Limited value of cabergoline in Cushing’s disease: a prospective study of a 6-week treatment in 20 patients

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Abstract

Context and objective: The role of cabergoline in Cushing’s disease (CD) remains controversial. The experience is limited to case reports and few open studies that report the effects determined after ≥1 month of treatment. In prolactinomas and dopamine-responsive GH-secreting tumours, effects of cabergoline are seen within days or weeks. Here, we searched for short-term effects of cabergoline in CD.

Design: Twenty patients (19 naïve and one recurrent) were included in a prospective study. Cabergoline was administered in increasing doses of 0.5–5 mg/week over 6 weeks.

Methods: Urinary free cortisol (UFC) 24 h, morning cortisol and ACTH, and salivary cortisol at 0800, 1600 and 2300 h were determined once weekly throughout. Diurnal curves (six samples) of serum cortisol were measured at start and end.

Results: At study end, the median cabergoline dose was 5 mg, range 2.5–5 mg/week. The prolactin levels, markers of compliance, were suppressed in all patients. During the treatment, hypercortisolism varied, gradual and dose-dependent reductions were not seen. Five patients had a >50% decrease of UFC, three had a >50% rise of UFC. Salivary cortisol at 2300 h showed a congruent >50% change with UFC in two of the five cases with decreased UFC, and in one of the three cases with increased UFC. One patient with decreases in both UFC and 2300 h salivary cortisol also had a reduction in diurnal serum cortisol during the course of the study.

Conclusions: Cabergoline seems to be of little value in the management of CD. Only one patient had a response-like pattern. Given the known variability of disease activity in CD, this might represent a chance finding.

Introduction

Cushing’s disease (CD) is caused by excess cortisol production driven by abnormal adrenocorticotropic hormone (ACTH) secretion from a pituitary tumour. Treatment is primarily surgical, for the patients not cured by an operation, medical treatment and/or radiotherapy remain (1, 2). Drugs used either interfere with adrenal steroid production, such as ketoconazole, metyrapone and mitotane, or block glucocorticoid action, e.g., mifepristone, or directly target pituitary tumour ACTH secretion, e.g., pasireotide, a somatostatin receptor analogue recently approved for treatment of CD (3). For almost 40 years following the first reports of the use of oral bromocriptine in Cushing’s syndrome, dopamine agonists have been explored as inhibitors of ACTH secretion in Cushing’s syndrome (4). The outcome has been markedly variable, with inconsistent effects on ACTH/cortisol levels in most studies that have included at least five patients (5, 6, 7, 8, 9, 10, 11, 12). Invitti et al. (13) performed a
3-month trial with monthly injections of 50–100 mg bromocriptine in six patients with CD. The injections suppressed prolactin, but did not influence ACTH, serum cortisol or urinary free cortisol (UFC) levels.

In recent years, three studies have reported an effect of cabergoline, a dopamine agonist more potent than bromocriptine, after ≥ 1 month of treatment in patients with recurrent/persistent CD after surgery (14, 15, 16, 17). In a single-centre study Pivonello et al. (14) treated ten patients with cabergoline up to 3 months and noted a normalization of UFC in 40%. In a subsequent report in 2009 (15), the same ten patients were included together with another ten patients from the same centre. A persisting pituitary tumour was detectable in 15 of the 20 patients, and mild hyperprolactinemia was present in eight patients (40%). Effect of treatment was monitored by UFC and measured monthly, and the dose of cabergoline adjusted accordingly to 1–7 mg/week. The final dose at 3 months ranged from 1 to 3, median 3 mg/week, and, at 12–24 months, 1 to 7, median 3.5 mg/week. UFC levels within the normal range were used as the single criterion for response. Sustained control of cortisol secretion after 12–24 months was described in eight of 20 (40%) of patients. Vilar et al. (16) treated 12 CD patients who had persistent hypercortisolism after surgery. The maximal cabergoline dose was 3 mg/week. All 12 patients reportedly had >15% reduction of UFC on the drug at 6 months; the three patients with the smallest increase in UFC at study start reached normalization at a dose of 2–3 mg/week. In a retrospective study, Godbout et al. (17) evaluated 30 patients treated for 12–60 months with doses up to 6 mg/week, mean 2.1 mg/week. UFC had been monitored every 1–3 months. Normalization of UFC was observed within 3–6 months in 11 (37%) of the patients, a partial response (defined as decrease of UFC to <125% of upper normal limit) in four patients, and in 15 patients (50%) UFC increased by a mean of 35%. There are no placebo-controlled studies reported in the literature. This should be an optimal design given the known variability in disease activity in CD, illustrated by an up to 50% day-to-day fluctuation in UFC (18), and the frequent occurrence of intermittent hypercortisolism in 17–36% of patients (19).

In the present study, we investigated treatment with cabergoline at increasing doses up to 5 mg/week over 6 weeks in unselected newly diagnosed patients with CD. The assumption was that analogous to the rapid effects induced by pasireotide in CD, i.e., a reduction in UFC in 76% (22/29) of patients, with a normalization in 17% after 15 days on drug (20), and the rapid effects of cabergoline, within hours or days, on prolactin secretion in prolactinomas (21), and in dopamine-responsive growth hormone (GH)-secreting adenomas (22), an effect of cabergoline on cortisol levels in CD should be apparent within a short period of treatment, i.e., within the present study duration.

Subjects and methods
Subjects

Twenty patients with ACTH-dependent CD were recruited at four academic pituitary centres. The diseases were newly diagnosed in 19 patients, and one patient had recurrent disease after previous surgery for a microadenoma. The diagnosis was based on clinical features indicating hypercortisolism, increased 24 h UFC on at least two occasions, loss of circadian cortisol rhythm in serum and lack of cortisol suppression at a dexamethasone suppression test. Sixteen patients had a pituitary adenoma (macroadenoma: n = 3 and microadenoma: n = 13) while four patients had no detectable tumour at the time of a magnetic resonance imaging (MRI). A pituitary source of ACTH secretion was confirmed by bilateral sinus petrosal sampling (BIPSS) in 15 patients, including the four patients with no visible adenoma at MRI. Five patients did not have a BIPSS; three of these had macroadenomas and one had a microadenoma. In these four patients, a diagnosis of an ACTH-producing adenoma was verified by immunohistochemistry of the removed tumour specimen. The fifth patient in whom BIPSS was not performed was the one with the recurrence of hypercortisolism subsequent to an earlier removal of an ACTH-secreting adenoma at pituitary surgery, i.e., the source of ACTH was known.

After completion of the study, 18 patients had pituitary surgery. A corticotroph adenoma was confirmed at histopathology in 13 of 18 patients, corticotroph hyperplasia was found in one of 18. In four patients no adenoma was identified at examination of the tissue specimens. One of these patients was biochemically cured by surgery, two were biochemically improved, while in one patient UFC remained high. This patient had a bilateral petrosal sampling prior to surgery strongly suggesting a pituitary source of ACTH. One patient with a microadenoma (as indicated by BIPSS) elected to have treatment with stereotactic gamma knife radiosurgery instead of transsphenoidal surgery, and the patient with recurrent disease with no visible adenoma was not operated but continued on cabergoline.
Study protocol

At study start, hypercortisolism was confirmed by elevated UFC >20% above the upper limit of normal (ULN=170 nmol/24 h) in two samplings in all cases. The patients were then given increasing doses of cabergoline; week 1: 0.5 mg (0.25 mg on 2 days in the week), week 2: 1.0 mg (0.5 mg on 2 days in the week), weeks 3–4: 3 mg (1 mg on 3 days each week) and weeks 5–6: 5 mg (1 mg on 5 days each week). Treatment was monitored by weekly samplings of UFC, morning serum cortisol and plasma ACTH, salivary cortisol at 1600, 2300 and 0800 h. At the study start and study end, the patients were hospitalized for 2 days during which, in addition to UFC and salivary cortisol, the diurnal variation of serum cortisol (at 1600, 2000, 2400, 0400 and 0800 h) was determined. S-prolactin served as a marker of compliance.

Serum and plasma were collected by routine procedures and samples stored frozen until analysis. All samples except prolactin were analyzed at a single laboratory. UFC was determined by liquid chromatography–tandem mass spectrometry (LC–MS/MS), upper reference level <170 nmol/24 h. Salivary cortisol was determined by an electrochemiluminescent assay (ECLIA), Roche Ltd, reference value at 2300 h <9.7 nmol/l (23). Measurement of salivary cortisol, probably due to cross reactivity, includes also a considerable amount of salivary cortisone, whereas urine cortisol by LC–MS/MS measures only cortisol and not cortisone. The differences in the two measurements are unlikely to confound the results as the secretion and turnover of cortisone and cortisol are tightly linked. S-cortisol was determined by ECLIA (Roche Ltd) and ACTH by ECLIA (Roche Ltd), upper reference level <14 pmol/l. All urine, saliva and serum samples of a given individual were analyzed in a same assay run. Adverse events were actively asked for at each visit.

Response criteria

More than 50% reduction of UFC was considered a significant response, in agreement with Pivonello et al. (14). Recently, in a study of baseline UFC levels in a large cohort of CD patients, an intra-patient variability of ~ 50% in 24 h UFC measurements was described, and suggested relevant as a target for estimation of treatment effects (18).

Statistical analyses

Statistical significance was evaluated by Friedman’s ANOVA using the Statistica Software (Statsoft, Inc., Tulsa, OK, USA). Wilcoxon’s paired t-test was used to examine changes between time-points, and the Bonferroni’s correction was used to adjust multiple comparisons. P values <0.05 would be considered significant.

The study was approved by the Ethics Committee, Lund University, Sweden, Dnr 2010/97, and by the Swedish Medical Agency, Eudra-CT nr 2010-018720-12, Dnr 151:2010/10925. The patients were informed about the purpose and procedure of the study and gave their written informed consent.

Results

The basal characteristics of the patients and the changes in UFC and 2300 h salivary cortisol during the study are presented in Table 1. All patients except two had normal prolactin at study start; all had suppressed prolactin at study end. Most patients – 17 of 20 – were able to follow the dose escalation schedule to a final dose of 5 mg/week. In three patients the final dose was reduced to 2.5, 3 and 3 mg respectively, due to side effects (visual hallucinations in one patient, dizziness and tiredness in one, and nausea/constipation in one patient). Side effects not leading to dose reductions were reported in another ten patients (mild nausea in three, moderate nausea in one, mild gastrointestinal discomfort in one, loose stools in one, mild dizziness, constipation and nasal congestion in one, tiredness in one, and tiredness and change in personality in one patient). In two of these patients, the side effects appeared already at a dose of 1 mg/week but resolved spontaneously in spite of dose escalations, while in eight patients side effects appeared at a dose of 3 or 5 mg/week and remained throughout the study period. Body weight, blood pressure, fasting glucose and HbA1c were determined throughout the 6 weeks of study. No changes of these parameters were detected.

The weekly median UFC and salivary cortisol 2300 h values over the 6-week treatment period are illustrated in Fig. 1. No significant changes in the study cohort were found. Likewise, there were no changes in median ACTH and morning S-cortisol values over the treatment period.

The urinary outputs of cortisol varied considerably over the 6 weeks on cabergoline, and dose-dependent gradual reductions were not seen. In five patients (cases 1, 4, 6, 10 and 17), a >50% fall in urinary cortisol (start vs end values) was determined. In two of these patients (cases 1 and 4), the 2300 h salivary cortisol levels were decreased >50% at 6 weeks, and in case 4 the mean diurnal serum cortisol levels also indicated an improvement. In the other three patients, the reduced UFC was not reflected in the
We found that several patients maintained a high cortisol production throughout the study, with only small fluctuations in urinary cortisol output and salivary cortisol levels, in spite of compliance with the cabergoline medication as indicated by suppressed prolactin levels. The correlation between UFC and 2300 h salivary cortisol or means of the three salivary cortisol samples (not shown) was modest, as reported by others regarding UFC and late night salivary cortisol (24). We also noted variations in morning serum cortisol and plasma ACTH levels in individual patients. This could be explained by the episodic secretion of ACTH known to occur in CD and in normal individuals (25). The variation in hypercortisolism observed in cases 4 and 6 may also reflect periodic hypercortisolism, as described in several publications (19, 26, 27, 28, 29). An observed increase in UFC by a mean of 35% in 15 of 30 patients treated with cabergoline for 4 months (17) likely represents another example of spontaneous fluctuations of cortisol production in CD. In establishing a diagnosis of CD, the use of multiple tests has been recommended in order to account for this variation, especially in mild and episodic disease (29). Neither a normal UFC, nor a normal midnight salivary cortisol excludes mild cyclic CD (24).

Table 1  Basal characteristics of 20 patients with Cushing's disease at start and end of a 6-week trial with cabergoline.

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UFC, urinary free cortisol, ref range <170 nmol/24 h. (↑) The arrows indicate a >50% change from basal UFC value. When a congruent >50% change in salivary cortisol 2300 h was found, an arrow has been inserted in the cortisol salivary 2300 h column.

Discussion

We found that several patients maintained a high cortisol production throughout the study, with only small fluctuations in urinary cortisol output and salivary cortisol levels, in spite of compliance with the cabergoline medication as indicated by suppressed prolactin levels.
possible fluctuations caused by non-treatments effects to become apparent.

The rationale for using a dopamine agonist in treatment of CD relies on dopamine receptors being present in corticotroph tumours. In the normal anterior pituitary about 70–90% of the cells express dopamine receptors, notably the subtype 2 receptor. In a detailed study of 89 pituitary tumours, D2R was detected by in situ hybridization (ISH) in 79/89 (89%), including 16/16 lactotroph, 7/7 mixed somatotroph/lactotroph, 12/14 somatotroph and 11/16 corticotroph (functioning and silent) adenomas, and, when examined by immunocytochemistry (ICC), in 60/62 adenomas. The ISH and ICC signals for D2R were strongest in the lactotrophic adenomas, intermediate in gonadotroph, null cell, thyrotroph and somatotroph, and lowest in corticotroph adenomas (30). Tateno et al. (31) examined DR subtypes in non-functioning pituitary tumours (NFT), silent corticotroph adenomas (SCA) and ACTH-secreting pituitary tumours (CD). DR2 mRNA was highest in NFT and markedly lower in SCA and CD. Collectively, these studies indicate that corticotroph tumours typically have lower levels of the D2R in comparison with other adenomas, in particular compared with lactotroph and gonadotroph/NFT.

In vitro studies on effects of dopamine agonists and bromocriptine, respectively, on ACTH release from human corticotroph tumours have yielded conflicting results. In comparison, dopamine agonists have shown consistent inhibitory effects on the release of prolactin from tissue cultures of prolactinomas, as have somatostatin analogues on GH release from somatotropinomas. Pivonello et al. (14) examined D2R expression in 20 tumours, ten from The Netherlands tissue bank and ten tumours from Naples. Four of the tumours were studied in vitro, two of them showed 43–52% inhibition with bromocriptine, and 53–60% inhibition with cabergoline after 72 h incubations. Both these tumours were D2R positive at immunohistochemistry. The two other tumour cell preparations showed no inhibition and were reported as D2R negative. Van der Pas et al. (32) studied cultures from corticotroph adenomas and reported a mean 41.9% inhibition of ACTH release in three of four adenomas upon 72 h incubation with cabergoline. The variable results may be influenced by technical difficulties inherent to this type of studies. Limited amount of tumour tissue precludes multiple incubations and tests of reproducibility. Mechanical and/or enzymatic liberation of cells for culture may result in cell death with release of proteolytic enzymes and affect the ACTH peptide, known to be easily degraded, particularly during long incubation times.

Since the first publication (1999) of an effect of cabergoline in a patient with Nelson’s syndrome (33), there have been another five case reports on successful use of the drug in ACTH-producing tumours (34, 35, 36, 37, 38). Most of these tumours have had characteristics different from the average ACTH-secreting adenomas. Two initially ACTH-silent macroadenomas considered to be completely removed by surgery subsequently recurred.
as large invasive macroadenomas (34, 35). Upon recurrence, one had evolved into an ACTH-producing tumour causing CD (35). Both tumours regressed on moderate doses of cabergoline, 1.5 and 2 mg/week respectively. In one of the cases, the tumour escaped control after 5 years on treatment, but was subsequently controlled by a high dose, 6 mg/week (35). Another large invasive macroadenoma (36) had a gradual lowering of ACTH, from about 50 to 29 pg/ml over 3 months on 0.25–0.5 mg/week. In two of the reported patients (34, 36) the DR2 mRNA with the medication was ascertained by measurements of prolactin levels; all cases suppressed at study end. The horizontal lines represent upper levels of normal, solid line UFC 170 nmol/24 h and dashed line salivary cortisol at 2300 h 9.7 pmol/l.

**Figure 2**

Individual urinary free cortisol/24 h (UFC, solid lines) and 2300 h salivary cortisol (broken lines) values determined weekly (days 1, 7, 14, 21, 28, 35 and 42) in the cohort of 20 patients with Cushing’s disease given escalating doses of cabergoline over 6 weeks; median dose at study end 5 mg/week. Compliance
expression was intense, and in the same order as that observed in control prolactinomas. In another unusual tumour, a macroadenoma co-secreting prolactin and ACTH, clinical and biochemical features of hypercortisolism disappeared upon treatment with cabergoline (37). A patient with Nelson’s syndrome and a macroadenoma had a lowering of ACTH from 112 to 38 pg/ml after 1 month on a low dose of cabergoline, 1 mg/week (38). After a year the tumour had disappeared, but to what extent this was a drug effect is difficult to evaluate, since pituitary irradiation had been given before commencement of cabergoline. Possibly, sensitivity to dopamine may develop in exceptional corticotroph tumours and explain positive effects of dopamine agonists in some patients with CD. In our view, such responsiveness is likely to be rare, and a publication bias may have contributed to a skewed impression of the usefulness of dopamine agonists in the management of CD.

There are several strengths with the present study: the prospective design, the inclusion of naïve (19/20) unselected patients with CD, the frequent assessments that enables spontaneous fluctuations to be observed, and the assessment of cortisol status in several compartments; urine, saliva and blood. The study did not have a placebo arm and did not include cases with marked hyperprolactinemia and/or large invasive macroadenomas. A limitation might be the relatively short study duration of 6 weeks. However, patients were exposed to ≥3 mg cabergoline/week for a total of 1 month, a dose which is slightly higher than the average dose of 2.5 mg/week reported to achieve normalization of UFC in the three other studies (15, 16, 17). We feel that treatment for a month should be sufficient to detect a drug effect, in particular as repeated hormonal measurements were performed. It could be argued that persistent/recurrent adenomas may have certain characteristics, including a dopamine receptor profile different from the naïve adenomas, and therefore respond better to dopamine agonists. This possibility has to our knowledge not been addressed in the literature.

To summarize, the present data indicate that cabergoline is of little clinical value in patients with CD. The findings do not exclude that dopamine agonists can be of benefit in patients harbouring exceptional tumours. In our view, a positive response to cabergoline should discernable within a few weeks, in line with the typical and rapid effects of dopamine agonists and somatostatin analogues acting on their cell surface receptors in patients with prolactinomas and somatotropinomas. If unaltered hypercortisolism prevails over a month, a change in therapy will be indicated.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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