ORIGINAL CONTRIBUTION

Acute Orthostatic Hypotension When Starting Dopamine Agonists in Parkinson's Disease

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Objective: To study the frequency and severity of acute orthostatic hypotension (OH) in patients with Parkinson's disease who are starting dopamine agonist therapy.

Patients and Methods: In the context of an outpatient clinical practice, 29 consecutive patients with Parkinson's disease who were starting dopamine agonist therapy were brought into the clinic for their first dose of agonist. After a baseline supine and standing blood pressure assessment, patients were given a test dose of either pergolide mesylate (0.025, 0.05, 0.125, or 0.25 mg), pramipexole dihydrochloride (0.125 mg), or ropinirole hydrochloride (0.125 or 0.25 mg). At 3 selected times, blood pressure readings were repeated in the supine and standing positions.

Main Outcome Measure: Orthostatic hypotension was defined as a drop in either systolic blood pressure of more than 25 mm Hg or diastolic pressure of more than 10 mm Hg. Patients with OH before the administration of the dopamine agonist were excluded.

Results: Ten subjects (34%) met the criteria for acute OH. There was no evidence that OH was related to the use of a specific dopamine agonist or the concurrent use of levodopa. Of the patients who met the criteria for OH, only 3 (30%) had symptoms of OH, such as lightheadedness or general malaise.

Conclusions: Acute OH occurs frequently when starting dopamine agonist therapy in Parkinson's disease, but is frequently not appreciated by patients. Knowledge of acute blood pressure responses may be useful when making decisions regarding agonist titration schedules in clinical practice.

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MEDICATIONS used to treat Parkinson's disease (PD), including levodopa,[1] may result in orthostatic hypotension (OH). Dopamine agonists can markedly reduce blood pressure, and precipitous changes can occur even with the first dose.[2] Dopamine agonists lower blood pressure primarily by venous and arterial dilation through inhibition of the sympathetic nervous system.[3] Because apomorphine hydrochloride and bromocriptine mesylate decrease blood pressure in normotensive and hypertensive subjects,[4] dopamine agonists have been used in the treatment of high blood pressure.[5] In PD, OH has been a well-recognized adverse effect of all available dopamine agonists, including bromocriptine, pergolide mesylate, and the newer agents, pramipexole dihydrochloride and ropinirole hydrochloride.[6,7] These studies reported OH as an adverse event associated with the administration of dopamine agonists at any point rather than as an acute effect of starting the medication. We studied the frequency and severity of acute changes in supine and standing blood pressure readings when patients took their first dose of a dopamine agonist. An acute change in blood pressure strongly suggests a direct dopamine agonist effect rather than an underlying illness (dehydration or infection) or concurrent medication (antihypertensive or antiparkinsonian) that may have resulted in an adverse event being reported in previous studies. This information would be useful when making decisions regarding subsequent titration and dosing schedules, to assure patient safety and drug tolerability.

RESULTS

Nine patients (31%) received pergolide; 16 (55%), pramipexole; and 4 (14%), ropinirole. After agonist ingestion, 10 patients (34%) met the criteria for OH (6 met the systolic criteria; 7, the diastolic criteria; and

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PATIENTS AND METHODS

PATIENTS

Thirty-three consecutive ambulatory patients with PD who planned to start dopamine agonist therapy under the care of a movement disorder specialist in our university tertiary care center were studied. All patients were brought into the clinic for their first nonrandomized, open-label dose during an appointment that was separate from their regular follow-up visit. In all cases, dopamine agonists were selected to treat progressive parkinsonism. The choice of agonist was not randomized but rather based on the treating physician's preference after consultation with the patient, and did not focus on concerns of OH. *Orthostatic hypotension* was defined as a change in systolic blood pressure of more than 25 mm Hg or a change in diastolic blood pressure of more than 10 mm Hg.[8] Four patients had OH before the administration of the dopamine agonist and were not included in the data analysis. The mean (±SD) age of the remaining 29 patients (18 men and 11 women) was 62.4±10.4 years (range, 38-83 years), and the mean (±SD) disease duration from the time of diagnosis was 11.2±6.0 years (range, 1-28 years). Twenty-three patients (79%) were receiving levodopa therapy at the time of the study, with a mean dose of 554.9 mg/d. Six patients (21%) were receiving antihypertensive medications at the time of the study, but none had OH at baseline. No changes were made to the patient's dose of antiparkinsonian or antihypertensive medications before this study. After obtaining baseline supine and standing (measured after 3 minutes in the upright position) blood pressure readings, patients were given an oral test dose of either pergolide mesylate (0.025, 0.05, 0.125, or 0.25 mg), pramipexole dihydrochloride (0.125 mg), or ropinirole hydrochloride (0.125 or 0.25 mg). The oral test dose was selected by the treating physician as the proposed dose for starting agonist treatment in an outpatient setting and considered the patient's overall disability and age. At 30 minutes, 1 hour, and 1½ to 2 hours after agonist ingestion, blood pressure readings were repeated by unblinded personnel, with the patient in the supine and standing positions. A single nurse, trained by a physician in the Movement Disorders section to take the recordings as described above, was responsible for all blood pressure readings for each study patient.

STATISTICAL ANALYSIS

Frequencies and percentages were calculated. Fisher exact test was used to determine the association of OH with specific dopamine agonists or the use of other medications.

3, both the systolic and diastolic criteria). Three of the patients with OH received a test dose of pergolide mesylate (0.025, 0.125, or 0.25 mg), while 7 were given pramipexole dihydrochloride (0.125 mg). There was no evidence that a specific dopamine agonist resulted in an increased frequency of OH ($P=.36$, Fisher exact test). All patients received a low dose of agonist (mean pergolide equivalent, 0.11±0.05 mg), where 1 mg of pergolide equals 1 mg of pramipexole equals 3 mg of ropinirole. Because of this lack of variation, no correlation could be tested between dose and the occurrence of acute OH. Of the 10 patients who met the criteria for OH, only 3 (30%) had symptoms of OH (lightheadedness or general malaise).

Orthostatic hypotension was not related to the concurrent use of other medications such as levodopa and antihypertensive agents. Although most patients in this study were receiving levodopa, among the 6 who were not, 2 demonstrated agonist-associated OH. Only 1 patient with OH was receiving an antihypertensive medication (nifedipine, 30 mg/d).

COMMENT

Orthostatic hypotension is a frequently reported manifestation of autonomic dysfunction in patients with PD, with prevalence rates from 8.7% to 58.2%.[9-11] Acute OH is not usually appreciated by patients as lightheadedness. A recent study by Senard et al[11] demonstrated that 38.5% of patients with OH were asymptomatic. Among 55 subjects enrolled in a double-blind trial of pramipexole, Hubble et al[7] found that all patients exhibited asymptomatic OH, regardless of treatment with placebo or pramipexole. In a study by Singer et al,[12] which used a questionnaire to determine autonomic symptoms in men with PD, 22% of patients complained of orthostatic dizziness.

The results of our study are similar to those of others that demonstrated OH with agonist therapy in PD. In 91 consecutive patients with PD evaluated for OH, Senard et al[11] found that 53 patients met criteria for OH, and more than half were receiving bromocriptine. Likewise, Hubble et al[7] found more symptomatic OH in patients receiving pramipexole than in those receiving placebo (25% vs 18.5%, respectively).

The treatment of OH in PD includes nonpharmacological as well as pharmacological measures to stabilize blood pressure. Nonpharmacological therapies include eliminating or decreasing medications that may cause OH (diuretics, vasodilators, antihypertensives, tricyclic antidepressants, and dopamimetics), increased consumption of salt and fluids, smaller but more frequent meals, avoidance of alcoholic beverages, and use of elastic Jobst stockings to increase venous return of blood to the heart. Since these conservative measures may be effective in patients who have only mild dysfunction, pharmacological agents are usually necessary to improve the patient's symptoms. The number of medications available is extensive and diverse, each with an associated profile of potential adverse effects, supine hypertension being the most common. Frequently used drugs in the treatment of OH include mineralocorticoids (fludrocortisone), sympathomimetics (ephedrine, and phenylpropanolamine), direct vasoconstrictors (midodrine hydrochloride), prostaglandin synthetase inhibitors (indomethacin) and prohemopoietic agents (erythropoietin).[13] The role of orthostatic hypotension—symptomatic or

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asymptomatic—as a cause of orthostatic instability and falling has not been systematically studied among patients with PD. We recognize that this was not a randomized, blinded, placebo-controlled study, but it was designed to mimic a regular clinical practice and used consecutive patients. Because the morbidity of falls includes hip fractures, expensive diagnostic procedures, multiple emergency department visits, and hospitalization, the identification of patients who have OH in response to antiparkinsonian medication is of practical importance. Despite the small number of subjects in this study, we believe that drug-induced OH may cause significant disability in this patient population and recommend that dopamine agonist therapy be started under the direct supervision of a physician or nurse. This monitoring can be accomplished easily during an extended outpatient clinic appointment. Because so many of our patients were asymptomatic despite large drops in blood pressure, we now modify titration schedules in patients who demonstrate acute OH. These patients are started on lower doses and, often, alternate-day therapy. The monitoring of blood pressure in the outpatient clinic is a simple and safe procedure that can assist in disease management.

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REFERENCES

1. Calne DB, Brennan J, Spiers ASD, Stern GM. Hypotension caused by L-dopa. *BMJ.* 1960;1:474-475.
2. Schoenberger JA. Drug-induced orthostatic hypotension. *Drug Saf.* 1991;6:402-407.
3. Johns DW, Ayers CR, Carey RM. The dopamine agonist bromocriptine induces hypotension by venous and arteriolar dilation. *J Cardiovasc Pharmacol.* 1984; 6:582-587.
4. Montastruc JL, Chamontin B, Rostin M, et al. Experimental and clinical approaches to treatment of hypertension by dopamine receptor agonists. *Clin Exp Hypertens.* 1987;9:1069-1084.
5. Luchsinger A, Velasco M, Urbina A, et al. Comparative effects of dopaminergic agonists on cardiovascular, renal, and renin-angiotensin systems in hypertensive patients. *J Clin Pharmacol.* 1992;32:55-60.
6. Dooley M, Markham A. Pramipexole: a review of its use in the management of early and advanced Parkinson's disease. *Drugs Aging.* 1998;12:495-514.
7. Hubble JP, Koller WC, Cutler NR, et al. Pramipexole in patients with early Parkinson's disease. *Clin Neuropharmacol.* 1995;18:338-347.
8. Bannister R, ed. *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System.* Oxford, England: Oxford University Press; 1983.
9. Netten PM, De Vos K, Horstink M, Hoefnagels W. Autonomic dysfunction in Parkinson's disease, tested with a computerized method using a Finapres device. *Clin Auton Res.* 1995;5:85-89.
10. Plaschke M, Trenkwalder P, Dahlheim H, Lechner C, Trenkwalder C. Twenty-four–hour blood pressure profile and blood pressure responses to head-up tilt tests in Parkinson's disease and multiple system atrophy. *J Hypertens.* 1998; 16:1433-1441.
11. Senard JM, Rai S, Lapeyre-Mestre M, et al. Prevalence of orthostatic hypotension in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1997;63:584-589.
12. Singer C, Weiner WJ, Sanchez-Ramos JR. Autonomic dysfunction in men with Parkinson's disease. *Eur Neurol.* 1992;32:134-140.
13. Freeman R, Miyawaki E. The treatment of autonomic dysfunction. *J Clin Neurophysiol.* 1993;10:61-82.

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