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ORIGINAL COMMUNICATION

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Conversion from dopamine agonists to pramipexole

An open-label trial in 227 patients with advanced Parkinson's disease

Abstract *Background* Pramipexole is a nonergoline dopamine agonist with D2 and preferential D3 dopamine receptor activity. This selective activity may result in clinically different effects. Small clinical trials indicate that overnight switching from one agonist to another can be performed safely. *Objective* To determine safety and efficacy of overnight switching from dopamine agonists to pramipexole in patients with advanced Parkinson's disease (PD). *Methods* Patients with advanced PD and motor complications not optimally controlled by levodopa and a stable dose of bromocriptine, pergolide or ropinirole were converted to pramipexole overnight. Clinical assessments were performed just prior to conversion and after 2, 6 and 12 weeks of treatment, when an optimal dose of pramipexole was achieved. *Results* Two hundred and seventeen patients were included in the trial. One hundred and twenty five were converted from pergolide to pramipexole, 58 from bromocriptine and 34 from ropinirole. After 12 weeks, the average dose of pramipexole was 2.8, 2.9 and 3.4 mg/d in patients converted from bromocriptine, pergolide, and ropinirole, respectively. UPDRS II, III and IV scores were reduced by 26–30 % in all patients ($p < 0.0001$). Mean levodopa dose was slightly reduced in all groups (p: NS). No serious or unexpected side effects were reported. The dose equivalences calculated from this trial were: bromocriptine: pramipexole 6.9:1, pergolide: pramipexole 0.9:1, ropinirole: pramipexole 1.5:1. *Conclusion* Switching from bromocriptine, pergolide or ropinirole to pramipexole in an overnight schedule is safe. The observed clinical improvement may be related to a placebo effect, to the use of low doses of dopamine agonists or to a direct effect of pramipexole.

Key words dopamine agonists · pramipexole · Parkinson's disease · motor complications

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Introduction

Motor fluctuations and dyskinesias affect more than 50 % of patients with Parkinson's disease (PD) after 5 years of chronic treatment with levodopa [13]. Dopamine agonists are considered standard therapy as adjuncts to levodopa in the management of this complex situation [12]. Considerable differences exist between dopamine agonists in terms of half-life, affinity for dopamine receptor subtypes, ergotic character, activity at noradrenergic and serotoninergic receptors, etc. [18]. For instance, pramipexole is a nonergoline dopamine agonist with D2 and preferential D3 dopamine receptor activity [14]. However, as no direct comparative studies between pramipexole and other dopamine agonists have been conducted, it is difficult to know the clinical significance of its pharmacological peculiarities. Nonetheless, some data suggest that they may result in clinically different effects. For instance, it has been shown that pramipexole may have antidepressive [2, 7, 17] and antitremor [15] effects that can positively influence the clinical condition of patients with PD and motor complications.

Although results of controlled clinical trials suggest that the efficacy and side effects profile of the different

dopamine agonists are quite similar [12, 18], a few studies indicate that in patients in whom efficacy waned from one dopamine agonist, renewed benefit may occur after switchover to another dopamine agonist [4, 5]. This has been documented in patients switched from bromocriptine to pergolide [4] and vice versa [5]. This apparent paradox can be explained by a selection bias inherent to clinical trials. Patients with PD and moderate motor complications are the usual population included in clinical trials and this is not a reflection of the real conditions found in daily clinical practice in which patients with more advanced disease, more severe complications and affected by many other diseases are treated. This may hide the true differences between dopamine agonists.

The switch from one agonist to another can be carried out gradually or abruptly. Small clinical trials indicate that overnight switching from one agonist to another may be performed safely [1, 6, 11, 16]. To our knowledge, this has not been studied in daily clinical practice with a big sample of non-selected patients. The present study has been conducted to determine the safety and efficacy of overnight switching from dopamine agonists to pramipexole in patients with advanced PD in real clinical conditions.

Methods

Patients with idiopathic PD according to the United Kingdom PD Brain Bank criteria [3] were included in this open, observational, prospective and multicenter study. All of them suffered from motor complications not optimally controlled by levodopa and a stable dose of bromocriptine, pergolide or ropinirole.

All patients stopped the former agonist on the day after the baseline evaluation and started pramipexole. Patients were switched to pramipexole overnight according to the following dose equivalency scheme: 1 mg of pramipexole = 1 mg of pergolide = 10 mg of bromocriptine = 4 mg of ropinirole. As no proper clinical studies have been performed to date to determine the equivalence of different dopamine agonists, this scheme was an approximation based on personal experience and extrapolations from previous clinical trials [6, 16]. After this, the dose of pramipexole could be increased until a maximum of 4.5 mg/d or optimal clinical control was achieved. Levodopa dosage could be adjusted if the neurologist considered it necessary. Other antiparkinsonian drugs (selegiline, amantadine, etc.) and complementary treatments (antidepressive drugs, benzodiazepines, etc.) were kept unchanged.

Patients were assessed with the UPDRS (subscales I–IV) which was administered in the "on" condition. The Hamilton rating scale was used to evaluate depression [9]. Both rating scales were administered just prior to conversion and after 2, 6 and 12 weeks of treatment, when patients were on an optimal dose of pramipexole. Adverse effects were assessed at every visit, following a checklist.

Results were analysed by an ANOVA and paired Student's *t* test. Significance in all cases was assigned when $p < 0.05$. SAS version 8.2 software was used to perform the statistical analysis.

Results

Two hundred and seventeen patients were included in the trial. One hundred and twenty five were converted from pergolide, 58 from bromocriptine and 34 from ropinirole. Demographics of patients are shown in table 1. Patients on bromocriptine had a longer duration of PD and the severity of symptoms was greater. Forty-four patients (20.3 %) did not complete the study. The distribution of these patients within the three groups was quite homogeneous (28 (22.4 %) were on the pergolide group, 10 (17.2 %) belonged to the bromocriptine group and 6 (17.6 %) were on the ropinirole group).

No serious or unexpected side effects were reported. Twelve patients (5.5 %) were withdrawn because of lack of efficacy (n = 5), adverse effect (n = 4) and protocol violation (n = 3). However, 44 patients were lost to follow-up and it is likely that in some of them this was due to a lack of efficacy or to the development of some adverse experience. Seventeen patients reported some kind of psychiatric adverse effects. Fifteen of them already had these problems before entering the trial. Five out of them reported visual hallucinations. All these problems could be easily controlled by adjusting the dose of pramipexole and, in fact, none of them was withdrawn of the study.

Clinical results are summarized in table 2. A significant improvement in the UPDRS II and III was obtained ($p < 0.0001$). Patients converted from pergolide and bromocriptine also experienced a significant improvement in the subscale I of the UPDRS whereas patients on ropinirole before entering the study showed a trend to improvement in this subscale. Motor fluctuations were significantly ameliorated in all groups. Levodopa-induced dyskinesias score was reduced in all groups although this reduction was statistically significant only in the group previously treated with bromocriptine. Depression was significantly ameliorated. Mean levodopa dose was slightly and not significantly reduced in all the groups.

After 12 weeks, the mean dose of pramipexole was 2.8, 2.9 and 3.4 mg/d in patients converted from bromocriptine, pergolide and ropinirole, respectively.

Table 1 Demographics of patients

	Previous treatment		
	Bromocriptine	Pergolide	Ropinirole
Mean (SD)			
Age (years)	68.1 (8.8)	67.2 (7.0)	65.3 (9.0)
Duration of PD	8.6 (4.2)	6.5 (3.8)	6.2 (3.5)
Gender (m/f)	29/29	73/52	21/13
UPDRS	44.9	38.2	36.8
Levodopa (mg)	603	613	595
Dose (mg)	19.2	2.6	5.4

Table 2 Summary of results

	Pergolide			Bromocriptine			Ropinirole		
	Basal	Final	%	Basal	Final	%	Basal	Final	%
UPDRS I	2.2	1.5	31.8	3.3	2	39.3	1.9	1.6	15.8*
UPDRS II	13.5	10.1	25.2	16	12.1	24.3	13	10	23
UPDRS III	18.8	13.9	26	21	15	28.6	18.1	12.9	28.7
Dyskinesias	1.4	1.1	21.4*	1.8	1.3	27.8	1.7	1.3	23.5*
Fluctuations	2	1.2	40	2.2	1.2	45.5	1.8	1.1	38.9
Hamilton scale	7.7	5.2	32.5	9.5	6.7	29.5	8	5.3	33.7
Ldopa dose	614	598.6	2.5*	604	574.1	4.9*	595	536.2	9.9*

%: Percentage of change. All the changes were significant ($p < 0.0001$) except those with an asterisk (*)

The dose equivalence calculated from this trial were: bromocriptine:pramipexole 6.9:1, pergolide:pramipexole 0.9:1, ropinirole:pramipexole 1.5:1.

Discussion

The results of the present study show that switching from pergolide, bromocriptine or ropinirole to pramipexole can be safely performed, supporting previous experience with small numbers of patients [6, 16]. Until the study by Goetz et al. [6], the general tendency was to slowly introduce the new agonist while the other agonist was slowly reduced and stopped. These authors compared rapid versus slow-titration schedules for starting pramipexole in 16 patients already on levodopa and bromocriptine or pergolide [6]. They showed that the conversion could be performed abruptly with a very good tolerance and with the possibility of obtaining additional clinical benefits, such as a reduction in the time required to reach an improvement in clinical rating scales without increased adverse effects [6]. The present study is in keeping with these conclusions and, furthermore, strongly supports the notion that a similar strategy may be applied to unselected patients in real practice conditions (such as aged patients with advanced PD and severe and complex motor complications, most of them suffering from other diseases and receiving more treatments).

A significant improvement in virtually all motor and psychological evaluations was found in our study. The improvement was seen from the firsts weeks of treatment and was maintained over the 12-week study. In a previous study including 21 patients, Shulman et al. [16] showed that 17 patients abruptly switched from bromocriptine, pergolide or cabergoline to pramipexole experienced a significant improvement in the total UPDRS and 60 % of patients were judged improved by the examining neurologist on a global assessment scale. Hanna et al. [10] studied the clinical evolution of 25 parkinsonian patients after changing pergolide to pramipexole over a one month period. Three patients were lost of follow-up, and one patient died. After a mean follow-up of 6 months on pramipexole, the mean levodopa daily dose was reduced from 618.7 mg to 581.2 mg (16.5 % reduction). The mean daily doses of pergolide and pramipexole were 2.1 mg/d and 3.2 mg/d 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 in the UPDRS on pramipexole, the difference was not statistically significant. In this study the conversion was made gradually. Although there are some methodological differences, the results of this study also points to a positive clinical effect of the change. In the study by Goetz et al, patients were randomized to two titration schedules: slow titration or immediate switchover [6]. Over the 8-week study, both groups showed statistically significant improvement over baseline function on the original agonists. However, patients abruptly switched spent less time in reaching the optimal clinical situation. Looking at the differences in clinical results observed in those studies involving rapidly and slowly converted patients, it is tempting to speculate that the rate of conversion can influence, at least in part, the final result.

Reasons for the clinical benefit encountered in our study could be multiple. First, this was an open label study and therefore all weaknesses related to this type of study design have to be acknowledged. A placebo effect can explain the improvement observed in all the scales administered. Moreover, this effect could be overestimated because of the short duration of the study. Additionally, many patients were aware of the release of pramipexole to the market and were anxiously waiting to try it, mainly if they were not well controlled with other antiparkinsonian drugs. In these cases the placebo effect can be determinant.

Secondly, the dosage of pramipexole was flexible (until a maximum dose of 4.5 mg/d tid was achieved) and adjusted to patients' needs in each visit. Therefore, it is

likely that the improvement observed was related to a global increase in the dopaminergic tone due to a relative increment in the dosage of pramipexole. However, despite the negligible decrease in daily levodopa dose, dyskinesias were also improved suggesting that other factors might be involved in these beneficial effects.

Thirdly, the switchover itself may be a likely explanation for the observed positive clinical outcome. In a five-year study of bromocriptine and pergolide, Goetz et al. found that patients whose bromocriptine efficacy waned, experienced renewed efficacy after switching to pergolide [4]. Similarly, in patients showing a progressive loss of efficacy from pergolide, conversion to bromocriptine stabilized motor function [5].

Finally, a direct effect of pramipexole could explain the results. Although this was not a study involving a change in the dopamine agonist used, Guttman compared pramipexole and bromocriptine in patients with advanced PD and found pramipexole to be more effective in reducing motor disability [8]. Pramipexole is a nonergoline dopamine agonist with D2 and preferential D3 dopamine receptor activity. This selective activity may result in clinically different effects. For instance, it has been claimed that pramipexole may exert special antitremor and antidepressive effects that can be important for PD patients [2, 7, 15, 17]. Although several studies strongly support the antitremor effect of pramipexole [14, 15], tremor was not individually assessed in this study. Nonetheless, all the cardinal symptoms and signs of the disease were improved (data not shown). A placebo-controlled trial in patients with depression has shown that pramipexole may exert an antidepressive effect comparable to fluoxetine [2]. Thus, the improvement in the Hamilton rating scale may be related to this apparently specific effect of pramipexole. However, other explanations, such as a causal relationship between the improvement in motor and emotional status, cannot be excluded.

The design of the study precludes the possibility of making any dosage equivalency recommendations. Up to the present, no such data exist because the question has not been adequately addressed. The dose equivalency estimates suggested in this study are based on prior clinical studies [1, 6, 13, 16] and expert opinions. However, there is considerable variability among the different published studies [1, 6, 13, 16]. In the study by Shulman et al. [16] the conversion ratio from bromocriptine to pramipexole was 5:1, from pergolide to pramipexole was 0.75:1 and from cabergoline to pramipexole was 2:1. In the study by Hanna et al. [10], the calculated conversion ratio from pergolide to pramipexole was 0.7:1. The ratio used by Hauser et al. in their pramipexole to ropinirole switchover study was 1:3 [11]. Finally, Canesi et al. selected a pergolide:ropinirole dose ratio of 1:6 after correcting the initial estimate which was 1:3 [1]. In this last study patients with pramipexole were not included [1]. However, extrapolating from other data [3, 6, 16], a similar pramipexole:ropinirole [1:3–4] ratio can be considered. These data are somewhat different from ours: 0.9:1 in the case of pergolide, 7:1 in the case of bromocriptine and 1.5:1 with ropinirole. Obviously the results are not comparable because of methodological differences. Also the heterogeneity of the population included in the present study could explain such differences. Nevertheless, and based on current experience, we believe that the conversion ratio from pergolide to pramipexole obtained in present study is quite adjusted but this is not the case with bromocriptine and much less with ropinirole (1.5:1 actual ratio vs 3–4:1 suggested ratio).

Twelve patients abandoned the study mainly because of inefficacy or side effects. Otherwise, the safety profile of pramipexole was similar to existent data with mild gastrointestinal and cardiovascular side effects as the principal adverse reactions. Psychiatric side effects are a major concern of the use of dopamine agonists. In this study; 17 patients experienced mild psychiatric disturbances; 15 of them had the same problem before entering the study which was not worsened by the change. These complications were easily controlled by slight dosage adjustments of pramipexole. These data are concordant with results of previous studies [6, 10, 16] in which adverse hyperdopaminergic effects were not more frequent after a rapid conversion. By contrast, Hauser et al. found that a gradual switch from pramipexole to ropinirole tended to be better tolerated than an acute switch [11].

In summary, switching from bromocriptine, pergolide or ropinirole to pramipexole in an overnight schedule is safe in levodopa-treated PD patients. The observed clinical improvement may be related to a placebo effect, to the use of proportionally high doses of pramipexole because of previous low doses of dopamine agonists (particularly ropinirole) or to a direct effect of pramipexole. Although this open label study failed to provide conclusive evidence of superior efficacy of either dopamine agonist, it is possible that some patients may obtain additional benefit from other DA agonists. Thus, further randomized, controlled, double-blinded therapeutic trials are needed to determine which, if any, dopamine agonist is superior in the treatment of PD.

Spanish dopamine agonists study group

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