The Medical Treatment of Cushing's Disease: Effectiveness of Chronic Treatment with the Dopamine Agonist Cabergoline in Patients Unsuccessfully Treated by Surgery

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Background: The role of dopamine agonists in the treatment of Cushing's disease (CD) has been previously debated.

Aim: The aim of this study was to evaluate the effectiveness of short-term (3 months) and long-term (12–24 months) treatment with cabergoline in patients with CD.

Patients and Methods: 20 patients with CD unsuccessfully treated by surgery entered the study. Cabergoline was administered at an initial dose of 1 mg/wk, with a monthly increase of 1 mg, until urinary cortisol levels normalized or the maximal dose of 7 mg/wk was achieved. The responsiveness to treatment was evaluated according to changes in urinary cortisol excretion. A decrease greater than 25% was considered as a partial response, whereas complete normalization was considered as a full response at short-term evaluation; persistence of normal cortisol excretion was the only criterion to evaluate the response at long-term evaluation.

Results: After short-term treatment, 15 (75%) patients were responsive to cabergoline treatment. Among these, normalization of cortisol excretion was maintained in 10, whereas treatment escape was observed in five patients after 6–18 months. Among the 10 long-term responsive patients, eight were followed for 24 months, whereas the remaining two were followed for 12–18 months, due to cabergoline withdrawal for intolerance. A sustained control of cortisol secretion for 24 month cabergoline treatment at the maximal dose ranging from 1-7 mg/wk (median: 3.5) without significant side effects, was obtained in eight of 20 (40%) patients.

Conclusions: The results of this study demonstrated that cabergoline treatment is effective in controlling cortisol secretion for at least 1–2 yr in more than one third of a limited population of patients with CD. If this evidence is confirmed by additional studies, this agent may be considered as a useful treatment option in patients with CD who are unsuccessfully treated by neurosurgery. **(*J Clin Endocrinol Metab* 94: 223–230, 2009)**

Cushing's disease (CD) is the most common form of Cushing's syndrome, caused by a corticotroph pituitary tumor, and often complicated by hypertension and impaired glucose tolerance and associated with increased morbidity and mortality for cardiovascular diseases (1–3). The first-line treatment of CD is surgery, with the objective of removing the pituitary tumor, although it is effective in inducing immediate disease remission in around 70% and late disease remission in around 50% of pa-

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Abbreviations: CD, Cushing's disease; HOMA-B, homeostasis model of assessment-β-cell function; HOMA-IR, homeostasis model of assessment-insulin resistance; MRI, magnetic resonance imaging; PRL, prolactin.

tients (4, 5). Pituitary irradiation and bilateral adrenalectomy are the alternative therapeutic approaches to CD, but they can be associated with significant complications. Pharmacotherapy is not currently used in the treatment of CD, except for adrenal blocking drugs, used as transient palliative treatment before definitive cure (4, 5). However, although no drug has demonstrated a sufficient effectiveness in controlling cortisol secretion and inducing tumor shrinkage in CD, the dopamine agonist bromocriptine was reported to inhibit cortisol secretion in a limited group of patients after short-term therapy, and in sporadic patients after long-term treatment (6–8). Recently, a preliminary report of this study described that a short-term treatment with the potent dopamine agonist cabergoline controlled cortisol secretion in six of 10 (60%) patients with CD, suggesting that cabergoline could be more efficacious than bromocriptine in the management of this disease (9).

The aim of the current study was to evaluate the effectiveness of short-term and long-term treatment with cabergoline on ACTH and cortisol secretion, tumor size, and systemic complications in patients with CD who are unsuccessfully treated by surgery.

Patients and Methods

Patients

Twenty patients (15 females, five males, 24–60 yr) with persistent CD after unsuccessful surgery entered the study after their informed consent had been obtained. The diagnosis of CD was mainly based on: 1) elevated daily urinary cortisol excretion (two or more times the upper limit of normal range) with inappropriately high plasma ACTH concentrations (>20 pg/ml); 2) failure of serum cortisol suppression (<18 μg/liter) after low-dose but greater than 50% decrease after high-dose oral dexamethasone suppression test; and 3) evidence of a pituitary tumor at magnetic resonance imaging (MRI) of the pituitary gland or at the bilateral inferior petrosal sinus sampling (1, 2). The diagnosis of the persistence of CD after surgery was based on: 1) documentation of a corticotroph pituitary lesion (adenoma or hyperplasia) at the histological and immunohistochemical study (19 patients), or the persistence of the presurgical clinical syndrome, hormonal pattern, and pituitary tumor (1 patient); and 2) elevated daily urinary cortisol excretion (1, 2). The inclusion criteria for the study included: 1) persistence of CD after surgery and 2) elevated urinary cortisol excretion 1.5 or more the upper limit of normal range. At the beginning of the study all patients included in the study had baseline urinary cortisol levels more than 2.0 times higher than the upper limit of the normal range. Mild hyperprolactinemia was present in nine of 20 patients (45%). Pituitary tumor was detectable in 15 of the 20 patients. Hypertension was present in 13 of 20 (45%) patients, and was treated by a different combination of antihypertensive drugs, whereas diabetes mellitus was present in six patients, which were under dietary treatment without or with the association of metformin. The patients included in the study had been operated 0.5–5 years before the study: those operated more than six months before, had been treated with ketoconazole since 3 months before the study. Patients' profile at study entry is shown in Table 1.

Study design

The study design was in accordance with the Helsinki Doctrine on Human Experimentation, and it was approved by the local Ethical Committee. The study protocol included the evaluation of short-term (3 months) and long-term (12–24 months) effectiveness of cabergoline treatment on clinical, biochemical, and radiological features, focusing on the complications of the disease. Cabergoline (Dostinex; Pharmacia-Pfizer, New York, NY) was administered at the initial dose of 1 mg/wk (0.5 mg twice a week), progressively increased by 1 mg every month until normalization of urinary cortisol levels or a maximal dose of 7 mg/wk (1 mg/d) had been reached. The study was performed in a single center (Federico II University of Naples).

Responsiveness to treatment

After short-term treatment, patients who achieved a normalization of urinary cortisol levels were considered full responders, whereas those who achieved a 25% or more decrease without normalization of urinary cortisol levels were considered partial responders. Patients who achieved less than a 25% decrease of urinary cortisol levels were considered resistant. After long-term treatment, the presence of urinary cortisol levels within the normal range was the only criterion to evaluate the responsiveness to treatment. A re-increase of urinary cortisol levels at least to the baseline levels after their normalization was considered an escape from treatment. The responsiveness to short-term treatment with cabergoline in terms of urinary cortisol changes in 10 of the 20 patients of the study (nos. 1–10 in Table 1) has been already described in a previous report (9).

Effectiveness and safety of treatment

The clinical study included the evaluation of body mass index, as index of general obesity and waist to hip ratio, as index and visceral obesity, systolic and diastolic blood pressure, and heart rate. The biochemical study included the evaluation of serum glucose and insulin levels, as well as the homeostasis model of assessment-insulin resistance (HOMA-IR) and homeostasis model of assessment-β-cell function (HOMA-B) indexes, markers of insulin resistance and insulin secretion, respectively, together with the evaluation of serum prolactin (PRL), plasma ACTH, serum and urinary cortisol levels, for which the mean of three urinary collections was considered. The prevalence of hypertension was evaluated by the measurement of blood pressure, considering a diagnosis of hypertension when systolic and diastolic blood pressure were above 140 and above 90 mm Hg, respectively. The prevalence of glucose intolerance was evaluated on the basis of glucose levels at fasting and/or after a oral glucose tolerance test. Diabetes mellitus was diagnosed when fasting serum glucose levels were more than 126 mg/dl in two consecutive determinations or more than 200 mg/d 2 h after the glucose load, whereas an impairment of glucose tolerance was diagnosed when fasting serum glucose levels were between 100 and 126 mg/dl, and between 140 and 200 mg/dl 2 h after the glucose load. In patients under treatment with antihypertensive or antidiabetics drugs, these were withdrawn for 1 wk to evaluate the presence of hypertension and/or glucose intolerance. Serum insulin was measured by solid-phase, two-site sequential chemiluminescent immunometric assay. The cross-reactivity of insulin with proinsulin was 8.5%. Plasma ACTH as well as serum PRL were measured by a solid-phase two-site sequential chemiluminescent immunometric assay, whereas serum and urinary cortisol were measured by a solid-phase competitive chemiluminescent enzyme immunoassay. The normal range for urinary cortisol levels was 35–135 μg/d, obtained measuring urinary cortisol levels on a large number of normal subjects of different age. The radiological study included the evaluation of the tumor volume by MRI, performed on clinical 1.5-T scanners, before and after gadolinium administration. A more than 25% shrinkage was considered significant. Tumor volume was evaluated only in the 15 patients with detectable tumor at MRI during the study. The presence of cardiac valve disease was investigated by an echocardiography performed at study entry and every 6 months during the entire period of treatment.

Statistical analysis

The statistical analysis was performed by SPSS for Windows (SPSS, Inc., Chicago, IL). The comparison between baseline and posttreatment parameters was performed by the Wilcoxon or Friedman test. The association study was performed by the χ^2 test corrected by the Fisher exact test, whereas the correlation study was performed with regression anal-

TABLE 1. Patients' clinical profile at study entry

Patient no. (sex/age)	Plasma ACTH (pg/ml)	0800-h serum cortisol (μg/liter)	1600-h serum cortisol (μg/liter)	Daily urinary cortisol (μg/24 h)	Serum PRL (μg/liter)	Presurgical radiological findings	Surgical findings	Postsurgical radiological findings	Histological findings	Immunohistochemical findings
1 (f/49)	54.0	299.0	134.2	471	22.0	Microadenoma	Microadenoma	Microadenoma	Basophilic adenoma	ACTH+++
2 (f/48)	69.3	340.3	110.0	906	7.8	Macroadenoma	Macroadenoma	Macroadenoma	Chromophobe adenoma	ACTH++, FSH+, LH+
3 (f/25)	67,2	288.4	213.2	815	27.9	Microadenoma	Microadenoma	Microadenoma	Basophilic adenoma	ACTH++
4 (f/35)	78.1	276.3	154.0	598	30.2	Microadenoma	Microadenoma	No tumor	acidophilic adenoma	ACTH++, GH+, PRL++
5 (m/31)	98.9	287.2	221.0	925	7.6	No tumor	Microadenoma	No tumor	Basophilic adenoma	ACTH+++
6 (f/42)	52.0	233.0	199.2	645	30.1	No tumor	Diffuse enlargement	No tumor	Basophilic hyperplasia	ACTH++
7 (m/45)	43.3	311.7	256.2	971	10.2	Microadenoma	Microadenoma	Microadenoma	Basophilic adenoma	ACTH+++
8 (f/43)	76.2	298.8	176.1	906	38.9	Macroadenoma	Macroadenoma	Microadenoma	Chromophobe adenoma	ACTH++, TSH+, PRL++
9 (f/47)	55.4	178.2	132.2	434	16.2	Microadenoma	Microadenoma	Microadenoma	Basophilic adenoma	ACTH+++, PRL++
10 (f/26)	99.1	213.2	145.2	544	15.2	Macroadenoma	Macroadenoma	Microadenoma	Basophilic adenoma	ACTH+++
11 (f/38)	71.1	245.3	187.3	560	21.2	Microadenoma	Microadenoma	Microadenoma	Basophilic adenoma	ACTH+++
12 (f/52)	77.0	178.4	170.2	389	25.2	Microadenoma	Microadenoma	Microadenoma	Basophilic adenoma	ACTH+++, PRL+
13 (f/55)	101.0	243.1	187.4	443	44.4	Microadenoma	Microadenoma	No tumor	Basophilic adenoma	ACTH+++
14 (f/29)	78.0	215.0	198.3	467	12.2	Macroadenoma	Macroadenoma	Macroadenoma	Basophilic adenoma	ACTH+++
15 (m/30)	32.9	166.9	143.2	333	33.3	Microadenoma	Microadenoma	Microadenoma	Chromophobe adenoma	ACTH2+, TSH+
16 (m/18)	59.4	188.4	178.4	299	31.4	Microadenoma	Diffuse enlargement	Microadenoma	Normal pituitary	ACTH+, PRL++, GH+
17 (m/31)	78.8	312.2	213.2	441	7.8	Microadenoma	Microadenoma	Microadenoma	Basophilic adenoma	ACTH+
18 (f/60)	59.2	299.0	199.2	654	45.1	Macroadenoma	Macroadenoma	Microadenoma	Basophilic adenoma	ACTH+++, PRL++
19 (f/46)	71.2	169.2	170.1	444	19.3	No tumor	Diffuse enlargement	Microadenoma	Basophilic hyperplasia	ACTH++
20 (f/48)	54.4	292.0	156.3	556	15.3	Microadenoma	Microadenoma	No tumor	Basophilic adenoma	ACTH+

Normal ranges for: plasma ACTH, 10–130 pg/ml; serum cortisol, 50–200 μg/liter; urinary cortisol, 35–135 μg/d; and serum PRL, 0–25 μg/liter for females and 0–15 μg/liter for males. Urinary cortisol levels represent the mean of three different urine collections. f, Female; m, male. The post surgical radiological findings were obtained before starting the study after 0.5–5 years from the surgical operation. Immunolistochemical findings: +, weak; ++, moderate; +++, strong.

ysis calculating the Pearson's coefficient. Data are expressed as mean ± SE. Significance was set at 5%.

Results

Responsiveness to treatment with cabergoline

At short-term treatment, 15 (75%) patients were responsive [eight (40%) partial and seven (35%) full responders], whereas five (25%) were resistant. Cabergoline was withdrawn in all resistant patients, except in one, who continued treatment for 12 months. Among the 15 responsive patients, six of the eight (75%) partial responders normalized cortisol levels after 6–12 month treatment with increasing cabergoline dose. However, two of the seven (28.6%) full responders and three of the eight (37.5%) partial responders experienced a treatment escape after 12–18 month treatment, and stopped treatment. At the 12-month follow-up, 10 (50%) patients were persistently controlled at the median cabergoline dose of 6 mg/wk (1–7 mg/wk). Cabergoline was discontinued during the second year of follow-up in two (10%) patients who did not tolerate the treatment because of severe asthenia associated with hypotension. At the 24-month follow-up, eight (40%) patients were persistently controlled at a median cabergoline dose of 3.5 mg/wk (1–7 mg/wk) (Figs. 1 and 2). In these patients, all multiple urinary cortisol levels were within the normal range, or very close to the upper limit of the normal range. A flowchart explaining the disposition of the different patients during the short-term and long-term study and the corresponding outcome of the treatment is shown in Fig. 3. The presence of hyperprolactinemia was significantly associated with the responsiveness to short-term ($\chi^2 = 5.455$; $P = 0.038$), but not long-term ($\chi^2 = 5.051$; $P = 0.070$), treatment.

Effectiveness of treatment with cabergoline

Short-term treatment (Table 2)

The clinical picture improved in the majority of responsive patients, whereas it mildly improved, remained stable, or mildly worsened in resistant patients. Despite a mild increase of body mass index, waist to hip ratio significantly decreased, as well as blood pressure, serum glucose and insulin, HOMA-IR, and tumor volume. Systolic and diastolic blood pressure significantly decreased in resistant patients as well, whereas HOMA-B did not change both in responsive and resistance patients. PRL levels were lower than the normal range in all patients.

Long-term treatment

Responsive patients (Table 3). The clinical picture further improved during treatment. Body mass index slightly increased during the first 3–6 months, but significantly decreased thereafter, whereas waist to hip ratio progressively decreased. The prevalence of overweight or obesity decreased from 87.5% at baseline to 62.5% at the 24-month treatment. The distribution of fat mass was modified from an abdominal to a generalized pattern in the majority of patients. Muscle mass and strength as well as skin features slightly or significantly improved in the majority of patients. Systolic and diastolic blood pressure values significantly decreased, becoming stable after 6–12 month treatment. The prevalence of hypertension decreased from 50% at

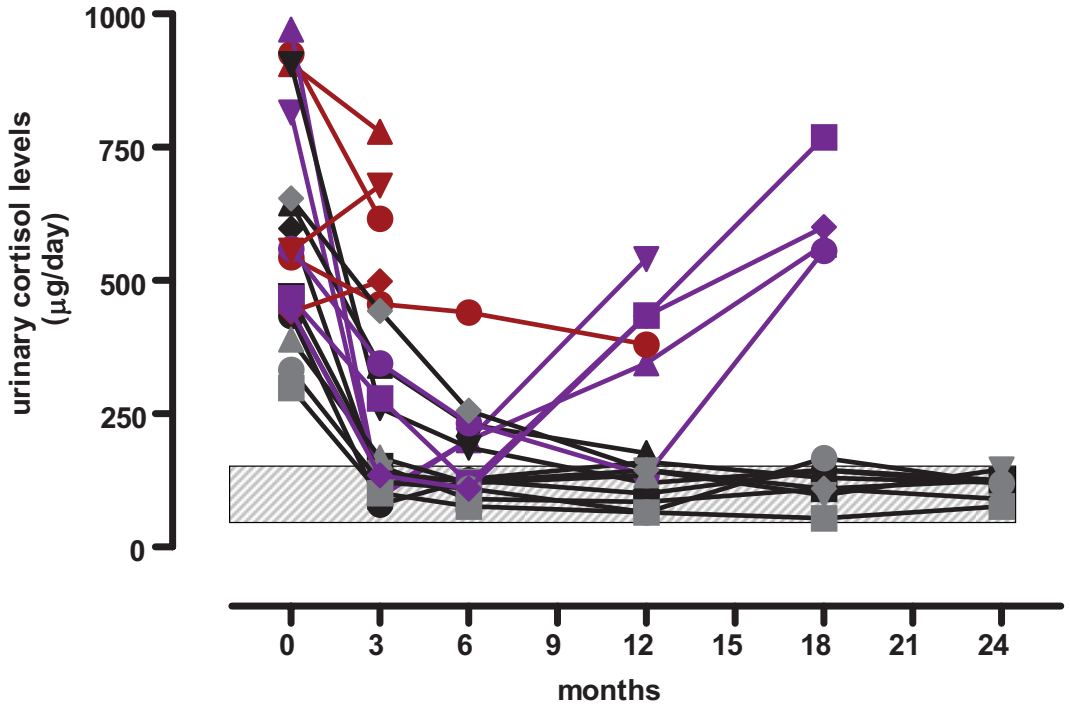

FIG. 1. Urinary cortisol levels during the entire period of treatment in all 20 patients treated with cabergoline. The patients long-term response to cabergoline treatment are shown with *black lines*, those with early response and late escape are shown with *purple lines*, and those nonresponders to the treatment are shown with *red lines*. The *shaded area* indicates the normal range of urinary cortisol levels (35–135 μg/d). Urinary cortisol levels represent the mean of three different urine collections performed on three different nonconsecutive days of the same week.

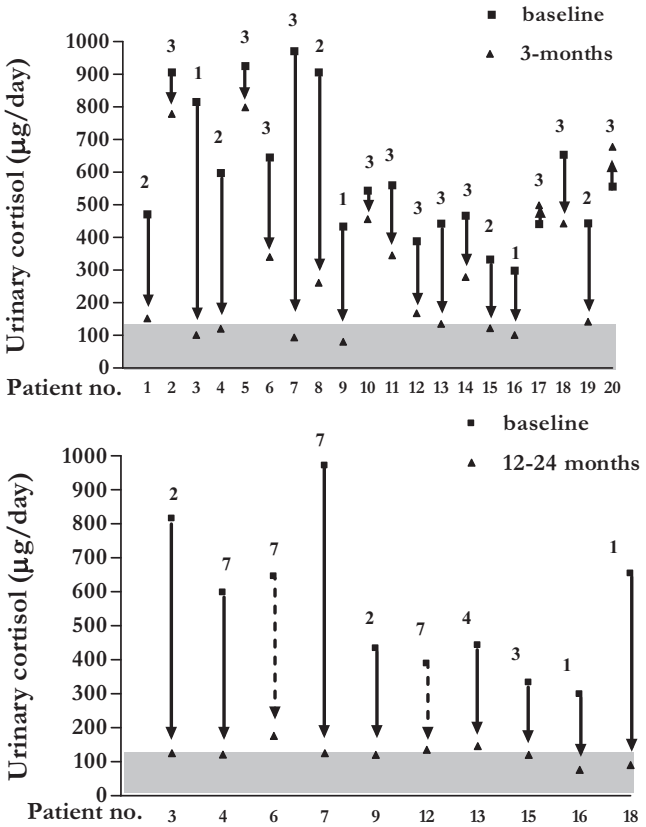

FIG. 2. Changes in urinary cortisol levels after short-term (*top*) and long-term (*bottom*) treatment with cabergoline. The eight patients with a 24-month follow-up are shown with a *continuous arrow*, whereas the two patients with 12–18 months of follow-up are shown with an *interrupted arrow*. The *number on each arrow* indicates the maximal dose of cabergoline expressed in mg per week administered to the patients during short-term and long-term treatment. The *gray area* indicates the upper limit of normal of the urinary cortisol levels (135 µg/d). Urinary cortisol levels represent the mean of three different urine collections performed on three different nonconsecutive days of the same week.

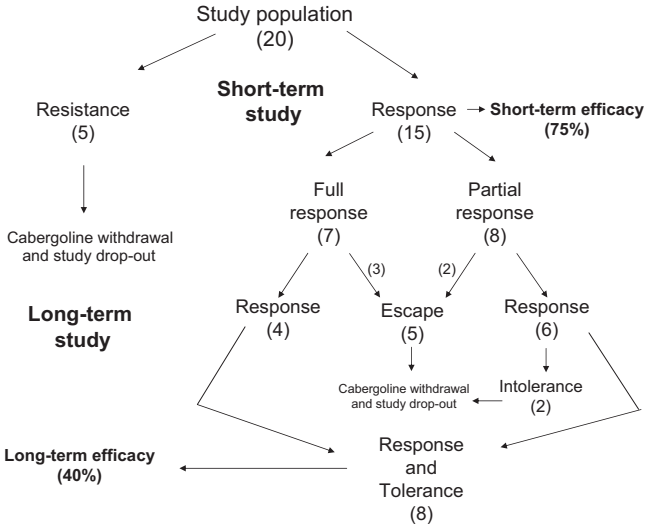

FIG. 3. Flowchart illustrating the disposition of the different patients during short-term and long-term study, and the corresponding outcome of the treatment.

baseline to 0% after 24 month treatment, when specific antihypertensive treatment (an angiotensin converting enzyme inhibitor plus a diuretic agent in two, an angiotensin receptor blocker plus a diuretic agent in one, and a calcium antagonist in one patient) was completely withdrawn. Fasting serum glucose and insulin levels, as well as HOMA-IR, but not HOMA-B, significantly decreased; the prevalence of diabetes mellitus and impairment of glucose tolerance changed from 25 and 37.5% at baseline to 10 and 20% after 24 month treatment, respectively. Metformin treatment was withdrawn in one of the two patients with diabetes, who became controlled by only a dietary treatment. PRL levels were lower than normal range in all patients. A decrease of tumor volume was observed during the entire period of treatment. In particular, tumor shrinkage was observed in four (50%), whereas a stable tumor volume was found in the remaining responsive patients.

Escaped patients (Table 4)

The clinical picture slightly worsened with the treatment escape. However, at the last follow-up, systolic and diastolic blood pressure, and HOMA-IR were still decreased compared with the baseline. No change of tumor volume was found after the treatment escape, whereas a slight increase was observed in the only resistant patient who continued treatment for 12 months.

Tolerance

No significant side effect was documented except hypotension (80/50 mm Hg) associated with severe asthenia in two patients, who stopped treatment after 12 and 18 months of treatment, respectively. A transient moderate asthenia was registered in four patients, whereas a transient mild dizziness with nausea was reported by another patient during the first period of treatment. These latter side effects did not require treatment withdrawal. No patient experienced any deterioration of cardiovascular function, or any significant symptom or sign related to cardiac disease; in particular, no development of cardiac valve insufficiency or worsening of previously diagnosed valve insufficiency was documented in the patients of the study, except in one who had a mild tricuspid regurgitation at baseline and a moderate tricuspid regurgitation with normal pulmonary pressure after 2 yr treatment.

Discussion

The current study represents the extension of a previously reported preliminary study (9). Indeed, this is the first study evaluating the chronic effectiveness of cabergoline treatment in CD. The results of the study demonstrated that a 24-month treatment with cabergoline, at a variable dose between 1 and 7 mg/wk, induces or maintains control of cortisol secretion in 40% and induces tumor shrinkage in 20% of a group of 20 patients with CD, improving hypertension and glucose intolerance in the majority of patients, regardless of the normalization of cortisol secretion.

Presently, a real medical treatment for CD, acting at the level of the pituitary tumor, does not exist. Indeed, although several neuromodulatory drugs were used, no single agent has ever been demonstrated to be effective sufficiently to achieve a widespread

TABLE 2. Clinical, biochemical, and radiological features of the 20 patients with CD treated with cabergoline at baseline and after short-term treatment

Parameter	Responsive patients (n = 15)			Resistant patients (n = 5)		
	Baseline	3-month treatment	*P* value	Baseline	3-month treatment	*P* value
Body mass index (kg/m^2)	27.5 ± 0.8	28.0 ± 0.8	0.115	27.7 ± 1.3	28.4 ± 1.3	0.066
Waist to hip ratio	1.10 ± 0.04	1.08 ± 0.04	0.001	1.05 ± 0.06	1.07 ± 0.06	0.221
Systolic blood pressure (mm Hg)	146.0 ± 3.6	135.7 ± 2.9	0.001	149.0 ± 5.8	138.0 ± 3.7	0.041
Diastolic blood pressure (mm Hg)	94.0 ± 2.4	87.3 ± 2.2	0.002	95.0 ± 4.2	88.0 ± 3.7	0.038
Heart rate (beats/min)	69.5 ± 1.8	74.1 ± 2.3	0.014	63.2 ± 1.3	65.0 ± 0.5	0.109
Fasting serum glucose (mg/dl)	129.3 ± 5.6	121.8 ± 4.0	0.004	124.2 ± 7.7	116.2 ± 3.1	0.136
Fasting serum insulin (μU/ml)	11.0 ± 1.2	10.1 ± 1.2	0.001	14.4 ± 1.2	13.7 ± 1.1	0.104
HOMA-IR	3.6 ± 0.5	3.1 ± 0.4	0.002	4.4 ± 0.5	4.0 ± 0.3	0.138
HOMA-B (%)	65.0 ± 7.2	65.4 ± 7.4	0.865	92.0 ± 17.1	94.0 ± 9.4	0.500
Plasma ACTH (pg/ml)	64.9 ± 3.3	56.3 ± 3.1	0.002	78.0 ± 10.3	78.6 ± 9.6	0.893
Serum cortisol (μg/liter)	239.3 ± 13.9	177.1 ± 13.4	0.001	288.8 ± 21.1	276.8 ± 14.5	0.686
Urinary cortisol (μg/d)	561.9 ± 52.5	192.0 ± 29.1	0.001	674.4 ± 100.5	642.2 ± 70.6	0.345
Tumor volume (mm^3)	246.5 ± 40.9	230.7 ± 41.5	0.047	565.3 ± 391.2	573.1 ± 394.3	0.109

Normal ranges for: fasting serum glucose, 60–110 mg/dl; serum insulin, 1–20 μU/ml; plasma ACTH, 10–130 pg/ml; serum cortisol, 50–200 μg/liter; urinary cortisol, 35–135 μg/d; and serum PRL, 0–25 μg/liter for females and 0–15 μg/liter for males. Urinary cortisol levels represent the mean of three different urine collections.

clinical use in the management of CD (4, 5). However, the dopamine agonist bromocriptine was reported to induce a significant inhibition or normalization of cortisol secretion in about 40% of patients after short-term treatment (5, 6, 10, 11), although controversial and variable results were obtained by different studies on short-term treatment (5), and normalization of cortisol secretion was rarely maintained and tumor shrinkage sporadically detected after long-term treatment (5, 7, 8). This evidence suggested that only a subset of patients with CD was able to respond to chronic treatment with bromocriptine. On the other hand, the potent dopamine agonist cabergoline induced a normalization of ACTH and/or cortisol secretion and/or a significant tumor shrinkage in two ACTH-secreting pituitary tumors associated with Nelson's syndrome (12, 13), a silent ACTH (14), an aberrant ACTH-secreting (15), and a mixed ACTH and PRL-secreting (16) pituitary tumors. Moreover, in a preliminary report of this study on the first 10 patients with CD, a short-term cabergoline treatment induced a significant inhibition of cortisol secretion in six (60%) and normalization in four (40%) patients, suggesting a higher effectiveness of cabergoline than bromocriptine in the treatment of CD (9). However, no study has ever evaluated the effectiveness of long-term treatment with cabergoline in patients with CD.

The results of the current study confirmed that a short-term treatment with cabergoline is able to induce an inhibition of cortisol secretion in 15 (75%), and normalization in seven (35%), out of 20 patients with CD. In addition, they demonstrated a successful effectiveness of cabergoline after long-term treatment as well. Among the patients with an initial responsiveness, five experienced a treatment escape and two drug intolerance. Therefore, half of the patients with a short-term responsiveness continued to respond with stable normal cortisol

TABLE 3. Clinical, biochemical, and radiological features of patients with CD long-term responsive to cabergoline treatment

Parameter	Baseline (10 patients)	12-month treatment (10 patients)	24-month treatment (8 patients)	*P* value
Body mass index (kg/m^2)	28.2 ± 0.9	28.0 ± 0.8	27.1 ± 0.7[a]	0.011
Waist to hip ratio	1.12 ± 0.06	1.03 ± 0.06[b]	1.01 ± 0.06[a]	0.002
Systolic blood pressure (mm Hg)	141.5 ± 4.4	118.0 ± 5.1[a]	123.1 ± 4.4[a]	0.015
Diastolic blood pressure (mm Hg)	91.0 ± 2.5	75.0 ± 3.8[b]	80.0 ± 3.4[a]	0.002
Heart rate (beats/min)	71.5 ± 2.3	79.7 ± 2.2[a]	76.9 ± 2.1	0.368
Fasting serum glucose (mg/dl)	128.2 ± 8.1	115.0 ± 3.2	106.0 ± 5.2[a]	0.002
Fasting serum insulin (μU/ml)	10.9 ± 1.5	8.4 ± 1.0[b]	7.2 ± 1.0[a]	0.002
HOMA-IR	3.47 ± 0.66	2.37 ± 0.29[b]	1.88 ± 0.29[a]	0.001
HOMA-B (%)	66.6 ± 9.2	61.0 ± 8.7	67.8 ± 11.3	0.607
Plasma ACTH (pg/ml)	62.4 ± 6.1	45.4 ± 3.6[b]	35.6 ± 3.2[a]	0.002
Serum cortisol (μg/liter)	236.2 ± 17.6	160.2 ± 6.0[b]	144.6 ± 10.5[a]	0.002
Urinary cortisol (μg/d)	558.1 ± 69.1	118.5 ± 12.2[b]	115.4 ± 7.8[a]	0.002
Tumor volume (mm^3)	224.3 ± 31.9	158.1 ± 46.2[a]	133.7 ± 56.7[a]	0.084

Normal ranges for: fasting serum glucose, 60–110 mg/dl; serum insulin, 1–20 μU/ml; plasma ACTH, 10–130 pg/ml; serum cortisol, 50–200 μg/liter; urinary cortisol, 35–135 μg/d; and serum PRL, 0–25 μg/liter for females and 0–15 μg/liter for males. Urinary cortisol levels represent the mean of three different urine collection. *P* values indicate the global significance.

[a] $P < 0.05$ compared with baseline.

[b] $P < 0.01$ compared with baseline.

TABLE 4. Clinical, biochemical, and radiological features of patients with CD who experienced a treatment escape during the long-term treatment with cabergoline

Parameter	Baseline (5 patients)	6-month treatment (5 patients)	12-month treatment (5 patients)	18-month treatment (4 patients)	*P* value
Body mass index (kg/m^2)	26.1 ± 1.6	26.6 ± 1.5	25.9 ± 1.3	26.6 ± 1.6	0.546
Waist to hip ratio	1.07 ± 0.05	1.00 ± 0.06[a]	0.99 ± 0.06[a]	1.08 ± 0.07	0.027
Systolic blood pressure (mm Hg)	155.0 ± 4.5	136.0 ± 4.0[a]	139.0 ± 3.7[a]	142.5 ± 2.5	0.040
Diastolic blood pressure (mm Hg)	100.0 ± 4.2	89.0 ± 2.9[a]	91.0 ± 3.7[a]	95.0 ± 2.9	0.027
Heart rate (beats/min)	65.6 ± 1.6	72.2 ± 4.5	66.6 ± 4.0	69.0 ± 2.6	0.557
Fasting serum glucose (mg/dl)	131.4 ± 5.6	119.0 ± 4.4[a]	119.8 ± 3.5[a]	125.3 ± 1.3	0.209
Fasting serum insulin (μU/ml)	11.4 ± 2.3	10.4 ± 2.4	9.6 ± 2.1[a]	8.2 ± 2.5	0.029
HOMA-IR	3.72 ± 0.82	2.99 ± 0.69[a]	2.84 ± 0.65[a]	2.53 ± 0.77	0.038
HOMA-B (%)	76.5 ± 6.9	82.0 ± 10.4	69.1 ± 7.2	61.4 ± 9.7	0.165
Plasma ACTH (pg/ml)	74.0 ± 3.6	57.5 ± 5.0[a]	59.0 ± 13.1	76.0 ± 10.4	0.022
Serum cortisol (μg/liter)	245.4 ± 25.0	157.4 ± 11.0[a]	200.6 ± 22.9	250.3 ± 23.3	0.112
Urinary cortisol (μg/d)	569.6 ± 86.4	172.6 ± 24.3[a]	377.8 ± 68.1	623.0 ± 49.5	0.019
Tumor volume (mm^3)	277.8 ± 92.0		268.7 ± 85.5		0.465

Normal ranges for: fasting serum glucose, 60–110 mg/dl; serum insulin, 1–20 μg/ml; plasma ACTH, 10–130 pg/ml; serum cortisol, 50–200 μg/liter; urinary cortisol, 35–135 μg/d; and serum PRL, 0–25 μg/liter for females and 0–15 μg/liter for males. Urinary cortisol levels represent the mean of three different urine collections. *P* values indicate the global significance.

[a] $P < 0.05$ compared with baseline.

levels for a period as long as two years. It has to be pointed out that although five patients were completely resistant and seven patients withdrew cabergoline for treatment escape or intolerance, six of eight patients partially responsive to short-term treatment became fully responsive after increasing the cabergoline dose, and three of them showed a persistent normalization of cortisol secretion during long-term treatment, suggesting that the cabergoline dose and the period of treatment necessary to normalize cortisol secretion were extremely variable for each patient with CD. Considering the entire population of 20 patients, cabergoline was able to stably control cortisol secretion in 50% patients after 1 yr and 40% of patients after 2 yr treatment. It is noteworthy that at the diagnosis, 45% of patients had a mild hyperprolactinemia, which were significantly associated with short-term but not long-term responsiveness to cabergoline treatment. This evidence seems to suggest that the presence of hyperprolactinemia could be considered a marker of responsiveness to initial but not chronic cabergoline treatment.

An important finding of the current study was the demonstration that cabergoline treatment improved hypertension and glucose intolerance in patients with CD. In fact, blood pressure and the prevalence of hypertension already decreased after short-term and nearly normalized in the majority of patients during long-term treatment. On the other hand, glucose and insulin levels as well as insulin resistance, and the prevalence of impaired glucose tolerance or diabetes mellitus decreased during long-term treatment. Moreover, the improvement of hypertension and glucose intolerance in patients who were resistant or escaped from treatment suggest that cabergoline might directly and positively influence blood pressure and glucose tolerance independently of the change in cortisol secretion. The direct effect of dopamine agonists on hypertension is largely documented and justified by the expression of dopamine receptors in the vascular system, where they mediate a relaxing effect, with a consequent reduction of peripheral resistance (17). The direct effect of dopamine agonists on glucose tolerance is supported by the evidence that bromocriptine is able to improve glucose homeostasis in patients with diabetes mellitus, probably due to a potentiation of insulin-mediated suppression of hepatic glucose production or stimulation of splanchnic glucose uptake (18). The results of this study concur with these hypotheses and suggest that even when no effect on cortisol secretion was found, cabergoline may have a consistent impact on blood pressure and glucose intolerance.

Another essential point of this study was the demonstration that cabergoline did not induce major side effects in patients with CD. Hypotension associated with severe asthenia was only found in two patients, probably because of the direct effect of cabergoline on the vascular system. It is noteworthy that no significant cardiac valve dysfunction was found in the patients of the study, with the exception of a slight worsening of tricuspid regurgitation in one patient. This is a crucial point because cabergoline treatment has been recently described to be associated with an increased prevalence of cardiac valve insufficiency in patients with Parkinson's disease (19, 20). However, patients with Parkinson's disease are often elderly patients, and are treated with a high dose of the drug for a long period of time. Although patients with CD often require higher doses of cabergoline than those with hyperprolactinemia, the doses are still sensibly lower than those used by patients with Parkinson's disease and the period of treatment was only 2 years. This could help to explain the reason for the lack of cardiac valve disease in the group of patients of this study with CD.

In conclusion, the current study demonstrated that cabergoline is effective in controlling cortisol secretion in more than one third of a limited population of patients with CD during chronic treatment, without major side effects. However, further studies on a larger population of patients are mandatory to confirm the results of the current study. If these data are confirmed, cabergoline could be considered a useful tool in the management of

persistent and/or recurrent CD, and may be proposed as the first real causative medical treatment for CD.

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