J Neural Transm (1997) 104:461–468

Journal of
Neural
Transmission

Pergolide: treatment of choice in restless legs syndrome (RLS) and nocturnal myoclonus syndrome (NMS). A double-blind randomized crossover trial of pergolide versus L-Dopa

J. Staedt[1], F. Waßmuth[1], U. Ziemann[2], G. Hajak[1], E. Rüther[1], and G. Stoppe[1]

Departments of [1]Psychiatry and [2]Clinical Neurophysiology, Georg August University, Göttingen, Federal Republic of Germany

Accepted February 13, 1997

Summary. A double-blind randomized crossover study of 0.125 mg Pergolide (Lilly®) at bedtime versus 250 mg L-Dopa + Carbidopa (Roche®) was conducted in 16-day phases in 11 patients with idiopathic restless legs syndrome. Two patients reported a partial and 9 patients a complete relieve of motor restlessness while receiving Pergolide. Only 1 patient experienced an improvement of restlessness after L-Dopa. The patients showed polysomnographically a mean decrease in NMS cluster disturbed time by 45% from control on L-Dopa ($p < 0.025$) and by 79% from control on Pergolide ($p < 0.001$). In addition, Pergolide increased the total sleep time compared to L-Dopa ($p < 0.05$). In conclusion, the dopamine agonist Pergolide is superior to L-Dopa in the treatment of RLS and NMS.

Keywords: Restless legs syndrome, RLS, nocturnal myoclonus syndrome, NMS, L-dopa, pergolide, PMS.

Introduction

The restless legs syndrome is a common condition and regulary associated with stereotypical jerks of the lower limbs during sleep (Ekbom, 1945; Lugaresi et al., 1965, 1966, 1968). Colemann et al. (1980) defined criteria for the frequency (0.5/min.–0.66/min.) and duration (0.5 sec-5 sec) of the jerks and introduced the term "Periodic Movements in Sleep" (PMS). This definition should describe the movement element, but disregards the fact that the jerks also occur during wakefulness in bed. In addition, the abbreviation can be mixed up with the "Permenstrual Syndrome". For this reason we introduced (Staedt et al., 1994) the term "Nocturnal Myoclonus Syndrome" (NMS) in Symonds' and Lugaresis' honor (Symonds, 1953; Lugaresi et al., 1965), even though the duration of the jerks is usually too long for a true myoclonus (Fahn et al., 1986). NMS is often associated with arousals or awakenings and may

cause severe sleep disturbances especially in the elderly (Staedt et al., 1994; Ancoli-Israel et al., 1991). The positive therapeutical effect of dopamine agonists (Brodeur et al., 1988; Staedt et al., 1995a; Trenkwalder et al., 1995; Walters et al., 1988) and the worsening of RLS/NMS by dopamine antagonists (Akpinar, 1982; Montplaisir et al., 1991) support the hypothesis of an underlying decreased dopaminergic activity. In support of this view, we recently found in in-vivo investigations, using [123I] labeled (S)-2-hydroxy-3-iodo-6-methoxy-([1-ethyl-2-pyrrolidinyl]methyl) benzamide (IBZM) (= [^{123}I]IBZM, a highly selective CNS D2 dopamine receptor ligand) and single photon emission tomography (SPET) a reduced striatal D2 dopamine receptor density in NMS (Staedt et al., 1993, 1995b). Since D2 dopamine autoreceptors are involved in synthesis and release of dopamine (Brown et al., 1985; Yarbrough et al., 1984), the reduced D2 receptor density in RLS/NMS may reflect a diminished tonic dopaminergic level. To date, L-Dopa is the treatment of first choice in RLS and NMS. But L-Dopa has a short duration of action and often requires a repeated dosing during night to prevent NMS-rebound phenomena (Brodeur et al., 1988; Montplaisir et al., 1986). Another drawback with L-Dopa is the daytime RLS-rebound (Guilleminault et al., 1993). From this it follows that, because of its 29 fold longer half life, the dopamine agonist Pergolide may be of therapeutical interest. One recent preliminary report indicated that Pergolide may be effective in the treatment of RLS symptoms (Silber et al., 1995). In the present study, we tested for the first time the effects of Pergolide and L-Dopa on RLS/NMS in a double-blind crossover fashion.

Materials and methods

Eleven patients with a history of restlessness and paresthesias that were present at night and/or daytime participated. Informed consent was obtained from all patients and approval was given by the local Ethics Committee and by the German Federal Health

Table 1. Patient data and medications

Patient No.	Age (years)	Sex (M/F)	Duration of RLS (years)	L-Dopa medication prior the study	Benzodiazepines
1	59	M	10	200 mg	∅
2	69	M	2	200 mg	∅
3	57	F	2.5	200 mg	Temazepam 20 mg
4	59	F	4	200 mg	∅
5	50	M	15	∅	∅
6	55	M	10	∅	∅
7	53	M	7	125 mg	∅
8	60	F	3	250 mg	Temazepam 20 mg
9	52	F	3	200 mg	∅
10	60	F	14	300 mg	∅
11	60	M	2	600 mg	Temazepam 20 mg

∅: none

Institute. All patients were healthy according to medical history and results of neurological examination, cCT scans, EEG and EMG examination of lower limbs. Blood and urine biochemistry revealed no abnormalities. Nine patients were treated with L-Dopa prior to this study and 3 patients were on temazepam to treat their sleep disturbances (for further information, see Table 1). The L-Dopa medication was withdrawn 3 days prior to entering the study. The temazepam medication was continued in the three patients during the whole investigation, since it is known that the NMS activity is not effected by temazepam (Mitler et al., 1986). Over a 16-day period, patients were given a daily dose of L-Dopa + Carbidopa (250 mg) or Pergolide (0.125 mg) 1 to 3 hours prior to sleep. An increase up to a total of dose of 500 mg L-Dopa or 0.25 mg Pergolide was possible.

Design

To conform to the regulations of the German Law for Medications from August 1976 (Deutsches Arzneimittelgesetz, August 1976), the study plan was submitted to the Federal Institute for Drugs and Medical Products (Bundesinstitut für Arzneimittel und Medizinprodukte) and registered with the District Government in Braunschweig, Lower Saxony.

As testing drug material, we used the customary Pergolide as traded by the company Lilly and supplied by our pharmacy and the standard L-Dopa/carbidopa combination, a Roche product. In order to carry out our double-blind design, both substances were, in the above mentioned dosages, concealed under and filled into identical coloured hard-gelatin-capsules (volume 0.95 ml) by the central pharmacy of the University of Göttingen. To keep the galinic of the standard substances, we opened the Madopar® (L-Dopa) capsules and emptied their contents into the larger test capsules, making up for the difference in volume by adding milk sugar. We then proceeded similarily with Parkotil® (Pergolide) tablets, i.e. one empty coloured test capsule received half a tablet of Parkotil® 0.25 mg and was then equally topped up with milk sugar.

During the *1 to 3 day* of the study, we carried out the polygraphical investigations of our patients' sleep. On the third day, they took the first capsule of their randomised testing mediation (first part) while still under control of hospitalization.

4.–16. day: Ambulatory treatment of the patients who received their testing medication (first part) for 13 nights. They thus disposed of up to two capsules for each day and were instructed to take them within the last two hours before going to bed. If a patient did not sufficiently respond to his medication, he was allowed to increase his dose to the limit of two capsules per night after consultation with the study doctor.

17.–20. day: Second polygraphical sleep investigation, on the 17. and 18. day with the testing medication of the first part, on the 19. day interruption of medication, on the 20. day start of the cross-over design, i.e. first intake of a capsule of the testing medication of the second part while the patients were under control of hospitalization.

21.–33. day: Second ambulatory treatment of patients who are now given the testing medication of the second part for 13 nights, that is two capsules for each of the 13 days, again with the option to take up to two capsules per day after consultation with the doctor.

34.–36. day: Third polygraphical sleep investigation, in which night 34 and 35 were investigated under the testing medication of the second part. Withdrawal of the testing medication (part two) on the 36. day.

To prevent a selection bias, we have chosen a washout period of only 24 hours duration between the phases. Apart from that, otherwise only a few patients would have participated. During this period the patients were drug-free, with the exception of temazepam (see above). After each phase, patients were asked whether restlessness or paresthesias had changed (not quantified).

In addition, we compared the averages of the polysomnographic data between day 1 and 2 with the averages of the day 17 and 18 as well as day 34 and 35 of part two. In order to quantify the drug response the periods of time spent in bed (TIB) disturbed by NMS were summarized to clusters as reported elsewhere (Staedt et al., 1995, 1996). All-night

polysomnographic recordings (PSG) including abdominal excursion, nasal air flow and electromyogram (EMG) of anterior tibialis muscles were done according the standard criteria (Rechtschaffen and Kales, 1968). Data for the three conditions (control, Pergolide, L-Dopa) were expressed as mean ± 1 standard deviation. Group comparisons were done with the nonparametric Wilcoxon rank-sum test.

Results

During the control phase, all patients showed a NMS-related insomnia. The mean NMS cluster disturbed time of sleep was 164 ± 80.4 min. Five patients complained about day- and nighttime-, six patients only about nighttime-RLS (not quantitated).

Therapeutic response (restlessness and paresthesias)

On *L-Dopa* (mean dose 363 mg/per night), only one patient reported a complete relieve of nighttime restlessness, all others had no subjective improvement.

On *Pergolide* (mean dose 0.159 mg/per night), nine patients reported a complete and the other two patients a nearly complete relieve of restlessness.

Serious adverse events did not happen during drug trials. A frequent side effect was initial nausea in nine patients on Pergolide and in one patient on L-Dopa (for further information, see Table 2). In these cases, the nausea was successfully treated with domperidone up to 60 mg/day.

Therapeutic response (NMS cluster)

During L-Dopa treatment, the mean NMS disturbed cluster time was 90.6 ± 72.3 min. This is a significant decrease in comparison to the control condition ($p < 0.025$). During Pergolide treatment, the mean NMS disturded cluster

Table 2. Patient subjective reports and side effects

Pat. No.	RLS	L-Dopa	RLS relieve	Side effects	Pergolide	RLS relieve	Side effects
1	+	500 mg	↔	constipation	0.25 mg	↓	initial nausea
2	+	500 mg	↔	∅	0.125 mg	↓	initial nausea, constipation
3	+	250 mg	↔	∅	0.125 mg	↓	initial nausea
4	+*	500 mg	↔	initial nausea	0.25 mg	↓	initial nausea
5	+	250 mg	↓	∅	0.125 mg	↓	constipation
6	+	250 mg	↔	∅	0.125 mg	↓	initial nausea
7	+*	250 mg	↔	∅	0.125 mg	↓	initial nausea
8	+	250 mg	↔	∅	0.125 mg	↓	initial nausea
9	+*	250 mg	↔	∅	0.125 mg	↓	initial nausea
10	+*	500 mg	↔	constipation	0.25 mg	(↓)	initial nausea
11	+*	500 mg	↔	∅	0.125 mg	(↓)	∅

+: nighttime RLS; +*: day and nighttime RLS; ↓: complete RLS relieve; (↓): nearly complete RLS relieve; ↔: no RLS relieve; ∅: none

Table 3. Average response of NMS cluster time to L-Dopa and pergolide

NMS cluster time (minutes)		
Control	L-Dopa	Pergolide
164.6 ± 80.4	90.6 ± 72.3	35.27 ± 35.81
Statistical group comparisons of NMS cluster times		
Control to L-Dopa	Control to pergolide	Pergolide to L-Dopa
$p < 0.025$	$p < 0.001$	$p < 0.01$

Data are mean ±1 standard deviation

time was 35.3 ± 35.8 min. This decrease in comparison to baseline is even more significant ($p < 0.001$). The comparison of NMS cluster time between L-Dopa and Pergolide revealed a significantly lower value under Pergolide ($p < 0.01$) (for further information, see Table 3).

Sleep parameters

There was no significant change in the classical sleep parameters during the drug trials in comparison to the control condition (see Table 4). However, we observed a decrease in sleep latency and nocturnal awakings on L-Dopa and

Table 4. Average response of sleep parameters on pergolide and L-Dopa

	Control						
	TIB	TST	SWS	S1 + S2	REM	Wake	SL
mean ± 1 s.d. (minutes)	458 ± 81	373 ± 115	17 ± 24	307 ± 98	48 ± 31	73 ± 63	42 ± 43
L-Dopa							
	TIB	TST	SWS	S1 + S2	REM	Wake	SL
mean ± 1 s.d. (minutes)	387 ± 117	345 ± 120	25 ± 28	259 ± 83	60 ± 26	32 ± 14	15 ± 15
	Pergolide						
	TIB*	TST*	SWS	S1 + S2	REM	Wake	SL
mean ± 1 s.d. (minutes)	461 ± 54	421 ± 62	23 ± 22	330 ± 60	67 ± 25	32 ± 19	22 ± 19

* $p < 0.05$ as compared to L-Dopa; *s.d.* standard deviation; *TIB* time in bed; *TST* total sleep time; *SWS* slow wave sleep; *S1 + S2* sleep stage 1 and 2; *REM* rapid eye movement sleep; *Wake* nocturnal awakenings; *SL* sleep latency

Pergolide. Additionally, in comparison to L-Dopa, patients on pergolide showed a significant increase in total sleep time and time in bed ($p < 0.05$, see Table 4).

Discussion

For the first time, the results of this double-blind controlled study definitely show that the dopamine agonist pergolide is more effective than the dopamine precusor L-Dopa in relieving restlessness and paresthesias in patients with RLS and NMS. In addition to the patients subjective data, the PSG recordings confirmed this finding. Patients receiving Pergolide showed a nearly complete NMS relieve and compared to L-Dopa a significant increase in total sleep time.

On L-Dopa, we observed the well known NMS rebound in the second half of the night (Montplaisir et al., 1986; Trenkwalder et al., 1995) and no relieve of daytime restlessness. One other explanation for the differential results could be a stimulation of different dopamine receptors by Pergolide and L-Dopa. However, that is not the case. Pergolide as well as dopamine both stimulate D1 and D2 dopamine receptors (Waddington and O'Boyle, 1989).

In our opinion, the NMS- rebound is related to the short half life of the dopamine precursor L-Dopa, because this rebound could be prevented by the administration of a second dose L-Dopa during the night (Brodeur et al., 1988). Based on these considerations, we believe that the excellent therapeutic effect of Pergolide on RLS and NMS is related to its long half life. However, whether the superior therapeutical effect of Pergolide is permanent cannot be decided by the results of our short-term treatment period. Nor is it possible to estimate whether an increase in dosage will be necessary in the long-term use of Pergolide. To obtain an answer to these questions, long-term follow up investigations are necessary. Nevertheless, in our opinion, the results clearly indicate that Pergolide should be the first choice in the treatment of RLS and NMS, since Trenkwalder et al. (1995) showed that L-Dopa is only for the first 4 hours after drug-intake superior to placebo. On account of the initial nausea on Pergolide we recommend an add-on treatment with the peripherally acting dopamine-antagonist domperidone by up to 60 mg/day for first week of treatment.

References

Akpinar S (1982) Treatment of restless Legs syndrome with levodopa plus benserazid. Arch Neurol 39: 739

Ancoli-Israel S, Kripke DF, Klauber MR, Mason W, Fell R, Kaplan OJ (1991) Periodic limb movements in sleep in community dwelling elderly. Sleep 14: 496–500

Brodeur C, Montplaisir J, Goudbout R, Marinier R (1988) Treatment of restless Legs syndrome and periodic movements during sleep with L-dopa. Neurology 38: 1845–1848

Brown F, Campbell W, Mitchell PJ, Randall K (1985) Dopamine autoreceptors and the effect of drugs on locomotion and dopamine synthesis. Br J Pharmacol 84: 853–860

Coleman RM, Pollack C, Weitzman ED (1980) Periodic movements in sleep (nocturnal myoclonus): relation to sleep-wake disorder. Ann Neurol 8: 416–421

Ekbom KA (1945) Restless legs. Acta Med Scand 158 [Suppl]: 1–123
Fahn S, Marsden CD, van Woert MH (1986) Definition and classification of myoclonus. In: Fahn S, Marsden CD, van Woert MH (eds) Myoclonus: advances in neurology, vol 43. Raven Press, New York, pp 1–5
Guilleminault C, Cetel M, Philip P (1993) Dopaminergic treatment of restless legs and rebound phenomenon. Neurology 43: 445
Lugaresi E, Coccagna G, Tassinari CA, Ambrosetto C (1965) Relievi poligrafici sui fenomeni motori nella syndrome delle gambe senze riposo. Riv Neurol 35: 550–561
Lugaresi E, Coccagna G, Gambi D, Berti-Ceroni G, Poppi M (1966) A propos de quelques manifestations nocturnes myocloniques (nocturnal myoclonus de Symonds). Rev Neurol 115: 547–555
Lugaresi E, Coccagna G, Berti-Ceroni G, Ambrosetto C (1968) Restless legs syndrome and nocturnal myoclonus. In: Gastaut H, Lugaresi E, Berti-Ceroni G, Coccagna G (eds) The abnormalities of sleep in man. Aulo Gaggi Editore, Bologna, pp 285–294
Mitler MM, Browman CP, Menn SJ, Gujavarty K, Timms RM (1986) Nocturnal myoclonus: treatment efficacy of clonazepam and temazepam. Sleep 9: 385–392
Montplaisir J, Godbout R, Poirier G, Bedard MA (1986) Restless legs syndrome and periodic movements in sleep: physiopathology and treatment with L-dopa. Clin Neuropharmacol 9: 456–463
Montplaisir J, Lorrain D, Godbout R (1991) Restless legs syndrome and periodic leg movements in sleep: the primary role of dopaminergic mechanism. Eur Neurol 31: 41–43
Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Brain Information Service/Brain Research Institute, UCLA, Los Angeles
Silber MH, Shepard JW, Wisbey JA (1995) The role of pergolide in the management of restless legs syndrome. Sleep Res 24A: 366
Staedt J, Stoppe G, Kögler A, Munz D, Riemann H, Rüther E (1993) Dopamine D_2 receptor alterations in patients with periodic movements in sleep (nocturnal myoclonus). J Neural Transm [Gen Sect] 93: 71–74
Staedt J, Stoppe G, Kögler A, Munz DL, Hajak G, Staedt U, Riemann H, Rüther E (1994) Nächtliches Myoklonie-Syndrom (NMS) und Restless-Legs-Syndrom (RLS)-Übersicht und Fallbeschreibung. Fortschr Neurol Psychiat 62: 88–93
Staedt J, Stoppe G, Kögler A, Riemann H, Hajak G, Munz DL, Emrich D, Rüther E (1995a) Single photon emission tomography (SPET) imaging of dopamine D2 receptors in the course of dopamine replacement therapy in patients with nocturnal myoclonus syndrome (NMS). J Neural Transm [Gen Sect] 99: 187–193
Staedt J, Stoppe G, Kögler A, Riemann H, Hajak G, Munz DL, Emrich D, Rüther E (1995b) Nocturnal myoclonus syndrome (periodic movements in sleep) related to central dopamine D2-receptor alteration. Eur Arch Psychiatry Clin Neurosci 245: 8–10
Staedt J, Stoppe G, Riemann H, Hajak G, Rüther E, Riederer P (1996) Lamotrigine in the treatment of Nocturnal Myoclonus Syndrome (NMS): two case reports. J Neural Transm 103: 355–361
Symonds CP (1953) Nocturnal myoclonus. J Neurol Neurosurg Psychiatry 16: 166–171
Trenkwalder C, Stiasny K, Pollmächer Th, Wetter Th, Schwarz J, Kohnen R, Kazenwadel J, Krüger HP, Ramm S, Künzel M, Oertel WH (1995) L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. Sleep 18: 681–688
Waddington JL, O'Boyle KM (1989) Drugs acting on brain dopamine receptors: a conceptual re-evaluation five years after the first selective D1 antagonist. Pharmacol Ther 43: 1–52
Walters AS, Hennig WA, Kavey N, Chokroverty S, Gidro-Frank S (1988) A double blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. Ann Neurol 24: 455–458

Yarbrough GG, Mcguffin-Clineschmidt J, Singh DK, Haubrich DR, Bendesky RJ, Martin GE (1984) Electrophysiological, biochemical and behavioral assessment of dopamine autoreceptor activation by series of dopamine agonists. Eur J Pharmacol 99: 73–78

Authors' address: PD Dr. J. Staedt, Department of Psychiatry, University of Goettingen, Von-Siebold-Strasse 5, D-37075 Goettingen, Federal Republic of Germany.

Received July 10, 1996