Transient Efficacy of Octreotide and Pasireotide (SOM230) Treatment in GIP-dependent Cushing's Syndrome

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- GIP-dependent Cushing's syndrome
- octreotide
- pasireotide

Abstract

We studied a 55-year old woman presenting with features of Cushing's syndrome associated with metabolic abnormalities including severe hypertension and type 2 diabetes. Urinary free cortisol excretion was within normal limits, but an unusual diurnal cortisol rhythm was observed with low morning and high postprandial levels, associated with the absence of cortisol suppression after dexamethasone, suggesting the possibility of GIP-dependent Cushing's syndrome. The diagnosis was confirmed by further investigations, showing significant plasma cortisol responses after a mixed meal test and after oral, but not intravenous glucose administration, as well as ACTH-independent bilateral macronodular adrenal hyperplasia (AIMAH). An aberrant increase in cortisol was also observed after glucagon and terlipressin injections. The patient was first treated with octreotide 100–250 µg thrice daily for 6 months, then with the new multi-ligand somatostatin analogue (SOM 230) 450–900 µg twice daily for 3 months. Although inducing a significant acute suppression of postprandial cortisol response, both drugs had no effects on the clinical and metabolic abnormalities associated with Cushing's syndrome and new tests performed at the end of each treatment period confirmed escape of post-meal cortisol suppression to therapy. The patient finally underwent a bilateral adrenalectomy, which markedly improved her medical condition and allowed in vitro confirmation by real time RT-PCR quantification of a high aberrant expression of GIP receptor mRNA in adrenal tissue. This case report illustrates the lack of sustained efficacy of somatostatin analogues on GIP-dependent Cushing's syndrome, independent of their affinity for the different somatostatin receptor subtypes.

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Introduction

GIP-dependent Cushing's syndrome (CS) is a rare cause of endogenous ACTH-independent hypercortisolism. GIP-dependent CS has been reported so far in less than 40 patients with either ACTH-independent macronodular adrenal hyperplasia (AIMAH) or unilateral adrenocortical adenoma [1,2]. In such conditions, cortisol secretion increases in response to physiological plasma elevation of GIP following meals, as the result of a high ectopic expression of non-mutated GIP receptors in zona fasciculata-type cells in AIMAH or unilateral adenomas [1,2]. The identification of aberrant adrenal hormone receptors in AIMAH provided new opportunities to use specific pharmacological therapies as alternatives to adrenalectomy. In particular, previous attempts to block the post-prandial release of GIP with octreotide led to some clinical and biological improvement of CS, which however did not persist in the long-term, likely because of an eventual desensitization of somatostatin subtype 2 receptors (sst-2) on GIP-secreting duodenal K cells [1–3]. Thus, in the absence of an effective pharmacological therapy, bilateral adrenalectomy has been the most widely used treatment for patients with GIP-dependent CS [4]. The development of new drugs which could inhibit GIP release or block the GIPR in a more sustained way would be of potential benefit for such patients, particularly for those at high risk of operative complications.

We had recently the opportunity to study and compare the efficacy of the new multi-receptor somatostatin analogue pasireotide (SOM 230) with that of octreotide in a female patient with GIP-dependent Cushing's syndrome secondary to AIMAH.

Primer Sense	Sequence Sense	Primer Antisense	Sequence Antisense
GIPR-S	CCAAGCTCGGCTTTGAGAT	GIPR-AS	GTAGAGGACGCTGACCAGGA
AVPR1A-S	ATCGTCTGCTGGGCGCCTTT	AVPR1A-AS	GGGTTTTCCGATTCGGTCCAGACG
AVPR2-S	AGGCAGAGGCTGAGTCCGCA	AVPR2-AS	GATGCCCAGGCACAGCGGAA
AVPR1B-S	TCGTGCTGGCCTACATCGCT	AVPR1B-AS	TGGTGGAATCTTCATCAGGGGCA
AGTR1-S	CAGAAAGTCGGCACCAGGTGTATT	AGTR1-AS	TGCCTTCCAGCTTTGGGACAATCA
AGTR2-S	GCAGCCTGAATTTTGAAGGAGTGTG	AGTR2-AS	TGGCAAGGGTGGAGTTGCCCT
LHCGR-S	CATTCAATGGGACGACACTG	LHCGR-AS	GCCTCCAGGAGATTGACAAA
GNRHR-S	TGGCCTGGATCCTCAGTAGT	GNRHR-AS	GAGTCTTCAGCCGTGCTCTT
HTR4-S	CAAGGCTGGAATAACATTGG	HTR4-AS	AGAGCAGGTGATGGCGTAG
HTR7-S	ACCGGAATATCAACCGGAAG	HTR7-AS	TAGCACCCACACAGATACCG
ADRB1-S	TCGTGTGCACCGTGTGGGCC	ADRB1-AS	AGGAAACGGCGCTCGCAGCTGTCG
ADRB2-S	ACCCACCAGGAAGCCATCAACTGCT	ADRB2-AS	GCCTATCCAATTTAGGAGGATGTAAACTTCC
ADRB3-S	GCTCCGTGGCCTCACGAGAA	ADRB3-AS	CCCAACGGCCAGTGGCCAGTCAGCG
MC2R-S	CCCAGAAAGTTCCTGCTTCA	MC2R-AS	TCTTCAGGATCTTTTCTTCCTTG
FSHR-S	TGGAGACGGCAAATCTCTG	FSHR-AS	CACGTCAACCACTTCATTGC
GCGR-S	AATCTGTTTGCGTCCTTCGT	GCGR-AS	ACCAGCAGCCAGCAGTAGTT
HPRT1-S	TGCTGACCTGCTGGATTACA	HPRT1-AS	CCTGACCAAGGAAAGCAAAG

Table 1 Primers used in the real-time PCR assays

Materials and Methods

In vivo studies

Dynamic endocrine testing was performed in the patient using previously reported protocols [5] in order to identify illegitimate or abnormal expression of membrane hormone receptors on adrenal cells. Serial cortisol and ACTH measurements were taken at 30-min intervals for 2–3 h during the following tests: standard mixed meal challenges (total caloric amount of 950 kcal; proteins 41 g (164 kcal, 17.3 %), lipids 54 g (486 kcal, 51.1 %) and carbohydrates 75 g (300 kcal, 31.6 %); conventional oral glucose tolerance test (75 g; OGTT); intravenous (i.v.) glucose tolerance test (0.3 g/kg glucose in 1 min; IVGTT); gonadotrophin-releasing hormone (100 µg GnRH i.v.), thyrotropin-releasing hormone (200 µg TRH i.v.) vasopressin (1 mg terlipressin i.v.), glucagon (1 mg i.m.) and propanolol (20 mg orally) tests. A result was arbitrarily considered as negative when the plasma cortisol increase was < 25 % over baseline at any time after stimulus and as positive when increase was ≥ 50 % over baseline at any time after stimulus. Intermediate increase (25–49 %) was considered as partial response. Plasma cortisol and ACTH were measured by conventional automated immunoassays using the DXI (Beckman Coulter, Brea, CA, USA) and Liaison (Diasorin, Saluccia, Italy) assays, respectively. Octreotide (Sandostatine®, Novartis Pharma, 100 µg or 250 µg) and pasireotide (SOM 230, Novartis Pharma, 450 µg or 900 µg) were administered subcutaneously (sc) 15 min before standard meal test to assess the effect of this therapy on postprandial cortisol release. The study was approved by the Ethics Committee of the Université Catholique de Louvain, and the patient signed written informed consent before use of pasireotide in this indication.

In vitro studies and real-time RT-PCR quantification

Tissues from both right and left adrenals were immediately frozen in liquid nitrogen after removal and stored at −80 °C. As a control group a commercially available pool of 61 normal adrenal glands was used (Clontech, Mountain View, CA, USA). Total mRNA extraction, cDNA synthesis, and SYBRgreen based real-time PCR were performed as described previously [6]. The mRNA levels of the following genes were evaluated: Gastric inhibitory polypeptide receptor (GIPR), arginine vasopressin receptors type 1A (AVPR1A), type 2 (AVPR2) and type 1B (AVPR1B), angiotensin II receptors type 1 (AGTR1) and type 2 (AGTR2), luteinizing hormone choriogonadotropin receptor (LHCGR), follicle stimulating hormone receptor (FSHR), gonadotropin-releasing hormone receptor (GNRHR), 5-hydroxytryptamine (serotonin) receptors 4 (HTR4) and 7 (HTR7), adrenergic receptors beta-1 (ADRB1), beta-2 (ADRB2) and beta-3 (ADRB3), melanocortin 2 receptor (MC2R) and glucagon receptor (GCGR). Some primers were used as previous described [7] and others were designed using the software Primer3 (http://frodo.wi.mit.edu/). The sequences of each pair of the primers used are shown in **Table 1**. The expression ratios were determined with these efficiencies using the comparative ΔΔCt method described by Pfaffl [8]. Data were evaluated by the Rotor Gene 6000 software (Corbett Research, Sydney, Australia). Results were normalized for expression of human hypoxanthine phosphoribosyltransferase 1 (hPRT) as a reference gene and were expressed relative to the mean mRNA expression levels of 61 normal adrenal glands.

Results

Case report and in vivo studies

A 55 year-old woman was admitted for investigation of Cushing's syndrome. She had been admitted 6 months before in another institution for acute dyspnea, bronchospasm and pulmonary edema. Severe hypertension was diagnosed, associated with diabetes and dyslipidemia. She required multiple drug therapy to control her blood pressure and metformin combined with insulin at a dose of 0.45 U/kg in a basal-bolus scheme to control hyperglycemia. A Cushing's syndrome was considered, but basal plasma and urinary free cortisol (UFC) measurements were normal. The patient was referred and admitted in our unit for complementary investigations. She presented typical CS features, including central obesity, moon face, easy bruising, oedema, hairiness, and proximal muscle atrophy. Body-mass-index was 32.4 kg/m^2, with a fat mass determined by impedance measurement of 40.2 % (normal 22–30) and a waist circumference of 105 cm. Her blood pressure was high at 175/105 mmHg despite multiple drug therapy. General laboratory tests were normal, except for hypokalemia at 3.1 mM/l and chronic hyperglycemia with glycated hemoglobin at 68 mmol/mol (8.4 %). A daily plasma cortisol profile showed a low fasting value of 86 nmol/l at 08:00 h (normal range 235–471), and higher values at 12:00 h (366 nmol/l), 16:00 h (272 nmol/l), 20:00 h (650 nmol/l), and

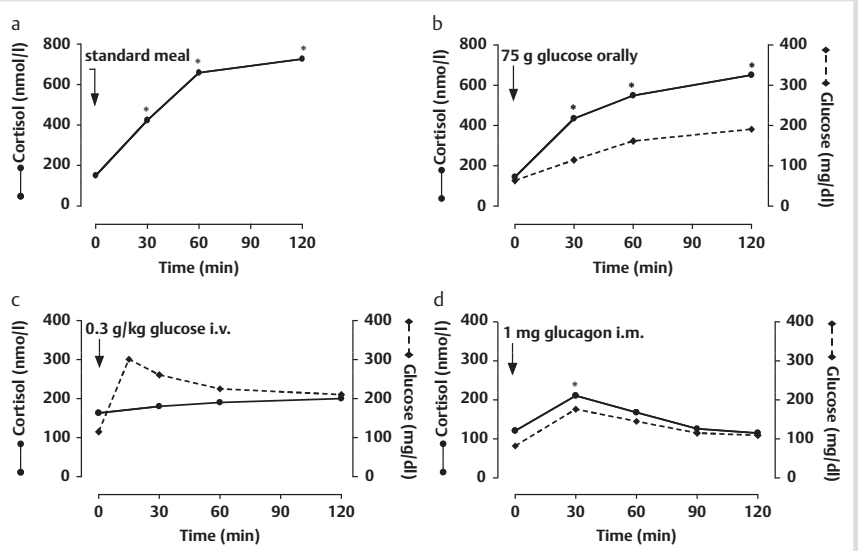

Fig. 1 Plasma cortisol (nmol/l) and glucose concentrations (mg/dl) measured during several stimulation tests. **a**: Standard mixed meal test (SMT) containing 41 g proteins (17.3 %), 54 g lipids (51.1 %), and 75 g carbohydrates (31.6 %) for a caloric amount of 950 kcal); **b**: OGTT, oral glucose tolerance test (75 g of glucose); **c**: IVGTT, intravenous glucose tolerance test (0.3 g/kg glucose in 1 min); **d**: Glucagon test (1 mg glucagon intramuscularly).

Table 2 Plasma cortisol concentrations (nmol/l) before and after a standard mixed meal test, in basal conditions, and after a subcutaneous injection of octreotide or pasireotide 15 min before meal, at the doses and times indicated

	0 min	30 min	60 min	120 min	180 min	Maximum increase over baseline (%)
Standard meal test (SMT*)	150	423	659	727	780	+420 %
Injection of octreotide 100 µg (first injection) + SMT	173	167	180	138	240	+39 %
Injection of octreotide 250 µg (after 6 months) + SMT	126	123	161	491	481	+289 %
Injection of pasireotide 450 µg (first injection) + SMT	210	257	291	268	233	+39 %
Injection of pasireotide 900 µg (after 3 months) + SMT	130	203	343	290	317	+164 %

* The standard meal test (SMT) contained 41 g proteins (17.3 %), 54 g lipids (51.1 %) and 75 g carbohydrates (31.6 %) for a caloric amount of 950 kcal

midnight (248 nmol/l). UFC was normal at 38, 34, and 58 µg/24 h on repeated controls (normal range <60). ACTH levels were below 15 pg/ml at all time points and no reduction in morning plasma cortisol was observed after dexamethasone suppression tests with low (2 mg) or high (8 mg) doses. A food-induced cortisol production was confirmed by a significant cortisol response after a standard meal test with a steady rise from a baseline value of 150 nmol/l to a peak value of 780 nmol/l (+420 %) observed 120 min after meal (**Fig. 1** and **Table 2**). An abdominal CT scan showed bilateral macronodular adrenal hyperplasia with nodules up to 5 cm of low density (8–15 UH) on both glands. We also observed a prompt and sustained cortisol response after oral but not intravenous glucose administration (**Fig. 1**). There was also a cortisol rise after glucagon (from 121 to 211 nmol/l, +75 %) and terlipressin administration (from 102 to 247 nmol/l, +142 %), but not after TRH, GnRH and propanolol (data not shown). ACTH values remained below 15 pg/ml every time they were measured, in a fasting state or after stimulation. Administration of octreotide (Sandostatine®) 100 µg s.c. 15 min before meal acutely reduced by about 4-fold the postprandial increase in plasma cortisol values (**Table 2**). However, chronic treatment did not improve the clinical manifestations of Cushing's syndrome or the control of glycemia and blood pressure, even after increasing the dose to 3×250 µg daily. After 6 months of treatment, a new meal test performed after sc injection of 250 µg octreotide showed no longer suppression of post-prandial cortisol rise (**Table 2**). We therefore tested the effects of the new multi-receptor somatostatin analogue pasireotide (SOM 230). We could also observe a significant 4-fold inhibition of meal-induced cortisol release after a sc injection of 450 µg SOM 230 (**Table 2**). Treatment was therefore started at the dose of 450 µg BID and readily increased to 900 µg BID after 1 month. This treatment also had no detectable effects on clinical and metabolic alterations and a new meal test performed after 3 months of treatment confirmed an escape in the effects of SOM 230 on cortisol release (**Table 2**).

Considering the worsening of CS features, a bilateral adrenalectomy was performed allowing a rapid and marked improvement in her medical condition, with a weight loss of 7 kg and a regression of most signs of hypercorticism after 2 months. Blood pressure was well controlled with reduction of antihypertensive drugs, and insulin therapy could be stopped and replaced by sulfonylurea (Gliclazide, 30 mg daily) and metformin, with a better metabolic control [HbA1c at 58 mmol/mol (7.5 %)].

Pathological examination and in vitro studies

On pathological examination, both adrenal glands were enlarged and included multiple large well-delineated nodules (left: 3.0 and 2.5 cm, right: 4.0, 1.5 and 1.2 cm) Histological diagnosis was that of bilateral macronodular adrenal hyperplasia in which the nodules were characterized by the predominance of eosinophilic cells with a small nucleus, while large cells with a clear cytoplasm constituted about 25 % of the nodular cell population. There were no histological signs of malignancy and the adrenal tissue outside the nodules was not atrophic. Real-time quantitative RT-PCR showed a marked overexpression of GIPR (15–18-fold) in both adrenal glands from the patient compared to the pool of control adrenal glands. In contrast, no mRNA overexpression could be demonstrated for all other receptor genes tested, including the vasopressin and glucagon receptors (**Fig. 2**).

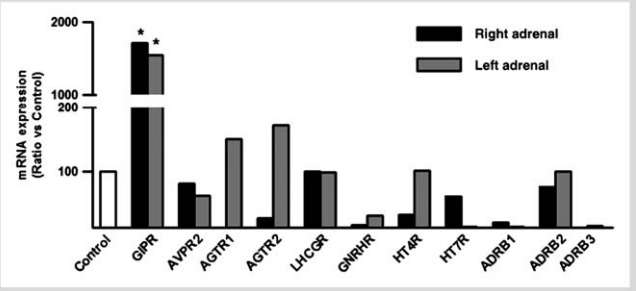

Fig. 2 Messenger RNA (mRNA) expression levels of several G-protein coupled receptors in the left and right adrenal gland tissue extracts of the patient, as determined by real-time quantitative PCR. The figure shows the mRNA levels for the receptors of GIP, AVP2, AGT1, AGT2, LHCG, GNRH, HT4, HT7, ADB1, ADB2 and ADB3. AVPR1A, AVPR1B, MC2R, and FSHR had no detectable expression compared to control (pool of 61 normal control adrenals from Clontech), and are not shown in the figure. For abbreviations of the receptors, see material and methods. * $p<0.05$ when comparing values obtained in each tissue with those in the control tissue.

Discussion

This patient presented several features of the rare etiology of GIP-dependent CS. She had characteristic clinical features and metabolic abnormalities of prolonged hypercorticism. However, the normal urinary free cortisol (UFC) excretion and low morning blood cortisol values in the fasting state, were atypical for a classical CS. This together with the combined findings of an unusual cortisol diurnal rhythm with higher values during the day, very low ACTH levels, the lack of suppression by low and high doses of dexamethasone, and a bilateral macronodular adrenal hyperplasia at imaging should evoke the diagnosis of an aberrant, ACTH-independent stimulation of cortisol release. When further tests were performed according to well-described protocol [1,2,5], we observed indeed a marked and sustained cortisol response to a standard mixed meal test and to oral but not intravenous glucose administration. This "incretin-like" effect is usually related to a physiological food-induced increase of the insulinotropic peptide GIP by the duodenum, and to an abnormal stimulation of cortisol secretion due to the illegitimate presence of GIP receptors on hyperplasic adrenals [1,2]. The GIP-dependent nature of this case of CS was indeed confirmed by the very large overexpression of GIPR in both adrenal tissues at levels comparable to those reported previously in such cases [1,2].

Food-dependent hypercortisolism associated with the presence of abnormal GIP receptors on adrenocortical cells represents a rare (<1%) and challenging form of Cushing's syndrome. Signs and symptoms are not different from classical CS, and diagnosis relies on specific pharmacologic testing, which is not included in the usual workup of the syndrome. Moreover, atypical laboratory findings may render confirmation of the diagnosis difficult. UFC often remains normal or is only moderately increased because of the peculiar rhythm of cortisol secretion, with very low levels during the post-absorptive states. Interestingly enough, Hsiao et al. showed that AIMAH patients excrete in their urines various glucocorticoid metabolites that are not detected by specific assays for UFC. They also reported high urinary excretion of 17-hydroxycorticosteroid (17-OHS) even when UFC levels were normal or low [9].

In the present case, we also observed a significant, albeit smaller, increase of cortisol secretion after the administration of glucagon. This response could have been a marker of the aberrant expression of glucagon receptors on adrenal cells, as it has been already reported in one patient with AIMAH [10]. However, in our case, we could not demonstrate an overexpression of adrenal glucagon receptor mRNA levels over those found in a normal control population. In a recent study, Libé et al. also found a significant in vivo cortisol response to glucagon in a majority of patients with a subclinical Cushing's syndrome related to AIMAH [11]. This could be due to more subtle alterations of adrenal receptors not detectable by mRNA quantification, or to modifications of post-receptor intracellular pathways in AIMAH.

Our patient also exhibited an increase of cortisol secretion after the administration of terlipressin. In fact, AVP induces a significant increase in cortisol release in a large proportion of AIMAH patients [12]. This response might be due to a direct action of AVP on adrenocortical cells, mediated through the V1a receptor, as demonstrated by cell culture experiments in vitro [12], but as in our case, most molecular studies have been unable to show an obvious overexpression of those receptors on tumor cells [13,14]. The ability of AVP to significantly stimulate cortisol secretion in AIMAH is more likely related to an increased coupling efficiency of V1a receptors normally expressed at the cell surface [12], the mechanisms of this being still unknown. Vasopressin could also have an indirect steroidogenic effect mediated by corticotrophin-releasing hormone or other peptides and ectopic expression of other AVP receptor subtypes such as V2 has also been reported [15].

Treatment of GIP-dependent CS is also a challenge. Octreotide therapy has been attempted with disappointing long-term results [1,3]. Likewise, in our patient, this medication markedly reduced the postprandial rise in cortisol values in an acute setting but was no longer effective after a few months of use. Such a transient effect of chronic octreotide therapy has been indeed reported, presumably due to a down-regulation of somatostatin receptors or the presence of other stimuli of cortisol secretion than GIP [3].

We also investigated the effects of the new multi-receptor somatostatin analogue pasireotide or SOM 230. Compared with octreotide and lanreotide, this drug has a 30-fold greater affinity for sst1, a 5-fold greater affinity for sst3, and a 40-fold greater affinity for sst5, while it has a comparable affinity for sst2 receptors [16]. This analogue could be a more potent inhibitor of GIP and other food-dependent gastro-intestinal peptides than octreotide, with less desensitization over time. Also, all 5 sst subtypes have been found in normal and tumoral adrenal tissue, including cortisol-producing adenoma cells [17], and it was therefore possible that pasireotide could directly inhibit cortisol production from hyperplastic adrenal tissue. We indeed observed a significant acute inhibition of meal-induced cortisol release after pasireotide, similar to that observed after octreotide. However, very much like for octreotide, this effect had disappeared 3 months after initiation of this treatment.

In summary, we have reported a case of typical GIP-dependent CS with AIMAH suspected on the basis of clinical and laboratory findings and confirmed by histological and molecular biology studies. Medical treatment with either octreotide or pasireotide was effective to acutely reduce the postprandial rise in cortisol, but failed to control the long-term effects of hypercortisolism, as a result of a rapid desensitization of cortisol suppression to both somatostatin analogues.

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Conflict of Interest

The authors have no conflicts of interest to declare. LMM was recipient of a partial support from Fundação de Amparo à Pesquisa do Estado de São Paulo (Fapesp), Brazil.

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