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Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease

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Abstract The expression of dopamine receptor subtypes has been reported in corticotroph adenomas, and this finding support the possibility for medical treatment of Cushing's disease (CD) with dopamine agonists when conventional treatment has failed. The aim of this study was to evaluate the effectiveness of cabergoline (at doses of up 3 mg/week), alone or combined with relatively low doses of ketoconazole (up to 400 mg/day), in 12 patients with CD unsuccessfully treated by transsphenoidal surgery. After 6 months of cabergoline therapy, normalization of 24 h urinary free cortisol (UFC) levels occurred in three patients (25%) at doses ranging from 2–3 mg/week, whereas reductions ranging from 15.0 to 48.4% were found in the remaining. The addition of ketonocazole to the nine patients without an adequate response to cabergoline was able to normalize UFC excretion in six patients (66.7%) at doses of 200 mg/day (three patients), 300 mg/day (two patients) and 400 mg/day (one patient). In the remaining patients UFC levels did not normalize but a significant reduction ranging from to 44.4 to 51.7% was achieved. In two of the six responsive patients to combination therapy, the weekly dose of cabergoline could be later reduced from 3 to 2 mg. Our findings demonstrated that cabergoline monotherapy was able to reverse hypercortisolism in 25% of patients with CD unsuccessfully treated by surgery. Moreover, the addition of relatively low doses of ketoconazole led to normalization of UFC in about two-thirds of patients not achieving a full response to cabergoline.

Keywords Cushing's disease · Cabergoline · Ketoconazole

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Introduction

Cushing's disease (CD), the most common form of endogenous Cushing's syndrome, is caused by an ACTH-secreting pituitary tumor and is associated with increased morbidity and mortality particularly due to metabolic and cardiovascular complications [1–3]. The treatment of choice for CD is transsphenoidal surgery (TSS) which yields immediate disease remission in about 70% of patients but the late disease remission rate is around 50% [4, 5]. Pituitary irradiation [6] and bilateral adrenalectomy [7] are alternative treatment approaches but they can be associated with serious complications, such as hypopituitarism and Nelson's syndrome, respectively [4, 5].

There is currently no medical therapy for CD that targets the pituitary adenoma. Pharmacotherapy, particularly ketoconazole (an adrenal blocking drug), is rather used before surgery or as a transient palliative treatment before definitive cure in patients submitted to pituitary radiotherapy [4, 8]. There are also few reports of successful primary therapy with ketoconazole in patients that refused

or had contraindications to surgery [9, 10]. In the past successful treatment of CD was also sporadically reported with drugs that modulate pituitary ACTH release, such as the dopamine agonist (DA) bromocriptine, cyproheptadine, and sodium valproate [11–13]. Recently, it was shown that longterm therapy with cabergoline, a DA more potent than bromocriptine, at weekly doses of 1–7 mg normalized 24 h urinary free cortisol (UFC) excretion in eight out 20 (40%) patients with CD not cured by surgery [14]. The effectiveness of cabergoline in normalizing ACTH levels and in inducing tumor shrinkage has also been demonstrated in some cases of Nelson's syndrome [15, 16]. Also recently, a multicenter phase II trial has shown normalization of UFC concentration in 17% of 29 patients with refractory or persistent CD after 15 days of treatment with pasireotide, a multireceptor ligand somatostatin analog [17].

The aim of this study was to evaluate the effectiveness of relatively low doses of cabergoline (up to 3 mg/week), alone or combined with ketoconazole, in patients with Cushing's disease unsuccessfully treated by surgery.

Materials and methods

Patients

Twelve patients (eight women and four men; mean age, 42.8 ± 6.2; age range 34–52) with persistent CD after unsuccessful surgery were included in this prospective study. Patients were selected from outpatients of the Division of Endocrinology of Pernambuco Federal University and Pernambuco Center for Diabetes and Endocrinology, Recife, Brazil.

The diagnosis of CD was mainly based on (1) the confirmation of the hypercortisolism by the demonstration of at least two of the following findings: elevation of daily UFC concentration and/or midnight salivary cortisol levels (two or more times the upper limit of normal range) and failure of cortisol suppression to less than 1.8 μg/dl after low-dose dexamethasone suppression tests, (2) plasma ACTH greater than 20 pg/ml, (3) serum cortisol suppression greater than 50% after high-dose oral dexamethasone suppression test and/or ACTH increase greater than 35% after CRH or desmopressin stimulation tests, (4) evidence of a pituitary tumor at magnetic resonance imaging (MRI) of the pituitary gland or at the bilateral inferior petrosal sinus sampling [1–3, 18].

The diagnosis of the persistence of CD after surgery was based on the persistent detection of high UFC levels. The inclusion criteria for the study were persistence of CD after surgery and UFC excretion 1.5 times or more the upper limit of normal range. At the beginning of the study all patients included in the study had UFC levels more than 2.0 times higher than the upper limit of the normal range, varying from 226 to 991 μg/24 h (mean ± SD, 592.4 ± 224.6). All patients had normal prolactin (PRL) levels. Pituitary MRI revealed microadenomas in six of the 12 patients (50%) with a median diameter of 4.5 mm (range 3–6 mm) whereas in the remaining patients there was no evidence of tumor. Immunohystochemistry showed positive staining for ACTH only in all patients.

Study protocol and assays

The study protocol included the evaluation of the effectiveness of cabergoline in monotherapy or in association with ketoconazole in normalizing UFC levels. Cabergoline was administered at the initial dose of 1 mg/week (0.5 mg twice weekly), which was progressively increased by 1 mg every month until normalization of UFC levels or a maximal dose of 3 mg/week were reached (1.5 mg twice weekly at bedtime). In cases with persistent elevation of UFC after 6 months of cabergoline treatment, the therapy with ketoconazole was added. This drug was given at initial dose of 100 mg/day that was progressively increased by 100 mg every month until normalization of UFC levels or a maximal dose of 400 mg/day were reached (200 mg twice a day after meals).

Patients were assessed clinically and by hormone and routine chemistry determinations once a month. Patients who achieved UFC normalization were considered full responders to cabergoline, whereas those who achieved a 25% or more decrease without normalization of UFC levels were labeled as partial responders. Patients who achieved less than a 25% reduction of UFC levels were considered resistant to cabergoline.

Plasma ACTH and serum PRL were measured by a solid-phase two-site sequential chemiluminescent immunometric assay, whereas serum cortisol and UFC were measured by a solid-phase competitive chemiluminescent enzyme immunoassay. The normal range for UFC levels was 10–90 μg/day. Midnight salivary cortisol levels were assessed by radioimmunoassay or by an electrochemiluminescent assay.

The radiological study included the evaluation of the sellar region by MRI (Sigma LX GE, Milwaukee, WI), 1.5T, and gradient of 23 mT/m. The slices were axial, coronal, and sagittal in T1, pre- and post-gadolinium, and in T2. Furthermore, all patients underwent an echocardiography at study entry and every 6 months during the entire period of treatment in order to investigate the presence of a cardiac valve disease.

The study was performed in accordance with the declaration of Helsinki and was approved by the local ethics committee. All study participants provided informed consent before enrollment had been reached.

Table 1 Characteristics of the patients and their response to the treatment with cabergoline (CAB)

Patients	Age/sex	IHC	CAB dose (mg/week)	Duration of treatment (months)	UFC normalization	UFC reduction (%)	UFC before CAB (μg/d)	UFC after CAB (μg/d)	Baseline PRL
No. 1	34/F	ACTH (+)	2.0	6	Yes	66.7	226	82	NI
No. 2	37/F	ACTH (+)	2.0	6	Yes	68.6	280	88	NI
No. 3	40/F	ACTH (+)	3.0	6	Yes	77.6	368	82.5	NI
No. 4	47/M	ACTH (+)	3.0	6	No	34.6	523	342	NI
No. 5	43/M	ACTH (+)	3.0	6	No	37.4	591	370	NI
No. 6	44/M	ACTH (+)	3.0	6	No	48.4	680	351	NI
No. 7	52/M	ACTH (+)	3.0	6	No	26.4	735	541	NI
No. 8	38/F	ACTH (+)	3.0	6	No	26.1	720	532	NI
No. 9	51/F	ACTH (+)	3.0	6	No	26.5	792	582	NI
No. 10	48/F	ACTH (+)	3.0	6	No	19.2	882	712	NI
No. 11	46/F	ACTH (+)	3.0	6	No	15.0	866	736	NI
No. 12	34/F	ACTH (+)	3.0	6	No	20.2	991	791	NI

IHC immunohystochemistry, *PRL* prolactin, *NI* normal

Urinary free cortisol (UFC) normal range = 10–90 μg/day

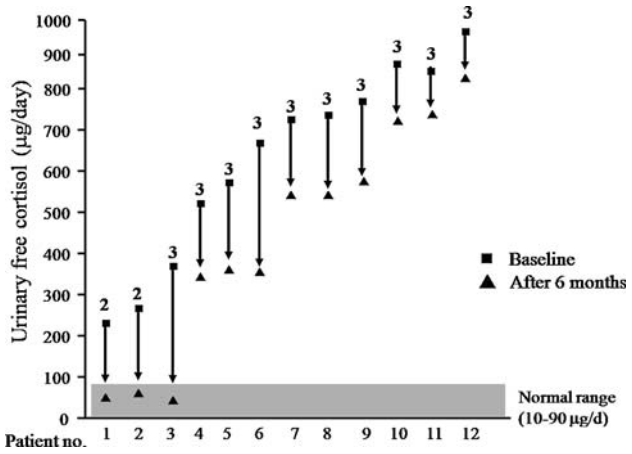

Fig. 1 Changes in 24 h urinary free cortisol levels after treatment with cabergoline. The number on each *arrow* indicates the maximal dose of cabergoline expressed in mg/week administered to each patient

Statistical analysis

In the analysis of qualitative variables, the χ^2 test or the Fisher exact test (when necessary) was used. The Student *t*-test was performed for the comparative analysis of quantitative variables. Results are expressed as percentages and mean values ± SD unless otherwise indicated. *P* values <0.05 were considered statistically significant.

Results

Responsiveness to treatment with cabergoline

Comparing the last value during cabergoline monotherapy with baseline (Table 1), mean ± SD UFC levels decreased from 637.8 ± 245.7 (range 226–991) μg/day to 434.1 ± 256.8 (range 82–791) μg/day ($P < 0.001$). Normalization of UFC levels occurred in three patients (25%) at cabergoline doses ranging from 2 to 3 mg/week (mean ± SD, 2.5 ± 0.5), whereas reductions ranging from 15.0 to 48.4% were found in the remaining. Three patients were labeled as resistant to cabergoline (UFC decrease <25%). In two patients, the normalization of UFC excretion was achieved at the dose of 2 mg/week (Table 1) (Fig. 1).

Regardless the UFC normalization, all patients reported improvement of clinical symptoms during the treatment with cabergoline.

Responsiveness to treatment with cabergoline and ketoconazole

The addition of ketonocazole, at doses ranging from 200 to 400 mg/day (mean ± SD, 325 ± 103.5), to the nine

patients without a full response to cabergoline yielded a mean ± SD UFC levels decrease from 520.7 ± 156.1 (range 342–791) μg/day to 149.6 ± 124.1 (range 72–385) μg/day ($P < 0.001$). Normalization of UFC levels were achieved at doses of 200 mg/day in three patients, 300 mg/day in two patients and 400 mg/day in one patient. In the remaining patients UFC levels could not be normalized but a significant reduction ranging from to 44.4 to 51.7% was achieved (Table 2) (Fig. 2). As shown in Table 2, UFC levels in patients that did not respond to combination therapy was significantly higher than those of responsive patients: 746.3 ± 40.5 (range 712–791) μg/day versus 453 ± 109.7 (range 342–582) μg/day ($P < 0.001$). By contrast, there was no correlation between the response to treatment and PRL levels (normal in all patients) or the expression of PRL by immunohystochemistry (negative in all subjects). In two out of the six responsive patients to combined therapy, the weekly dose of CAB could be later reduced from 3 to 2 mg without elevation UFC levels beyond the upper limit of the normal range.

Overall, normalization of daily UFC excretion could be obtained in nine patients (75%), three (25%) submitted to cabergoline monotherapy and in six (66.7%) undergoing the combination of cabergoline with ketoconazole. The response was not infleuTreatment escape, manifested as relapse of hypercortisolism and elevation of UFC levels during the use of cabergoline alone or combination therapy, was not observed in any patient.

Tolerability

Cabergoline and ketoconazole were well tolerated and none of the patients had to interrupt the treatment. Transient moderate dizziness and/or nausea were reported by three patients treated with cabergoline. After the addition of ketoconazole, mild transient elevation of transaminases was found in one out of nine patients (11.1%). No patients developed symptoms of hypoglycemia while on cabergoline or combined therapy. Moreover, none of the patients experienced any significant symptom or sign related to cardiac disease; particularly, no patients developed cardiac valve regurgitation.

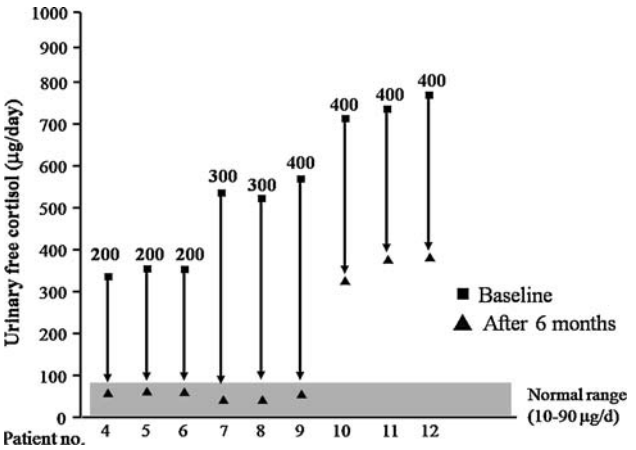

Fig. 2 Changes in 24 h urinary free cortisol levels after treatment with cabergoline and ketoconazole. The number on each *arrow* indicates the maximal dose of ketoconazole expressed in mg/day administered to each patient

Discussion

Unlike prolactinomas and acromegaly, currently there is not an effective medication to treat Cushing's disease that acts at the level of the pituitary gland inhibiting ACTH secretion by the corticotroph tumor [1, 2]. Some neuromodulatory drugs were used in the past, however, due to

Table 2 Characteristics of the patients and their response to the treatment with cabergoline (CAB) + ketoconazole (KTCZ)

Patients	CAB dose (mg/wk)	KTCZ dose (mg/d)	Duration of treatment (months)	UFC normalization	UFC reduction (%)	UFC before KTCZ (μg/d)	UFC after KTCZ (μg/d)
No. 4	3.0	200	6	Yes	75.1	342	85
No. 5	3.0	200	6	Yes	76	370	89
No. 6	3.0	200	6	Yes	74.3	351	90
No. 7	3.0	300	6	Yes	86.7	541	72
No. 8	3.0*	300	6	Yes	85.3	532	78
No. 9	3.0*	400	6	Yes	85.2	582	86
No. 10	3.0	400	6	No	44.4	712	316
No. 11	3.0	400	6	No	51.7	736	381
No. 12	3.0	400	6	No	48.7	791	385

In patients No. 8 and 9 the dose of cabergoline could be later reduced to 2 mg/week

Urinary free cortisol (UFC) normal range = 10–90 μg/day

their limited efficacy, they never reached a widespread clinical use for the treatment of CD [4, 8, 10]. The most effective was the DA bromocriptine that was reported to induce a significant inhibition or normalization of cortisol secretion in up 40% of patients after short-term treatment [11, 19–21], but normalization of cortisol secretion was rarely maintained and tumor shrinkage was only sporadically found after long-term treatment [19, 22, 23].

Better results have been reported with the potent DA cabergoline, such as normalization of ACTH and/or cortisol secretion and/or significant tumor shrinkage in two ACTH-secreting pituitary tumors associated with Nelson's syndrome [15, 16], a silent ACTH [24], an aberrant ACTH-secreting [25], and a mixed ACTH and PRL-secreting [26] pituitary tumors. Moreover, it was recently demonstrated a sustained control of cortisol secretion for 24 months during cabergoline treatment at doses ranging from 1 to 7 mg/week (median 3.5) in eight of 20 patients (40%) with CD unsuccessfully treated by surgery [14]. In this study, after short-term treatment, 15 out of 20 patients (75%) were responsive to cabergoline treatment [14].

The rationale for the use of cabergoline in CD was the demonstration that the dopamine receptor subtype 2 (D_2) is expressed in approximately 80% of human corticotroph adenomas and that these adenomas can be responsive to the ACTH-inhibiting actions of D_2-agonists in vitro [27, 28]. In other studies, this rate varied between 51 and 75% in initial responders (both complete and partial) observed in vivo with cabergoline monotherapy [14, 27, 29]. In the pituitary, the response to dopamine agonists is related to the activity of the D_2 receptor [27]. Compared to bromocriptine, cabergoline has a higher specificity and affinity for the D_2 receptor and a longer duration of action, and is much better tolerated [30]. All these factors explain the greater efficacy of cabergoline in the management of pituitary tumors [30].

It was also suggested in the early 1980s that some ACTH-secreting adenomas may originate not only from the anterior but also from the neurointermediate lobe, which is under hypothalamic dopaminergic control [31]. These patients would be therefore more likely to respond adequately to dopamine agonists. However, in the study by Croughs et al. [32] the response to bromocriptine was associated with hyperplastic anterior pituitary gland and not only with neurointermediate lobe hyperfunction. More recently, it was shown in six normal human pituitary glands that the expression of D_2 receptors was more intense and more homogeneous in corticotrophs from the intermediate lobe than in those from the anterior lobe [33].

In the current study, among the 12 patients with CD that underwent treatment with cabergoline monotherapy, three (25%) achieved normalization of 24 h UFC levels whereas a reduction ranging from 44.4 to 85.2% was observed in the remaining. The lack of full response to this drug in 75% of our patients could be rather attributed to low expression or lack of expression of D2 receptors in tumor cells. Although we did not aim at correlating the response to the treatment to the expression of D2 receptors, it was shown in a previous study that the response to cabergoline was strongly correlated to the presence of these receptors in corticotrophs tumors cells. Other likely explanations would be downregulation of D2 receptor expression by high cortisol levels and inadequate dose of cabergoline. Indeed at a maximal dose of 3 mg/week fully responsive patients had an UFC increase of no more than 4.0 times higher than the upper limit of normal range. As mentioned, UFC normalization was found in 40% of patients from the series by Pivonelo et al. [14]. This better response might be perhaps attributed to the fact that 45% of these patients had mild hyperprolactinemia whereas prolactin levels were normal in all our patients. Moreover, the maximal dose of cabergoline used in that study was higher than in ours (7 versus 3 mg/week). It is therefore possible that we might have had better results if we had used higher cabergoline doses. However, in our protocol we decided that that maximal dose would be 3 mg/week as there is some evidence that higher doses may be associated with an increased risk of valve heart abnormalities [34].

We did not assess the effect of cabergoline on the tumor size as only half of the patients had an abnormal pituitary MRI that revealed small microadenomas. However, in the series by Pivonello et al. [14], tumor shrinkage was observed in four of the eight (50%) who were followed for 24 months, whereas a stable tumor volume was found in the remaining responsive patients.

Ketoconazole, an imidazole derivative, is a potent inhibitor of gonadal and adrenal steroidogenesis [35]. It has been used at doses of 200–1,200 mg/day but, in most cases, 600–800 mg/day is required to keep UFC levels within the upper limits of normal, which should be the goal of therapy to avoid the risk of adrenal insufficiency [9, 10, 35]. Compared to lower doses, 600–1,200 mg/day implies a greater risk for endocrine side-effects, such as gynecomastia, impairement of testicular function, and adrenal insufficiency [10, 35].

Some patients undergoing longterm cabergoline or ketoconazole monotherapy may show relapse after having been in full remission [8, 10, 14, 29]. A treatment escape was observed in two of the seven (28.6%) full responders and three of the eight (37.5%) partial responders to cabergoline from the series by Pivonello et al. [14] after 12–18 months of treatment but in none of our patients that were given cabergoline alone or in combination. The mechanisms that cause these escapes from cabergoline monotherapy are not known. Receptor downregulation or various postreceptor desensitization mechanisms may be involved in this process [28]. Regardless of the cause, these

treatment escapes may limit the efficacy of cabergoline monotherapy as a long-term treatment option for CD [28]. Adrenal stimulation by high ACTH levels is believed to be the main mechanism of escape during chronic ketoconazole therapy for CD [10, 35].

We also demonstrated that, among the nine unsuccessfully treated by cabergoline, UFC normalization was achieved in six of them (66.7%) after the addition of relatively low doses of ketoconazole (200–400 mg/day). The addition of ketoconazole also enabled reduction of cabergoline dose from 3 to 2 mg/week in two patients who had successfully responded to combination therapy. Similarly the three patients who did not respond to combined therapy had more severe hypercortisolism than patients who achieved UFC normalization.

There are only scant data in the literature regarding the benefits from the combined treatment with cabergoline and ketoconazole for CD [36, 37]. Recently Pivonello and coworkers [37] reported that the addition of ketoconazole at very low doses (50–200 mg/day) led to normalization of UFC excretion in all six patients who were partially responsive to cabergoline (3.5 mg/week). In our series, one-third of patients that were given ketoconazole had been shown to be resistant to cabergoline (UFC reduction <25%). These patients did not benefit from the combination therapy.

The rationale for the combined treatment would be the utilization of drugs with complementary pharmacologic mechanisms. Indeed, while the main action of cabergoline is inhibiting ACTH secretion by the corticotroph adenoma, ketoconazole blocks many steps of adrenal steroidogenesis, including the enzymes 17,20-lyase, 11β-hydroxylase and 17α-hydroxylase [8, 35]. The potential advantages of the combination of cabergoline with ketoconazole compared with either monotherapy would include a higher probability of longterm control of the hypercortisolism at lower doses, a lower incidence of side-effects and, possibly, a lower rate of treatment escapes.

In conclusion, our findings demonstrate that cabergoline may be helpful for patients with Cushing's disease unsuccessfully treated by surgery. We could also observe that the addition of relatively low doses of ketoconazole (200–400 mg/day) led to normalization of 24 h urinary free cortisol levels in two-thirds of patients that were not full responders to cabergoline. However, further evidence is necessary from studies involving a larger number of patients to confirm the results of the present study.

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