. These assessed the efficacy and safety of ropinirole vs. placebo as adjunctive therapy in stage II-IV patients not optimally controlled by levodopa alone. In the first study, the primary endpoint was the reduction in "off time". In this study, ropinirole was gradually increased from 0.5 mg up to 4 mg bid. About 65% of patients in the ropinirole group had a greater than 30% reduction in "off time", although this did not reach statistical significance ($p = 0.077$). However, the clinicians' global evaluation did show a significant difference with the ropinirole-treated group improved by 78% compared to 35% with placebo ($p = 0.04$). Adverse events were frequent and similar in treated and control groups, reaching 91% and 76% respectively. In the second study, levodopa dose was kept constant for the initial six weeks, but was then reduced as appropriate for the following six weeks. Ropinirole dose was gradually titrated from 0.5 mg to a maximum of 5 mg bid. The primary outcome measures were a reduction in levodopa intake by 20% or more and an improvement in the total UPDRS. In this study, 49% of the ropinirole group demonstrated a reduced levodopa requirement vs. 36% in the placebo group but this difference was not statistically significant. About 66% of patients receiving ropinirole had an improvement in the clinicans' global evaluation at endpoint, compared with 54% in the placebo-treated group (not significant). Dizziness, headache, nausea, and somnolence were the most frequent side effects, leading to withdrawal in about 15% of cases in both groups.

A three month, randomized, double blind, placebo controlled trial on 46 patients with a history of motor fluctuations (defined by end of dose "wearing off" or "on/off" phenomenon) was published by Rascol et al.[47] Criteria for entry included a duration of levodopa treatment of 3 to 10 years, and the need for between 3 and 7 doses of levodopa per day. Daily diary cards allowed the assessment of "on" vs. "off" time as a primary outcome. Ropinirole was slowly titrated from 0.5 mg to 4 mg bid or to the maximal tolerated dose. The addition of ropinirole was associated with a marked reduction in "off" time (50% greater on ropinirole than on placebo), but this difference did not reach statistical significance for the intent to treat population. The clinician's global evaluation indicated a higher proportion of improved patients in the ropinirole group (70% vs. 35% $p = 0.004$). Side effects occurring more frequently with ropinirole vs. placebo included nausea (30% vs. 13%), postural hypotension (17% vs. 4%), and vomiting (13% vs. 0%). Increased dyskinesia occurred (35% vs. 22% on placebo) but did not cause withdrawal.

Larger trials with ropinirole as adjunctive therapy in fluctuating patients have been reported in abstracts and await full publication.[48,49] 148 patients (stage I-IV) with fluctuations were randomized to either ropinirole (2.5 to 8 mg BID) or placebo. After 6 months, 28% of ropinirole-treated patients had both a 20% reduction in "off time" and a 20% reduction in levodopa dose.[48] About 11% of placebo-treated patients had similar reductions.

Preliminary results of a multi-center comparison trial of ropinirole and bromocriptine in 555 patients (including both fluctuators and non-fluctuators)[49] at 6 months showed no significant difference although there was a trend for a greater percentage of responders in the ropinirole group. The effect was statistically significant in a subgroup of patients with severe fluctuations (based on a high baseline levodopa dose). The occurrence of nausea (22%) in this advanced population was less than that seen in patients receiving ropinirole as monotherapy. In this study, dyskinesia (35%) was more frequently reported in the bromocriptine group.

In summary, ropinirole appears to be a useful adjunct therapy comparable to bromocriptine in terms of efficacy and tolerance with a tendency to superiority in subgroups of patients needing more powerful dopaminergic stimulation. No routine lab monitoring is required with this medication.

Pramipexole

The first pramipexole trial in advanced Parkinson's disease (single blind, 11 week, placebo controlled, on 24 patients) demonstrated it to be well tolerated and of potential efficacy.[50]

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Subsequently, Lieberman et al[51] studied 360 patients with advanced PD, randomized to pramipexole or placebo. These patients all had motor fluctuations in response to levodopa. The trial consisted of a seven week ascending dose phase followed by a six month maintenance period. The primary outcome measures were the mean UPDRS ADL and motor score. The ADL and motor scores improved by 22% (vs. 4% in placebo; p<0.0001) and 25% (vs. 12% in placebo; p <0.01) respectively in pramipexole-treated patients. When analyzing the individual components of the motor score, the greatest percentage reduction for pramipexole vs. placebo occurred in resting tremor (65% vs. 46%), rigidity (98% vs. 55%), finger tapping (89% vs. 40%), hand movements (61% vs. 21%), and rapid alternating movements (63% versus 41%). Total "off" time was reduced by 31%, and "off" scores improved by 17% in the pramipexole group. The levodopa dose was decreased by 27% in the pramipexole group. Adverse effects (vs. placebo) were somewhat different than in the early Parkinson's disease studies. Dyskinesia was the most common side effect (61% versus 41%). Visual hallucinations (19%) and symptomatic hypotension (16%) also occurred more commonly on pramipexole. Nausea, vomiting, heart rhythm/rate disorders, urinary frequency, insomnia, confusion, and agitation were equally frequent in the two treatment groups. Although not statistically significant, the investigators commented on an impression of decreased anxiety and apathy as well as improved attention span among patients treated with pramipexole.

There is only one published trial of advanced PD in which pramipexole was compared with another agonist. This was a multi-center, double blind, parallel-group trial in 246 patients,[52] divided into three groups (bromocriptine, pramipexole, and placebo) and followed over 10 months. The medication was titrated over seven weeks to a maximum of 30 mg of bromocriptine and 4.5 mg of pramipexole. The aim of the study was to determine whether pramipexole was superior to placebo. The study was not powered to show statistical differences between active treatment groups. The UPDRS ADL score showed the greatest benefit with pramipexole (27%) vs. placebo (5%; p = 0.0002). Bromocriptine improved the ADL score by 14% (p = .017). Similarly motor scores improved by 35% (p = 0.0006) with pramipexole, and 24% (p = 0.0113) with bromocriptine compared to 6% with placebo. The differences between bromocriptine and pramipexole did not reach statistical significance. Secondary outcomes showed a trend on a global clinical assessment of efficacy in favor of pramipexole. The percent "off" time demonstrated an earlier onset of benefit (at 2 to 3 weeks) and better maintenance of this effect over the 36 weeks with pramipexole compared to bromocriptine. "Off" time was reduced by 46% on pramipexole (p = 0.007), by 30% on bromocriptine (not significant) and by 6% on placebo. The dropout rate was 20% in both treatment arms and 40% in the placebo arm. Dyskinesia, and nausea occurred more commonly in both active groups than with placebo.

In summary, pramipexole appears to be effective as an adjunctive therapy in advanced disease where it results in a 25% reduction in ADL and motor scores as well as a 30 to 45% decrease in "off time". Encouraging findings include the early onset of efficacy (2-3 weeks) and the relatively low instance of hypotension, cardiac, and gastrointestinal side effects. Patients do need to be cautioned, however, about the potential for somnolence (especially drivers), postural hypotensive symptoms, and visual hallucinations. It seems that about 25% of patients in the advanced group will be unable to reach the 4.5 mg dose because of hallucinations.

Formulations and Dose

Ropinirole

This product has been produced in a uniquely shaped pill (pentagonal tilting tablet) designed to be easy to pick up. It is available in 0.25, 1.0, 2.0, and 5.0 mg tablets. Currently it is recommended that the patients start on one 0.25 mg tablet three times a day and increase by weekly 0.25 tid increments over 4 weeks to 1 mg tid. This is the lowest efficacious dose. The medication can then be titrated by 1 mg tid increments as required and as tolerated up to a total of 24 mg/day. Most patients receive 6-10 mg/day.

Pramipexole

This product is available in three tablet sizes; 0.25, 1.0, and 1.5 tablets. The tablets are scored. The pills will turn brown if exposed to light so they should be kept in a light proof container. The effect of the color change on efficacy is unknown. The titration schedule starts at half a 0.25 mg tablet tid for the first week, a full 0.25 mg tablet the second week and then continues to increase the dose by a 0.25 mg tid as tolerated. The optimal dose ranges between 1.5 and 4.5 mg per day.

Agonist Dose Equivalents and Comparative Cost

It is generally accepted that the dose equivalents of the older agonists (bromocriptine versus pergolide) provide an approximate 10:1 ratio. This information allows for rapid and safe switch from one agonist to another. Recommended doses have been in the range of 30mg/day of bromocriptine or 3.0mg of pergolide. As there are few trials comparing the old with the new agonists, and no trials directly comparing the new agonists, it is difficult to be certain of dose equivalency. In a comparative trial between pramipexole and bromocriptine, the patients were titrated randomly up to an average of 23 mg/day of bromocriptine or 3.4 mg/day of pramipexole suggesting a dose ratio of about 7:1.[52] In a three year study of ropinirole vs bromocriptine in early PD, at 6 months the mean dose levels were 17 mg/day of bromocriptine and 8 mg/day of ropinirole, i.e., approximately 2:1.[43] In an advanced Parkinson's disease study, 20 mg/day of bromocriptine seemed to be approximately equivalent in terms of efficacy to about 12 mg/day of ropinirole, again approximately 2:1.[49]

This information would suggest the following approximate dose equivalents: 30 mg of bromocriptine, 15 mg of ropinirole, 4.5 mg of pramipexole, and 3.0 mg of pergolide. Based on these dosages, comparative daily costs (based on published Alberta Blue Cross figures) are $9.24 for bromocriptine (Parlodel), $6.90 for generic bromocriptine, $10.00 for ropinirole, $5.94 for pramipexole and $9.30 for pergolide. It is suggested, based on available information, and one of the authors' (Hobson) clinical experience with conversion, that the ratio of ropinirole to pramipexole may be close to 5:1 or 6:1. This ratio has also been suggested by other authors.[53] Because these dose equivalencies are estimates, when changing patients from one of the older agonists to one of the newer agonists the authors prefer to make

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the transition gradual, changing one daily dose at a time. At this point, there is insufficient comparative efficacy data between agonists upon which to base a general recommendation regarding agonist choice.

Conclusions

Ropinirole and pramipexole are effective anti-parkinsonian drugs with side-effects profiles linked to peripheral and central dopaminergic stimulation, amenable to tolerance through a slow titration or the addition of domperidone in sensitive patients. They do not share the ergot chemical structure of bromocriptine and pergolide, and can therefore be expected to be free of the uncommon but serious adverse events related to this structure, including refractory edema of the lower limbs, erythromelalgia, and pleuropulmonary and retroperitoneal fibrosis. The potential levodopa delaying effect has been confirmed. Both of these compounds have been shown to be efficacious as monotherapy in early PD, and have been suggested as being less likely than levodopa to lead to the early development of motor fluctuations and dyskinesias in this clinical setting. There is no longer the excuse of lack of efficacy to withhold initiating dopamine agonist use to control symptoms in medically well younger patients (less than 65-70). They can be continued as monotherapy as long as symptom control is satisfactory.

A levodopa sparing effect has been confirmed in advanced stages of the disease, perhaps offering a neuroprotective potential inherent in reduction of the dopamine oxidation metabolism. Long-term results from levodopa controlled studies, however, are still lacking. The potential of these new compounds to improve the future occurrence of fluctuations, dyskinesia, and psychiatric complications is exciting to ponder while awaiting the outcome of ongoing and future trials.

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