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Treatment with low doses of cabergoline is not associated with increased prevalence of cardiac valve regurgitation in patients with hyperprolactinaemia

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None for all authors and authors have nothing to declare. There is no conflict of interest that would prejudice impartiality of reported data.

SUMMARY

Introduction and aim: Dopamine agonists have been reported to increase the risk of cardiac valve regurgitation in patients with Parkinson's disease. However, it is unknown whether these drugs might be harmful for patients with hyperprolactinaemia (HyperPRL). The aim of the study was to evaluate whether HyperPRL patients treated with dopamine agonists had a higher prevalence of cardiac valves regurgitation than that of general population. **Methods and patients:** One hundred consecutive patients (79 women, 21 men, mean age 41 ± 13 years) with HyperPRL during treatment with cabergoline were enrolled in an observational case–control study and compared with 100 matched normal subjects (controls). Valve regurgitation was assessed by echocardiography according to the American Society of Echocardiography recommendations. **Results:** Seven HyperPRL patients (7%) and six controls (6%) had moderate (grade 3) regurgitation in any valve ($p = 0.980$). All were asymptomatic and had no signs of cardiac disease. Mean duration of cabergoline treatment was 67 ± 39 months (range: 3–199 months). Mean cumulative dose of cabergoline was 279 ± 301 mg (range: 15–1327 mg). Moderate valve regurgitation was not associated with the duration of treatment ($p = 0.359$), with cumulative dose of cabergoline ($p = 0.173$), with age ($p = 0.281$), with previous treatment with bromocriptine ($p = 0.673$) or previous adenomectomy ($p = 0.497$) in patients with HyperPRL. **Discussion:** In conclusion, treatment with cabergoline was not associated with increased prevalence of cardiac valves regurgitation in patients with HyperPRL. Mean cumulative dose of cabergoline was lower in patients with HyperPRL than that reported to be deleterious for patients with Parkinson's disease: hence, longer follow-up is necessary, particularly in patients receiving weekly doses > 3 mg.

What's known

- Dopamine agonists have been linked to increased prevalence of cardiac valve disease in patients with Parkinsons' disease. The employed doses of cabergoline are usually much higher than those used in patients with hyperprolactinaemia.
- Dopamine agonists (particularly, cabergoline) are frequently used for treating hyperprolactinaemia.

What's new

In this observational study, we found that patients with hyperprolactinaemia treated with cabergoline have not an increased prevalence of cardiac valve disease.

Introduction

Dopamine agonists are widely used for treating patients with either Parkinson's disease or hyperprolactinaemia (HyperPRL) (1,2). Relatively new and long-acting dopamine agonists (cabergoline) are frequently employed for several years, and often for all the fertile period in patients with HyperPRL (1,3). Dopamine agonists interact with dopamine receptors thus reducing prolactin (PRL) secretion (4). Treatment is considered safe in the long term as well as during pregnancy (5,6). A relationship between treatment with cabergoline or pergolide and occurrence of cardiac valves regurgitation has been reported in patients with Parkinson's disease (7). In addition, abnormalities of cardiac valves have also been shown in patients treated with bromocriptine (8).

Recently, it has been reported that patients with Parkinson's disease had a fivefold increase prevalence of cardiac valve regurgitation, when treated with cabergoline or pergolide, than that of general population (9,10); in addition, a dose- and time-dependent relationship between these drugs and development of cardiac valve disease was shown (9,10), suggesting a causative effect of cabergoline and pergolide on cardiac valve regurgitation. The underlying mechanism might be the interaction of drugs with serotonin receptor subtype 5-HT_{2B} which is expressed in cardiac valves and might affect mitogenesis, as reported for fenfluramine (11).

However, it is unknown whether cabergoline might be harmful for patients with pituitary PRL-secreting adenoma when employed at low doses for treating HyperPRL.

The aim of this study was to evaluate the prevalence of cardiac valve regurgitation in a series of consecutive patients with HyperPRL treated with cabergoline and in a group of control subjects.

Patients and Methods

Study population

The study group consisted of 100 consecutive patients with HyperPRL during treatment with cabergoline (79 women, 21 men, mean age 41 ± 13 years) referred to the Department of Endocrinology of University of Pisa during the period January to December 2007. Sixty patients had pituitary microprolactinoma (adenoma diameter < 10 mm), 39 patients had pituitary macroprolactinoma (adenoma diameter ≥ 10 mm) and a patient had HyperPRL without evidence of pituitary lesions at magnetic resonance imaging (MRI).

Eight patients had arterial hypertension: two patients were treated with calcium-channel blockers, three with beta-blockers and three with angiotensin receptor antagonists. A patient had diabetes mellitus treated with appropriate dietary therapy. Seven patients had hypercholesterolaemia: two were under any therapy and five were treated with hydroxymethylglutaryl coenzyme A reductase inhibitors.

Diagnosis of HyperPRL was made according to clinical and laboratory features, including increased serum PRL concentrations (12,13). Macroprolactin was excluded in all cases by measuring serum PRL after polyethilenglycole precipitation (14).

Twenty-one patients (21%) were previously treated with bromocriptine and 17 patients (17%) had recurrence of PRL-secreting macroadenoma after transfenoidal adenomectomy (see Results). Normal subjects (controls) were recruited among the medical staff of our Departments: they were matched for sex, age and body mass index.

No patients or controls had a positive history for cardiovascular or cardiac valve disease (see Cardiac evaluation). Control of HyperPRL under cabergoline or bromocriptine was defined by normal serum PRL concentrations and regression of clinical signs of HyperPRL. Duration of cabergoline treatment was expressed in months and consisted in the time interval between the onset of drug treatment and echocardiography. Previous treatment with bromocriptine consisted in the period, expressed in months, between starting bromocriptine and its switch to cabergoline. Mean cumulative dose of cabergoline was 279 ± 301 mg (range: 15–1327 mg) and mean weekly dose was 1.1 ± 0.9 mg (range: 0.25–3.5 mg). All patients included in the study, which was approved by the Internal Review Board, gave their written informed consent.

Assay of pituitary function

Serum PRL was measured by commercial kit (Unicell; Beckman Coulter, Fullerton, CA). Normal range in our laboratory was 12–25 ng/ml. Pituitary function was evaluated by basal blood samples or dynamic tests, as appropriate, in all patients, as previously reported (15,16) (data not shown).

Cardiac evaluation

Two-D-Color Doppler echocardiography was performed as previously reported (17). Comprehensive transthoracic echocardiography was performed using commercial equipment (Philips–Envisor C; Eindhoven, The Netherlands). Two-dimensional and colour Doppler was performed in standard parasternal and apical views by a single operator (SB).

Qualitative and quantitative parameters for evaluating mitral, aortic or tricuspid valve regurgitation were recorded on optical disk for off-line analysis according to the American Society of Echocardiography recommendations (17). Valve regurgitation was defined and quantified as follows: zero, absent; one, trace; two, mild; three, moderate; four, severe. To evaluate the total regurgitant valve disease, a composite scoring system derived from the sum of mitral, aortic and tricuspid scores was used (range: 0–12, being zero the absence and 12 the most severe regurgitation). No patient had history of coronary artery disease, neither showed symptoms nor signs of cardiac heart failure or cardiac valve disease. Smoking habit, systolic and diastolic blood pressure, baseline serum glucose, total cholesterol, high-density lipoprotein cholesterol and triglycerides were evaluated in all patients at enrolment.

Statistical analysis

Data were expressed as mean ± SD for quantitative variables and as absolute frequency and percentage for qualitative variables. Relationship between two qualitative variables was analysed by the two-side Fisher's exact test. Comparison between groups for quantitative variables was performed by ANOVA; $p < 0.05$ was considered as significant.

Results

Clinical and biochemical findings of the study groups are shown in Table 1. Among patients and controls, women were predominant (79% and 84% respec-

Table 1 Clinical and biochemical features of study groups

	HyperPRL (n = 100)	Controls (n = 100)	p-value
Age (years)	41 ± 13	38 ± 7	0.701
Sex (M/F)	21/79	16/84	0.531
BMI (kg/m^2)	26 ± 5	26 ± 7	0.803
PRL (ng/ml) at diagnosis	1307 ± 2169	N/A	
PRL (ng/ml) at enrolment	17 ± 9	15 ± 5.1	0.249
Diabetes (yes/no)	1/99	0/100	0.970
SBP (mmHg)	121 ± 7	116 ± 19	0.518
DBP (mmHg)	75 ± 11	77 ± 9	0.671
Hypertension (yes/no)	8/92	7/93	0.782
Cholesterol (mg/dl)	216 ± 17	227 ± 31	0.471
HDL (mg/dl)	79 ± 11	71 ± 17	0.490
LDL (mg/dl)	124 ± 17	121 ± 31	0.710
Triglycerides (mg/dl)	100 ± 51	94 ± 47	0.611
Hypercholesterolaemia (yes/no)	7/93	8/92	0.707
Cigarette smoking (yes/no)	15/85	18/82	0.391

Data were expressed as mean ± SD. HyperPRL, patients with hyperprolactinaemia; controls, normal subjects. Normal values in our laboratory were as follows: PRL: 12–25 ng/ml. Hypertension was defined when ≥ 140/90 (or on antihypertensive drugs); diabetes and hypercholesterolemia were defined according to the National Cholesterol Education Program Adult Treatment Panel III guidelines (28). SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

tively), and mean age was 41 ± 13 years and 39 ± 7 years respectively.

Sixty patients had pituitary microadenomas (60%), 39 pituitary macroadenomas (39%) and one (1%) had HyperPRL without evidence of pituitary lesions at MRI. Among patients with PRL-secreting macroadenoma, one had multiple endocrine neoplasia type 1 (HyperPRL associated with primary hyperparathyroidism) (Table 2). A patient had diabetes mellitus, eight had arterial hypertension and seven had hypercholesterolaemia. Patients with HyperPRL and controls did not differ as prevalence of arterial hypertension, diabetes, hypercholesterolaemia and smoking habit (Table 1).

Table 2 Clinical and biochemical features of patients with hyperprolactinaemia

	n	Percentage
MacroPRLoma	39	39
MicroPRLoma	60	60
Functional HyperPRL	1	1
MEN-1*	1	1
Previous bromocriptine treatment	21	21
Previous adenomectomy	17	17
Cumulative CAB dose (mg)	279 ± 301	N/A
Duration of CAB therapy (months)	67 ± 39	N/A

*One patient with macroPRLoma had MEN-1 (primary hyperparathyroidism and PRLoma).
MacroPRLoma, prolactin (PRL)-secreting macroadenoma; microPRLoma, PRL-secreting microadenoma; MEN-1, multiple endocrine neoplasia 1; CAB, cabergoline.

Overall, patients with HyperPRL were treated with a mean cumulative dose of 279 ± 301 mg (range: 15–1327 mg) cabergoline for a mean of 67 ± 39 months (range: 3–199 months). Among them, 21 received a previous treatment with bromocriptine (mean dose, 13670 ± 17105 mg) for a mean of 61 ± 43 months (range: 6–169 months). Four patients received a weekly dose of 3.5 mg cabergoline for a mean of 73 ± 11 months.

Prevalence of regurgitation grade for each valve and the total regurgitation score are shown in Table 3. Echoardiographic grading at each valve was not different in HyperPRL patients and controls (Table 3). It is worth noting that neither patients nor control subjects had clinical symptoms (dyspnoea, oedema, syncope, arrhythmia or chest pain) referred to cardiac disease; in addition, none had severe regurgitation in any cardiac valve (grade 4). Mean total score was 1.52 ± 1.23 and 1.58 ± 1.61 in HyperPRL patients and controls respectively (p = 0.52). Seven HyperPRL patients (7%) and six controls (6%) had moderate (grade 3) asymptomatic regurgitation (p = 0.980). HyperPRL patients with moderate regurgitation in any valve (score 3)

Table 3 Echocardiographic findings in the study groups

		HyperPRL	Controls	p-value
VC, aorta (cm)		0.101 ± 0.15	0.095 ± 0.091	0.213
EROA, aorta (cm^2)		0.039 ± 0.041	0.037 ± 0.036	0.476
Jet width, aorta (%)		7.01 ± 7.25	6.57 ± 6.10	0.563
VC, mitral (cm)		0.111 ± 0.137	0.100 ± 0.123	0.707
EROA, mitral (cm^2)		0.079 ± 0.081	0.067 ± 0.074	0.546
VC width, tricuspid		0.059 ± 0.097	0.061 ± 0.101	0.911
Countor CW, tricuspid(dense/soft parabolic)		4/100	5/100	0.871
Grading of aortic regurgitation no of patients (%)	0	66 (66)	68 (68)	0.371
	1	15 (15)	17 (17)	
	28	18 (18)	15 (15)	
	3	1 (1)	0 (0)	
	4	0 (0)	0 (0)	
Grading of mitral regurgitation no of patients (%)	0	66 (66)	62 (62)	0.285
	1	10 (10)	15 (15)	
	2	19 (19)	17 (17)	
	3	5 (5)	6 (6)	
	4	0 (0)	0 (0)	
Grading of tricuspid regurgitation no of patients (%)	0	70 (70)	75 (75)	0.891
	1	20 (20)	17 (17)	
	2	9 (9)	8 (8)	
	3	1 (1)	0 (0)	
	4	0 (0)	0 (0)	
Total score no of patients (%)	0	37 (37)	39 (39)	0.407
	1	15 (15)	13 (13)	
	2	21 (21)	19 (19)	
	3	17 (17)	17 (17)	
	4	7 (7)	6 (6)	
	5	2 (2)	4 (4)	
	6	1 (1)	2 (2)	

Grading of regurgitation was: zero absent; one trace; two mild; three moderate; four severe (17). To evaluate the total regurgitant valve disease, a composite scoring system derived from the sum of mitral, aortic and tricuspid scores was used (range: 0–12, being zero the absence and 12 the most severe regurgitation). It is worth noting that no patients or controls had a total score > 6. VC, vena contracta; EROA, effective regurgitant orifice area; CW, continuous wave; HyperPRL, patients with hyperprolactinaemia.

received lower mean cumulative dose of cabergoline (117 ± 71 mg) for shorter period (42 ± 27 months), than those with lower grading of regurgitation (scores: 0–2), although not reaching a statistical significance (261 ± 293 mg, $p = 0.131$ and 58 ± 40 months, $p = 0.379$). Moderate valve regurgitation was not associated with the duration of treatment ($p = 0.359$), the cumulative dose of cabergoline ($p = 0.173$) or age ($p = 0.281$).

Patients previously treated with bromocriptine had mean aortic score (1.10 ± 0.79), mitralic score (0.858 ± 0.91), tricuspidal score (0.170 ± 0.477) and total score (2.01 ± 1.87) not different from that of HyperPRL patients who did not received a previous treatment with bromocriptine (aortic 0.873 ± 0.98, $p = 0.571$; mitralic 0.907 ± 0.96, $p = 0.890$, tricuspid 0.297 ± 0.601, $p = 0.483$; total 2.193 ± 1.63, $p = 0.875$ respectively).

Seventeen patients (17%) with macroadenoma had recurrence of PRL-secreting adenomas after neurosurgery (the latter performed before enrolment). These patients were older (49 ± 13 years) and received a slight higher cumulative dose of cabergoline (439 ± 410 mg) than those not submitted to adenomectomy (age, 34 ± 11 years, $p < 0.05$; cumulative dose of cabergoline, 209 ± 175 mg, $p < 0.05$ respectively); however, mean score for aortic, mitral or tricuspidal valve and total score did not differ from that of patients not submitted to adenomectomy [aortic: (0.69 ± 0.71 and 1.01 ± 0.99 respectively, $p = 0.671$); mitral: (0.97 ± 1.21 and 1.13 ± 1.14 respectively, $p = 0.790$); tricuspid: (0.44 ± 0.71 and 0 ± 0 respectively, $p = 0.123$); total: (2.07 ± 1.41 and 1.99 ± 1.67 respectively, $p = 0.776$) as well distribution of grading (aortic: $p = 0.215$, mitral: $p = 0.747$, tricuspid: $p = 0.361$ and total: $p = 0.135$).

Discussion

Dopamine agonists are widely used for treating either HyperPRL or neurological disorders, including Parkinson's disease (1,2,6,13,18). To evaluate cardiac valve effects of cabergoline in patients with HyperPRL and Parkinson's, disease, at least three main findings should be considered: patients age, doses and duration of drug treatment. The typical patient with HyperPRL is a young woman in her fertile period; control of PRL secretion is usually obtained, on average, with 0.5–1 mg cabergoline weekly (13), and treatment is often protracted for decades or until menopause (13,19). The features of our patients well fit those mentioned above, being mean age < 40 years and mean weekly cabergoline dose 1.1 mg, which was taken for up to 16 years. This is at variance with patients with Parkinson's disease who are usually older (60–70 years old) and mostly men (9,10); in addition, mean weekly dose is usually much higher (up to 25 mg), although treatment could be protracted for several years, as reported in recent papers (9,10). In fact, in the paper by Zanettini et al. (9) and by Schade et al. (10), the risk of developing cardiac valve regurgitation was found in patients who received 3 mg or greater cabergoline daily for at least 6 months, suggesting that the high daily dose of the drug might be the more harmful risk factor. The results reported by Zanettini et al. (9) and by Schade et al. (10) were in keeping with many previous case reports, which suggested a relationship between ergot-derivate treatment and cardiac valve disease (7,20–24).

In addition, studies on patients with neurological diseases reported a relationship between severity of valve regurgitation and dose of dopamine agonists (9); in our series, the mean cumulative (and weekly) dose of cabergoline received by HyperPRL patients with moderate valve regurgitation did not differ from that received by patients with absent to mild valve regurgitation; moreover, patients with grade 3 and those with lower grades received cabergoline for similar period, thus, ruling out that lack of association with mean drug doses was due to a different treatment duration. It is worth noting that all patients, including those with grade 3 score had no symptoms of cardiac valve disease at variance with patients described in two recent studies (9,10). Likewise, another study reported a low incidence of restrictive valvulopathy in patients with Parkinson's disease treated with lower pergolide doses (25). Our results show that patients with HyperPRL have a prevalence of asymptomatic moderate valve regurgitation superimposable to that of matched controls, a percentage similar to that found in population-based studies (26,27). Four patients received a weekly dose of cabergoline > 3 mg for more than 6 years; although their cardiac valve score was not different from that of the remaining subjects, they likely require an echocardiographic follow-up.

Seventeen per cent of our patients were submitted to pituitary adenomectomy before enrolment in the present study and received a significantly higher cumulative dose of cabergoline than the remaining HyperPRL subjects. However, this subset of patients had prevalence of valve regurgitation (expressed either as mean total regurgitation score or number of subjects with moderate vs. absent-to-mild regurgitation in any valve) not different from those who received lower cabergoline doses.

In conclusion, our data suggest that treatment with low cabergoline doses, even in the long term, is not associated with significant increased prevalence of cardiac valve regurgitation in HyperPRL patients. However, results of the present study need to be confirmed in larger and longitudinal studies.

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