Medical Treatment in Cushing's Syndrome: Dopamine Agonists and Cabergoline

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Key Words

Dopamine agonists · Cabergoline · Cushing's disease · Adrenocorticotrophic hormone · Cortisol · Adenoma · Ectopic

Abstract

Dopamine (DA) is a catecholamine with a wide range of functions and whose five subtype receptors are found in different organs where they exert a mainly inhibitory action. Since this action may also appear in a number of secretory tumors in various locations, DA agonists have elicited some interest as a medical treatment for hypercorticism. Non-iatrogenic Cushing's syndromes are due in 70% of the cases to a pituitary adrenocorticotrophic hormone (ACTH)-producing adenoma, and, less frequently, to an adrenal adenoma or an ectopic ACTH secretion by a neuroendocrine tumor. First-line treatment in Cushing's syndrome consists of the surgical removal of the secreting tumor. However, surgery may not achieve a complete cure in a number of cases, hence emphasizing the potential benefit of a medical complementary treatment, which could also benefit patients as an alternative approach, either when waiting for, or when the patient is not eligible for surgery. Studies of corticotrophic adenomas have shown that 80% of these tumors express D2 receptors. Clinical trials of DA agonists in Cushing's disease have shown an inhibitory effect of these drugs with an inhibition of ACTH secretion and/or a decrease of tumor size. There are only a

few cases of documented use of DA agonists in ectopic ACTH secretion, but when the tumor expresses DA receptors, DA agonists may represent a useful complementary treatment. DA receptors are also expressed in normal and tumoral adrenals, suggesting a potential use of DA agonists in Cushing's syndrome secondary to adrenal tumors. However, clinical data regarding this specific situation are very scarce, maybe due to the relatively high rate of surgical cure of adrenal adenomas. In conclusion, DA agonists represent a potential preparatory or complementary treatment for endogenous Cushing's syndrome, especially in Cushing's disease. These compounds may be underused as suggested by the scarce number of publication and case reports in the literature. In the future, association of these drugs with somatostatin analogs may also prove beneficial.

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Introduction

Cushing's syndrome [1] is a pathology which is often easy to suspect, sometimes difficult to demonstrate, frequently with elusive etiology, and seldom treated by the clinician. Indeed in most cases, surgery is the first-line treatment of noniatrogenic Cushing's syndrome, whether due to a pituitary or adrenal adenoma or a paraneoplastic adrenocorticotrophic hormone (ACTH) secretion. This is probably why medical treatment of Cushing's syndrome

has not elicited a lot of interest from the endocrine community in comparison to other conditions like acromegaly. Medical treatment is, however, mandatory in some situations. Surgery may not be always curative. Sometimes patients' general condition contraindicates surgery, which may be delayed, calling for a preparatory or secondary medical treatment.

Historically, compounds interfering with the synthesis of cortisol were the main drugs used in these patients. Later, drugs interfering with the physiological control of hormone secretion have been tested in vitro or in vivo. Dopamine (DA) agonists are one of these new potential treatments [2].

Physiology

DA is a catecholamine hormone with a short half-life of about 1 min. It has a wide range of physiological properties, acting as a neurotransmitter, controlling hormonal secretions, cardiovascular tone and renal filtration. The effect of DA is the result of the activity of its receptor (DR) [3, 4] which belongs to the family of G-protein-coupled receptors. G-protein-coupled receptors are located in the cells' membranes and comprise seven transmembranes domains. DRs are made of five subtypes D1–D5 which are divided in two groups: D1-like (D1 and D5) and D2-like (D2, D3, D4). D1-like receptors are generally considered as triggering a stimulatory effect, whereas D2-like receptors are generally associated with an inhibitory action. The D2 receptor is itself made of two isoforms: the short and the long isoforms.

Localization of DA Receptors

DA receptors have been demonstrated in a variety of organs [5], on par with their wide physiologic effects. They are present in the brain, the pituitary, the adrenals, the kidneys, the gastrointestinal track and the cardiovascular system. These receptors being present in the neuroendocrine system, one may expect them to be expressed in tumors deriving from these tissues and, possibly, to exert an inhibitory effect when activated [4].

Pituitary

Immunohistochemistry, receptor-ligand-binding and RT-PCR studies have demonstrated that D2-type receptors may be present in up to 80% of pituitary corticotrophic adenomas. The presence of these receptors correlated

quite well with in vitro ACTH secretion control: tumoral cells that highly expressed D2 receptors showed an inhibition of ACTH secretion of 43–60%, whereas cells that did not express the D2 receptor did not respond to DA agonists [6].

Ectopic

A study on a small cell lung cancer cell [7] line showed an inhibition of pro-opiomelanocortin mRNA by bromocriptine. In a series of six carcinoid tumors (four lung, one pancreas and one thymic), five expressed D2 receptors on immunohistochemistry [8].

Adrenals

Both D1- and D2-type receptors are present in normal adrenals, where they play a role in the secretion of cortisol, aldosterone and androgens. In tumoral cells, both D2 and D4 subtypes are expressed. However, adenomas expressed both D2 isoforms, whereas carcinomas expressed only the long D2 isoform [9].

Clinics

Cushing's Disease

The first studies of DA agonists in Cushing's disease were performed with bromocriptine. A decrease in ACTH production was generally observed in 50% of the cases; however, this effect did not appear to be very strong and was maintained for longer term only in a smaller subset of cases [10]. Better results were expected with cabergoline which has a higher binding capacity to D2 receptors and a longer half-life.

The first cases in the literature are two case reports describing tumor shrinkage in a silent ACTH-adenoma expressing D2 receptors [11] and decreased ACTH with tumor shrinkage in a secreting adenoma [12]; both patients were treated with cabergoline.

Pivonello and co-workers studied the use of cabergoline in short- [6] and long-term [13] treatment in 20 patients. In the short term (3 months), urinary free cortisol was normalized or decreased in 15 patients. Ten of these patients showed a remission during the long-term treatment (12–24 months). Clinical data showed good correlation with the expression of D2 receptors by tumoral cells.

Ectopic ACTH Secretion

Pivonello et al. [8] describe 6 cases with ACTH-secreting carcinoid tumors who had been operated. Three of these patients were not cured and therefore treated with

Table 1. Cabergoline used in Cushing's syndrome

First author, year	Cases n	Dose mg/ week	Duration months	Biological results	Tumor	Notes
<i>Cushing's syndrome</i>						
Petrossians, 2001 [11]	1	1.75	12	NA	shrinkage	silent adenoma
Miyoshi, 2004 [12]	1	0.25–0.5	6	decreased ACTH	shrinkage	
Pivonello, 2004 [6]	20	1–3	3	UFC: 40% normalization, 20% decrease	NA	5 micro-, 15 macroadenomas
Illouz, 2006 [21]	3	1–3	1–9	UFC: normalized in 2 cases	no change	
Godbout, 2007 [22]	8	0.75–3	20–28	UFC: normalized in 38%, decreased in 38%	shrinkage	
Pivonello, 2009 [13]	20	1–7	3–24	UFC: normalized in 10 cases	NA	long-term results of patients described in 2004
Vilar, 2009 [23]	12	2–3	6	UFC: normalized in 3 cases	NA	ketoconazole combined with cabergoline normalized UFC in 6 patients out of 9 remain- ing patients
<i>Ectopic ACTH secretion</i>						
Pivonello, 2007 [8]	3	3.5	6	UFC: normalized in 2 cases	NA	1 escape

NA = Not available; UFC = urinary free cortisol.

cabergoline (3.5 mg/week for 6 months). Two of these 3 patients normalized their urinary free cortisol, although 1 of them who had the weakest D2 isoform expression exhibited treatment escape.

Adrenal Adenomas

There are currently no firm data related to the use of DA agonists in adrenal adenomas causing Cushing's syndrome. Indeed, in these pathologies, treatment is mainly surgical with a relatively high cure rate.

Discussion

A summary of the available publications on the use of cabergoline in Cushing's syndrome is represented in table 1. Due to its higher affinity to D2-type receptors and longer half-life, this compound may play a more important role in the medical treatment of Cushing's syndrome than its predecessor bromocriptine. However, although the interest in the medical use of DA agonists is not new, one cannot fail to observe the scarcity of publications on this subject. There may be two explanations for the lack of data. Adrenal adenomas represent a small percentage of Cushing's syndromes. They are usually treated surgically and, in the case of true benign adenomas, with good surgical results, thus alleviating the need of com-

plementary medical therapy. Ectopic ACTH secretion by a neuroendocrine tumor represents a small group of Cushing's syndromes, and is also treated surgically. When the originating tumor is correctly localized, up to 80% of surgical success is described [14]. When the tumor is not localized or surgery is not curative, patients undergo bilateral adrenalectomy, and they may also be treated by steroidogenesis inhibitors or chemotherapy. For these tumors, DA agonists may thus appear as an unusual therapeutic alternative and not be envisioned in everyday practice.

For Cushing's disease, however, the scarcity of the literature may seem more surprising. True, ACTH secreting pituitary adenomas represent only $\pm 7\%$ of pituitary adenomas (with acromegaly $\pm 12\%$ and prolactinomas $\pm 50\%$, with a prevalence of 1:1,064 for pituitary adenomas [15]), but they are usually explored and treated by endocrinologists experienced in pituitary tumors and who routinely use DA agonists. So one may expect to see more trials with cabergoline in Cushing's disease.

The available literature for this topic is mainly made of case reports and four series for Cushing's disease, one series in ectopic ACTH secretion and, to the authors' knowledge, no series in adrenal adenomas. It is difficult to assess if these data represent the only therapeutic trials that have been made in different centers. One could not exclude that a number of cases have not been published

(either because of the lack of good results or the lack of interest in the publication process) [16, 17]. Another point is that study durations are rather short, knowing that a secondary treatment could imply a life-long use. Nonetheless, despite these restrictions, the available data do encourage us to try DA agonists when looking for a medical treatment of Cushing's disease. And, in the case of Cushing's syndrome, the in vitro data at least, may legitimize therapeutic trials associating DA agonists. One point of concern, however, is the safety of cabergoline in chronic treatment. Cardiac valve disease has been associated with the use of DA agonists in Parkinson disease [18, 19]. These patients were receiving doses of cabergoline higher (avg. dose of 3.6 mg/day) than those routinely used in endocrine practice. A study of endocrinology patients taking cabergoline for 12–228 months with doses between 0.25 and 4.5 mg/week did not show a significant increase of clinically relevant cardiac valve disorders [20].

Conclusions

A review of the recent literature shows a scarce number of publications and an even scarcer series on the use of DA agonists in Cushing's syndrome [21–23]. The main clinical data concern Cushing's disease. Less data are available regarding ectopic ACTH secretion and basically none on cortisol secreting adrenal adenomas. In vitro studies showing the presence of D2-type receptors in tumors of different origin sometimes with a good correlation with in vitro and even in vivo response to DA agonists suggests that these compounds may present a therapeutic interest as complementary or alternative treatment in some cases of noniatrogenic Cushing's syndrome. Some other options may rely in the joint use of DA agonists with somatostatin analogs or with some new chimeric molecules.

Disclosure Statement

The authors have nothing to disclose.

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