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Quick Titration of Pergolide in Cotreatment with Domperidone Is Safe and Effective

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Summary: The purpose of the study was to analyze efficacy and safety of quick pergolide titration combined with domperidone. In an open-label prospective study, pergolide was titrated in 16 days to a maximum of 3 mg/d doses as adjunctive treatment to L-Dopa in 10 elderly patients with Parkinson's disease. Sixty milligrams domperidone was started 2 days before and and continued during the pergolide titration period to prevent side effects. Adverse events were studied for 6 weeks. Efficacy was measured with the motor part ("on" condition) of the Unified Parkinson's Disease Rating Scale (UPDRS), the 2-minute walking test, the Timed Up and Go test, and the Postural-Locomotor-Manual test. After quick titration of pergolide with domperidone cotreatment, no symptomatic side effects were seen except for lightheadedness in one patient, which disappeared after dose reduction. The UPDRS motor score improved significantly from 21 ± 8 at baseline to 16 ± 7 and 12 ± 7 after 1 and 2 weeks, respectively. The 2-minute walking distance improved significantly from 123 ± 36 m at baseline to 136 ± 41 m after 6 weeks. The Timed Up and Go and Postural-Locomotor-Manual test results, overall, did not show significant changes. Quick titration of pergolide to a maximum of 3 mg/d with domperidone cotreatment is safe and effective. Therefore, we recommend domperidone cotreatment in the titration period to prevent unnecessary failure of dopamine agonist treatment because of adverse effects. **Key Words:** Pergolide—Domperidone—Parkinson's disease—Elderly patients—Dose titration

Pergolide is a mixed D1/D2 dopamine receptor agonist, which improves the motor functioning of patients with Parkinson's disease as monotherapy or as adjunctive therapy to L-Dopa (1,2). Studies with pergolide have suggested that dose levels of 1.5–5 mg/d are necessary to reach adequate effects (2,3). A study in very elderly patients showed a success rate of 47% to 53% at doses of 1.4 to 1.8 mg (4). To reach this optimal clinical benefit, pergolide has to be titrated slowly to prevent side effects, mainly, nausea (17%–30%) and orthostatic hypotension (5%–17%). The current dose-titration regime for pergolide takes 6 weeks to reach a dose of 3 mg/d. To overcome the adverse events with dopamine agonists, the use of domperidone, a peripherally acting dopamine antagonist, is suggested (5).

In our experience, the pergolide titration schedule is difficult to follow for elderly patients. To confirm our experience, we used the PHARMO database, containing all prescriptions and hospitalization of 450,000 inhabitants of 12 Dutch cities, to analyze pergolide titration in daily practice. The method of this database is described elsewhere (6). Exact dose calculations were possible for 156 elderly patients (median age, 75 y) first using pergolide. The course of the L-Dopa dose was also analyzed. After the recommended titration period of 6 weeks, the mean dose of pergolide was 0.54 mg (18% of the recommended dose) and after 3 months, 0.69 mg. The number of patients using pergolide decreased 22% within 3 months. The L-Dopa dose remained stable.

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We attempted to determine whether an easier-to-follow regimen involving quick titration of pergolide to the mean recommended dose of 3 mg in 16 days with domperidone cotreatment is safe and effective.

METHODS

Patients older than 65 years of age with Parkinson's disease (Hoehn-Yahr stages 2–4) and with suboptimal reaction on a regimen of L-Dopa were consecutively recruited from the Department of Geriatrics of University Medical Center Utrecht and from the Department of Neurology of Eemland Hospital in Amersfoort, The Netherlands. All patients had had a good response to L-Dopa therapy in the first years of the disease but needed extended therapy because of worsening motor symptoms. All patients were on a stable regimen of L-Dopa therapy combined with a decarboxylase inhibitor. None of the patients had L-Dopa–induced dyskinesias. A choice was made to add pergolide to the regimen to keep the L-Dopa dose low (7). Cotreatment with other medication for Parkinson's disease, except for dopamine receptor agonists, was allowed. Also, use of benzodiazepines was allowed. Patients using antipsychotic drugs were excluded. Patients with a history of orthostatic hypotension, nausea, dizziness, and hallucinations were excluded.

Twenty milligrams domperidone in three daily doses was started 2 days before the initiation of pergolide therapy. Pergolide was started with 0.05 mg/d and gradually increased to a maximum dose of 3 mg/d at 16 days (Table 1). Blood pressure was measured after 5 minutes with the patient supine and after 1–3 minutes of standing each day during the first week and once a week during the next 6 weeks with an Omron automatic blood pressure device (8). Orthostatic hypotension was defined as a reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg measured in the supine position and within 3 minutes of standing (9). We inquired actively and daily about nausea, vomiting, dizziness, and confusion during the first week and once a week during the next 6 weeks. The motor part of the Unified Parkinson Disease Rating Scale (UPDRS) was assessed in the "on" condition at baseline and weekly for 6 weeks after the start of pergolide therapy. Functional mobility was measured by the 2-minute walking distance (10), the Timed Up and Go test (11), and the Postural-Locomotor-Manual test (12) at baseline and on days 21 and 42. The Postural-Locomotor-Manual test is a multiple-task test consisting of three phases: postural, locomotor, and manual. The study was approved by the ethical committee or our institution. All patients were informed about the study and gave written consent.

TABLE 1. *Quick titration schedule of pergolide*

Day	Per-tablet Dose	No. of Tablets
1	0.05 mg	1-0-0
2		1-1-0
3		1-1-1
4		2-2-2
4		3-3-3
6		4-4-4
7	0.25 mg	1-1-1
8		2-1-1
9		2-2-1
10		2-2-2
11		3-2-2
12		3-3-2
13		3-3-3
14		4-3-3
15		4-4-3
16	1 mg	1-1-1

TABLE 2. *Patient characteristics*

Characteristic	Data
N	10
Sex (F/M)	7/3
Mean age (mean ± SE)	77.2 ± 5.8
Hoehn-Yahr stage (± SE)	2.3 ± 0.48
Mean L-Dopa Dose (mg ± SE)	281 ± 107
Duration of PD (mean ± SE)	4.8 ± 3.6

Statistical Analysis

The changes in the UPDRS and functional mobility test results were analyzed for significance with use of the paired-sample Student *t* test . The accepted level of significance was set at $p < 0.05$ (two-tailed). All statistical analyses were performed with SPSS (version 8.0; SPSS, Chicago, IL).

RESULTS

The characteristics of the patients are summarized in Table 2. One patient used selegiline as cotreatment for Parkinson's disease. During the study period, orthostatic hypotension was measured in 4 of the 10 patients. On a total of 96 blood pressure measurements, these four patients had a drop of systolic blood pressure of more than 20 mmHg (mean value, 26 mmHg ± 4) 11 times and a drop of diastolic blood pressure of more than 10 mmHg (mean 20 mmHg ± 9) five times after change from supine to standing position. None of these episodes led to clinical symptoms. No relationship with the strength of the dose was found either. One patient complained of lightheadedness after 14 days on a regimen of 2.5 mg/d pergolide, which disappeared after reduction of the dosage to 1.5 mg/d; she had no orthostatic hypotension at that moment. In the other patients, no

symptomatic side effects, such as nausea, vomiting, dizziness, or confusion, occurred, and a dose of 3 mg pergolide was reached. In half the patients, the domperidone dose was decreased and stopped within 3 months without reports of nausea or dizziness.

Figure 1 shows the course of the UPDRS score in the "on" condition. The score improved significantly after 1 week of treatment with a further significant improvement after 2 weeks. The 2-minute walking distance increased significantly ($p = 0.043$) from 123 m ± 36 at baseline to 136 m ± 41 after 6 weeks. The Timed Up and Go and Postural-Locomotor-Manual test results, except for the manual phase on day 42, did not show significant changes.

DISCUSSION

The basic objective of our open-label study was to investigate whether prevention of orthostatic hypotension and nausea with domperidone co-treatment would provide the opportunity for an easier and quicker titration schedule of pergolide, as described earlier. Indeed, our schedule, with pergolide titration up to 3 mg in 16 days, showed a safe and quick onset of improvement of parkinsonian symptoms. Domperidone not only prevents nausea and vomiting but also plays an important role in the regulation of blood pressure. In patients without Parkinson's disease, 30 mg domperidone three times daily has proven to be effective in the treatment of orthostatic hypertension, probably caused by an increase of sympathetic outflow (13). The preventive action of domperidone in patients with Parkinson's disease using different dopamine agonists has also been reported (14–17). All studies reported fewer adverse events, including both gastrointestinal tract side effects and orthostatic hypotension, compared with dopaminergic medication alone. The dose of domperidone in these studies ranged from 30 to 120 mg/d. Domperidone is a benzimidazole derivative, acting as a dopamine antagonist, which does not cross the blood–brain barrier in dosages below 100 mg/d (18,19). Possible sites of action include presynaptic noradrenergic terminals and postganglionic cells in sympathetic ganglia (20). Domperidone blocks nausea and vomiting by its action on dopamine receptors in the area postrema. Because this area postrema is also known as an important blood regulation center, this may also contribute to the preventive effect of domperidone on hypotension (21).

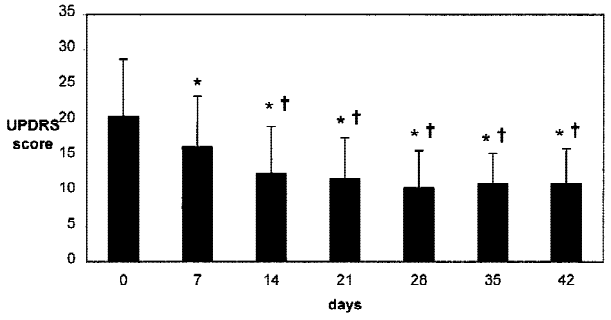

FIG. 1. Unified Parkinson's Disease Rating Scale (UPDRS) score (UPDRS motor part, "on" condition) (mean ± SD) of 10 patients treated with a quick-titration regimen of pergolide up to 3 mg in 16 days.

This study has several limitations. The number of patients is small, and a control group was lacking. A quick elevation to 3 mg is not always necessary. However, our proposal for the quick titration regimen of pergolide allows for elevation of the dose to 1 mg within 14 days and can be followed up by an observation period to determine whether a further elevation of the dose is needed.

Although our pergolide titration regime, according to our experience, was easier to explain than the conventional schedule, it is still complex, and written instruction is advisable.

In conclusion, pergolide is titrated very slowly in daily practice in The Netherlands. Our data show that domperidone allows titration of dopamine agonists up to effective levels in general and that domperidone even allows a forced quick titration of pergolide up to 3 mg in 16 days in elderly patients with Parkinson's disease. Our data should be confirmed by a controlled study in a larger population.

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REFERENCES

1. Barone P, Breve D, Bermajo-Pareja F, et al. Pergolide monotherapy in the treatment of early PD: a randomized, controlled study—Pergolide Monotherapy Study Group. *Neurology* 1999;53:573–9.
2. Olanow CW, Fahn S, Muenter M, et al. A multi-center double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. *Mov Disord* 1994;9:40–77.
3. Kulisevsky J, Lopez-Villegas D, Garcia-Sanchez C, et al. A six-month study of pergolide in *de novo* Parkinson's disease patients. *Clin Neuropharmacol* 1998;21:358–62.
4. Shulman LM, Minagar A, Rabinstein A, et al. The use of dopamine agonists in very elderly patients with Parkinson's disease. *Mov Disord* 2000;15:664–8.
5. O'Sullivan J, Lees A. Oral dopamine agonists adverse drug reaction profile. *Prescrib J* 1999;39:166–71.
6. Herings RMC. PHARMO: *A Record Linkage System for Postmarketing Surveillance of Prescription Drugs in The Netherlands* [PhD dissertation]. Utrecht, The Netherlands: Department of Pharmacoepidemiology, Utrecht University, 1993:207.
7. Watts RL. The role of dopamine agonists in early Parkinson's disease. *Neurology* 1997;49(suppl 1):34–48.
8. O'Brien E, Mee F, Atkins N. An accurate automated device for home blood pressure measurement at last! The Omron HEM-705CP. *J Hypertens* 1994;12:1317–8.
9. The Consensus Committee of the American Autonomic Society and

the Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology* 1996;46:1470.
10. Butland RJA, Pang J, Gross ER, et al. Two-, six-, and twelve-minute walking tests in respiratory disease. *Br Med J* 1982;284:1607–8.
11. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; 39:142–8.
12. Valls M, Ingvarsson B, Johnels B, et al. Age-related slowing and fragmentation of a complex movement quantified by opto-electronic kinesiology. *Clin Rehabil* 1990;4:111–22.
13. Montastruc JL, Chamontin B, Senard JM, et al. Domperidone in the management of orthostatic hypotension. *Clin Neuropharmacol* 1985;2:191–2.
14. Agid Y, Pollack P, Bonnet AM, et al. Bromocriptine associated with a peripheral dopamine blocking agent in the treatment of Parkinson's disease. *Lancet* 1979;1:570–2.
15. Morello M, Pirtosek Z, Bishop S, et al. Cardiovascular reflexes in Parkinson's disease: effect of domperidone and apomorphine. *Clin Auton Res* 1992;2:215–9.
16. Pollak P, Mallaret M, Gaio JM, et al. Blood pressure effects of apomorphine and domperidone in parkinsonism. *Adv Neurol* 1986;45: 263–6.
17. Quinn N, Illas A, Lhermitte F, et al. Bromocriptine and domperidone in the treatment of Parkinson disease. *Neurology* 1981;31: 662–7.
18. Laduron PM, Leysen JE. Domperidone, a specific in vitro dopamine antagonist, devoid of in vivo central dopaminergic activity. *Biochem Pharmacol* 1979;28:2161–5.
19. Parkes JD. Domperidone and Parkinson's disease. *Clin Neuropharmacol* 1986;9:517–32.
20. Clark BJ. Dopamine receptors and the cardiovascular system. *Postgrad Med J* 1981;57:45–54.
21. Tangri KK, Saxena AK, Misra N, et al. Area postrema and cardiovascular regulation: role of monoaminergic receptors [abstract]. *Eur J Pharmacol* 1990;183:406.

Erratum

In the article entitled "Incoherence of Neuroimaging Studies of Attention Deficit/Hyperactivity Disorder," by Baumeister and Hawkins, in the January–February 2001 issue of Clinical Neuropharmacology (23:2–10), the passage in the section entitled "Frontal Lobes" on page 6 that read:

> Of the studies that reported significant effects in frontal lobe activity (41–45); five found decreased activity exclusively, although activity was increased in some frontal loci (46–50); three reported no differences between subjects with ADHD and control subjects (51–53); and one reported that subjects with ADHD had increased frontal lobe activity (54).

Should have read:

> Of the studies that reported significant effects in frontal lobe activity, five found decreased activity exclusively (41–45); five found predominantly decreased activity, although activity was increased in some frontal loci (46–50); three found no differences between subjects with ADHD and control subjects (51–53); and one reported that subjects with ADHD had increased frontal lobe activity (54).

We regret any confusion that this error may have caused.