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Evaluation of pulmonary side effects in prolactinoma patients treated with cabergoline

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Abstract

Introduction: Cabergoline (CAB) is the most used dopamine agonist in the treatment of prolactinomas. Studies related to the treatment of Parkinson's disease have shown that dopamine agonists can lead to fibrotic syndromes affecting the heart and the lung. The aim of this study was to evaluate the possible pulmonary side effects of CAB in prolactinoma patients.

Material and methods: Chest X-ray imaging and pulmonary function parameters like forced vital capacity (FVC), total lung capacity (TLC), and diffusion capacity for carbon monoxide (DLCO) were evaluated in 73 prolactinoma patients. The cumulative dose of CAB and the total duration of CAB use were also calculated, and all data were reviewed retrospectively.

Results: The median cumulative CAB dose was 192 mg, and the median duration of CAB use was 64 months. Only 13 patients (17%) among this cohort had abnormal DLCO results that could be an indirect sign of pulmonary fibrosis. These abnormal DLCO results were found not to be associated with cumulative CAB dose in these 13 patients.

Conclusions: CAB appears to be safe in terms of pulmonary functions with a median cumulative dose of 192 mg in prolactinoma patients.
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Key words: *pleural fibrosis; pulmonary fibrosis; dopamine agonist; prolactinoma; cabergoline*

Introduction

Medical treatment with dopamine agonists (DAs) is the first choice in prolactinoma treatment [1]. The most commonly used DAs are the ergot derivatives: bromocriptine (BRC), cabergoline (CAB), and to a lesser degree pergolide. Along with known gastrointestinal and psychiatric side effects of DAs, these agents are powerful 5-hydroxytryptamine 2B (5-HT2B) receptor agonists, which have been implicated in fibrotic disorders such as retroperitoneal or pleuropulmonary fibrosis and valvular heart disease. The pathogenesis of pleuropulmonary fibrosis is not clear, but a potential mechanism is that the activation of the serotonergic receptor induces both proliferative and fibrotic signals in various mesothelial cell types [2, 3]. Agarwal et al. reported pulmonary fibrosis related to pergolide treatment in patients with Parkinson's disease (PD) or restless leg syndrome [4]. Also, there are case reports of interstitial lung disease and pleuropulmonary fibrosis with pergolide treatment [5–7]. CAB on the other hand is the most commonly used drug in the treatment of prolactinoma, with its long-lasting, highly selective dopamine agonist activity and good tolerability [8]. There are many publications about the cardiac side effects of CAB, which are mostly fibrotic changes in cardiac valvular structure, and there are also a few case reports about the pulmonary side effects of CAB use, which include pleuropulmonary fibrosis [3, 9–14]. Based on these publications about CAB and interstitial pneumonitis and alveolitis, in 2002 the Committee on Safety of Medicines advised caution about possible side effects of ergot dopamine agonists, (BRC, CAB, and pergolide) in PD and recommended screening of pulmonary functions in these patients [15]. This study aims to evaluate the pulmonary functions of prolactinoma patients who received CAB treatment for a long time.

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Material and methods

The study protocol was approved by the local Ethics Committee of Istanbul University, Istanbul Medical Faculty (19.02.2020/304), and the procedures used in this study adhere to the tenets of the Declaration of Helsinki. Seventy-three patients with the diagnosis of prolactinoma, who received CAB for at least one year were recruited from 4 medical centres in Istanbul (Istanbul Medical Faculty, Bakırkoy Dr. Sadi Konuk Research and Training Hospital, Acibadem University — Maslak Hospital, Haydarpasa Numune Research and Training Hospital). For screening, chest X-ray and pulmonary function tests were performed at the last visit of each patient. Data were reviewed retrospectively. Patients with a history of pulmonary disease before prolactinoma treatment and patients who were using drugs that may deteriorate pulmonary function were excluded from the study. The prolactin (PRL) level at the time of diagnosis and tumour size before initiation of treatment, last PRL level and last tumour size while receiving treatment, and smoking history were obtained from patient files. The cumulative CAB dose and the total duration of CAB use were calculated from the records. The weight (kg), height (cm), and body mass index (BMI) (kg/m^2) were also obtained from the files, which were measured during the pulmonary screening. Pulmonary function tests were performed by trained technicians and included the measurement of forced vital capacity (FVC), total lung capacity (TLC), and diffusion capacity monitoring for carbon monoxide (DLCO) in accordance with American Thoracic Society standards (ZAN74N device, Sidney, Australia) [16, 17]. The results of pulmonary function tests were expressed as a percentage of predicted values according to the sex, age, weight, and height of the individual. Abnormal values were accepted to be < 80% of the predicted value. All patients were evaluated by the same pulmonologist, and those with abnormal results were referred for additional tests such as high-resolution computed tomography (HR-CT) of the chest.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, United States). Numerical variables were presented as median and interquartile range (IQR). Categorical variables were presented as numbers and percentages. In the comparison of the 2 groups (normal *vs.* low DLCO), the Mann Whitney-U test was used for numerical variables and the chi-square test was used for categorical variables. Spearman's rho test was used in the cumulative CAB dose and DLCO value correlation analyses. $P < 0.05$ was considered significant.

Results

The study consisted of 34 male and 39 female patients with a median age of 41 years [interquartile range (IQR): 36–51]. None of the patients had symptoms of dyspnoea, cough, or any finding compatible with pulmonary disease in physical examination. The clinical characteristics and pulmonary function test results of the patients are shown in Table 1.

The median cumulative CAB dose was 192 mg (IQR: 77–310), and the median duration of CAB use was 64 months (IQR: 37–110). Median values of FVC, TLC, and DLCO were 103%, 103.5%, and 93%, respectively. None of the study patients had abnormal chest X-ray findings. Only 13 asymptomatic patients (13/73, 17%) had abnormal DLCO levels in the study. Among these 13 patients, 2 (#8 and #12) had significantly decreased DLCO levels, but their physical examination and chest HR-CT revealed no pathology (Tab. 2). The mean cumulative CAB doses of these 2 patients were 120 and 175 mg, respectively. The remaining 11 patients had DLCO values just below the lower limit of the normal range but had a normal physical examination and chest X-ray imaging findings. Abnormal DLCO results were not associated with cumulative CAB dose or duration

Table 1. *The baseline clinical characteristics and pulmonary function test results of study patients*

Number of patients; n	73
Gender	
Male; n (%)	34 (46.6)
Female; n (%)	39 (53.4)
Age [years]; median (IQR)	41 (36-51)
BMI [kg/m^2]; median (IQR)	27 (25-32)
Highest pre-treatment PRL level [ng/mL]; median (IQR)	213 (136-794)
Size of the tumour	
Microadenoma (< 10 mm); n (%)	33 (45)
Macroadenoma (≥ 10 mm); n (%)	40 (55)
Disease duration [years]; median (IQR)	7 (3-11)
Total cumulative dose of CAB [mg]; median (IQR)	192 (77-310)
Total duration of CAB use [months]; median (IQR)	64 (37-110)
Pulmonary Function	
FVC (Percentage of individual predicted value); median (IQR)	103 (96-115)
TLC (Percentage of individual predicted value); median (IQR)	103.5 (94-110)
DLCO (Percentage of individual predicted value); median (IQR)	93 (84-107)

IQR — interquartile range; BMI — body mass index; PRL — prolactin; CAB — cabergoline; FVC — forced vital capacity; TLC — total lung capacity; DLCO — diffusion capacity for carbon monoxide

Table 2. *Characteristics of patients with abnormal diffusion capacity for carbon monoxide (DLCO) levels*

Patient number	Sex	Age [years]	Hb [g/dL]	BMI [kg/m^2]	Cumulative CAB dose [mg]	Duration of CAB use [months]	Smoking	DLCO (%)	Chest X-ray	Thorax HRCT
1	F	29	12.3	22	44	22	–	73	N	–
2	F	41	12.6	23	912	228	+	73	N	–
3	M	53	14.5	40	252	56	+	76	N	–
4	M	45	12	40	336	168	–	74	N	–
5	F	36	11.2	20	284	70	–	77	N	–
6	F	22	13.1	23	864	108	–	73	N	–
7	F	31	11.7	31	200	48	–	73	N	–
8	F	30	13.1	26	120	48	–	58	N	N
9	F	41	11.7	23	144	73	–	73	N	–
10	M	28	15.2	30	67	63	–	74	N	–
11	M	41	14.1	25	180	64	–	77	N	–
12	F	35	13.2	25	175	114	–	64	N	N
13	F	24	11.8	22	83	35	–	79	N	–

F — female; M — male; Hb — haemoglobin; BMI — body mass index; CAB — cabergoline; DLCO — diffusion capacity for carbon monoxide; N — normal; HR-CT — high-resolution computed tomography

Table 3. *Comparison of patients with low diffusion capacity for carbon monoxide (DLCO) to patients with normal DLCO levels*

	Group with normal DLCO	Group with low DLCO	Total patient group
Age [years]; median (IQR)*	42 (38–53)	35 (29–41)	41 (36–51)
Gender; n (%)			
M	30 (50.0)	4 (30.8)	34 (46.6)
F	30 (50.0)	9 (69.2)	39 (53.4)
Smoking; n (%)			
Yes	18 (30.0)	2 (15.4)	20 (27.4)
No	42 (70.0)	11 (84.6)	53 (72.6)
BMI [kg/m^2]; median (IQR)	28 (26–32)	25 (23–30)	27 (25–32)
Disease duration [years]; median (IQR)	8 (3–11)	6 (5–15)	7 (3–11)
Total cumulative dose of CAB [mg]; median (IQR)	195 (73–321)	180 (120–284)	192 (77–310)
Total duration of CAB use [months]; median (IQR)	63.5 (36–110)	64 (48–108)	64 (37–110)
FVC; median (IQR)*	104 (97–116)	98 (85–104)	103 (96–115)
TLC; median (IQR)*	105 (96–111)	93 (86–105)	103.5 (94–110)
DLCO; median (IQR)*	96 (89–109)	73 (73–76)	93 (84–107)

BMI — body mass index; CAB — cabergoline; FVC — forced vital capacity; TLC — total lung capacity; DLCO — diffusion capacity for carbon monoxide; *$p < 0.05$

of CAB use in these patients ($p > 0.05$), as shown in Table 3. Correlation analyses also revealed no significant association between cumulative CAB dose and DLCO value ($p > 0.05$).

Discussion

CAB, one of the most commonly used DAs in the treatment of prolactinoma, is reported to be associated with pleuropulmonary fibrosis, with limited evidence in the literature [13, 14]. In this study, we evaluated the pulmonary functions of patients with prolactinoma receiving CAB with a median cumulative dose of 192 mg for a long duration (median; 64 months). In clinical practice, the diagnosis of pulmonary fibrosis is based primarily on pulmonary function tests, chest imaging, and histopathological studies. The use of pulmonary function tests including FVC, TLC, and DLCO is recommended by the Committee on Safety of Medicines in 2002 for diagnosis [15, 18]. The results of these tests are

expressed as a percentage of predicted values in consideration of the sex, age, weight, and height of the individual, and abnormal values are accepted to be < 80% of the predicted value. While low FVC and low TLC are supporting findings of pleural fibrosis, low DLCO level is one of the expected findings in the case of pulmonary fibrosis. In our study, only 13 out of 73 patients were found to have low DLCO levels, but none of them had symptoms of pulmonary disorder and abnormal chest X-ray imaging. The 2 patients (#8 and #12) with significantly low levels of DLCO (58% and 64%, respectively) were also evaluated with chest HR-CT, which showed no pathology. The mean cumulative dose of CAB use in these 2 patients (120 mg and 175 mg, respectively) was lower than the mean cumulative dose value of the total cohort. The remaining 11 patients with borderline abnormal DLCO results (range; 73-79%) but with normal chest X-rays and without symptoms were also evaluated for anaemia and smoking (Tab. 2). Because these patients had no symptoms and no findings of any other specific disease, no additional tests were performed. As a result, our study revealed no association between CAB use and pleuropulmonary fibrosis. In the study by Dhawan *et al.*, among 234 cases with the diagnosis of PD receiving CAB, 15 were identified with symptoms suggestive of cardiac, pulmonary, and retroperitoneal fibrosis. This symptomatic patient group was treated with a mean dose of 3.74 mg daily CAB for a mean duration of 3.3 years. Subsequent investigations in these 15 patients showed no definite association of fibrotic side effects with CAB except in 2 cases who had a cough but normal chest X-ray and normal DLCO. These 2 patients were considered to have alveolitis resulting from the resolution of cough after CAB was discontinued [19]. The dose of CAB used in our study was much lower (median cumulative dose 192 mg), but the median duration of CAB use was longer (5 years and 4 months) than the study of Dhawan *et al.* Unlike PD, the doses of DAs used in endocrine diseases (hyperprolactinaemia and acromegaly) are significantly lower. In patients with PD, the duration of treatment is limited, but the daily dose is relatively high. Kars *et al.* reported the mean cumulative dose of CAB to be far higher (2500–6600 mg) compared with hyperprolactinaemic patients. On the other hand, patients with hyperprolactinaemia are treated for a longer period of time with a lower dose of daily CAB [20]. Previous studies of patients treated with CAB for acromegaly or hyperprolactinaemia are scarce and did not show an increase in pleuropulmonary fibrosis with CAB, consistent with our study [21, 22]. In the study of Lafeber *et al.* 119 patients treated with CAB for prolactinoma (n = 95), acromegaly (n = 14), nonfunctional pituitary tumour with hyperprolactinaemia due to stalk compression (n = 6), and mixed growth hormone and PRL secreting pituitary tumour (n = 5) were evaluated for fibrotic adverse reactions other than valvular pathology [21]. In that study, the median total cumulative dose of CAB was found to be 277 mg and the median total duration of CAB use was 115 months. Only a 66-year-old male with the diagnosis of prolactinoma and symptoms of chest pain, dyspnoea, and cough showed possible early signs of pulmonary fibrosis with a decreased DLCO (75%) and suspicious findings in HR-CT. The cumulative dose of CAB of that patient (236 mg) did not differ from the median dose of the total population (277 mg). Therefore, the authors concluded that there is no seriously increased risk of clinically relevant pleuropulmonary fibrosis in patients with hyperprolactinaemia treated with CAB. Our study group consisted only of patients with prolactinoma (n = 73), and our results were similar to the aforementioned study. Recently, a prospective study from our country investigated the effect of CAB treatment for a year on pulmonary function tests in patients with prolactinoma (n = 32). They found no deterioration in pulmonary function tests with a cumulative dose of 31 ± 22 mg in this period [22]. In this study, the cumulative dose and duration of CAB treatment were much lower and shorter than in our study.

On the other hand, when we compared patients with normal and low DLCO levels in terms of cumulative CAB dose and total CAB usage time, there was no significant difference between these 2 groups (Tab. 3).

The retrospective character and the small sample size of the study are its main limitations.

Conclusion

CAB can be considered safe in terms of pleuropulmonary side effects in prolactinoma patients who are usually treated with relatively low doses of CAB.

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Conflict of interests
The authors declare that they have no conflict of interest.

Ethics committee approval
The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine.

Data availability
All the data is available.

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