

Cushing's Disease

Sustained remission in five cases induced by medical therapy with the dopamine agonist cabergoline

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مرض كوشينج الاستجابة الكاملة والمستمرة للعلاج بواسطة عقار الكابرجولين

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المخلص: نُدرج هنا وصفاً لخمس حالات مصابة بمرض كوشينج في مستشفى جامعة السلطان قابوس عولجت لأول مرة باستخدام دواء الكابرجولين لمعرفة مدى فعاليته. كانت مستويات هرمون الكورتيزول (في الصباح والمساء) والهرمون الموجه لقشر الكظر مرتفعة، وأثبت الرنين المغناطيسي وجود ورم في الغدة النخامية عند ثلاثة مرضى فقط، ولم يثبت وجود ورم فارز للهرمون الموجه لقشر الكظر خارج الغدة النخامية عند المرضين الآخرين. تم استخدام دواء الكابرجولين بجرعة 1 ملجم يومياً، وكانت هناك استجابة كاملة عند أربعة مرضى حيث انخفض مستوى هرمون الكورتيزول إلى الحد الطبيعي، وأثبتت زيارات المتابعة استقرار الحالة السريرية والكيميائية الحياتية عندهم بعد 14 و 28 و 44 و 378 يوماً على التوالي. أما المريض الخامس فلم يستجب للعلاج. نوصي بعلاج كل حالات مرض كوشينج بدواء الكابرجولين حتى يرجع الهرمون لمعدله الطبيعي قبل إجراء العملية، أو يمكن تفادي العملية واستخدامه على المدى البعيد.

مفتاح الكلمات: مرض كوشينج، الهرمون الموجه لقشر الكظر، مستقبلات دوبامين، دواء كابرجولين، تقرير حالة، عُمان.

ABSTRACT: We report five cases of Cushing's disease where the patients were given a therapeutic trial of cabergoline. Morning serum cortisol, adrenocorticotrophic hormone (ACTH), and sleeping cortisol concentrations were significantly raised. Magnetic resonance imaging (MRI) scans revealed pituitary microadenomas in 3 patients but were normal in the others. Ectopic ACTH production was excluded in the 2 patients with normal MRI scans. All were given a therapeutic trial of cabergoline (1 mg daily). Four patients responded with a prompt fall in serum cortisol levels and had a sustained clinical and biochemical remission for 378, 44, 28 and 14 days, respectively. One patient failed to respond. In conclusion, we suggest that all patients with Cushing's disease should undergo a therapeutic trial of cabergoline. Responders can then be prepared for surgery or, if needed, treated medically in the long term.

Keywords: Cushing's disease; Adrenocorticotrophic hormone; Dopamine receptors; Cabergoline; Case report; Oman.

CUSHING'S DISEASE DUE TO PITUITARY adenoma is the most common cause of adrenocorticotrophic hormone-(ACTH) dependent Cushing's syndrome. Magnetic resonance imaging (MRI) may show the adenoma, but the scan may be normal in up to 40% of patients.¹ The remaining 15% of cases of ACTH-dependent Cushing's syndrome are due to ectopic ACTH secretion, usually from bronchial, pancreatic, or neuroendocrine tumours (NETs) or, rarely, due to tumours that produce corticotropin releasing hormones (CRH).²

Most NETs express somatostatin receptors, mainly types 2 and 5, and thus are amenable to inhibition by somatostatin analogues such as octreotide as opposed to ACTH-producing adenomas which usually do not respond due to lack of expression or down regulation of somatostatin receptors.³

We report a series of five cases of Cushing's disease, four of which responded successfully to cabergoline, which has been used sporadically in Cushing's disease, but is not yet the standard of care. The patients and their families were all made aware

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Table 1: Serum cortisol and adrenocorticotrophic hormone (ACTH) data on admission

Case number	1	2	3	4	5
Cortisol (nmol/L)					
Fasting level (morning) (n = 184–580)	752	612	961	933	751
Sleeping level (n <128)	458	430	398	704	--
Post 1 mg dexamethasone (n <50)	523	317	660	---	--
ACTH (pmol/L)					
Fasting level (n = 1.6–13.9)	14.4	12.9	37	24	27

ACTH = adrenocorticotrophic hormone

that this drug is not yet the standard of care and consented to its use. We suggest that a therapeutic trial of cabergoline should be given to all patients in preparation for surgery, as well as to those who are not candidates for surgery.

Case One

A 32-year-old married Omani woman with three children was admitted to our hospital with a recurrent thigh abscesses which required surgical drainage and antibiotics. Four years previously, she had presented with type 2 diabetes mellitus (DM) and hypertension. She had been amenorrhoeic for the previous year. She was on 90 daily units of insulin mixtard and 10 mg daily of lisinopril. On examination, she was severely Cushingoid with central obesity, a moon face, male pattern baldness, hirsutism, thin skin, and easy bruising. The patient's blood pressure was 185/104 and fasting blood sugar was 14 mmol/L with a HbA1c of 10.9%. Liver, bone, renal, and thyroid profiles were within normal limits.

The patient's serum cortisol and ACTH levels, both fasting and sleeping, were in keeping with ACTH-dependent Cushing's syndrome [Table 1]. The pituitary MRI, chest and abdominal computed tomography (CT) scans, and the serum chromogranin A levels were normal (56 µg/L,

normal range 27–94).

A therapeutic trial of somatostatin analogue octreotide 100 µg three times daily was carried out for three days but failed to lower serum cortisol levels [Table 2]. A laparoscopic bilateral adrenalectomy was offered but the patient refused; thus, treatment with the dopamine agonist cabergoline was attempted at a dose of 1 mg/day. The response was dramatic, with normalisation of serum cortisol levels within one week of the treatment. Levels subsequently remained normal for up to 378 days in this case [Table 3].

After 4 months, there was a complete disappearance of the patient's Cushingoid features, resumption of normal menses, normalisation of blood pressure to 123/86, and a HbA1c of 5.7% without any antihypertensive or diabetic medications. After 52 weeks, the cabergoline was reduced to 0.5 mg daily. Two weeks later, she remained in biochemical remission with normal cortisol values [Table 3]. She currently remains in remission and is taking 0.5 mg of cabergoline 3 times a week and is now pregnant after 10 years of secondary infertility.

Case Two

A 28-year-old woman presented with hypothyroidism, hypertension, mild type 2 DM, obesity, irregular periods, and hirsutism. She was taking thyroxine 75 µg daily for central hypothyroidism, and irbesartan/hydrochlorothiazide 150/12.5. Examination revealed central obesity and a small buffalo hump. The patient's blood pressure was controlled at 125/70 and the fasting blood sugar was 6.3 mmol/L on diet alone. HbA1c was 6.5% (n <6.0) with normal bone, liver, electrolyte and

Table 2: Serum cortisol levels before and during the administration of octreotide (100 mcg) subcutaneously

Time/Hours	Fasting cortisol levels (nmol/L)			
	0	24	48	72
Case 1	650	590	680	920
Case 2	752	-	-	750

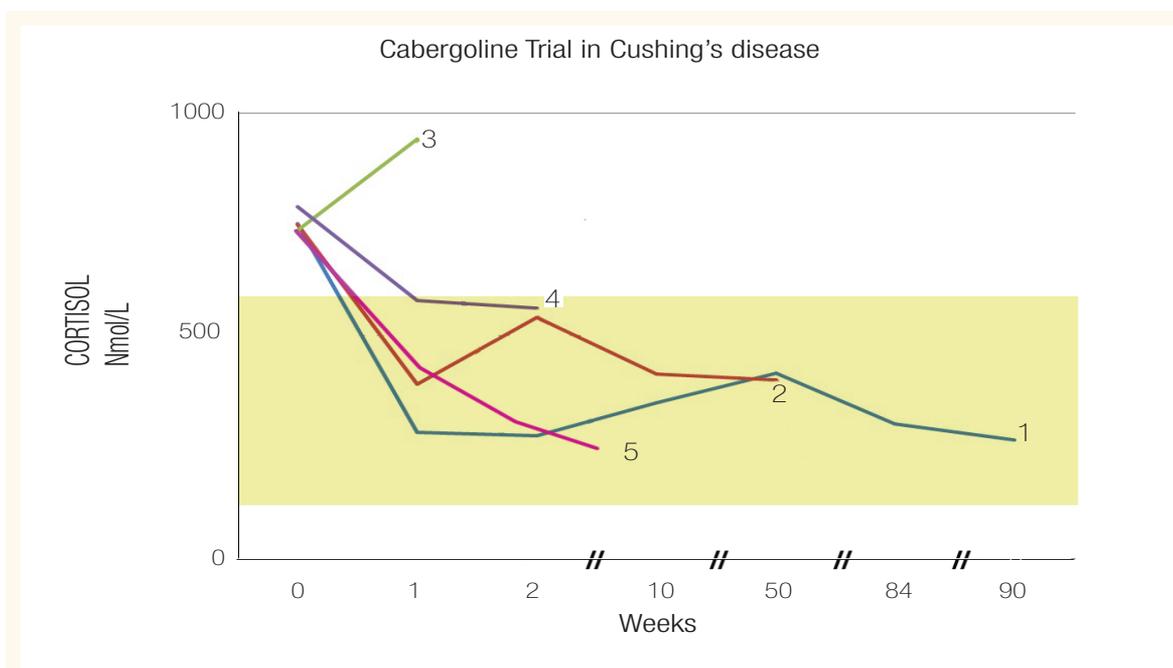


Figure 1: Response to cabergoline therapy in 5 patients with Cushing's disease. The normal range is shaded.

thyroid profiles. Serum chromogranin A was 43 ug/L (normal range 27–94). A pituitary MRI and adrenal CT scan revealed a microadenoma and nodular enlargement of the left adrenal gland. Fasting serum cortisol, ACTH and sleeping cortisol concentrations were in keeping with ACTH-dependent Cushing's syndrome [Table 1].

A 72-hour therapeutic trial of octreotide failed to lower serum cortisol levels [Table 2]. A trial of cabergoline, however, produced a rapid and sustained fall in serum cortisol levels [Table 3].

Case Three

A 46-year-old female patient presented with clinically severe Cushing's syndrome with hypertension, DM, recurrent abscesses, and

osteomyelitis of the foot. Cushing's disease was confirmed by raised serum cortisol and ACTH levels, and sleeping and post-dexamethasone cortisol levels [Table 1]. A pituitary MRI revealed a 6 x 4 mm microadenoma. A CT scan of the abdomen revealed normal adrenal glands. She failed to respond to a one-week trial of cabergoline [Table 3]. Surgery was advised but the patient discharged herself against medical advice. She later underwent transsphenoidal surgery in India and was cured.

Case Four

A 45-year-old Omani woman was admitted to our hospital for assessment and possible adrenalectomy. She presented with type 2 DM and hypertension

Table 3: Cabergoline trial serum cortisol levels before and during the daily administration of cabergoline

Days	Fasting Cortisol Levels (nmol/L) (n = 184–580)								
	0	7	14	21	28	44	196	364	378
Case 1	752	284	276				415	513	303
Case 2	612	392	541			414			
Case 3	736	914							
Case 4	789	578	561						
Case 5	751	406		274	250				

and was taking 2 mg of glimepiride and 150 mg/12.5 mg of valsartan and hydrochlorothiazide (Novartis Pharmaceuticals UK Ltd.) daily. The CT scan initially revealed a right-sided 8 x 8 mm adrenal nodule.

On examination, she was severely Cushingoid, with hyperpigmentation, a moon face, supraclavicular fat pad, and central obesity. The patient's blood pressure was 170/85 and fasting blood glucose level was 6.4 mmol/dL with a Hb1Ac level of 7.5%. Liver, bone, renal, and thyroid profiles were within normal limits. Fasting serum cortisol levels, and sleeping ACTH levels were in keeping with ACTH-dependent Cushing's syndrome [Table 1]. A pituitary MRI scan showed a 10 x 10 mm microadenoma.

A therapeutic trial of cabergoline was carried out for 2 weeks [Table 3]. The response was dramatic, with normalisation of serum cortisol levels within a week of treatment [Table 3]. She subsequently underwent successful transsphenoidal pituitary surgery.

Case Five

A 19-year-old female presented to the Emergency Department with severe psychosis. Eight months earlier she had presented with Cushing's syndrome and was found to have an ACTH-secreting pituitary tumor and had undergone transsphenoidal surgery. She remained well for one year but relapsed and presented with amenorrhoea and all the clinical features of ACTH-induced Cushing's syndrome. She was normotensive and not diabetic. Morning serum cortisol and ACTH levels were in keeping with this diagnosis [Table 1]. Treatment was started with 1 mg of cabergoline daily. The response was dramatic, with a reversal of the psychotic state within a week, associated with a progressive reduction of serum cortisol levels over the following month [Table 3].

Discussion

Five patients with Cushing's disease and raised ACTH levels were given a therapeutic trial of cabergoline. Four of them responded with a prompt fall in serum cortisol levels [Figure 1]. In Cases 1 and 2, their normal menses resumed and associated comorbidities, namely DM and hypertension, were

reversed. Pituitary MRIs were normal in two of the patients as may be the case in up to 40% of all Cushing's disease patients.¹ In these circumstances, the diagnosis of Cushing's disease should ideally be confirmed by inferior petrosal sinus sampling with ACTH measurements. Since this technique is not yet available in Oman, we used indirect methods to exclude ectopic ACTH production and as a result are confident that both had Cushing's disease.

NETs almost invariably express somatostatin receptors 2 and 5 and respond to treatment with octreotide.^{4,5} As noted, there was no fall in serum cortisol levels during the therapeutic trial of octreotide in either patient, and no evidence of ectopic tumours was seen on CT scans of the neck, chest, or abdomen. Furthermore, serum chromogranin-A levels, which are frequently elevated in patients with NETs, were also normal.² High dose dexamethasone suppression can also be used to differentiate pituitary from ectopic diseases. Since this test was considered potentially harmful, it was not performed. One patient was septicaemic with several abscesses (Case 1) and the other had a steroid psychosis (Case 5).

Somatostatin receptors are also expressed on normal pituitary ACTH-producing cells, but their expression is down-regulated by elevated glucocorticoid levels which explains why octreotide is not useful therapeutically in the majority of patients with Cushing's disease.³ So why is cabergoline effective? Up to 80% of ACTH-secreting pituitary adenomas express dopamine receptors and many respond well to treatment with dopamine agonists.⁶ A sustained response to bromocriptine is unusual but so far cabergoline has been shown to induce clinical and biochemical remission in 20–50% of cases.^{7,8} The beneficial effect of cabergoline was first demonstrated in a patient with Nelson's syndrome in 1999, which resulted in normalisation of the patient's ACTH levels and disappearance of the tumour.⁹

Because of these observations, we have started to give a therapeutic trial of 1 mg of cabergoline daily to all patients with Cushing's disease. Four of the five patients treated so far responded with a rapid normalisation of serum cortisol levels, and a reversal of associated comorbidities in the two patients treated for one or more months. Indeed, the patient refusing surgery has elected to remain on medical treatment and is still in complete

remission after 378 days, having reduced the dose of cabergoline to 0.5 mg three times per week.

We have so far studied only 5 patients and were pleasantly surprised to find that four of them responded to cabergoline [Figure 1]. This may be because we used a higher dose than reported earlier—usually not more than 0.5 mg daily.⁷ Further studies need to be carried out to find the optimal cabergoline dose required for treatment of this disease. Other medical therapies have been used in the medical management of Cushing's disease in preparation for surgery. These act either by inhibiting the release of ACTH or by inhibiting cortisol secretions.⁷ However, many have unpleasant side effects and are frequently ineffective, unlike cabergoline which has few short-term side effects even in large doses.⁷ Lightheadedness on the first day of treatment was the only reported side effect in these patients.

Conclusion

In conclusion, we recommend that a therapeutic trial of cabergoline, starting at 1 mg daily, be carried out in every patient with Cushing's disease and, if successful, can then be used to induce a remission prior to surgery or, if indicated, taken long term, as in Case 1.

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