Risk Factors for the Development of Pedal Edema in Patients Using Pramipexole

Galit Kleiner-Fisman, MD; David N. Fisman, MD, FRCPC, MPH

Objective: To determine risk factors for pedal edema among patients with Parkinson disease (PD) using pramipexole hydrochloride therapy.

Design: A retrospective medical record review.

Setting: Philadelphia Veterans Administration Parkinson’s Disease Research, Education and Clinical Center (PADRECC).

Patients: All consecutive patients at the PADRECC receiving pramipexole from December 2002 to December 2004.

Main Outcome Measures: Bivariable and multivariable logistic regression models were used to identify comorbid illnesses, demographic characteristics, other medications, and PD features associated with increased risk of pedal edema among individuals taking pramipexole. Estimation of time to development of pedal edema in individuals taking pramipexole was performed using Kaplan-Meier survival methods and multivariable Cox proportional hazards models.

Results: Two hundred thirty-seven PADRECC patients received pramipexole and met criteria for inclusion in the analysis. Of these, 38 (16%) developed pedal edema. Multivariable regression models identified idiopathic PD (odds ratio [OR], 4.80; 95% confidence interval [CI], 1.54-14.98; \( P = .007 \)), history of coronary artery disease (OR, 3.35; 95% CI, 1.51-7.46; \( P = .003 \)), and history of diabetes mellitus (OR, 3.12; 95% CI, 1.01-9.60; \( P = .05 \)) as strong independent risk factors for development of edema. There was no relationship between dose of pramipexole and incidence and severity of pedal edema. The risk of development of pedal edema was 7.7% (95% CI, 4.5%-12.9%) in the first year after initiation of pramipexole therapy, with more rapid development of edema among those with a history of coronary artery disease.

Conclusions: Pedal edema is a relatively common outcome in patients with PD receiving pramipexole. History of coronary artery disease increases the risk for developing edema.

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OPAMINE AGONISTS HAVE become an acceptable treatment option as both initial monotherapy in early Parkinson disease (PD) and as adjunctive therapy to levodopa in more advanced disease. These agents have proven efficacy and safety for treatment of the motor symptoms of PD.1-7

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Pramipexole hydrochloride is a nonergot-derived dopamine agonist with potent D2 dopamine receptor activity with highest affinity to the D3 receptor subgroup. Commonly recognized adverse effects of pramipexole and agonists in general include nausea, hallucinations, and somnolence.3-8,9 Though not identified in early safety and efficacy studies,3-8,10 anecdotal experience as well as data from more recent publications3,11 suggest that pedal edema is a relatively common treatment-related adverse event with an estimated prevalence of between 5% to 22.5%.1,11 The morbidity related to edema may counteract the benefit to quality of life that is achieved because of reduction in motor complications.12

We performed a retrospective cohort study in individuals taking pramipexole and attending a specialty PD clinic to determine cumulative incidence of pedal edema in such individuals and to identify risk factors that may predispose patients receiving pramipexole to the development of pedal edema.

STUDY SUBJECTS

Patients who received pramipexole therapy at the Philadelphia Veterans Administration Parkinson’s Disease Research, Education and Clinical Center (PADRECC) at any point between December 2002 and December 2004 were identified through pharmacy records and in-
cluded in the database. The PADRECC is a multidisciplinary center providing subspecialty care to veterans with PD and other movement disorders and serves a catchment area that covers New England and the mid-Atlantic States, as well as Pennsylvania.

Data extracted from patient records (including both paper and electronic medical records) included demographic characteristics, medical comorbidities, length of time of pramipexole and other medication use, maintenance doses and highest doses of pramipexole achieved, whether pedal edema developed while the individual was using pramipexole, and its severity, rated as mild, moderate, or severe. Details of investigations and/or interventions undertaken following the development of edema were collected. Resolution of edema and information pertaining to this were documented when available. Individuals were excluded from the analysis if inspection of medical records did not corroborate the use of pramipexole documented in pharmacy records or if there was a history of pedal edema or lower extremity deep venous thrombosis prior to initiation of pramipexole use as this could confound the analysis.

ANALYSIS

Risk factor analyses were performed using several methods. Descriptive analyses were performed using tabular and graphical methods. Univariable statistical testing ($\chi^2$ for proportions, unpaired $t$ test or Wilcoxon rank sum test as appropriate) was performed to identify differences between individuals who developed pedal edema while taking pramipexole and those who did not develop pedal edema. Odds ratios (ORs) and 95% confidence intervals (CIs) for pedal edema were calculated through creation of univariable logistic regression models for exposures that were found to be associated with risk of pedal edema on univariable statistical testing. Best-adjusted estimates were then calculated by creating a multivariable logistic regression model through the use of a backward elimination algorithm, such that all characteristics with a $P$ value $<.15$ were retained in the model. The possibility of effect modification was assessed through creation of multiplicative interaction terms that were added individually to multivariable models.

We also performed “time-to-event” analyses to estimate the rate at which pedal edema developed among individuals taking pramipexole. Time to development of pedal edema was estimated using the Kaplan-Meier method, with time at risk estimated as time from first use of pramipexole until the last available evaluation or until the development of pedal edema. Differences in event-free survival according to the presence of patient demographic characteristics, medical histories, and other factors were tested using the log-rank test. Finally, univariable and multivariable hazard ratios for candidate risk factors were generated through creation of Cox proportional hazards models, with proportionality of hazards tested using both graphical inspection and testing of Schoenfeld residuals.

The study was approved by the institutional review board of the Philadelphia VA Hospital. All analyses were performed using Intercooled Stata Version 8.0 (StataCorp, College Station, Tex).

RESULTS

Two hundred fifty-one individuals of a total of 553 patients attending the PADRECC were identified through pharmacy records as having been prescribed pramipexole while receiving care at the PADRECC. Of these, 14 individuals were excluded: 3 had no record of receipt of pramipexole in their medical record; 9 had a history of pedal edema due to other causes prior to receipt of pramipexole; and 1 had a history of deep venous thrombosis.

Among the remaining 237 individuals included in the study cohort, 38 (16.0%) had developed pedal edema while taking pramipexole. All were male. Among 30 (79%) of 38 individuals for whom severity of edema was recorded in medical records, approximately equal numbers were classified as having developed mild (n=7), moderate (n=8), or severe (n=7) edema while taking pramipexole. Other adverse events that occurred in individuals taking pramipexole included hallucinations (8%) and fatigue or drowsiness (8%) and confusion or cognitive difficulty (2%). Psychosis, aggression, depression, hypersexuality, nausea, numbness, rash, syncope, and feeling “dizzy” or “jittery” were also reported, but each occurred in less than 2% of the study population.

Among individuals who developed pedal edema, 35 (92%) of 38 did not undergo investigation as to the cause of the edema. Two individuals underwent echocardiography, and 1 individual had a lower extremity Doppler ultrasound to investigate possible deep venous thrombosis. In 27 (71%) of 38 individuals, pedal edema was documented to have resolved, most commonly after discontinuation of pramipexole use (Figure 1). In the remaining individuals, edema persisted despite discontinuation of pramipexole use.

Univariable statistical testing showed that individuals who developed pedal edema were older at first use of pramipexole ($P = .007$), older at onset of parkinsonian symptoms ($P = .03$), more likely to have idiopathic PD as opposed to other causes of parkinsonism ($P = .009$), and more likely to have a history of coronary artery disease (CAD) ($P < .001$), diabetes mellitus ($P = .05$), or peripheral vascular disease ($P = .001$) than those who did not develop pedal edema. Individuals who developed pedal edema were less likely to have concurrent use of calcium channel antagonists than those who did not develop pedal edema. Differences were seen between groups (those with pedal edema compared with those without pedal edema) with respect to race, PD severity, or the use of other antiparkinsonian agents (Table 1). There was also no relationship between the dose of pramipexole and incidence of pedal edema while taking pramipexole hydrochloride.

Figure 1. Outcome of pedal edema in 38 patients who developed edema while taking pramipexole hydrochloride.
pedal edema, nor was there a relationship between severity of edema and dose of pramipexole. Those with pedal edema had a significantly shorter period taking pramipexole compared with those who did not develop edema.

Univariable and multivariable ORs for the development of pedal edema, estimated through creation of logistic regression models, are presented in Table 2. In multivariable models, age at onset of parkinsonism and age at first use of pramipexole were not found to be independent predictors of pedal edema; however, diabetes mellitus, and a history of idiopathic PD remained strong predictors of pedal edema risk. No interaction between predictors was detected through creation of multiplicative interaction terms (data not shown). Neither calcium channel antagonist use nor history of peripheral vascular disease could be assessed using logistic regression models because of the absence of the former risk factor among individuals who developed pedal edema and the absence of the latter risk factor among individuals who did not develop pedal edema.

The median duration of follow-up in study subjects was 73 weeks (interquartile range, 18-143 weeks). Using Kaplan-Meier methods, pedal edema was estimated to occur at a rate of 7.7 per 100 person-years (95% CI, 4.5-12.9 per 100 person-years) during the first year of pramipexole use. A significant difference again was found in time

### Table 1. Characteristics of Individuals Taking Pramipexole at the Philadelphia PADRECC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Individuals (N = 237)</th>
<th>Pedal Edema (n = 38)</th>
<th>No Pedal Edema (n = 199)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months of pramipexole use, median (range)</td>
<td>16.8 (0-89.7)</td>
<td>10.6 (0-53.8)</td>
<td>18.5 (0-89.7)</td>
<td>.002</td>
</tr>
<tr>
<td>Age at first use of pramipexole, y, mean (SD)</td>
<td>67.9 (11.5)</td>
<td>74.6 (8.2)</td>
<td>67.1 (11.9)</td>
<td>.007</td>
</tr>
<tr>
<td>Age at symptom onset, y, mean (SD)</td>
<td>61.3 (12.6)</td>
<td>65.5 (11.0)</td>
<td>60.6 (12.7)</td>
<td>.03</td>
</tr>
<tr>
<td>Idiopathic Parkinson disease, No. (%)</td>
<td>171 (72.2)</td>
<td>34 (89.5)</td>
<td>137 (68.8)</td>
<td>.009</td>
</tr>
<tr>
<td>African American, No. (%)</td>
<td>14 (5.9)</td>
<td>2 (5.3)</td>
<td>12 (6.0)</td>
<td>.85</td>
</tr>
<tr>
<td>Hoehn and Yahr score, median (range)</td>
<td>2.5 (1-5)</td>
<td>3 (2-4)</td>
<td>2.5 (1-5)</td>
<td>.18</td>
</tr>
<tr>
<td>UPDRS motor score, mean (SD)</td>
<td>28.1 (12.5)</td>
<td>30.5 (13.6)</td>
<td>27.5 (12.2)</td>
<td>.25</td>
</tr>
<tr>
<td>Pramipexole dosage, mg, median (range)</td>
<td>Highest dose 1.5 (0.125-10)</td>
<td>1.5 (0.125-9.0)</td>
<td>1.5 (0.125-10.0)</td>
<td>.82</td>
</tr>
<tr>
<td>Maintenance dose 1.5 (0.125-10)</td>
<td>1.5 (0.125-10)</td>
<td>1.5 (0.125-9.0)</td>
<td>1.5 (0.125-10.0)</td>
<td>.76</td>
</tr>
<tr>
<td>Other medications used, No. (%)</td>
<td>Pergolide mesylate 3 (1.3)</td>
<td>1 (2.6)</td>
<td>2 (1.0)</td>
<td>.41</td>
</tr>
<tr>
<td></td>
<td>Ropinirole hydrochloride 1 (0.4)</td>
<td>0</td>
<td>1 (0.5)</td>
<td>.66</td>
</tr>
<tr>
<td></td>
<td>Bromocriptine mesylate 3 (1.3)</td>
<td>1 (2.6)</td>
<td>2 (1.0)</td>
<td>.41</td>
</tr>
<tr>
<td></td>
<td>Amantadine hydrochloride 32 (13.5)</td>
<td>3 (7.9)</td>
<td>29 (14.6)</td>
<td>.27</td>
</tr>
<tr>
<td></td>
<td>Levodopa 155 (65.4)</td>
<td>25 (65.8)</td>
<td>130 (65.3)</td>
<td>.96</td>
</tr>
<tr>
<td></td>
<td>Controlled-release levodopa 52 (21.9)</td>
<td>9 (23.7)</td>
<td>43 (21.6)</td>
<td>.78</td>
</tr>
<tr>
<td></td>
<td>Entacapone 42 (17.7)</td>
<td>6 (15.8)</td>
<td>36 (18.1)</td>
<td>.73</td>
</tr>
<tr>
<td></td>
<td>Fludrocortisone acetate 5 (2.1)</td>
<td>1 (2.6)</td>
<td>4 (2.0)</td>
<td>.81</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blocker 19 (8.0)</td>
<td>0</td>
<td>19 (9.6)</td>
<td>.05</td>
</tr>
<tr>
<td>Medical history, No. (%)</td>
<td>Hypertension 81 (34.2)</td>
<td>13 (34.2)</td>
<td>68 (34.2)</td>
<td>.99</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease† 45 (19.0)</td>
<td>15 (39.5)</td>
<td>30 (15.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus 23 (9.7)</td>
<td>7 (18.4)</td>
<td>16 (8.0)</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular disease 2 (0.8)</td>
<td>2 (5.3)</td>
<td>0</td>
<td>.001</td>
</tr>
</tbody>
</table>

### Table 2. ORs and 95% CIs for Predictors of Pedal Edema at PADRECC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariable Logistic Regression Models</th>
<th>Multivariable Logistic Regression Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) P Value</td>
<td>OR (95% CI) P Value</td>
</tr>
<tr>
<td>Idiopathic PD</td>
<td>3.85 (1.31-11.31) .01</td>
<td>4.80 (1.54-14.98) .007</td>
</tr>
<tr>
<td>History of CAD</td>
<td>3.67 (1.72-7.84) .001</td>
<td>3.35 (1.51-7.46) .003</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>2.58 (0.98-6.79) .05</td>
<td>3.12 (1.01-9.60) .05</td>
</tr>
<tr>
<td>10-y Increase in age at first pramipexole hydrochloride use*</td>
<td>1.56 (1.09-2.24) .02</td>
<td></td>
</tr>
<tr>
<td>10-y Increase in age at first symptoms of PD*</td>
<td>1.41 (1.03-1.93) .03</td>
<td></td>
</tr>
</tbody>
</table>

### Abbreviations
- PADRECC, Philadelphia Veterans Administration Parkinson’s Disease Research, Education and Clinical Center
- UPDRS, Unified Parkinson’s Disease Rating Scale
- CI, confidence interval
- OR, odds ratio
- PD, Parkinson disease

*P > .15; not retained in multivariable regression model because of lack of statistical significance.
to edema in individuals with a history of CAD (P = .05 by log-rank test) compared with those who did not develop pedal edema (Figure 2). No significant differences were detected in time to edema for other exposures of interest. In a univariable Cox proportional hazards model, the hazard ratio for pedal edema in individuals with a history of CAD was 2.29 (95% CI, 0.99-5.32; P = .05).

Figure 2. Kaplan-Meier curve demonstrating time to development of pedal edema in subjects with and without coronary artery disease. Coronary artery disease was associated with a significant increase in edema risk. Pramipexole was given as pramipexole hydrochloride.

This retrospective cohort study of veterans receiving care at an outpatient movement disorders clinic found that the development of pedal edema was a common adverse effect in this population and occurred in 16% of those taking pramipexole. Initial studies of safety and efficacy of pramipexole in PD did not identify pedal edema as a common complaint; however, larger longitudinal studies, such as CALM-PD, reported peripheral edema in up to 14.6% of patients assigned to the pramipexole treatment arm, consistent with findings in this study.

Several patient characteristics were identified as markers of risk for the development of pramipexole-associated pedal edema. These included older age, idiopathic PD (in contrast to other diagnoses of parkinsonism), CAD, and diabetes, with the latter 3 factors emerging as independent predictors of risk in multivariable models. Coronary artery disease was also identified as a risk factor for more rapid development of pedal edema in a time-to-event analysis (ie, Kaplan-Meier analyses and Cox proportional hazards model).

The association between a prior diagnosis of CAD and the development of pedal edema while taking pramipexole seen in this study could represent 1 of several possibilities: (1) pramipexole use might be a cause of pedal edema in individuals with CAD; (2) CAD may be a confounding variable related to edema risk but not causal, or (3) individuals in this study might have developed pedal edema as a result of CAD, independent of pramipexole use. The absence of a group of subjects not using pramipexole makes it difficult to state with certainty that pedal edema risk was actually increased by pramipexole use; nonetheless, this finding highlights a testable hypothesis that can be assessed in future prospective studies that do include such a control group.

Idiopathic PD and diabetes were identified as additional risk factors for pedal edema using logistic regression but were not identified as increasing the rate at which edema developed in time-to-event analyses. A possible mechanism for this discrepancy might relate to error in measurement of the timing of the development of pedal edema (misclassification error), which could result in loss of statistical power for the detection of subtle effects in time-to-event analyses.

The pathophysiology of pramipexole-induced peripheral edema is unknown. One limited retrospective series did not identify any clear predisposing factors, though premorbidity conditions were not considered. In this same study, development of edema was concluded to be both idiosyncratic and dose related depending on the patient. In our study, we did not find a relationship between dose of pramipexole, incidence of pedal edema, or severity of edema. Results of time-to-event analyses (Kaplan-Meier analyses and Cox proportional hazards model) suggest that those who developed pedal edema did so early on and this occurrence was more likely an idiosyncratic reaction rather than dose related.

Though dopamine agonists such as bromocriptine mesylate and pergolide mesylate have been reported to cause edema, it is generally accepted that it is likely related to their ergot-alkaloid properties. However, development of edema also has occurred in patients taking ropinirole hydrochloride, a selective nonergoline dopamine agonist similar to pramipexole in this capacity. This suggests that edema is likely an agonist class effect that is independent of ergot properties. Lack of studies regarding edema in these agents for both patients with and without PD limits further speculation as to the mechanism of this effect as well as the mechanism of the relationship between CAD, pramipexole, and development of pedal edema.

Few of our patients underwent extensive evaluation or interventions in response to the edema. This was likely due to the fact that specialist physicians at a PD specialty clinic who were highly conscious of pedal edema as a potential adverse effect of pramipexole use were managing patient care. It is likely that more aggressive investigations and/or interventions would be undertaken if patients were treated by general practice physicians who may have lesser experience with the subtleties and adverse effects of this medication. Increasing awareness of this potential adverse effect may serve to limit unnecessary and potentially costly evaluations as this medication becomes more widely used in the community.

Like any observational study using clinical records as a data source, this study has limitations. Designation of edema as a clinical outcome was based on reports of treating health care professionals and was not independently validated, so edema may have been overdiagnosed based on the accepted association between pramipexole use and pedal edema. However, the incidence of edema in this study was remarkably similar to that reported in the CALM-PD study, a prospective double-blind randomized controlled study, suggesting that the degree of overdiagnosis may not have been great. A second important limitation is that some patients in-
cluded in the analysis may have had exposure to prami-
pexole prior to attending the PADRECC clinic so their
earlier exposure would not have appeared on their VA
pharmacy record. If such individuals had discontinued
pramipexole use because of pedal edema, this would re-
sult in underestimation of the true risk of pedal edema
among individuals taking pramipexole.

We sought to ascertain the prevalence of edema and to
determine whether there are specific risks that predis-
pose certain populations to developing edema. Knowl-
edge of risk factors may optimize benefit and minimize
adverse effects.

The relatively high prevalence of edema found sug-
gests that this is a common outcome in those exposed to
this medication. The relationship to CAD, though un-
clear with respect to mechanism, heightens our aware-
ness about the implications of this medication in at-risk
patients. Prospective, controlled, longitudinal studies with
adequate information regarding exposure, severity, and
comorbidities, among other factors, need to be con-
ducted for a definitive risk assessment and further ins-
ights into the mechanism of edema.

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Correspondence: Galit Kleiner-Fisman, MD, Morton and
Gloria Shulman Movement Disorders Center, Toronto
Western Hospital, University of Toronto, 399 Bathurst
St, McL-7, Toronto, Ontario M5T 2S8, Canada (gklein-
erfisman@yahoo.com).

Author Contributions: Study concept and design: Kleiner-Fisman and Fisman. Acquisition of data: Kleiner-Fisman. Analysis and interpretation of data: Kleiner-Fisman and Fisman. Drafting of the manuscript: Kleiner-Fisman and Fisman. Critical revision of the manu-
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