ORIGINAL ARTICLE

Optimal effective doses of cabergoline and bromocriptine and valvular leasions in men with prolactinomas

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Abstract

OBJECTIVES: Prolactinoma is the most common pituitary adenoma, and dopamine agonists(BRC, and CAB) is the primary therapy. Recently, the increased prevalance of cardiac valvular disease in patients treated with DAs for Parkinson's disease has raised concerns about the safety of this drug in patients with prolactinoma. CAB and pergolide are frequently reported to cause valvulopathy, there are very few studies showing this side effect in BRC administiration which has less potent agonism of 5-HT2B receptors. Male patients who are known to have higher prevalance of macroadenomas compared to women. The dosage of DAs administered were rarely evaluated.

METHODS: We performed a retrospective chart to evaluate the medical management and treatment outcomes of male patients with macro/giant prolactinomas. We evaluated 22 patients with prolactinoma managed with DAs therapy alone for at least 1 year. All patients were followed for a mean of 61 months. Pretreatment echocardiographic examination were not available at that time. Results:None of them had any resistance or intolerance to DAs. The mean tumor shrinkage was 62%. In three patients the macroprolactinoma disappeared, in two patients the tumor shrinkage was 93% and 70%. The DAs therapy was discontinued in these patient. After a follow up neither MRI showed a recurrence or enlargement of the adenoma, nor prolactin levels showed any elevation. The echocardiography were performed at the last visit of each patient and no valvulopathy in any of the patients on DAs therapy were detected.

CONCLUSIONS: DAs are effective, and safe for valve morphology with mean cumulative doses of 155 mg CAB, and 7 301 mg BRC in patients with macroprolactinoma

Abbreviations:

DAs	- Dopamine agonists
BRC	- Bromocriptine
CAB	- Cabergoline
MRI	- Magnetic resonance imaging
fT4	- Free thyroxine
PD	- Parkinson's disease
5-HT	- 5-hydroxytryptamine receptors
TSH	- Thyroid-stimulating hormone
LH	- Luteinizing hormone
FSH	- Follicle-stimulating hormone
PRL	- Prolactine
TR	- Tricuspide regurgitation

INTRODUCTION

Prolactinomas are the most common type of pituitary adenomas in adults, and microadenomas are common in women, whereas macro and giant adenomas are more common in men (Vance *et al.* 1987; Delgrange *et al.* 1997). In literature, the long-term therapeutic responses of DAs therapy in men with macroprolactinomas have been partially studied compared to women (Grisoli *et al.* 1980; Hulting *et al.* 1985; Berezin *et al.* 1995; Pinzone *et al.* 2000; Shrivastava *et al.* 2002; Nishioka *et al.* 2003). Dopamine agonists (BRC and CAB) are used as the first line treatment for prolactinomas. However, recently, there have been numerous studies on CAB associated valvulopathy in Parkinson's disease, whereas the risk of valvular heart disease in these patients on BRC has not been properly evaluated except a previous case report of valvular heart disease related to bromocriptine use, and two prospective studies that included a subgroup of Parkinson's disease patients on bromocriptine (Serratrice *et al.* 2002; Kim *et al.* 2006; Tan *et al.* 2009). The latest data indicate that valvulopathic effect of CAB depends on a cumulative dose in patients with prolactinomas (Shade *et al.* 2007; Zanettini *et al.* 2007). Bromocriptine is the first oral DA, and understanding the risk of developing valvular heart disease in patients on BRC is important as this drug is widely used in developing countries as first-line treatment for prolactinoma. But, it is uncertain that BRC, an ergot-derived dopamine agonist with partial 5-HT2B activity, is associated with a similar risk. Besides whether lower doses of CAB or BRC are also associated with significant valvulopathy is unknown and present a dilemma fort the endocrinologists about the management of these patients. Clinical studies and results will be important in this area. The aim of this retrospective study is to evaluate the medical management and long term treatment outcomes and to observe the risk of valvular heart disease among male patients with macro and giant prolactinomas treated on BRC and CAB.

METHODS

We retrospectively reviewed our experience in male patients (ages range 20–67 year; mean 45 yr) with macro (n:18) and giant (n:4) prolactinomas treated with only DAs (BRC, and CAB) for at least 1 year. According to the medical history, the patients in this study had no prior heart disease or other predisposing conditions for valvular heart disease. BRC administration was the primary therapy for prolactinomas before CAB was approved in our country. On admission, clinical and hormonal evaluations (fT4, TSH, LH, FSH, testosteron, basal cortisol and PRL levels) and tumor size on MRI were measured before initiation of medical therapy and sequentially thereafter. Secondary hypothyroidism was defined as a fT4 level <10.0 mmol/l and a basal TSH level <0.3 μU/ml in the absence of thyroid replacement therapy. Secondary hypogonadism was defined as a testosteron level <3 ng/ml and subnormal levels of gonadotrophins, and hypocortisolism was defined as low serum basal cortisol level (<3 μg/dl). After the initiation of DAs therapy all patients had at least two follow-up visits and serum prolactin measurements during the first year. MR images were obtained before therapy, and sequentially at least 16 weeks after initiation of DAs therapy and yearly thereafter. After the diagnosis, the patients were prescribed BRC (n=8) at a dose range of 2.5–5.0 mg/nightly (mean; 4.5±1.05 mg), and CAB (n=14) at a dose range of 0.5–1.0 mg/weekly (mean; 0.80±0.25 mg) and the doses were increased gradually as tolerated, and to achive a PRL level as normal as possible [maximum dose 12.5 mg/daily, and 4 mg/weekly, respectively]. The mean maintaining dose (range) of BRC and CAB were 3.75±0.66 mg daily (2.5–7.5) and 0.96±0.14 mg weekly (0.5–2.0), respectively (Table 2).

All patients were followed for a mean of 61 months (range, 12–128). The most recent hormonal values and MRI scan were reported for clinical endpoint in an individual patient. Although there were no pretreatment echocardiographies of the patients, transthorasic echocardiography was performed to patients at the clinical endpoint. Echocardiograms were recorded in supine position turned 30° on the left side, using commercially echocardiography machine (Vivid 7, GE Systems, Oslo, Norway) with a 2.5 MHz transducer. Two-dimensional guided M-Mode echocardiograms were obtained just below the mitral valve leaflets at the chordal level. All echocardiograms were recorded and stored in a hard disk and were analyzed later. Septal and posterior wall thickness and left ventricle chamber dimensions were measured according to the American Society of Echocardiography (ASE) guidelines. Ejection fraction (EF%) was derived from diastolic and systolic left ventricle volumes calculated with Teicholz's formula Endocardial fractional shortening ($_e$FS%) was calculated as:

$$'_eFS\% = 100 \times (LVID_d - LVID_s) / LVID_d'$$

where LVID was left ventricular internal dimension; $_d$ was end-diastole; $_s$ was end-systole. Valve regurgitation obtained and quantified as follows; 0: absent, 1: trace, 2: mild, 3: moderate, 4: severe (Lang RM *et al.* 2005). We analyzed the sum of mitral, aortic and tricuspid scores (value range of the composite scores from 0 to 12, higher scores indicate more severe disease). Leaflet thickening was identified to be present when the thickness was more than 5 mm. We also measured the mitral valve tenting area which is a quantitative index for leaflet stiffening and abnormal valve coaptation. The mitral tenting area was determined from the parasternal long-axis view and was analyzed as the area enclosed between the annular plane and the mitral leaflets at end systole. Stiffening of the leaflets cause an increse in this area and result abnormal coaptation and regurgitation.

RESULTS

Clinical and hormonal characteristics of the patients on admission are summarized on Table 1.

The most recent hormonal values, tumor size, cumulative dose of DAs, and echocardiographic examination were reported for clinical endpoint for every patient (Table 2).

After the initiation of DAs, serum PRL levels returned to normal in all patients (100%). The patients noted marked improvement in sexual function within 2–3 months of therapy, and one had a child. Complete resolution of visual field defects were observed in all. No side effect of DAs was observed (such as resistance or intolerance) in the patients. During the follow-up period, three patients (14 %; no:15,19,20) with secondary hypothyroidism, three patients (14%; no: 7,19,20) with secondary hypocortisolism, and seven patients (32%, no: 4,7,15,16,17,19,20) with secondary hypogonadism needed replacement therapy (Table 1). None of the patients had any serious clinical symptomatology causing referral to the department of the neurosurgery after the initiation of DAs. Based on serial radiological reports, in most patients tumor shrinkage was in progress with time (Figures 1–3). The mean tumor shrinkage was 62% (range; 20–100%).

Tab. 1. Initial clinical and hormonal characteristics of the patients.

Impotence [no. (%)]	16 (73)
Diminished libido [no. (%)]	15 (68)
Headache [no. (%)]	13 (59)
Visual field defect [no. (%)]	13 (59)
PRL [ng/mL; median (range)]	1228 (250–10382)
The mean maximal tumor diameter (mm; range)	29 (14–55)
Testosteron deficiency [<3 ng/ml; (%)]	7 (32%)
Secondary hypothyroidism (n, %)	3 (14%)
Secondary hypocortisolism (n, %)	3 (14%)

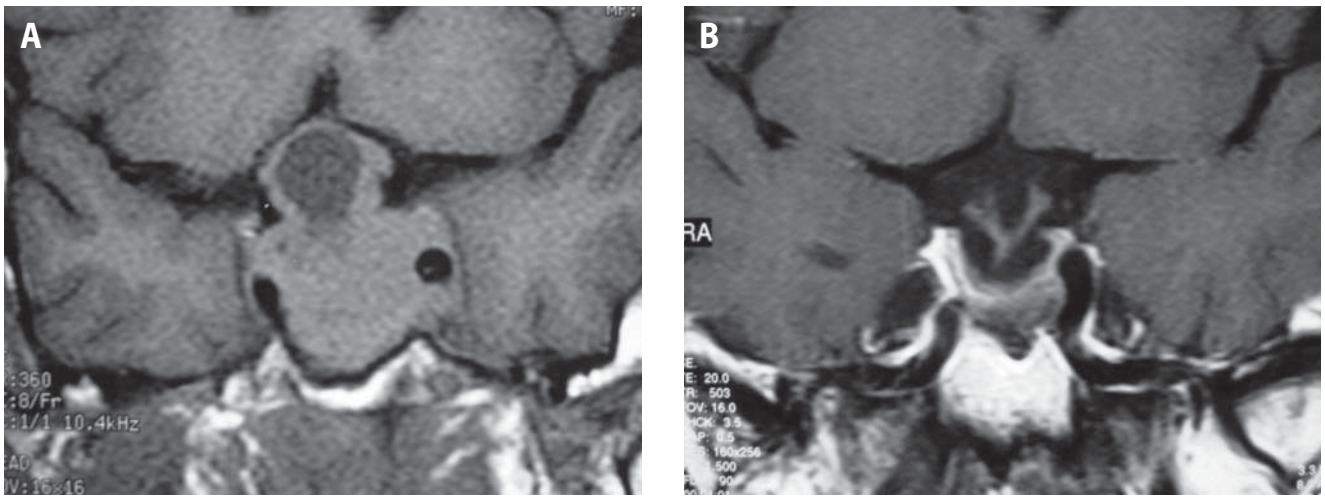

Fig. 1. Case 2. **A**: at 3 months of DAs cystic degeneration; **B**: at 42 months of DAs significant reduction.

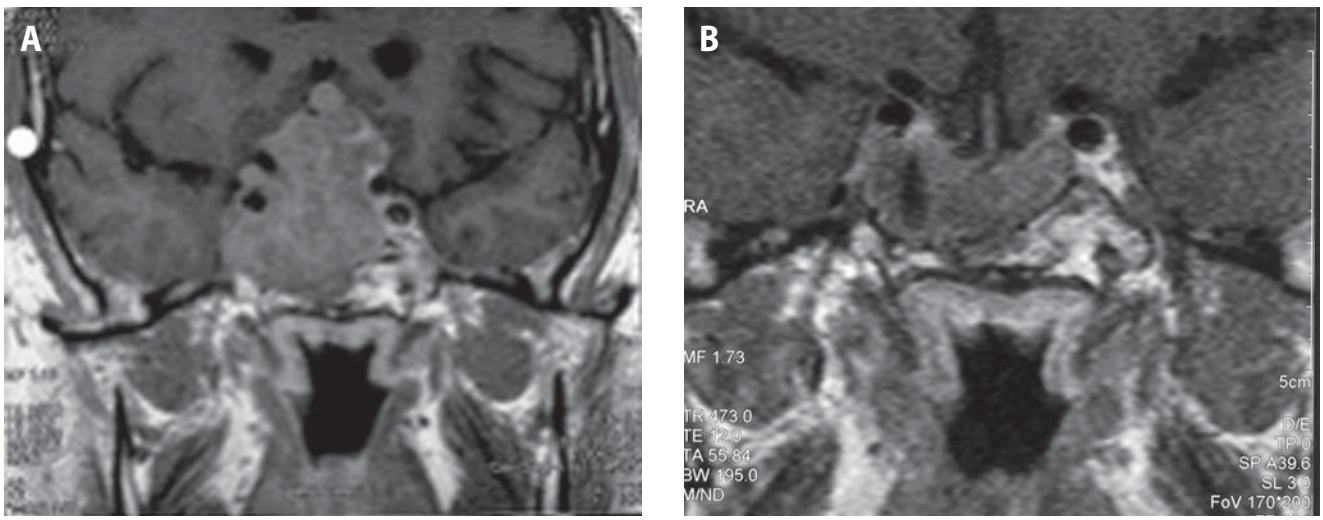

Fig. 2. Case 16. **A**: Before DAs; **B**: at 38 months significant shrinkage.

Tab. 2. The basal PRL, tumor size, DAs dose, most recent MRI, and cumulative dose of DAs.

no	age	Basal PRL level (n:1.0–20.8 ng/ml)	tumor size (mm) (basal CT or MRI)	BRC dose (mg/day) max maintain	CAB dose (mg/w) max maintain	tumor shrinkage at most recent CT/MRI (%)	Follow-up period/duration of stopping DAs (months)	Cumulative dose (at the clinical endpoint) BRC CAB
1	53	1613	28		0.5 0.5	50	57	127.0
2	38	10382	42		1.5 0.5	95	70	204.5
3	41	2279	40		1.5 0.5	90	62	351.0
4	52	482	22		1.0 0.5	86	43	88.8
5	60	1150	30	10.0 5.0*		93	112/57	17917.5
6	48	250	14	7.5 2.5		71	128	10733.5
7	48	1198	25	12.5 7.5		48	55	863.8
8	35	850	25	5.0 2.5		88	34	3300.0
9	56	250	26	7.5 2.5		100	111	15538.8
10	47	250	20	7.5 2.5*		70	105/55	2887.5
11	27	370	30	7.5 2.5*		100	99/58	572.5
12	26	4800	43	12.5 5.0		30	111	6595.0
13	67	1334	30		1.0 0.5	33	31	59.0
14	54	1258	20		1.0 0.5	40	21	77.0
15	37	1817	30		1.0 1.0	100	24	105.0
16	50	4700	30		1.0 1.0	75	46	240.0
17	41	264	15		3.0 1.5	20	67	114.0
18	42	707	15		1.0 1.0	75	55	220.0
19	20	1746	55		4.0 2.0	54	43	298.0
20	47	1815	34		1.0 1.0	65	31	120.0
21	43	7629	38		2.5 2.0	50	12	113.0
22	49	427	29		1.0 1.0	31	15	50.0

(*) stop medication

The first echocardiographic evaluation which was performed at the latest control showed no valvulopathy under DAs in any of the patients.

During the follow-up period (Table 2), in three patients macroprolactinomas disappeared (no: 9,11 and 15), in two patients (no: 5 and 10) the tumor showed a shrinkage of 97 % and 70 %, respectively. After the DAs therapy was discontinued in one patient with total disappearance of the adenoma (no: 11) and in the other two patients (no: 5 and 10) with significant shrinkage of the tumor, a follow up for a mean of 57 months revealed neither a recurrence or enlargement of the adenoma on MRI scan, nor elevation of serum prolactin levels. On the other hand, after the cessation of therapy in the other two patients showing a total disappearance of the adenoma (no: 9 and 15) hyperprolactinemia and gonadal dysfunction redeveloped and the former DAs therapy was initiated again.

The first echocardiographic evaluation which was performed at the latest control showed no valvulopathy in patients on DAs therapy with mean cumulative doses of 155 mg CAB (range 50–351 mg), and 7301 mg BRC (range 572.5–17917.5 mg).

DISCUSSION

Prolactinomas in male patients are known to be more invasive and charactarised with rapid growth (Delgrange *et al.* 1997). DAs therapy is the first line treatment with tolerability and efficiency, and typical responses of a macroprolactinoma include a rapid fall in serum PRL levels (within hours), tumor shrinkage (within days/weeks), visual improvement (often within hours/days) and recovery of pituitary functions. Most patients would be expected to respond satisfactorily to lower doses of DAs within 3 months of treatment (Colao *et al.* 2002; Chattopadhyay *et al.* 2005). Although BRC is the first oral DA, and is being widely used in developing countries as first-line treatment for prolactinoma, because of the patient compliance CAB is increasingly becoming the first-line agent for treatment of prolactinoma. Mean prolactine levels decreased by 93.6%, and normal levels were attained in 73% of patients at doses of 0.5–3.0 mg per week and most tumors were shown to shrink by at least 50% with CAB therapy (Biller *et al.* 1996). In three prospective studies, effectiveness of CAB treatment in series of male patients with giant prolactinomas has been reported with doses of 3.4, 3.3, and 1.6 mg CAB weekly (Minniti *et al.* 2002**;** Corsello *et al.* 2003; Shimon *et al.* 2007). In two retrospective studies, CAB and BRC therapy resulted with 95% and 99.8% reduction in PRL levels in men with giant prolactinomas, respectively (Shrivastava *et al.* 2007; Cho *et al.* 2009). On the other hand, the normalization of PRL in male patients with macroprolactinoma were 75%,75.6%, and 79 % after CAB therapy (Pinzone *et al.* 2000; Verhelst *et al.* 1999; Colao *et al.* 2004). In our study, the median dose of 1.0 mg CAB weekly are provided with a 67% tumor shrink-

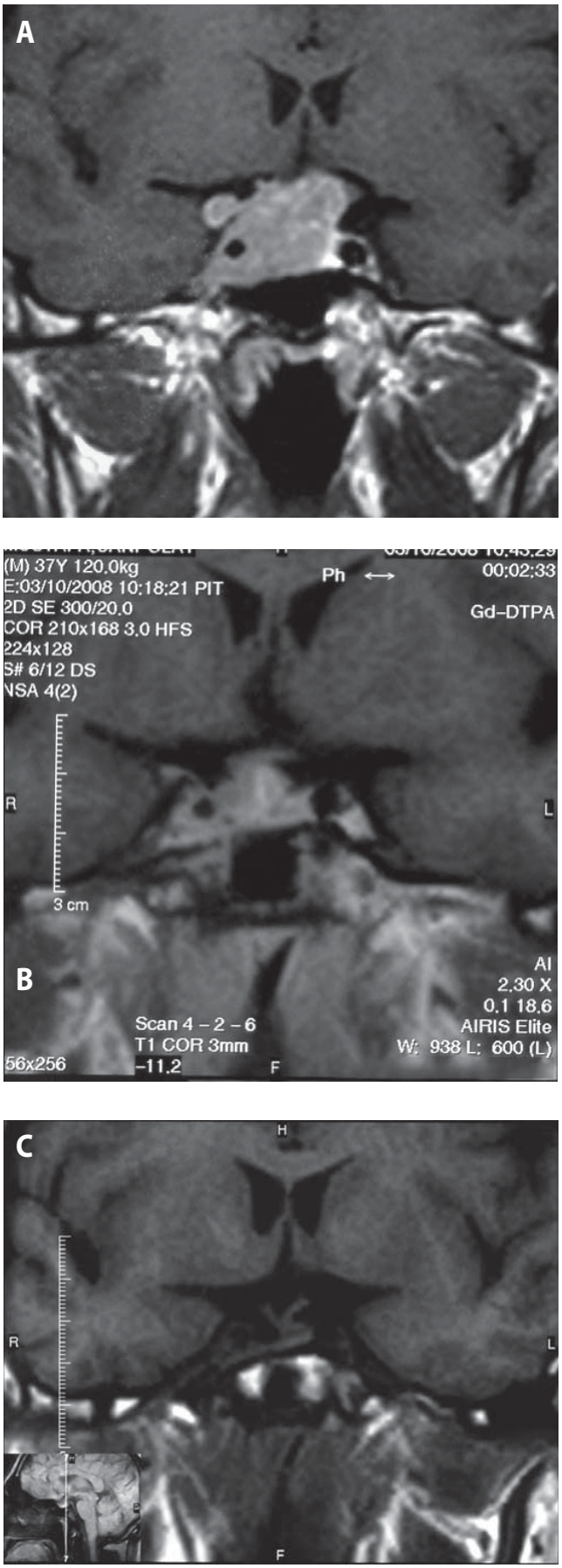

Fig. 3. Case 15. **A:** Before DAs; **B:** at 17 months of DAs; **C:** at 24 months of DAs (tumor disappeared).

age, and we found 100% normalization of PRL levels in male patients with macro and giant prolactinomas with BRC and CAB.

Treatment with DAs can be withdrawn in some patients, without following recurrence of hyperprolactinemia. The probability of treatment success is highest when CAB has been used for at least 2 yrs. However recurrences are most likely to occur in the year after withdrawal (Kharlip *et al.* 2009; Dekkers *et al.* 2010). In this study, only 3 patients were off therapy for a mean of 57 months, PRL levels remained normal, and no tumor regrowth was observed after the cessation of BRC therapy. But hyperprolactinemia and gonadal dysfunction redeveloped after the withdrawal of CAB in two patients who had no tumor on the latest MRI scan, and CAB therapy initiated again.

CAB is still being used for the treatment of hyperprolactinemia. In spite of the effectiveness of CAB, the increased prevalance of cardiac valvular disease in patients treated with CAB for Parkinson's disease has raised concerns about the safety of this drug in the patients with prolactinoma (Shade *et al.* 2007; Zanettini *et al.* 2007). But in these studies, CAB dose is much higher (average dose of 3.6 mg/day) than that used in our endocrine practice. In a study, patients taking CAB for 12–228 months, in doses between 0.25 and 4.5 mg/week did not show a significant increase of clinically relevant cardiac valve disorders (Lancellotti *et al.* 2008). In our study, only one of the patients on CAB therapy for 12–70 months had a maximum dosage of 4 mg/week and the weekly range was between 0.5–4.0 mg. Moreover, the other six studies in the literature did not find an association between clinically relevant valve regurgitation with the long-term administration of the commonly used lower doses (0.25–3 mg/week) and cumulative doses (range; 146–443 mg) of CAB for prolactinoma treatment (Lancellotti *et al.* 2008; Devin *et al.* 2008; Nachtigall *et al.* 2010; Bogazzi *et al.* 2008; Vallette *et al.* 2009; Herring *et al.*). The cumulative dose range was 50–351 mg in our study which can be accepted as a safe dosage for valvulopathy.

On the other hand, moderate TR was more prevalent in patients with respect to controls, and moderate TR was significantly more prevalent in patients receiving a cumulative dose of CAB above the mean (414 mg) than in those receiving a lower dose as reported by Colao (Colao *et al.* 2008). However other two studies showed an increase in the prevalence of CAB-induced valvulopathy, but it is not associated with cumulative doses (311 and 363 mg) (Wakil *et al.* 2008; Kars *et al.* 2008). In general, only two study suggested a relationship of valvulopathy with the mean cumulative dose of cabergoline (Colao *et al.* 2008; Valassi *et al.* 2010). The risk of developing clinically evident valvular heart disease for patients with prolactinoma who are treated with DAs seems to be low.

To the best of our knowledge, the risk of valvular heart disease in patients on BRC (less potent agonism of 5-HT2B receptors) has been evaluated in only a previous case report and two prospectives studies (Serratrice *et al.* 2002; Kim *et al.* 2006; Tan *et al.* 2009). The findings in these studies suggest that BRC is not as safe as previously thought (Antonini *et al.* 2007; Roth *et al.* 2007). In a prospective study of Tan *et al.* in patients with parkinsonism treated with modest BRC dose for 64 months (mean daily dose 19 mg), when the correlation of valvulopathy with the cumulative BRC dose was investigated, both mild and moderate-severe valvular regurgitations were excesively diagnosed on very high cumulative doses (median cumulative dose 20054 mg). This was the first study to suggest that the use of BRC in PD patients was associated with valvular heart disease (Tan *et al.* 2009). In our study, daily mean dosage of 3.75 mg (range: 2.5–7.5 mg) of BRC with a cumulative dosage of 7301 mg were effective in patients with macro and even giant prolactinomas and did not lead to valvulopathy. According to our follow-up findings, macro and giant prolactinomas are exquisitely responsive to DAs therapy, and we did not detect an increased risk for clinically relevant valve regurgitation or changes in valve morphology with the lowest maintaining doses of CAB (0.5–2.0 mg/week) and with mean cumulative doses of 155 mg CAB, and 7 301 mg BRC. This cumulative dose of CAB and BRC are lower than those stated in the literature for both parkinson disease and prolactinomas.

CONCLUSION

CAB and BRC administered in much lower doses then they are used in PD did not cause any valvular disease in our patients. Although most reports do not show any association between the use of DAs and valvulopathy, especially in patients with macroadenomas with the higher possibility of prolonged use of these drugs showing high or low 5-HT2B activity clinicians should recommend the lowest possible of CAB and BRC even for giant prolactinomas. Beyond that, countries having BRC as the first line treatment for prolactinoma needs further evaluation for the valvulopathic effect of these drugs.

Declaration of interest

There is no conflict of interest.

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