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Original Article

Pedal edema in Parkinson's disease patients treated with dopamine agonists

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ABSTRACT

Objectives: The purpose of this study was to determine the presence of pedal edema (PE) and its risk factors in Parkinson's disease (PD) patients.

Materials and methods: Between November 2008 and April 2009, a total of 75 outpatients (48 males, 27 females; mean age: 71±7.1 years; range, 58 to 82 years) with PD treated with levodopa and/or dopamine agonist (DA) were included in the study. Fifty patients were taking DAs such as pramipexole, piribedil, cabergoline, and ropinirole, while 25 patients were taking levodopa alone. Age, sex, disease duration, type, dose and duration of medication, and concomitant diseases were assessed as part of the study.

Results: Sixty-four percent of patients in the DA group and 40% in the levodopa group had PE, a significant difference. In the more detailed evaluation of the DA group, we found no significant difference between patients taking pramipexole, piribedil, cabergoline, and ropinirole. Pedal edema did not lead to treatment discontinuation. The association between PE and age, sex, disease duration, type, dose, duration of medication, and comorbidity was analyzed. No predisposing factors were found in PD patients with PE.

Conclusion: In conclusion, PE is more common and severe in PD patients treated with DA than in patients treated with levodopa. Levodopa can also cause PE, but the severity is mild and dose-dependent. No relationship has been established between the type of DA and PE. Therefore, PE is believed to be a class effect in patients treated with dopaminergic agents. Clinicians should be cautious about this side effect and routinely check PE after starting dopaminergic treatment.

Keywords: Dopamine agonist, levodopa, Parkinson's disease, pedal edema.

Parkinson's disease (PD) is a neurodegenerative disorder characterized by rigidity, tremor, bradykinesia, and postural instability.[1] The main treatment for PD is levodopa. Dopamine agonists (DAs) are another effective therapy of choice for PD in both early and advanced stages.[1-3]

Edema is a poorly recognized side effect and affects the quality of life of PD patients.[1,3] Pedal edema (PE) in PD is caused by the treatment or the disease itself, and DAs are a group of drugs often suspected of causing this complication.[4,5]

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There are several treatment options available at PD. Among the first are DAs, which are often used both as early monotherapy and as add-on therapy to levodopa.[1,3-5]

Although DAs can successfully control the motor symptoms of PD, the side effects associated with DAs, such as PE, can lead to poorer treatment adherence.[3,5,6] To improve treatment adherence, the risk factors that may cause side effects should be identified and taken into account when selecting medications.[3]

In this study, we aimed to determine the PE rate and its risk factors in PD patients.

MATERIALS AND METHODS

This two arm, open label, prospective, observational study was conducted at Marmara University, Faculty of Medicine, Department of Neurology, between November 2008 and April

2009. A total of 75 patients with AD (48 males, 27 females; mean age: 71±7.1 years; range, 58 to 82 years) were included in the study. The study was conducted in patients who met the United Kingdom Brain Bank criteria for PD and were prescribed at least one antiparkinsonian drug including levodopa and DAs. Fifty of patients take DAs such as pramipexole, piribedil, cabergoline, or ropinirole, and 25 take levodopa. Patients taking combined DAs were excluded. Patients' age, sex, disease interval, type and dose of antiparkinsonian medication, concomitant diseases, and other medications were all recorded. Edema was assessed by examination. The localization (pretibial, or dorsum of the foot) and laterality were also considered. The severity of the edema was classified as mild, moderate, or severe. To determine extrapyramidal symptoms, we used the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr scale. Patients who had severe cardiac insufficiency and kidney disease were excluded.

Statistical analysis

Descriptive statistics of the measured variables according to medication were expressed as mean ± standard deviation (SD), and categorical variables were expressed as numbers and percentages. Continuous variables were compared with the independent sample t-test and categorical variables were compared using the Chi-square test. P value of less than 0.05 was considered statistically significant for all tests. Statistical analysis was performed with SPSS software version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic characteristics

Baseline demographic characteristics of PD patients treated with levodopa or DAs were compared. No significant differences were found in age, sex, disease interval, disease severity, drug dose, and concomitant diseases between the two groups. Demographic characteristics and medication information are summarized in Table 1.

Medication data

Medication was classified according to the dose of the antiparkinsonian agent. Patients taking levodopa at a dose of 500 mg, pramipexole at a dose of 3 mg, cabergoline at a dose of 4 mg, ropinirole at a dose of 10 mg, and piribedil at a dose of 150 mg or more were classified as the "high-dose group," whereas patients taking lower doses formed the "low-dose group". Forty-four percent of patients in the levodopa group and

Table 1. Demographic features of the PD patients

	Levodopa (n=25)				Dopamine agonist (n=50)				
Parameter	n	%	Mean±SD	Min-Max	n	%	Mean±SD	Min-Max	*p*
Age (year)			72.7±6.6	62-82			69.3±7.6	58-82	0.061
Sex									0.610
Female	10	40			17	34			
Male	15	60			33	66			
Disease interval (year)			5.1±3.5	1-13			6.9±4.5	1-24	0.08
Disease severity									
UPDRS			19.9±9.1	8-36			20.8±76	5-41	0.646
Hoehn and Yahr Scale			2.1±0.6	1-3			2.1±0.5	1-3	0.878
Treatment duration (month)			30.4±25.4	2-108			25.7±18.9	1-72	0.373
Treatment dose									0.139
High dose	14	56			19	38			
Low dose	11	44			31	62			
Concomitant disease									0.845
Hypertension	11				21				
Diabetes mellitus	2				5				
Coronary artery disease	6				8				

PD: Parkinson's disease; SD: Standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

Table 2. Edema risk in treatment groups

	Edema						
	–		+		Total		
	n	%	n	%	n	%	*p*
Levodopa (n=25)	15	60	10	40	25	100	
Dopamine agonist (n=50)	18	36	32	64	50	100	0.048
Total (n=75)	33	44	42	56	75	100	

Table 3. Edema risk related to treatment doses

	Low dose LD		High dose LD			Low dose DA		High dose DA		
Edema	n	%	n	%	*p*	n	%	n	%	*p*
–	11	78	4	36	0.032	9	47	9	29	0.132
+	3	22	7	64		10	53	22	71	

LD: Levodopa; DA: Dopamine agonist.

Table 4. Relationship between edema severity and treatment

	Levodopa		Dopamine agonist		Total		
Edema severity	n	%	n	%	n	%	*p*
Mild	10	100	17	53.1	27	64.3	0.026
Moderate	0	0	11	34.4	11	26.2	
Severe	0	0	4	12.5	4	9.5	
Total	10	100	32	100	42	100	

62% in the DA group were in the high-dose group, and there was no significant difference between the two groups in terms of dose classification (Table 1).

Edema

Ten patients (40%) in the levodopa group had PE compared with 32 patients (64%) in the DA group. Pedal edema was significantly more common in the DA group than in the levodopa group (p=0.048), as shown in Table 2.

There was no correlation between the dose of PE and DA. However, we found a positive correlation between the levodopa dose and PE (p=0.032), as demonstrated in Table 3.

We described the severity of edema as mild, moderate, or severe, depending on the physician's assessment. PE was more severe in the DA group (p=0.026) as shown in Table 4. No significant difference was found according to the type of DA (p=0.145).

Of the 50 patients taking DAs, 27 used DA with levodopa. The risk for PE was the same in the DA group as in the DA + levodopa group (p=0.449). No association was found between the risk for PE and sex, age, or concomitant disease (p=0.304, p=0.450, and p=0.086, respectively). Disease severity and disease interval also did not correlate with PE (p=0.840, and p=0.753, respectively).

DISCUSSION

The quality of life of PD patients may be affected by PE. This adverse complication may be related to PD itself or to the drugs used for treatment.[3-5,7-16] The use of DAs as initial treatment has increased, and it is believed that the

complication of PE is usually related to DAs.[3,5-8] To improve treatment adherence, risk factors for PE need to be identified in PD patients, and these factors should be considered when selecting medications.[3,8]

One of the main questions in this study was which of the drug groups was more likely to trigger PE. Previous studies have shown that patients taking DAs have a higher risk of developing PE than patients taking levodopa.[3,5,6,9,11] As expected, the risk for PE was significantly higher in the DA group in our study (p=0.048). Studies investigating the development of PE in PD patients found an incidence of 16-45%.[4-6,16] In our study, the incidence of PE was 40% in the levodopa group and 64% in the DA group, indicating a higher risk of PE in PD patients taking DAs. It is suggested that the difference between these and previous results is related to the different methods of determining PE in our study and in previous studies. Most studies used retrospective surveys, prospective open-ended questions, patient self-report, and examinations to determine PE, which explains why mild cases may have been missed.[4,5,15-17] However, we examined each patient at PE and recorded mild cases as well.

We found no association between PE and sex, age, disease interval, disease duration, and concomitant diseases. However, a previous study of pramipexole showed that older patients with longer disease duration were more likely to have PE. Coronary artery disease, diabetes mellitus, and peripheral arterial disease were also identified as independent risk factors for PE.[1] In another study, Biglan et al.[5] found that female sex and concurrent heart disease were associated with the development of PE. The reason for the lack of association between PE and concomitant diseases such as chronic heart disease may be that patients with heart failure or renal disease were excluded. The number of patients with concomitant diseases was small, which could also explain the lack of an association.

In our study, we found no relationship between the type and dose of DA and PE. A previous study comparing pramipexole, ropinirole, and cabergoline showed that PE occurred less frequently with ropinirole.[7] The role of the dose of DA in the development of PE is controversial. Some studies concluded that the dose of DA is a factor,[6,14,16] whereas others did not.[4,5] Kleiner-Fisman and Fisman[4] pointed out that PE occurs early in PD patients and that it is probably an idiosyncratic response rather than a dose-dependent response.[16] Our results also showed that PE was not related to the dose of DA, suggesting an idiosyncratic response. We compared ergot and non-ergot groups in relation to PE, but found no difference, suggesting that the relationship between PE and DA may be a group effect. Previously, PE was thought to be related to the use of ergot-type DAs,[11,13] but it was later shown that DAs without ergot can also cause PE as a complication.[4-6,9,10,16] Pedal edema was more severe in the DA group than in the levodopa group (p=0.026) (Table 4). In the levodopa group, PE was observed significantly more often in patients taking high-dose levodopa (p=0.032), (Table 3), but the severity of PE was milder in the levodopa group (p=0.026) (Table 4). Therefore, patients treated with levodopa should be evaluated at PE. Although the severity of PE was low in our cases, this issue may be important for patients who are prone to develop PE due to concomitant diseases or co-medication factors.

A limitation of our study was the small sample size. In addition, the control group consisted of patients treated with levodopa, and PE could also be observed with the levodopa regimen. In a future prospective study, the control group could be selected immediately after diagnosis from patients not yet taking medication. Pedal edema in PD treated with dopaminergic agents is thought to be a class effect since dopamine is an important regulator of the sympathetic nervous system, aldosterone secretion, and adenosine triphosphate-mediated sodium and potassium channels.[1,18] However, the details of this mechanism have yet to be investigated further.

In conclusion, PE is more common and severe in PD patients treated with DA than in patients treated with levodopa. Levodopa can also cause PE, but the severity is mild and dose-dependent. No relationship has been established between the type of DA and PE. Therefore, PE is believed to be a class effect in patients treated with dopaminergic agents. Clinicians should be cautious about this side effect and routinely check PE after starting dopaminergic treatment.

Pedal edema is more common and severe in PD patients treated with DA than in patients treated with levodopa. Levodopa can also cause PE, but the severity is mild and dose-dependent. No relationship has been established between the type of DA and PE. Therefore, PE is believed to be a class effect in patients treated with dopaminergic agents. Clinicians should be cautious about this side effect and routinely check PE after starting dopaminergic treatment.

Ethics Committee Approval: The study protocol was approved by the Marmara University Faculty of Medicine Ethics Committee (date: 28.03.2008, no: MAR-YC-2008-0060). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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