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Brief Report

Double-Blind, Single-Dose, Cross-Over Study of the Effects of Pramipexole, Pergolide, and Placebo on Rest Tremor and UPDRS part III in Parkinson's Disease

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Abstract: Tremor is one of the cardinal signs of Parkinson's disease (PD) but its response to antiparkinsonian medication is variable. It has been postulated that pramipexole may have a stronger antiparkinsonian tremor effect than pergolide, another direct acting dopamine agonist medication, possibly because the former has preferential affinity for the dopamine D3 receptor. The purpose of this pilot study was to compare the effects of a single oral dose of either pramipexole (Pr) or pergolide (Pe) or placebo (Pl) on parkinsonian tremor and the motor (part III) subsection of the UPDRS. Ten patients (6 men, 4 women), mean age 65.3 years, mean duration from diagnosis of 2.6 years, with tremor dominant PD were recruited. On three separate occasions a single dose of pramipexole (salt) 500 μg, pergolide 500 μg or placebo were administered in random order to each patient, who were pretreated with domperidone and had their antiparkinsonian medication withheld from midnight before study. After each medication patients were assessed at baseline and then every 30 min for 4 hr using a 0 to 10 tremor rating scale and the UPDRS (part III) in a double-blind protocol. Adverse effects were systematically recorded. The results demonstrate that 500 μg of either pramipexole or pergolide reduced PD rest tremor scores to a similar degree, which at peak effect was significantly greater than placebo (respectively Pe v Pl: $P < 0.006$, Pr v Pl: $P < 0.033$). The two active drugs also had weaker beneficial effects on the UPDRS part III. Pergolide, however, was significantly more likely than pramipexole to cause nausea ($P = 0.005$) or vomiting ($P = 0.014$). © 2003 Movement Disorder Society

Key words: Parkinson's disease; tremor; pergolide; pramipexole

Tremor is the most frequently reported initial symptom of Parkinson's disease (PD) and may become intrusive. PD tremors respond variably to standard medical therapy with L-dopa (L-dopa), direct acting dopamine agonists, anti-cholinergics and propranolol.[1] Interest in the direct acting dopamine agonist class of medications has increased recently because chronic L-dopa utilisation is associated with the development of motor fluctuations and dyskinesias in about 40% of PD patients after 4 to 6 years, whereas the former drugs have a significantly lower propensity to produce these problems.[2] It is not clear, however, whether differences in the anti-tremor potencies of the individual direct-acting dopamine agonist medications exist. It is, therefore, reasonable to speculate that these drugs may have different influences on PD tremor as they possess different potency ratios for their effects on dopamine receptors. For example, pergolide mainly stimulates D2 receptors but also has some

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TABLE 1. *Patients' baseline demographics*

Subject no.	Gender	Age (yr)	H&Y	S&E (%)	Disease duration (yr)	UPDRS-III	Rest tremor rating (0–10)
1	F	46	1	95	4	10/108	2.5
2	M	62	1.5	85	1	21/108	4
3	M	68	2	100	0.5	26/108	5
4	M	75	2	85	2	27/108	2.5
5	M	50	1	85	1	27/108	2
6	F	76	1	80	1	27/108	2
7	F	84	1	95	8	15/108	2.5
8	M	71	2	80	0.6	15/108	2
9	F	56	1	90	5	15/108	3
10	M	65	3	75	3	47/108	5

H&Y, Hoehn and Yahr score; S&E, Schwab and England score.

activity at the D1 and D3 receptor sites, whereas pramipexole has preferential affinity for the D3 receptor subtype.[3–8]

We explore this hypothesis by examining the effects of single doses of two different dopamine agonists, namely pramipexole and pergolide, on rest tremor and UPDRS part III (motor subsection score) in PD.

PATIENTS AND METHODS

The study was approved by the Riverside Research and Ethics Committee and written informed consent obtained from all the participants before enrollment. The assessments were carried out from July to October 2000 in the tremor laboratory at Charing Cross Hospital.

Patients

Patients had: 1) idiopathic PD, according to UK brain bank criteria; 2) a rest tremor of an upper limb that reached at least Grade 2/10 in severity on a 0 to 10 tremor rating scale[9,10]; and 3) had not previously been on any direct-acting dopamine agonist class medication. Patients were recruited from the neurological clinics of the Charing Cross and West Middlesex University Hospitals, London. Twelve sequential patients attending these clinics and fulfilling the study's entry criteria were asked to take part in the study, and 2 patients declined. Demographics of the 10 participating patients are given in Table 1. Nine of the patients were on antiparkinsonian medication: 6 were on L-dopa (mean daily dose, 635.4 mg; range, 187.5–1,125 mg); 5 were on propranolol (mean daily dose, 100 mg; range, 40–160 mg); 2 were on trihexyphenidyl hydrochloride (both on 4 mg/day) and 1 was on amantadine (200 mg/day).

Study Design

The patients' anti-PD medications were stopped from midnight before each study day. After baseline assessments single doses of 500 μg pramipexole (salt), 500 μg pergolide, or placebo was administered to each patient. The medications were encapsulated in an identical fashion and given in random order by the research pharmacist. Patients were assessed on three separate mornings at weekly intervals, commencing at the same time of day. On each occasion assessments were carried out at half-hourly intervals for 4 hours using a double-blind protocol. All the patients were pre-treated with domperidone for 24 hours before each study day and received a further dose on the study mornings.[11] The first 5 patients received domperidone 10 mg t.d.s., followed by 10 mg on assessment days, whereas the second 5 were administered 30 mg t.d.s., followed by 30 mg. An increase in anti-emetic dosage was required because nausea or vomiting occurred in Subjects 1 to 5 on at least one of their three visits.

The primary and secondary outcomes were mean [area under the curve (AUC)] and minimum rest tremor in the most affected arm and mean and minimum UPDRS part III (motor score subsection) respectively.[9,10,12] The severity of rest tremor was scored using the 0 to 10 tremor rating scale by a blinded examiner. Patients were asked

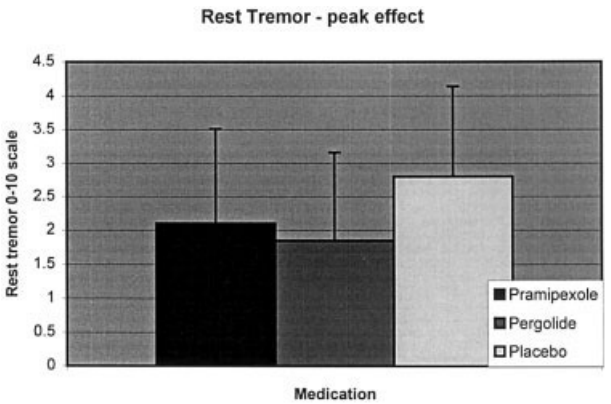

FIG. 1. Rest tremor severity (mean + SD) in the most affected arm by medication, at peak effect. The tremor is scored on a 0 to 10 rating scale.

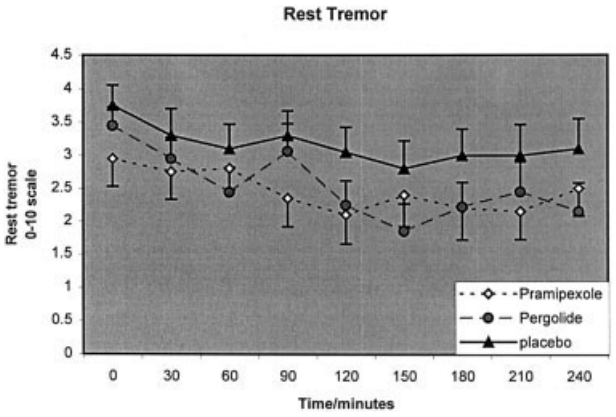

FIG. 2. Mean rest tremor (±SEM) in patients' most affected arm at each 30-minute interval after administration of medications. The tremor is scored on a 0 to 10 rating scale.

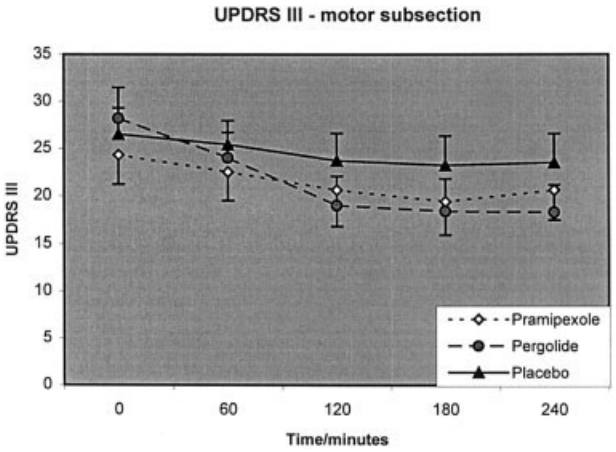

FIG. 4. Mean UPDRS part III (motor subsection) scores (±SEM) at each 30-minute interval after administration of medications.

to perform a verbal fluency task for 1 minute while the tremor was scored. Standardised video recordings were made of each patient performing the elements of UPDRS part III, which were subsequently scored by another blinded examiner. We also collected data on the following for subsequent reliability and validity sub-analysis: 9-hole pegboard test, a finger-tapping task, severity of postural and intention tremor and tremor in spirals, accelerometry of rest and postural tremor and UPDRS Sections 20 (rest tremor) and 21 (action tremor). The sitting and standing pulse rates and blood pressures were measured hourly and the incidence of adverse effects systematically collected.

Data Analysis

The effect of treatment on the UPDRS part III and rest tremor (scored from 0–10) were examined separately using ANOVA with period, subject, and treatment effects, using Type 1 sums of squares looking at both AUC (exactly equal to mean score over the 0–240-minute epoch) and peak effect (minimum score over the 0–240-minute epoch). Differences between pairwise comparisons of treatment (Pl vs. Pr, Pe vs. Pl, Pr vs. Pe) were made using contrasts. A Bonferroni correction was made for multiple comparisons and significance set at the 5% interval. The incidence of adverse effects experienced on each of the three treatments was compared, ignoring period effects, in a pairwise fashion using McNemar's test.

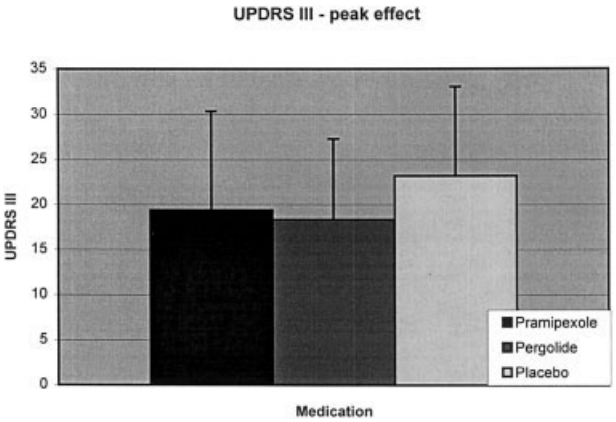

FIG. 3. UPDRS part III (motor subsection) scores (mean + SD) by medication, at peak effect.

RESULTS

All 10 recruited patients completed the study.

Rest Tremor

There was a good correlation between our 0 to 10 tremor ratings and the UPDRS section 20 (tremor at rest; correlation coefficient: 0.67, $P = 0.034$) and also 0 to 10 ratings of action and rest tremor (correlation coefficient: 0.47, $P = 0.011$).

Peak Effect Analysis—Minimum Rest Tremor.

There was a significant difference in the peak effect of the medications on rest tremor (ANOVA for minimum rest tremor, $P = 0.005$) (Fig. 1). Post hoc analysis contrasts for minimum rest tremor (Bonferroni corrected) showed that the mean difference between the

TABLE 2. *Number of patients experiencing adverse events with each medication*

Treatment	Nausea	Vomiting	Drowsiness	Sleep
Placebo	0	0	7	1
Pramipexole	1	0	8	1
Pergolide	9	6	10	3

active drugs was not significant at the 5% level, but both active drugs were significantly different (superior) to placebo:

[Pl − Pe] = 1.02, 95% CI (0.27, 1.77), $P = 0.006$
[Pl − Pr] = 0.82, 95% CI (0.06, 1.58), $P = 0.033$
[Pe − Pr] = −0.21, 95% CI (−0.98, 0.57), $P = 1.000$.

AUC Analysis—Mean Rest Tremor.

There was a significant difference in the effects of the medications on mean rest tremor over the 4-hour study period (ANOVA for tremor AUC, $P = 0.045$) (Fig. 2). Post hoc analysis contrasts showed no significant difference between the active drugs, nor were either of the active drugs significantly different from placebo at the 5% level, although at the 10% level pramipexole was superior to placebo.

[Pl − Pe] = 0.64, 95% CI (−0.15, 1.43), $P = 0.140$
[Pl − Pr] = 0.76, 95% CI (−0.04, 1.56), $P = 0.067$
[Pe − Pr] = 0.12, 95% CI (−0.7, 0.94), $P = 1.000$.

UPDRS PART III (MOTOR SUBSECTION SCORE)

Peak Effect Analysis—Minimum UPDRS Part III Score.

There was a significant difference in the peak effect of the medications on the UPDRS part III scores (ANOVA, $P = 0.040$) (Fig. 3). Post-hoc contrasts showed that the differences between the active drugs was not significant; although pergolide was significantly different from placebo at the 5% level, pramipexole was not:

[Pe − Pl] = −5.27, 95% CI (−10.49, −0.04), $P = 0.048$
[Pl − Pr] = 3.97, 95% CI (−1.34, 9.28), $P = 0.189$
[Pe − Pr] = 1.30, 95% CI (−6.69, 4.09), $P = 1.000$.

AUC Analysis—Mean UPDRS Part III Score.

There was no significant difference between the treatments on the UPDRS part III AUC (mean UPDRS part III score over the 4-hour study period; ANOVA, $P = 0.091$) (Fig. 4). Post hoc contrasts showed that there were no significant differences between the two active drugs or either of the active drugs and placebo:

[Pl − Pe] = −5.27, 95% CI (−1.48, 6.83), $P = 0.314$
[Pl − Pr] = 3.55, 95% CI (−0.67, 7.78), $P = 0.117$
[Pe − Pr] = 0.88, 95% CI (−3.41, 5.17), $P = 1.000$

TABLE 3. *Exact significance levels for the difference in the proportions of patients experiencing a specific adverse-effect with each medication using McNemar's test*

Adverse event	Pe vs. Pl	Pe vs. Pr	Pl vs. Pr
Nausea	0.004*	0.005**	0.317
Vomiting	0.014***	0.014***	1.000
Drowsiness	0.083	0.157	1.000
Sleep	0.625	0.625	1.000

*$P < 0.01$; **$P < 0.005$; ***$P < 0.05$.
Pe, pergolide; Pr, pramipexole; Pl, placebo.

TABLE 4. *Sitting and standing pulse rate and blood pressure*

Treatment	Posture	Pulse rate beats/min	Systolic BP mm Hg	Diastolic BP mm Hg
Placebo	Sitting	70.4 ± 12.0	130 ± 25.7	79 ± 7.9
	Standing	73.4 ± 12.1	128 ± 27.2	78 ± 11.7
Pramipexole	Sitting	68.7 ± 9.6	129 ± 16.6	80 ± 6.4
	Standing	72.5 ± 12.1	131 ± 19.4	81 ± 10.5
Pergolide	Sitting	69.5 ± 7.6	130 ± 19.0	77.5 ± 9.8
	Standing	74.2 ± 9.8	124 ± 19.6	78 ± 11.7

Dose Equivalency

Scatter plots of each patient's minimum and mean rest tremor on pramipexole (*y*-axis) versus those on pergolide (*x*-axis) produced gradients (slopes) of 1.16 for minimum rest tremor (intercept: −0.05) and 0.95 for mean rest tremor (intercept: 0.09). Similarly, plots of each patients minimum and mean UPRDS part III on pramipexole (*y*-axis) versus those on pergolide (*x*-axis) produced gradients of 0.94 for minimum UPDRS part III (intercept 3.46) and 0.93 for mean UPDRS part III (intercept: 1.39). These results indicate that 500-μg doses of the active drugs had approximately equivalent anti-tremor and anti-UPDRS III effects.

Adverse Effects

The incidences of the main adverse-effects encountered in this study are given in Table 2. Nausea usually appeared at the 1-hour assessment (mean, 1.3; range, 1–3 hours) and lasted between 1 and 1.5 hours. Pergolide was significantly more associated with nausea or vomiting than either placebo or pramipexole (Table 3). There were, however, no significant differences in the incidence of drowsiness or sleep between treatments (Table 3). The patients' pulse rates and sitting and standing blood pressures are shown in Table 4. Symptomatic postural hypotension was not encountered. A two-way repeated measures ANOVA (treatment group vs. hourly standing systolic blood pressure) showed no significant effects of treatment group, time, or time by treatment interaction.

Blinding

The high incidence of adverse events contributed to a degree of un-blinding of the patients. They correctly ascertained that they had received placebo in 70% of

placebo administrations (χ^2: 0.8, not significant), active treatment in 85% of active administrations (χ^2: 4.9, $P < 0.05$) but were unable to discriminate (50% correct) between the two active medications.

DISCUSSION

The main purpose of this study was to ascertain whether or not there was a difference between the anti-PD tremor actions of identical doses of pramipexole (salt) and pergolide, the former having more affinity for the D3 receptor subtype and the later for the D2 dopamine receptors.[7] Our results indicate that at peak effect both drugs, at doses of 500 μg, caused a significant but modest reduction of rest tremor compared to placebo (Fig. 1). No significant difference between the anti-tremor effects of the two drugs was detected.

No previous study has directly compared the anti-PD tremor potencies of these two drugs. Pogarell and colleagues[13] suggested that pramipexole may have additional therapeutic potential against PD rest tremor, and recommended that further studies should be conducted to examine this issue. It is possible, nevertheless, that a difference in the anti-tremor profiles of the two drugs may emerge with higher dose chronic administration, as daily maintenance doses are typically between 1.0 to 1.5 mg three times per day for both drugs.[8]

The influence of 500-μg doses of pramipexole (salt) or pergolide at peak effect on UPDRS part III (motor subsection) was modest (Fig. 3). Analysis of variance indicated that there was a significant treatment effect, but no significant difference between the two active drugs was found and only pergolide was significantly better than placebo at the 5% level. Although higher doses of the active treatments might have produced greater effects, it is possible that a floor effect in the UPDRS part III rating scale may have been encountered as the patients generally had mild PD.

The most statistically significant findings of the study were the marked differences in the incidence of adverse events encountered with the active drugs, despite pretreatment with domperidone (Tables 2 and 3). It is likely that this contrast was the result of the pharmacological profiles of these two drugs rather than simply a matter of dose, as the gradients obtained from the scatter plots suggest that pergolide and pramipexole had approximately equivalent anti-rest tremor and UPDRS part III potencies. One possible explanation for this is that pergolide, unlike pramipexole, is an ergot-derived drug (an ergoline) and is thus perhaps more likely to stimulate other monoamine receptor sites than a synthetic non-ergoline dopamine agonist.

Before the study 500 μg was considered to be a potentially useful dose level for as required or 'top-up' anti-PD tremor therapy. Our results, however, demonstrate that although pramipexole (salt) may have potential for this mode of deployment, pergolide certainly does not.

We conclude that single 500-μg doses of pergolide or pramipexole have a significant anti-rest–tremor effect in patients with Parkinson's disease. The adverse event profile, specifically the incidence of nausea and vomiting, was significantly worse with pergolide than pramipexole.

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