Clinical Characteristics of Pramipexole-Induced Peripheral Edema

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Background: Pramipexole, a new dopamine agonist, effectively treats early and advanced Parkinson disease and restless legs syndrome.

Objectives: To report the clinical features of and to investigate the predisposing factors and eventual outcomes in patients who developed peripheral edema (PE) following treatment with pramipexole.

Design: Retrospective case series in a tertiary referral center.

Results: Of the 300 patients who were receiving pramipexole therapy, 17 patients had mild to severe PE, which was attributable to the medication. Fifteen patients had Parkinson disease and 2 patients had restless legs syndrome. The mean (±SD) time of onset of PE after pramipexole therapy was started was 2.6 ± 3.6 months (range, 0.25-11 months). The mean (±SD) dose at onset of PE was 1.7 ± 1.0 mg/d (dose range, 0.75-3 mg/d) and the mean (±SD) dose when PE was at its maximum was 2.6 ± 0.7 mg/d (dose range, 1.5-3 mg/d). In all cases, the PE rapidly abated with discontinuation of therapy, and in all cases that we rechallenged, it rapidly returned. The condition seemed to be dose dependent but also idiosyncratic, as we could not identify any predisposing features. It resulted in extensive medical evaluation in some patients and was only minimally responsive to diuretic therapy.

Conclusion: Peripheral edema should be included among the potential adverse events associated with pramipexole therapy.

Arch Neurol. 2000;57:729-732

Pramipexole, a new dopamine agonist, has been shown to be an effective treatment of early and advanced Parkinson disease (PD) and restless legs syndrome. It is a potent agonist at the D2 dopamine-receptor group, with highest affinity to D3 dopamine-receptors. Pramipexole is usually well tolerated. Commonly reported side effects include nausea, somnolence, and visual hallucinations. Recently, sleep attacks have also been reported. Peripheral edema (PE) as a side effect of dopamine agonists, has been rarely reported with bromocriptine mesylate, ropinirole hydrochloride, and cabergoline. However, this adverse effect is not demonstrated in other studies. To our knowledge, PE has not been shown to be significantly associated with pramipexole therapy. We describe the clinical features and investigate possible predisposing factors and eventual outcomes in patients who developed PE after starting pramipexole therapy.

REPORT OF CASES

CASE 1

A 66-year-old woman (patient 6) had symptoms of parkinsonism for 4 years. She was initially started on a combined regimen of levodopa/carbidopa and amantadine hydrochloride. Pramipexole therapy was added 1 year ago. She noticed some ankle PE within 1 week of adding pramipexole therapy. Nevertheless, she followed the dosing schedule and subsequently increased to a maintenance dose of 3 mg/d. Pramipexole therapy improved PD, but the PE extended up to both of her knees resulting in discomfort and difficulty wearing her shoes.

The results of an extensive evaluation including a 2-dimensional echocardiogram, Doppler ultrasound of her lower extremities, and hepatic and liver function tests were unremarkable. The PE improved only mildly with leg elevation and diuretic therapy. Amantadine therapy...
PATIENTS AND METHODS

Of the 300 patients who were receiving pramipexole therapy and evaluated at our outpatient clinic, 17 satisfied the following inclusion criteria and were enrolled in this study: (1) taking pramipexole therapy for parkinsonism or restless legs syndrome, (2) no history of PE prior to initiation of pramipexole therapy, (3) development of PE while receiving pramipexole therapy and resolution or marked improvement of PE shortly after stopping the medication, and (4) no clinical and biochemical evidence of renal, cardiac, and hepatic failure.

The following information was documented for patients who were enrolled in the study: (1) demographics, (2) duration of disease, (3) total duration of pramipexole therapy, (4) duration of pramipexole therapy until the onset of PE, (5) dose of pramipexole per day when PE was at its worst, (6) severity of PE (ie, at the level of ankle, midshin, knee, thigh, or generalized), (7) functional disability, as measured by difficulty wearing shoes, walking, or exertional dyspnea, (8) outcome (either still receiving therapy or no longer receiving therapy), (9) history of other medication usage, (10) effects of rechallenge with pramipexole, and (11) potential dose response.

All study patients were asked to taper and then completely stop pramipexole therapy. Those patients who found the drug to be effective for their disease symptoms, were given the choice to restart the medication, after the PE had subsided.

was discontinued, as her internist thought this may be culpable; however, there was no improvement in the PE.

At the time of our physical examination, she had moderate bradykinesia and rigidity in her extremities. Pitting PE of both her lower extremities were present up to her knees, with thickening of overlying skin, indicating chronicity of the PE. There was no livedo reticularis or erythromyalgia. She had no evidence of renal, hepatic, or cardiac failure. We instructed her to taper off the dosage of pramipexole over a course of 1 week without adjusting her levodopa dosage. One week after she was no longer receiving pramipexole therapy, she reported at least an 80% improvement of her PE, and she was able to wear her usual shoes. As pramipexole therapy improved her PD, and was otherwise well tolerated, she elected to restart pramipexole therapy, but at a lower dose of 0.75 mg/d. Within 2 weeks, she had noticed an increase of her PE at her ankles, but to a lesser degree than before. She continued usage of pramipexole therapy at this dosage.

CASE 2

A 60-year-old man (patient 11) has a 3-year history of PD, presently complicated by levodopa-induced dyskinesias and motor fluctuations. Pramipexole therapy, at an initial dose of 0.375 mg/d, was started 1 year ago. At that time, he was receiving a combined therapy of levodopa and selegiline hydrochloride. Bilateral ankle swelling was noticed about 3 weeks after initiating pramipexole therapy, while taking 1.5 mg/d. He titrated up to 3 mg/d. The PE at the ankles increased in severity and progressed above both of his knees to the midthigh. The severity of the PE limited his mobility and caused significant distress. Treatment with diuretics gave only mild improvement in his condition. His liver and renal function test results were within normal limits. He also underwent a series of cardiac studies the results of which were unremarkable.

After 1 year of receiving 3 mg/d pramipexole therapy with persistent PE, he was instructed to taper the dosage and then discontinue taking the medication. Three days after discontinuing the drug, the PE completely resolved. Because pramipexole therapy significantly improved his PD symptoms, he restarted the drug. At 1.5 mg/d, he noticed a gradual return of the PE at his ankles. The dose has not been increased, and the PE remains restricted to his ankles.

RESULTS

Seventeen patients (8 males) were studied, with a mean (±SD) age of 63.8 ± 10.6 years (age range, 44-82 years). The mean (±SD) duration of PD was 7.3 ± 5.0 years (range, 2-28 years). Fifteen patients were treated for PD, 13 in Hoehn stage 2 in stage III. Two patients had restless legs syndrome.

The mean (±SD) time of onset of PE after pramipexole therapy was started was 2.6 ± 3.6 months (range, 0.25-11 months) (Table). The mean (±SD) dose at onset of PE was 1.7 ± 1.0 mg/d (dose range, 0.75-3 mg/d) and the mean (±SD) dose when PE was maximum was 2.6 ± 0.7 mg/d (dose range, 1.5-3 mg/d) (Table). Seven patients (41.2%) had PE restricted to the ankles, 5 (29.4%) at the calves, and 5 (29.4%) at or above the knees. Sixteen patients (94.1%) reported difficulty wearing their shoes, and 13 (76.5%) had difficulty walking. No patient had concurrent livedo reticularis or erythromyalgia. All except 1 patient reported complete resolution of PE after the medication was stopped for a few days. The remaining patient had an 80% reduction of her PE. Eleven patients (64.7%) decided to restart pramipexole therapy, but at a lower dosage. Ten reported return of the PE within 1 week, but to lesser severity, and 2 patients discontinued use of the drug.

Other possible concurrent causes of PE included 2 patients with quiescent malignancy of the prostate and uterus, and 1 patient with hypothyroidism. Three were receiving amantadine therapy, and 2 were receiving a calcium antagonist. None of these patients had a history of PE.

COMMENT

We report mild to severe PE in patients that is attributable to pramipexole therapy. In all cases, the PE rapidly abated within 1 week after discontinuation of the drug, and in all cases that we rechallenged with pramipexole therapy, PE rapidly returned. The condition seemed to be dose dependent but also idiosyncratic, as we could not identify any predisposing features. It resulted in exen-
sive medical evaluation in some patients and was only minimally responsive to diuretic therapy. In some cases, gait and balance difficulties caused by the PE were interpreted as worsening PD.

Because many patients initially seen by us already were receiving pramipexole therapy and others follow-up elsewhere after being prescribed pramipexole by us, we were unable to accurately determine the exact prevalence of PE in our practice, but we estimate it to be as high as 5% to 7%. We cannot ascertain whether amantadine, or calcium antagonists, both recognized causes of PE,14,15 may increase the risk or severity of PE when pramipexole is added to the regimen. Of the 5 patients who had severe PE (up to the knee), 1 was receiving amantadine therapy, and 1 was receiving a calcium antagonist. Our small sample size precludes any meaningful analysis of their contribution.

Shannon et al1 reported PE to be present in 7.9% of the patients receiving pramipexole compared with 3.3% in the placebo group. However, the difference was not statistically significant. None of the patients in the pramipexole-treated group discontinued the drug therapy because of PE and no further information was provided. Other large studies of pramipexole therapy have not reported any PE.2-6 Reports of PE as a side effect of other dopamine-agonist therapy have been inconsistent. Conflicting reports regarding this complication indicate that it is likely to be uncommon.

Ergot dopaminergic-agonists, such as bromocriptine and pergolide mesylate have actually been used to treat patients with cyclical PE.23-25 Their effectiveness could be a result of dopamine-mediated inhibition of mineralocorticoid activity. However, others have also reported severe generalized PE with bromocriptine therapy.14,15 Whether the PE caused by bromocriptine therapy in such cases is due to its ergot effects, α₁-adrenoceptors, or dopaminergic affinity is unknown. Some have suggested that because of its rarity, this may represent an idiosyncratic reaction.13 The mechanism by which pramipexole induces PE is unknown. It is not an ergot and has high affinity for the D3-receptor subtype, moderate affinity for α₁-adrenoceptor, and, unlike ergots, low affinity for α₁-adrenoceptor.10 It may have different propensity to induce PE compared with other dopamine agonists.

This study draws attention to our clinical observation that pramipexole therapy can induce PE and that this may be severe in some patients with PD and restless legs syndrome. The PE seems to be dose related, poorly responsive to diuretics, and easily reversed by stopping the medication. Recognition of this adverse effect can avoid unnecessary investigations and morbidity. The decision whether to continue treatment with the drug in patients with mild to moderate PE should be individualized. We do not think our experience is unique, and this complication may be unrecognized and underreported. As more centers acquire experience with pramipexole, the true magnitude of this potential problem may become clearer.

Accepted for publication September 22, 1999.

We thank Joseph Jankovic, MD, Parkinson’s Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, Tex.

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### Characteristics of Pramipexole-Induced Peripheral Edema (PE) in 17 Patients With Parkinson Disease and Restless Legs Syndrome

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Duration of Disease, y</th>
<th>Duration of Treatment Until PE Onset, mo</th>
<th>Dose at PE Onset, mg/d</th>
<th>Dose at Maximal PE, mg/d</th>
<th>PE Severity</th>
<th>Functional Disability*</th>
<th>Effect of Dose Reduction of Pramipexole Therapy</th>
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* Includes patients who had difficulty wearing shoes and/or who had difficulty with gait. Ellipses indicate not applicable.
† Peripheral edema was less severe after rechallenging with pramipexole therapy at a lower dose.
‡ Peripheral edema improved with reduction of the initial dose of pramipexole therapy.
REFERENCES