Case Report

Withdrawal from Glucorticosteroids Therapy: A Role for Tetracosactide 1 mg?

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Abstract

We present the case of a 31-year-old woman who underwent a right surrenectomy for cortical adenoma secreting cortisol responsible of Cushing's syndrome. After surgery, she was first treated with cortisone acetate 37.5 mg/die and then with hydrocortisone 20 mg/die. Fludrocortisone was administered at the dosage of 0.05 mg/die. Patient complained of severe asthenia and drowsiness and decided to stop therapy. Reduction and subsequent withdrawal from this therapy lasted four months and it took advantage of intramuscular tetracosactide injection. One-year follow-up showed normal values of both basal and stimulated serum cortisol level; the patient was in good physical condition and did not complain any more with asthenia.

Keywords: Tetracosactide; Cushing; adenoma; Glucocorticosteroids; Cortisol; Synacthen

Abbreviations: GCs- Glucocorticosteroids; CRH- Corticotrophin releasing hormone; ACTH- Adrenocorticotropic hormone; CA- Cortisone acetate; HC- Hydrocortisone; SST- Synacthen stimulation test; EGDS- Esophagogastroduodenoscopy; HPA- Hypothalamus-pituitary-adrenal

1. Introduction

In the endocrine practice hypocorticosurrenalism following steroid therapy represents a frequent challenge to deal with for the clinician. Glucocorticosteroids (GCs) are frequently used at high dosage in clinical practice for the treatment of many different pathologies considering their potent anti inflammatory effects and, besides, because it is thought to have immunosuppressive activity [1]. Practically, in every specialty of medicine, GCs represent an

effective treatment; in particular, oncology, hematology, dermatology, immunology, rheumatology, infectivology represent the medical specialties where GCs are more extensively used, and, sometimes, misused (Table 1). This widespread use of GCs poses a serious risk of iatrogenic hypocorticosurrenalism when GCs are withdrawn if medium or long acting GCs are used at high dosage and for more than three weeks, as often prescribed [2, 3]. Indeed, up to 1% of the population is now prescribed long-term GCs therapy [4]. Sometimes, GCs euphoric effect may increase well-being even in absence of objective improvements in underlying disease parameters [5, 6]. In these patients a careful evaluation of clinical and biochemical status is necessary to schedule a correct withdrawal from GCs therapy in order to avoid adrenal crisis and severe acute adrenocortical insufficiency [7]. A more subtle endocrine challenge is represented by withdrawal from short acting GCs used for long-term therapy after pituitary neurosurgery for functioning or non functioning micro or macroadenoma, craniopharyngioma and disorders of the pituitary and hypothalamic region or after monolateral surrenectomy for cortisol secreting adrenal carcinoma or adenoma. From a pathophysiological point of view, the difficulty in withdrawal process from GCs lies in the fact that prolonged use of GCs brings about a negative feedback on hypothalamus and pituitary gland decreasing corticotrophin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) secretion. Furthermore, this suppression prevents adrenal glands from proper functioning causing adrenal atrophy [1, 8]. Long term administration of long acting GCs at high dosage is a risk factor for adrenal atrophy, and recovery from this event requires several months [4, 7-9]. Unfortunately, GCs and mineralcorticosteroids are necessary for life and it is not thinkable to stop abruptly GCs therapy without posing serious health risks [8].

Endocrine system	Replacement therapy (Addison's disease, pituitary disease, congenital adrenal hyperplasia) Graves' opthalmopathy
Integumentary system	Dermatitis, pemphigus
Haematological system	Leukemia, lymphoma, haemolytic anemia, idiophatic thrombocytopenic purpura
Gastrointestinal apparatus	Inflammatory bowel disease (Crohn's disease, ulcerative colitis), chronic acitve hepatitis, transplantation, organ rejection
Urinary tract	Nephrotic syndrome, vasculitides, transplantation, organ rejection
Central Nervous system	Cerebral edema, raised intracranial pressure
Respiratory apparatus	Angioedema, anaphylaxis, asthma, sarcoidosis, tubercolosis, obstructive airway disease
Musculo-skeletal apparatus	Polymialgia rheumatica, myasthenia gravis
Immune system	Systemic lupus erythematosus, polyarteritis, temporal arteritis, rheumatoid arthritis

Table 1: Therapeutic use of GCs adapted from (Stewart 2008).

2. Case Report

A 30-year-old woman came to our attention complaining of severe asthenia, weight gain, drowsiness and gastritis. Her medical history revealed a monolateral right surrenectomy performed twenty months before our visit in order to

remove cortisol-secreting adrenocortical adenoma and responsible for Cushing's Syndrome. After surrenectomy, patient was treated with oral cortisone acetate (CA), being the initial dosage of 25 mg administered at 8.00 and 12.5 mg administered at 16.00, and with fludrocortisone 0.05 mg administered once daily. However, after four months of this therapy patient revealed low quality of life, being affected by deep asthenia; for this reason CA was replaced with hydrocortisone (HC) administered three times daily according to the following dosage: 10 mg at 8.00, 5 mg at 14.00, 5 mg at 19.00. Meanwhile, three Synacthen stimulation test (SST) were performed injecting intravenously 250 mcg of Synacthen to evaluate adrenal function drawing baseline cortisol and collecting blood samples at 60 minutes suggesting incomplete adrenal function.

When patient came at our attention, she was willing to stop GCs replacement therapy because her quality of life has been negatively affected by this therapy limiting deeply her daily activities forcing her to quit work in her patissierie. Following on, she had mild arterial hypertension treated with propranolol 40 mg/die once a day. Her weight was 58.6 kg.

An esophagogastroduodenoscopy (EGDS) with multiple biopsies, urea breath test for lactose intolerance and urea breath test for helicobacter pylori were performed with negative results for evaluation of gastritis. First, we immediately anticipated second dose to 12.00 and third dose to 16.00. Then, we scheduled a gradual and slow withdrawal from HC (Table 2).

	8.00	**12.00**	**16.00**
I-IV weeks	10 mg	5 mg	2.5 mg
V-VIII weeks	10 mg	2.5 mg	2.5 mg
IX-XII weeks	10 mg	2.5 mg	-
XIII-XVI weeks	7.5 mg	2.5 mg	-
XVII settimana	7.5 mg	-	-

Table 2: Tapering regime.

We decreased 2.5 mg of hydrocortisone every four weeks and, meanwhile, we administered 1 mg of tetracosactide, a depot (sustained-release) synthetic ACTH formulation, every seven days, for a total of sixteen administration in sixteen weeks by intramuscular route. During the third week, we stopped fludrocortisone taking into account arterial blood pressure, sodium, and potassium values. After two more weeks, we also stopped propranolol according to the results of 24 hours blood pressure monitoring. At the end of sixteenth week, we suspended HC therapy monitoring clinical status of the patient. Seven days after stopping HC and ten days after the last intramuscular injection of tetracosactide, we performed a SST to evaluate adrenal function drawing baseline ACTH and cortisol and collecting ACTH and cortisol blood samples at 60 minutes (Table 3).

Synacthen test 250 mcg	**0 min**	**+60 min**
ACTH (pg/ml)	29.5	15.7
Cortisolemia (nmol/L)	255.0	531.0

Table 3: Results of SST after the end of tapering regime.

Results of SST revealed a serum cortisol level of 531 nmol/L which suggested adequate adrenal function, therefore not requiring adrenal replacement therapy [8]. One year after the end of HC therapy, we evaluated the patient performing another SST which suggested full activity of adrenal gland, being also basal serum cortisol value maximal, and even higher than the previous stimulation test [10]. Serum cortisol of 609.0 nmol/l after stimulation confirmed proper adrenal function excluding hypocorticosurrenalism according to the existing guidelines [8, 11] (Table 4).

Synacthen test 250 mcg	**0 min**	**+60 min**
ACTH (pg/ml)	76.1	-
Cortisolemia (nmol/L)	519.0	609.0

Table 4: Results of SST one year after the end of tapering regime.

Clinically, patient referred an improved quality of life resuming full-time work in her patisserie and did not complain any more of asthenia and drowsiness. Gastritis and dyspeptic symptoms disappeared during the third month of tapering and only occasionally they reappeared again. Finally, she lost 7.2 kg during the tapering without any significant change in her lifestyle.

3. Discussion

Long term GCs therapy suppresses hypothalamus-pituitary-adrenal (HPA) axis causing adrenal atrophy; recovery of HPA axis from this condition in order to sustain a physiological secretion of adrenal hormones is a slow process requiring months or years [1]. Nevertheless, an adequate adrenal function is required to healthy living and its absence may bring about acute adrenal crisis which represent a life-threatening condition [10]. For these reasons withdrawal from GCs therapy should be carefully evaluated to avoid unnecessary and dangerous risks. In particular, it is crucial to make a slow and steady taper when a physiological dose of GCs is administered which corresponds to about 20 mg/die of HC or 5 mg/die prednisone (Table 5).

GCs	Anti-inflammatory action	HPA axis suppression	Salt retention	Plasma half-life (min)	Biologic half-life (h)
Hydrocortisone	1	1	1	90	8-12
Cortisone acetate	0.8	0.8	0.8	80-118	8-12
Prednisone	4	4	0.3	60	18-36
Prednisolone	4	4	0.3	115-200	18-36
Methylprednisone	6.2	4	0.5	180	18-36
Methylprednisolone	5.0	4	0	180	18-36
Triamcinolone	5.0	4	0	30	18-36
Betamethasone	25-40	-	0	300	36-54
Dexamethasone	30	17	0	200	36-54
Fludrocortisone	12	12	250	200	18-36

Table 5: Relative biologic potency of GCs adapted from (Chrousos 2007).

In this case, a reduction of the dose should be compensated by adrenal gland. A good rule of thumb consists of reducing 5 mg of HC every 2-4 weeks or 2.5 mg of HC every 1-2 weeks, starting from afternoon or evening dose. Indeed, doses administered in the late hours of the day result in a greater suppression of early morning ACTH secretion. When the daily dose has been reduced to 10 mg/die of HC, a SST should be performed to evaluate if withdrawal from GCs is indicated [5]. Before performing SST, therapy with HC or CA should be stopped for at least 24 hours in order to avoid cross reaction with cortisol assay [8]. A value of serum cortisol of 550 nmol/L 60 minutes after the intravenous injection of 250 mcg of Synacthen exclude hypocorticosurrenalism [2, 12, 13]. Otherwise, in case of therapy with GCs at pharmacological level (i.e. more than 20 mg/die of HC) for treating the underlying disease, the first part of tapering from pharmacology level to physiological level (i.e 20 mg/die of HC or 5 mg/die of prednisolone) may be fast if the condition of the underlying pathology permits GCs reduction. In this case, a reduction of 10 mg of HC or 2.5 mg of prednisone in 3-4 days is possible [8]. Generally, long or medium acting GCs are preferred for treating any form of disease, aside from hypocorticosurrenalism, and it is possible to switch from a long/medium acting GCs to a short acting GCs, such as HC or CA, in order to limit HPA suppression during GCs withdrawal [5, 14].

In our withdrawal from adrenal replacement therapy, we opted for a very slow taper from GCs considering the will of our patient to avoid any kind of symptoms associated with hypocorticosurrenalism. Indeed, we reduce 2.5 mg of HC every 4 weeks starting from the last dose of the day and after seventeen weeks of tapering the patient was administered 7.5 mg of HC in the morning (Table 1). We stopped fludrocortisone in the third week considering natraemia, kalaemia, and arterial blood pressure values in the physiological range. During tapering we closely monitored the patient to evaluate the presence of signs and/or symptoms related to adrenal insufficiency, such as:

anorexia, nausea, weight loss, arthralgia, lethargy, skin desquamation, postural dizziness, low grade fever, and depression [7]. No symptoms were reported by the patient who started to feel better from the ninth week. In order to speed up the process, and to avoid the presence of adrenal symptoms we administered 1 mg of tetracosactide depot every seven days by intramuscular route, for a total of sixteen administrations. After 20 months of adrenal replacement therapy, we supposed that a certain degree of adrenal atrophy might be present as suggested by three SST performed by our patient before tapering and we hypothesized that tetracosactide depot might be helpful in stimulating adrenal gland. Drug was well tolerated and no signs or symptoms of hypercorticosurrenalism were reported and/or observed. One year after stopping treatment, the patient reported well-being, spontaneous reduction of body weight, and she resumed her previous activities. From a biochemical point of view, adrenal gland was fully functional presenting maximal cortisol output, even at rest.

4. Conclusion

A long and steady tapering is necessary when facing withdrawal from long-term GCs therapy; however it may be not sufficient for restoring adequate adrenal function. Taking into account the essential physiologic requirement of proper adrenal function, the use of 1 mg intramuscular injection of tetracosactide, a depot synthetic ACTH formulation, may be helpful to support the recovery of adrenal glands from iatrogenic atrophy.

Informed Consent

Informed consent was obtained from the patient included in the study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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