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Switching from pergolide to pramipexole in patients with Parkinson's disease

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Summary. *Objective/Background*. To compare the safety and efficacy of pramipexole and pergolide in the treatment of mild to moderate Parkinson's disease (PD). In contrast to pergolide, a D_1 and D_2 dopamine agonist, pramipexole is a nonergoline dopamine agonist with D_2 and preferential D_3 dopamine receptor activity. This selective activity may result in clinically different effects. No prospective head-to-head comparison studies of pergolide and pramipexole have been reported.

Methods. Patients with PD who were maintained on an optimal dose of pergolide were converted to pramipexole, typically over a one-month period. Clinical assessments were performed just prior to conversion and after an optimal dose of pramipexole was achieved.

Results. Twenty-five patients were converted from pergolide to pramipexole during the period of July, 1997 to January, 1999. Three patients were lost to follow-up, and one patient died. Of the remaining 21 patients there were 11 men and 10 women, mean age was 67.3 years ± 10.0 (range 51–84). Mean duration of symptoms prior to conversion was 12.5 years ± 3.4 (range 5–19). All patients (except one) were on concomitant carbidopa/levodopa and experienced motor fluctuations. After a mean follow-up of 5.9 ± 2.9 months on pramipexole, the mean levodopa daily dose was reduced from 618.7 mg to 581.2 mg (16.5% reduction, $p = 0.61$). The mean daily doses of pergolide and pramipexole (in milligrams per day) were 2.1 ± 1.5 (0.15–6) and 3.2 ± 1.1 (0.75–6) respectively. Thirteen patients (62%) reported overall improvement (subjective global response) on pramipexole as compared to pergolide, 5 (24%) were unchanged and 3 (14%) reported worsening. Eighteen of the 21 patients (86%) remained on pramipexole after the study period. Although there was a slight trend toward improved scores on pramipexole, the difference was not statistically significant.

Conclusion. This open label study failed to provide evidence of superior efficacy of either dopamine agonist. It is possible, however, that while some

patients may benefit more from either pergolide or pramipexole, other patients may obtain additional benefit from other DA agonists or combination therapy. Future randomized, controlled, double-blinded therapeutic trials are needed to determine which, if any, dopamine agonist is superior in the treatment of PD.

Keywords: Dopamine agonists, pergolide, pramipexole, ropinirole, Parkinson's disease, therapy.

Introduction

Until the introduction of pramipexole and ropinirole in 1997, only two dopamine (DA) agonists, bromocriptine and pergolide (both ergot derivatives), were clinically used in the United States for the treatment of Parkinson's disease (PD) (Jankovic, 1999) while additional DA agonists including apomorphine, lisuride and cabergoline have been used in other countries for PD (Tulloch, 1997; Van Laar et al., 1992, 1996; Ondo et al., 1999; Ahlskog et al., 1994; Inzelberg et al., 1996; Rinne et al., 1998). Pramipexole is a nonergoline dopamine agonist with D_2 and preferential D_3 receptor activity (Piercey, 1998) which has proven to be safe and effective in the treatment of early (Hubble et al., 1995; Parkinson Study Group, 1997) and mild to moderate PD (Shannon et al., 1997). Furthermore, pramipexole has been helpful in controlling motor fluctuations in patients with advanced PD and in reduction of required levodopa doses (Molho et al., 1995; Lieberman et al., 1997; Dooley and Markham, 1998).

Few head-to-head comparisons of different DA agonists have been reported in the literature (LeWitt et al., 1983; Pezzoli et al., 1994; Inzelberg et al., 1996; Guttman et al., 1997). There are no published studies, without serious methodological limitations, definitely proving that one DA agonist is superior to another, so that the only possible conclusion at the moment, regarding evidence-based medicine, is that all DA agonists should be considered as "me-too" drugs. In particular, no prospective head-to-head comparison studies of efficacy and safety of pergolide and pramipexole have been reported. Since the two DA agonists have different DA receptor selectivities, which may result in differing clinical effect, we evaluated the efficacy and tolerability of pramipexole in patients who were previously taking pergolide.

Materials and methods

The study design was a single center (Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine), prospective, open label trial in patients with PD. All patients were on an optimal dose of pergolide, along with stable doses of carbidopa/levodopa (except one patient) at time of enrollment. All consecutive patients optimally treated with pergolide (typically to the maximal tolerate dose (though this was not forced) – up to 6 mg/day) were converted to pramipexole to determine if additional benefit could be derived from the new DA agonist. Each patient's DA agonist regimen was converted from pergolide to pramipexole, typically over a one-month period. The pergolide dose was decreased by one-half every week until the patient was off this medication. Simultaneously with the pergolide tapering, patients were started on

pramipexole with escalating doses (0.125 mg 3 times/day for a week, 0.25 mg 3 times/day for a week, 0.5 mg 3 times/day for a week, and 1.0 mg 3 times/day thereafter). Based on effect and tolerability, patients were subsequently allowed to increase the dose to as much as 2.0 mg 3 times/day.

Clinical assessments were performed just prior to conversion and after an optimal dose of pramipexole was achieved. The variables assessed during both conditions included the following: daily levodopa dose, Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987) I and II (ADL) subscores both "on" and "off", % daily "on" time (based on patient diaries/historical information), Schwab and England ADL scores "on", dyskinesia severity (0–4 scale) and % daily dyskinesias (UPDRS IV/historical information), and other levodopa-related complications such as nausea, orthostatic hypotension, and sleep disturbance (UPDRS IV). Each patient reported whether overall they were improved, unchanged or worse on pramipexole or pergolide as compared to levodopa. Since patients were not examined in their true "off" state (in the morning at least 12 hours after their last dose of levodopa) and during their peak "on" state (typically one hour after taking their first daily dose of levodopa), and UPDRS III (motor) scores were not included in the study analysis.

Results

A total of twenty-five patients were converted from pergolide to pramipexole during the period of July, 1997 to January, 1999. Of these, three patients were lost to follow-up, while one patient died, resulting in 21 patients (11 men, 10 women) available for analysis. Table 1 describes the demographic characteristics of the patients included in this study. At time of entry, all patients (except one) were taking carbidopa/levodopa at time of entry and were clinical fluctuators. The mean duration of pergolide treatment prior to conversion was 41.7 months ± 27.5 (range 5–94) (Table 1). Patients lowered their mean levodopa daily dose from 618.7 mg, while on pergolide, to 581.2 mg, on pramipexole, which is a 16.5% decrease ($p = 0.61$) (Table 2). The mean daily doses of pergolide and pramipexole are provided in Table 2. The inter-drug ratio between both agonists was comparable in most patients.

Thirteen patients (62%) reported overall improvement on pramipexole as compared to pergolide, 5 (24%) were unchanged, and 3 (14%) reported worsening. Eighteen of the 21 patients (86%) remained on pramipexole after the study period. Two of the patients who stopped pramipexole reported increased "off" time; one resumed the use of pergolide, while the other switched to ropinirole but adequate follow-up is not available. The third patient subsequently enrolled in a experimental drug trial. Six patients

Table 1. Pergolide vs. pramipexole study. Demographic data (N = 21)

Age	67.3 years ± 10.0 (range 51–84)
Gender	11 men (52%), 10 women (48%)
Duration of symptoms	12.5 years ± 3.5 (range 5–19)
Concumitant levodopa use	20 patients (95%)
Hoehn and Yahr stage	Stage 1: n = 1; 1.5: n = 1; 2: n ± 6; 2.5: n = 2 3: n = 9; 4: n = 2
Duration on pergolide (months)	41.7 ± 27.5 (range 5–94)
Pramipexole treatment (months)	5.9 ± 2.9 (range 1–12)

Table 2. Pergolide vs. pramipexole study (N = 21)

Variable	Pergolide	Pramipexole	p-value[3]
% daily "on" time[1]	74.7%	72.1%	0.894
Schwab/England ADL score[2]	80.5%	80.5%	0.856
% daily dyskinesias[1]	21.2%	16.8%	0.225
Dyskinesia severity	0.90	0.81	0.480
Levodopa daily dose in mg	618.7 ± 397.9	581.2 ± 336.5	0.61
Dopamine agonist dose in mg	2.1 ± 1.5 (0.15–6)	3.2 ± 1.1 (0.75–6)	N/A
UPDRS 1 subscore "on"	3.62 ± 3.3	3.29 ± 2.9	0.633
UPDRS 1 subscore "off"	3.76 ± 3.3	3.57 ± 3.0	0.752
UPDRS 2 subscore "on"	18.67 ± 7.8	16.95 ± 8.3	0.236
UPDRS 2 subscore "off"	24.19 ± 7.8	23.90 ± 8.7	0.384

[1]N = 17, [2]N = 20, [3]Wilcoxon. All above represent mean values

specifically reported improved energy on pramipexole while one patient reported decreased energy; two patients reported less depression. Three patients noted increased hallucinations on pramipexole. In one patient, the hallucinations resolved after discontinuing amantadine, one patient switched back to pergolide and one remained on pramipexole. Further specific symptoms which were noted to increase after conversion were sweating (1 patient), edema (1), and dyskinesia (1) while a decrease in the following symptoms were noted: nausea (1), falls (1), and dyskinesia (1). All of these patients remained on pramipexole. A further patient had an increase of tremor on pramipexole and subsequently underwent thalamic deep brain stimulation placement.

Percent "on" time was 74.7% (pergolide) and 72.1% (pramipexole), while dyskinesias dropped from 21.2% to 16.8% after conversion (p = 0.23). UPDRS I and II (ADL) subscores both "on" and "off" (Fig. 1), % daily "on" time, Schwab and England ADL scores while "on" (Fig. 2), % daily

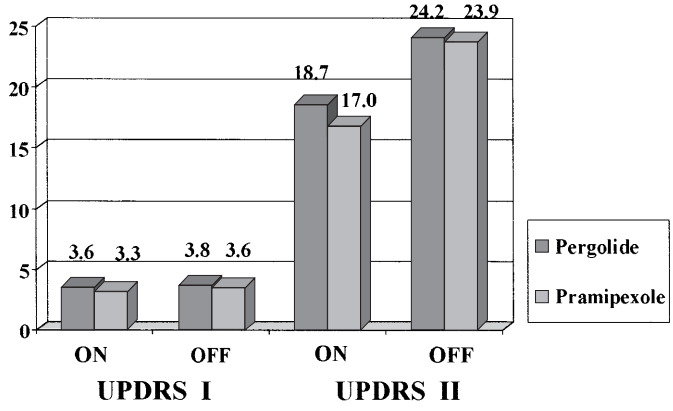

Fig. 1. Mean UPDRS I and II scores while on pergolide (shaded) or pramipexole (unshaded)

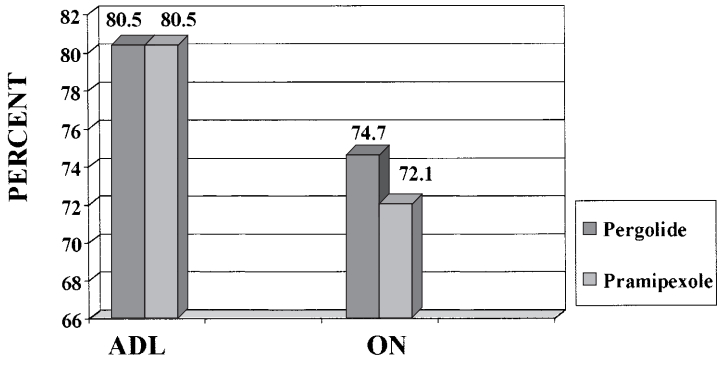

Fig. 2. Mean Schwab and England ADL (activities of daily living) score and percentage daily "on" time on pergolide (shaded) or pramipexole (unshaded)

dyskinesias (Fig. 3) and dyskinesia severity (0–4) are outlined in Table 2. Wilcoxon signed rank test was used for the statistical analysis for these data points. Nausea was reported in 4.8% of patients on either medication while no patients reported orthostatic hypotension on either agonist. Sleep disturbance (UPDRS IV) was reported in 31.6% with pramipexole vs. 25% on pergolide ($p = 0.65$) (Fig. 4).

Discussion

As the number of DA agonists available for the treatment of PD continues to expand, the clinician is faced with increasingly more complex choices of therapeutic options. In the present study, patients tolerated the conversion from pergolide to pramipexole well with the vast majority (18/21, 86%) remaining on pramipexole after conclusion of the study. There was no clear evidence, however, of superior efficacy or tolerability of either DA agonist as comparison of UPDRS I and II, Schwab and England ADL scores, "on" and "off" duration, dyskinesia severity and duration did not reveal statistically significant differences.

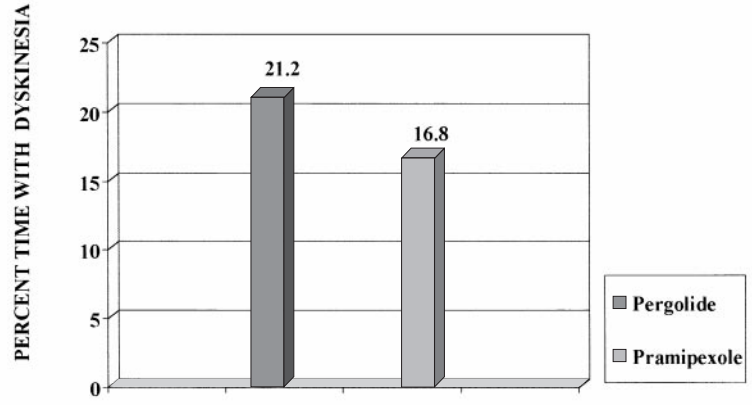

Fig. 3. Mean percentage of daily time with dyskinesia on pergolide (shaded) or pramipexole (unshaded)

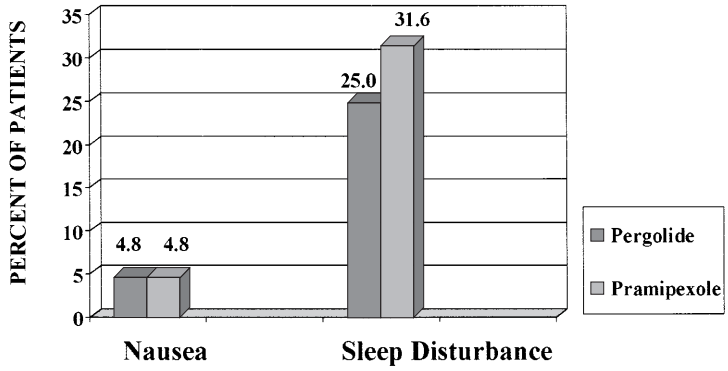

Fig. 4. Percentage of patients with levodopa-related complications (nausea, sleep disturbance) on pergolide (shaded) or pramipexole (unshaded)

There are recognized shortcomings to this study. The study was an open-label, crossover, trial with the possible biases favoring a "new" treatment. The dose ratio of 3:2 pramipexole to pergolide may not necessarily be the optimal conversion ratio since neither of the drugs was "forced" to the maximum tolerated dose. Although we did not report UPDRS motor scores in true "on" and "off" state, these assessments have a limited value in fluctuating patients; duration of "on" "off" and of dyskinesia may be more relevant to the assessment of overall motor functioning. It is also possible that the sample size of this study was too small to detect significant differences in outcomes.

The pharmacological activity of DA agonists is to directly activate DA receptors. Pergolide is an ergot derivative and as such it can cause potential vasoconstrictive complications, exacerbation of peptic ulcer disease, erythromelalgia, as well as pulmonary and retroperitoneal fibrosis. Pramipexole is a non-ergoline agonist and should have a lower risk of such complications. Pramipexole also differs from the older ergot agonists due to its preferential D_3 DA receptor activity (Piercey, 1998). This preferential D_3 DA receptor activity of pramipexole has been postulated to be a mechanism in the reported anti-depressant effects of this drug (Maj et al., 1997; Willner, 1997). In the present study, the depression subscore on the UPDRS I was lower in the pramipexole-treated patients, both in the "on" and "off" state, but the results did not reach statistical significance. One patient reported the development of lower extremity edema (Tan and Ondo, 2000) on pramipexole and no patients reported sleep attacks which have recently been described in patients on pramipexole and ropinirole (Frucht et al., 1999).

We used a fairly "slow" titration, tapering off one agonist while simultaneously increasing the dose of the other agonist, compared to the more rapid titration described by Goetz et al. (1999) in which patients "received the full converted dose the day after stopping the former agonist (8 patients) with subsequent weekly dose adjustments". Canesi et al. (1999) performed an overnight switch of dopamine agonists (to ropinirole) in sixty-eight PD patients with inadequate response to either pergolide (n = 46) or bromo-

criptine (n = 22). This approach was well tolerated, may improve compliance and reduce cost in comparison to slow titration schedules.

Despite its limitations, this open label study failed to provide evidence of superior efficacy of either DA agonist evaluated. There were trends toward improved efficacy on pramipexole and this agent was well tolerated by the vast majority of patients choosing to remain on this agent. Each agonist has particular DA receptor affinities and while some patients may benefit from pergolide the same or other patients may obtain additional benefit from pramipexole. Combination therapy may also be theoretically beneficial.

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