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Pergolide as adjunct therapy in Parkinson's disease evaluated using SPES

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ABSTRACT

Thirty-two patients suffering from idiopathic Parkinson's disease (PD) (mean age 65.3; mean disease duration 7.4 years) with motor fluctuations were enrolled in five out-patient clinics throughout Israel. After a basic clinical evaluation the patients were treated with pergolide in increasing doses as add-on therapy in an open trial, lasting three months. The clinical evaluation was performed applying the Short Parkinson's Evaluation Scale (SPES), a new friendly score, recently created by a joint European team (Rabey et al., Clinical Neuropharmacology, 1997). During the trial 13 patients withdrew: nine due to side effects: (persistent hypotension in three; nausea and dizziness in three; constipation in one; chest pains in one and headaches in one); protocol violations in one, and lost to follow up in three. Of the 19 patients who completed the study, there was improvement in the motor scoring (according to SPES) p = 0.01, and also in activities of daily living (p = 0.001). We have thus confirmed the benefit of pergolide as add-on therapy for PD patients and advise that in view of possible side-effects the dose be carefully and gradually increased. In addition, SPES seems to be a useful tool for the clinical evaluation of new therapies for PD.

Key words: Pergolide, Parkinson, Short Parkinson's Evaluation Scale (SPES).

RESUMEN

En cinco clínicas de pacientes externos en Israel se registraron treinta y dos pacientes con padecimiento de enfermedad idiopática de Parkinson (edad promedio de 65.3 años y 7.4 años de duración de la enfermedad) con fluctuaciones motoras. Después de evaluación clínica básica los pacientes fueron tratados con dosis crecientes de pergólido como terapéutica coadyuvante en un estudio abierto que duró tres meses. La evaluación clínica se llevó a efecto aplicando la Escala de Evaluación Corta de Parkinson (SPES = Short Parkinson's Evaluation Score), una marca amistosa creada recientemente por un equipo europeo unido (Rabey y cols., Clinical neuropharmacology, 1997). Durante el estudio se eliminaron 13 pacientes: nueve de ellos debido a los efectos colaterales (hipotensión persistente en tres; náusea y mareo en tres; constipación en uno; dolor torácico en uno; cefalea en uno), errores en el protocolo en uno y pérdida del seguimiento en tres. De los 19 pacientes que pudieron completar el estudio, hubo mejoría en los resultados motores (de acuerdo a las escalas de evaluación corta de Parkinson (SPES) p = 0.01, y también en las actividades cotidianas p = 0.001. Por lo tanto, confirmamos los beneficios del pergólido como coadyuvante en la terapéutica de la enfermedad de Parkinson y aconsejamos que en vista de posibles efectos colaterales la dosis se incremente cuidadosa y gradualmente. Además, la escala de evaluación parece ser una herramienta útil en la valoración clínica de nuevas terapias contra la enfermedad de Parkinson.

Palabras clave: *Pergólido, Parkinson, escala de evaluación corta.*

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Dopamine agonists have been introduced in the treatment of Parkinson's Disease (PD) in an attempt to reduce the adverse effects of long-term levodopa treatment, especially motor fluctuations and dyskinesia and also to combat the loss of efficacy of levodopa as the disease progresses.[1,2]

The dopamine agonist pergolide mesylate is a semisynthetic ergoline derivative with longer duration and higher potency than the other ergot derivatives, bromocriptine and lisuride.[3-6] It acts on both the D_1, and D_2 dopamine receptor[7] and has a half life of 27 hours. Pergolide has been shown to be effective in the treatment of PD[8-15] when used as monotherapy and in combination with levodopa. The addition of pergolide may allow for a reduction in the dosage of levodopa thus reducing levodopa side effects. Chronic treatment with pergolide has been shown to be effective in PD for up to 5 years.[16]

The purpose of this study was to evaluate the efficacy and safety of pergolide as an adjunctive therapy to levodopa in PD patients who had declining response and/or increasing side effects on levodopa.

Response to treatment was evaluated using the Short Parkinson's Evaluation Scale (SPES), as well as Clinical Global Impression, Clinical Global Improvement and Patient Global Impression Scores. The SPES[17] has been developed to overcome some of the short-comings of the Unified Parkinson's Disease Rating Scale (UPDRS).[18] The UPDRS is time consuming with low inter-rater reliability in some items and redundancy in others.[19] The SPES has been shown to be easier to apply and quicker to complete with good internal consistency and inter-rater reliability. It has a 0-3 point grading scale and is composed of motor and mental evaluation, activities of daily living, complications of therapy, scoring of motor fluctuations and the Hoehn-Yahr staging[17] [Addendum].

PATIENTS AND METHODS

This open label add on trial, involving 5 centers in Israel, was designed to assess the efficacy and safety of pergolide as adjunctive therapy in poorly controlled PD patients on levodopa alone, or in combination with selegiline.

Patient selection

Subjects enrolled in the study were of both sexes between 35-75 years of age, suffering from PD requiring levodopa and on stable dosage for at least one month. If patients were on other dopamine agonists, a washout period of at least one week was required.

Patients were excluded if they had severe adverse effects on any other dopamine agonist previously, had been on pergolide during the previous three months, had other chronic neurological cardiovascular or medical diseases and if they were pregnant, lactating or of child bearing potential.

Dosage regimen

Administration of pergolide was initiated with a daily dose of 0.05 mg/day for the first 2 days. The dose was then increased by 0.1 or 0.15 mg per day every third day over the next 12 days and subsequently, by 0.25 mg/day every third day until an optimal therapeutic dosage was achieved, but not exceeding 5 mg/day. Pergolide was administered in divided doses three times per day. During dosage titration, the dosage of current levodopa could be decreased.

Study procedures

The total study period was 12 weeks during which the patients were assessed at five visits. The first being the baseline visit after which pergolide was started thereafter at two weeks, four weeks, eight weeks and 12 weeks. At each visit blood pressure (sitting and standing) and pulse rates were measured, as well as drug monitoring and adverse events. Clinical global impression (CGI)[20] and patient global impression (PGI) were assessed at visits 3 till 5. Patients assessment and CGI were assessed independently. SPES was performed at baseline and at visit 5. Adjustment of levodopa dose was done when clinically indicated.

Efficacy end-points

The response of patients to treatment was measured using SPES, comparing the SPES score at week 12 with that of baseline (visit I), as well as CGI and PGI scores.

The assessments were performed by the same investigator at each visit.

Statistical methods

Paired t-test was applied in order to examine within group changes from baseline in quantitative pa-

rameters (SPES components). Spearman correlation were calculated and examined for significance in order to assess linear relationships between CGI and PGI scores. MacNumar's Chi square test was used to examine within groups changes (at each visit) differing from baseline in categorical parameters. All tests applied were two-tailed and p value of 5% or less was considered statistically significant.

RESULTS

Thirty-two patients were enrolled into the study, comprising 15 males and 17 females. Demographic data of the patients entering the trial are summarized in *Table I*. Of these patients, 19 (11 males and eight females) completed the study, and in those remaining, nine withdrew because of adverse events, three were lost to follow up, and one withdrew because of protocol violation. Thus 56% of participants completed the study. In those patients who completed the study (n = 19), statistically significant improvements in motor evaluation (mean =-2.4 ± 4.0, p = 0.01) and in activities of daily living (mean = 1.9 ± 2.2, p = 0.001), were observed. No differences were found between components of the "motor part" of the SPES. No significant change from baseline in Hoehn-Yahr staging nor in motor fluctuation were observed at the final visit.

Table II shows the distinct changes from baseline of the SPES scores as obtained at the final visit. The p values inside the table present the levels of significance for comparisons between baseline and the final visit.

CGI: At baseline over 80% of patients were considered mildly or moderately ill. Of the 19 patients with completed the study, at baseline five patients were considered mildly ill, 11 patients moderately ill and three patients markedly ill. At the end of the study, two were considered border-

Table I. Baseline demographic information (n = 32).

			Mean	*Range*
Age [n = 32]			65.3	60 - 75
Duration of PD (years) [n = 32]			7.4	1 - 16
Duration of tremor (years) [n = 25]			7.0	2 - 16
Duration of rigidity (years) [n = 31]			6.3	1 - 16
Duration of bradykinesia (years) [n = 32]			6.0	1 - 16
Hoehn-Yahr (during on)	Stage	2	6	
		3	20	
		4	6	

n = number of patients. PD = Parkinson's disease.

Table II: Clinical characteristics of the patients before and after pergolide treatment.

	SPES (Short Parkinson's Evaluation Scale)				
	Score at baseline (Visit 1) n = 19		*Differences from baseline mean Scores (Visit 5) n = 19*		
	Mean	*S.E.*	*Mean*	*S.E.*	*p value*
Motor evaluation	14.4	1.25	-2.42*	0.91	0.0168**
Complications of therapy	3.9	0.62	-0.105*	0.54	0.8474
Mental	1.1	0.18	-0.105*	0.16	0.5416
Activities of daily living	8.5	0.65	-1.95*	0.49	0.0010**

* Low score indicates improvement. **Significant differences (paired t-test).

Table III. Severity of disease assessed by clinical global impression at different visits during the study.

	Baseline *n = 32*		*Visit 3* *n = 24*		*Visit 4* *n = 22*		*Visit 5* *N = 19*	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Borderline III	—	—	—	—	3	13.6	2	10.5
Mildly III	8	25	9	37.5	7	31.8	8	42.1
Moderately III	17	53.1	13	54.2	11	50.0	8	42.1
Markedly III	6	18.8	2	9.3	1	4.5	1	5.3
Severely III	1	3.1	—	—	—	—	—	—

The percentages refer to the number of patients at each visit.

Table IV: Clinical global improvement during the study (compared to baseline).

	Visit 3 *n = 24*		*Visit 4* *n = 22*		*Visit 5* *n = 19*	
	n	*%*	*n*	*%*	*n*	*%*
Much improved	4	16.7	5	22.7	8	42.1
Minimally improved	12	50.0	12	54.5	8	42.1
No change	7	29.2	4	18.2	2	10.5
Minimally worse	1	4.2	1	4.5	1	5.3

n = number of patients evaluated.

Table V. Patients global impression.

	Visit 3 *n = 24*		*Visit 4* *n = 22*		*Visit 5* *n = 19*	
	n	*%*	*n*	*%*	*n*	*%*
Very much better	—	—	1	4.5	1	5.3
Much better	3	12.5	8	36.4	8	42.1
A little better	15	62.5	9	40.9	7	36.8
No change	3	12.5	3	13.6	2	10.5
A little worse	2	8.3	1	4.5	1	5.3
Much worse	1	4.2	—	—	—	—

n = number of patients evaluated.

line ill, eight mildly ill, eight moderately ill and one markedly ill. *Table III* summarizes the CGI as assessed at one, two and three months. As can be seen, there is a tendency of improvement at each visit during the study, but this was not statistically significant (c^2 statistical analysis). *Table IV* presents the clinical global improvement at visits.[3-5] As is shown, there is an improvement that increased from visit to visit during the study. An improvement was also found in the PGI as assessed during the study and this improvement increased during the study *(Table V)*. There was a very good positive correlation (Spearman analysis) between the CGI and the PGI at each visit; visit 3 ($r = 0.7657$, $p < 0.0001$), visit 4 ($r = 0.8322$, $p < 0.0001$), visit 5 ($r = 0.8072$, $p < 0.0001$).

Table VI presents all recorded adverse events, the most common being nausea, constipation, dizziness, postural hypotension, dyskinesia and headache. Most adverse events were of mild to moderate severity and patients continued the medication. These events did not require additional treatment. The reasons for dropping out because of adverse events in the 9 patients are listed in *Table VII*.

No significant changes in pulse or in sitting and standing blood pressure was found when comparing baseline and last visit.

The mean levodopa dose at the baseline (n = 19) was 572.8 mg (187.5 – 1,312.5). This being reduced to a mean 488.8 mg (125 – 1,000) by the end of the trial which means a levodopa sparing effect of about 15%, this being not significant.

The mean daily pergolide dose at the end of the trial was 1.3 mg (0.2 - 3.0). In those patients who withdrew because of adverse events (n = 9), the mean dose at the time of withdrawal of pergolide was 0.4 mg (0.1 - 1.5) with a mean levodopa dose of 428.1 (125 - 800).

DISCUSSION

The results presented indicate that pergolide was of benefit in the patients studied and this was reflected by the motor performance and activities of daily living. There was also very good correlation between the investigators assessment of patient improvement and that of the patients themselves as reflected in the significant correlation between the clinical global improvement and the patients global impression at each visit. A major weakness of this study was its open nature which could bias results. However, our results are in accordance with the findings of the American Multi Center Study,[16] which was a double blind placebo controlled trial of pergolide as an adjunct to Sinemet in which significant improvement in activities of daily living and in motor performance were found. Our study confirms these results and thus further confirms the usefulness and reliability of the SPES scoring test.

Some points should be clarified, however, concerning the grade of improvement measured in our study. In a detailed meta-analysis of eight previously published[9-16] controlled trials of pergolide versus placebo, Pezzoli et al.[3] summarized a total of 545 patients treated. In these studies the mean dose of pergolide ranged from 2.5 to 4.6 mg (mean 3 mg). The activities of daily living in those studies improved about 35% and the severity of the disease, measured with various rating scales was reduced about 35%. In our study utilizing the SPES, we measured a 23% improvement in the activities of daily living and 17% improvement in the motor performance. The differences observed in our study (activities of daily living 23% instead of 35%, and motor performance improvement 17% instead of 35%) may be the result of the lower mean dose of pergolide in our patients (1.3 mg in our study *vs.* 3 mg pergolide in the other studies).

Table VI. Number of patients with adverse events by visit.

	Visit				
	2	*3*	*4*	*5*	*All*
Dizziness	1	1		1	3
Nausea	4	3			7
Weakness		1			1
Constipation	2	2	1	1	6
Urticaria				1	1
Sweating		1			1
Chest pain				1	1
Headache	2	2	2		6
Vertigo	1		1		2
Hypotension		1			1
Somnolence	1				1
Taste abnormalities	1				1
Orthostatic hypotension	2	1			3
Dyskinesia			2	1	3
Visual hallucinations	1				1
Restlessness				1	1
Chin tremor				1	1

Table VII. Adverse events resulting in withdrawal.

Patient	*Last visit No.*	*Adverse effect*
1	3	Postural hypotension, nausea and dizziness
2	2	Postural hypotension and somnolence
3	2	Postural hypotension and dizziness
4	2	Visual hallucinations
5	2	Nausea
6	2	Nausea
7	3	Dyskinesia and constipation
8	4	Headache
9	4	Chest pain

Two important observations concerning adverse events. Firstly, adverse events were most often related to gastrointestinal symptoms or to postural hypotension and secondly they occurred early, within one month often within the first two weeks, of starting pergolide. These side effects were most likely due to the structure of the protocol in which the pergolide dose was relatively rapidly increased.

Because of the potential side effects a more gradual increase of the pergolide dose is therefore recommended in the future.

The levodopa sparing effect of pergolide was also confirmed. In our study a 14.7% reduction in the levodopa dose was obtained while still on a relatively low dose of 1.3 mg of pergolide. In the American Multi Center Study a 25% reduction of the levodopa was achieved on a mean pergolide dose of 3 mg.[16]

In summary, we think that pergolide is a useful add-on medication for use in PD patients. However, a careful slow build up titration should be utilized to avoid side effects. Furthermore, this study confirms the usefulness of the SPES in the evaluation of patients with PD.

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Addendum

SHORT PARKINSON'S EVALUATION SCALE (SPES)

I. MOTOR EVALUATION (specify if the patient was examined when "on" or "off")

A. Speech

0 = normal
1 = slight loss of expression, diction and/or volume
2 = monotonous, slurred, not always understandable
3 = unintelligible always or most of the time

Score _____

B. Tremor. Check each upper limb separately. When tremor is present only in lower limbs, or is more pronounced in them, score and specify only the most affected two limbs.
If tremor is not evident at rest, try to keep the patient attentive, e.g, by having him count backwards with eyes closed while walking (for rest tremor) and while extending upper limbs (for postural tremor)

1. Rest tremor (arms should be resting on the thighs)

0 = absent
1 = occasionally present (or obtained while keeping the patient attentive)
2 = present most of time - small amplitude
3 = present most or all of the time - marked amplitude

RUE _____
RLE _____
LUE _____
LLE _____

2. Postural tremor (check with arms outstretched, pronated and semipronated, and when the index finger in each hand is almost touching the other with flexion of the elbows. Record the worst performance).

0 = absent
1 = small amplitude
2 = moderate amplitude
3 = severe

RUE _____
LUE _____

C. Rigidity (judge on passive movements of major joints with the patient relaxed in a sitting position, cogwheeling to be ignored; each upper limbs checked separately).

0 = absent
1 = mild or moderate rigidity, detectable only on activation of the contralateral limb
2 = moderate rigidity detectable at rest
3 = severe rigidity

RUE _____
LUE _____

D. Rapid alternating movements of hands (check pronation - supination of hands horizontally, each hand separately, asking the subject to perform movements, striving for the largest possible amplitude. Each hand should slap the contralateral palm).

0 = normal
1 = mild slowing and/or reduction in amplitude
2 = definate and early fatiguing; may have occasional arrests in movement
3 = shows hesitation in initiating movement or frequent arrests in ongoing movements, or can barely perform the task

RUE _____
LUE _____

E. Arising from chair (Use a straightback chair; patient's arms to be folded across the chest)

0 = normal
1 = slow, may need several attempts, does not need to use arms
2 = needs use of arms but can get up without help
3 = unable to rise without help

SCORE _____

F. Gait

0 = normal
1 = mild slowing and/or reduction of amplitude of steps
2 = walks with difficulty, may shuffle or have festination; may require assistance
3 = severe disturbance of gait, requiring assistance most or all of the time

SCORE _____

G. Postural stability (Stand behind the patient and pull him backwards towards you while the patient is erect with eyes open and feet spaced slightly apart; patient is prepared)

0 = normal/may take 2 steps to recover
1 = retropulsion but recovers unaided
2 = retropulsion but will fall if unaided
3 = unable to stand unaided

SCORE _____

TOTAL MOTOR SCORE _____

II. COMPLICATIONS OF THERAPY (by history)

A. Dyskinesias (peak or biphasic)

1. General (consider frequency and intensity)

0 = absent
1 = mild
2 = moderate
3 = severe

SCORE _____

2. Disability (how disabling are the dyskinesias)

0 = not at all
1 = mildly
2 = moderate
3 = severe

SCORE _____

B. Painful cramps or dystonias

0 = absent
1 = mild
2 = moderate
3 = severe

SCORE _____

C. Fluctuations

0 = absent
1 = mild end-of-dose or early morning akinesia which do not affect activities of daily living
2 = marked and/or frequent end-of-dose akinetic periods which affect activities of daily living
3 = unpredictable on-off oscillations

SCORE _____

D. Freezing episodes

0 = absent
1 = occasional and not disabling events
2 = frequent and mildly disabling episodes
3 = severe disabling events

SCORE _____

TOTAL SCORE _____

III. MENTAL

A. Memory

0 = normal
1 = mild, occasional forgetfulness with partial recollection of events and no other difficulties
2 = moderate memory loss which interferes with daily activities
3 = severe memory loss, needs regular assistance for personal safety

SCORE _____

B. Thought disorder

0 = none
1 = benign hallucinations/hallucinosis with retained insight
2 = benign hallucinations/hallucinosis or delusions without insight; could interfere with daily living
3 = persistent hallucination and/or delusions; cannot be alone

SCORE _____

C. Depression

0 = not present
1 = periods of sadness greater than "normal"
2 = sustained depression
3 = severe depression affecting activities of daily life

SCORE _____

TOTAL SCORE _____

IV. ACTIVITIES OF DAILY LIVING

A. Speech

0 = normal
1 = mildly affected; no difficulty being understood
2 = moderately affected, asked to repeat sentences
3 = unintelligible most of the time

SCORE _____

B. Eating (chewing, swallowing) (patients should be asked if choking constitutes a problem)

0 = normal
1 = normal diet: chewing and swallowing are slow and laboured
2 = occasional choking
3 = frequent choking. May require soft food or substitute methods for food intake (nasogastric tube or gastrostomy)

SCORE _____

C. Feeding (cutting, filling cups, etc.)

0 = normal
1 = some difficulties but does not need help
2 = help required to carry out feeding tasks
3 = needs to be fed

SCORE _____

D. Dressing

0 = normal
1 = somewhat slow but no help needed
2 = some help needed (e.g., buttoning, getting arms into sleeves)
3 = almost totally or totally dependent

SCORE _____

E. Hygiene (washing, combing hair, shaving, brushing teeth, using toilet)

0 = normal
1 = slightly slow but independent
2 = requires some assistance to perform fine motor activities
3 = requires complete assistance and/or special devices

SCORE _____

F. Handwriting

0 = normal
1 = slightly slow and/or small letters, all words are legible
2 = severely affected; not all the words are legible; may need to use block letters
3 = the majority of words are illegible

SCORE _____

G. Walking

0 = normal
1 = walks slowly, does not require help or support
2 = may have difficulty with walking and/or turning; may require assistance or support in certain situations
3 = unable to walk, or walks only with assistance and great effort

SCORE _____

I. Turning and getting out of bed

0 = normal
1 = difficulty turning in bed and/or getting out of bed; does not need help
2 = difficulties in turning in bed and/or in getting out of bed; may need help
3 = unable to turn in bed and/or to get out of bed unaided

SCORE _____

TOTAL SCORE _____