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REVIEW

Primary symptomatic adrenal insufficiency induced by megestrol acetate

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ABSTRACT

Megestrol acetate (MA) is a progestational agent for the treatment of metastatic breast cancer and endometrial cancer. MA has also been used to promote weight gain in malnourished elderly patients, in patients with immunodeficiency virus and in cancer-induced cachexia. In addition to thromboembolic disease, MA may induce hyperglycaemia, osteoporosis, suppression of the gonadal axis, and Cushing's syndrome. MA has also been shown to cause symptomatic suppression of the hypothalamic-pituitary-adrenal (HPA) axis owing to its intrinsic glucocorticoid-like effect. Three additional patients are presented who developed symptomatic adrenal insufficiency while they were receiving 160-320 mg MA daily. The patients were treated with cortisone acetate supplements, had clear evidence of HPA-axis suppression but recovered fully after MA was discontinued. Patients receiving MA might have an inadequate adrenal response during stressful conditions, possibly because 160-320 mg MA daily may not provide adequate protection to prevent the symptoms of adrenal insufficiency. The adverse MA effect on the HPA axis is probably not well recognised in clinical practice, and clinicians need an increased awareness of the endocrine complications secondary to MA treatment.

KEYWORDS

Adrenal insufficiency, failure to thrive, megestrol acetate

INTRODUCTION

Megestrol acetate (MA) is a synthetic progestin that has been used for the treatment of breast cancer, advanced endometrial carcinoma and, subsequently, as second-line hormone therapy in advanced stages of other neoplastic diseases. Since the drug promotes weight gain, MA is frequently used for stimulating appetite in patients with wasting illnesses, including patients with cancer-associated anorexia and human immunodeficiency virus.

Multiple side effects have been reported in relation to the chronic use of MA, including hyperglycaemia and thromboembolic events. Chronic administration of MA has also been reported to induce Cushing's syndrome together with suppression of the hypothalamic-pituitary (HPA) axis. The mechanisms underlying these MA effects are thought to be mediated by the inherent glucocorticoid activity of progesterone and its derivatives. In particular, MA displayed considerable affinity toward the glucocorticoid receptors, which was significantly greater than that of the naturally occurring ligand cortisol. Although these pharmacological properties of MA may explain the majority of its side effects, the impact of the drug on the HPA axis still represents a clinical problem which should alert physicians to the possibility of adrenal suppression in patients taking MA.

Our case series identifies three symptomatic cancer patients who were being treated with MA, who presented with severe adrenal insufficiency (*table 1*).

PATIENT 1

An 81-year-old man with a past history of prostate cancer treated with prostatectomy, medical castration and chemotherapy was admitted to the hospital for suspected pneumonia. His medications included MA at a dose of 160 mg/daily for one year, oxycodone, ramipril, furosemide, and spironolactone.

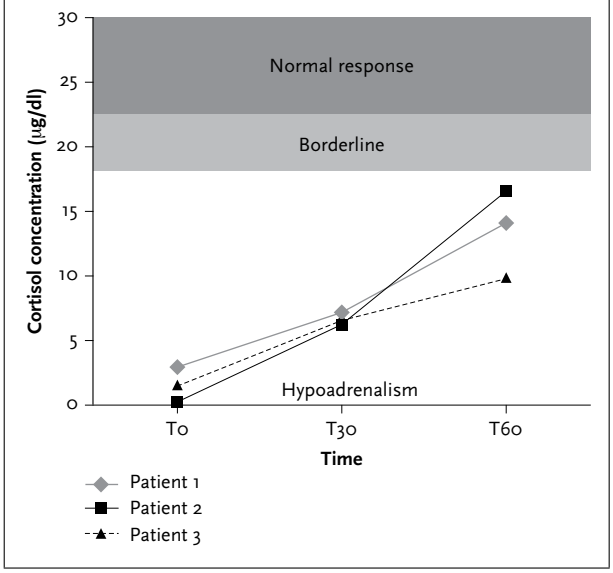
Blood count revealed megaloblastic anaemia (haemoglobin (Hb) 10.8 g/dl with a reference range of 13.1-17.1) due to

Table 1. *Summary of main features of the three case reports*

	Patient 1	Patient 2	Patient 3
Age (years)	81	70	70
Sex	Male	Female	Female
Disease	Prostate cancer	Breast cancer	Breast cancer
Dose of MA	160 mg/ daily	160 mg/ daily	320 mg/ daily
Duration of therapy	1 year	2 weeks	5 months
ACTH, pg/ml (10-60)	10	5	8
Cortisol, µg/ dl (3.7-19.4)	< 0.5	0.3	1.6
TSH, µUI/ml (0.35-4.94)	1.58	0.61	1.2
LH, mUI/ml (3.1-36.4)	0.07	11.47	14.2
FSH, mUI/ml (1.5-9.3)	2.11	21.5	18.5
Prolactin, ng/ml (2.58-18.12)	13.02	16.02	15.04

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; LH = luteinising hormone; MA = megestrol acetate; TSH = thyroid-stimulating hormone.

Figure 1.



folic acid deficiency and mild leukocytosis. Blood tests showed hyponatriaemia (129 mEq/l with a reference range of 135-145), The patient was treated with fluid replacement and broad spectrum intravenous antibiotics, as a chest X-ray was consistent with the diagnosis of pneumonia. Additional laboratory testing revealed undetectable morning cortisol and adrenocorticotropic hormone (ACTH) levels, low luteinising hormone, and low total and free testosterone. Follicle-stimulating hormone, thyroid-stimulating hormone, and prolactin were normal. Low-dose cosyntropin stimulation test revealed an inadequate adrenal response (*figure 1*). We also performed magnetic resonance imaging (MRI) of the pituitary, which was normal. We discontinued MA and replaced it with cortisone acetate 25 mg in the morning and 12.5 mg in the afternoon. After a few days the patient reported progressive improvement of the symptoms and disappearance of the fever. Chest X-ray confirmed that the pneumonia had resolved.

PATIENT 2

A female patient was admitted to our ward for severe asthenia, and weight loss. She had a clinical history of invasive ductal carcinoma of the left mammary gland treated with surgical removal of the upper outer quadrant, local radiotherapy, and adjuvant hormonal therapy. No tumour relapse occurred during the follow-up period of 20 years since the original diagnosis. Two weeks before admission to the hospital she started MA 160 mg daily for weight loss despite reported appropriate food intake. The physical examination revealed a low weight (36.5 Kg) with a body mass index (BMI) of 15.8 kg/m^2. Initial laboratory tests were normal with the exception of decreased Hb (10.4 mg/dl) and low ACTH (5 pg/ml with a reference range of 10-60) and cortisol (0.3 µg/dl, normal value 3.7-19.4). Low-dose cosyntropin stimulation test was consistent with adrenal insufficiency, as cortisol reached a value of 164.88 ng/ml 60 minutes after infusion. The other pituitary hormones were all in the normal range for age and sex. Antibodies against 21 hydroxilase were negative as well. The MRI of the pituitary was normal. We discontinued MA and prescribed cortisone acetate 25 mg in the morning and 12.5 mg in the afternoon. The patient reported improvement of the asthenia after just a few days. Three months later cortisone acetate was discontinued and cortisol and ACTH were both in normal range.

PATIENT 3

A 70-year-old woman was admitted to the hospital for evaluation of profound fatigue, decreased appetite and light-headedness on standing. She had undergone surgery for ductal carcinoma of the left breast three years previously, which was treated by mastectomy, axillary lymph node resection with adjuvant chemoradiotherapy. Approximately five months before hospitalisation she was started on MA 320 mg/day to stimulate her appetite and improve her nutrition. Laboratory tests were normal with the exception of mild hyponatraemia (130 mEq/l). Approximately 24 hours after admission, the patient developed worsening fatigue, nausea and became hypotensive. Infectious, cardiac, and neurological causes for hypotension were ruled out;

suspecting adrenal insufficiency, baseline cortisol serum levels were determined (1.6 µg/dl) and a low-dose cosyntropin stimulation test was performed. Cortisol levels 30 and 60 minutes after stimulation were 6.8 and 10 µg/dl, respectively, indicating a suboptimal adrenal response. ACTH level was 8 pg /ml. Normal saline and hydrocortisone (50 mg iv every six hours) was started with marked improvement of clinical parameters including blood pressure. MRI studies of the pituitary were then carried out, which showed no abnormalities of pituitary anatomy. The patient was discharged home on cortisone acetate taper, which was progressively reduced and finally discontinued with normalisation of ACTH and cortisol plasma levels.

DISCUSSION

MA is a synthetic progestin agent that has been used as second-line treatment for advanced endometrial and breast cancer,[1] although the exact mechanism of its antitumoral action is not known. More recently, its use has been suggested to reduce flushes in postmenopausal women, and in males with prostate cancer.[2,3] MA might act through a reduction of plasma oestrogen induced by MA-mediated inhibition of gonadotropin, although discordant data have been reported.[4]

An additional hypothesis suggests that MA might alter oestrogen metabolism via a downregulation of oestrogen receptors.[5-7] MA, at the dose of 400-800 mg per day, has been used increasingly in the treatment of cachexia related to AIDS and disseminated cancer, resulting in an increase in appetite and sustained weight gain.[8,9] MA may increase fat mass, mainly at the central level, without modifying body water content or lean mass.[10,11] This is the most common effect, although a few patients did not display weight gain. This possibility is more frequent in patients with AIDS, particularly in patients with lower $CD4^+$ counts and more severe disease.[10].

MEGESTROL ACETATE AND GLUCOCORTICOID ACTIVITY

High doses or a prolonged treatment period with MA have been reported to produce a clinical appearance of Cushing's syndrome and to reduce plasma ACTH and cortisol secretion, leading to adrenal insufficiency secondary to prolonged suppression of the HPA axis. This action of MA on the HPA axis is currently attributed to the glucocorticoid-like activity of the drug. The affinity of MA for the glucocorticoid receptor was shown in the 1980s by Kontula *et al*. who demonstrated that MA displayed affinity to glucocorticoid receptors of human mononuclear leucocytes, with a binding capacity of 46% as compared with the reference compound dexamethasone. The affinity of MA was notably greater than that of the natural ligand cortisol, which had a relative binding affinity of only 25%. The authors concluded that MA possessed inherent glucocorticoid activity, and that it could alter cortisol synthesis by suppressing HPA axis when used in humans.[12]

MEGESTROL ACETATE AND PITUITARY-ADRENAL AXIS

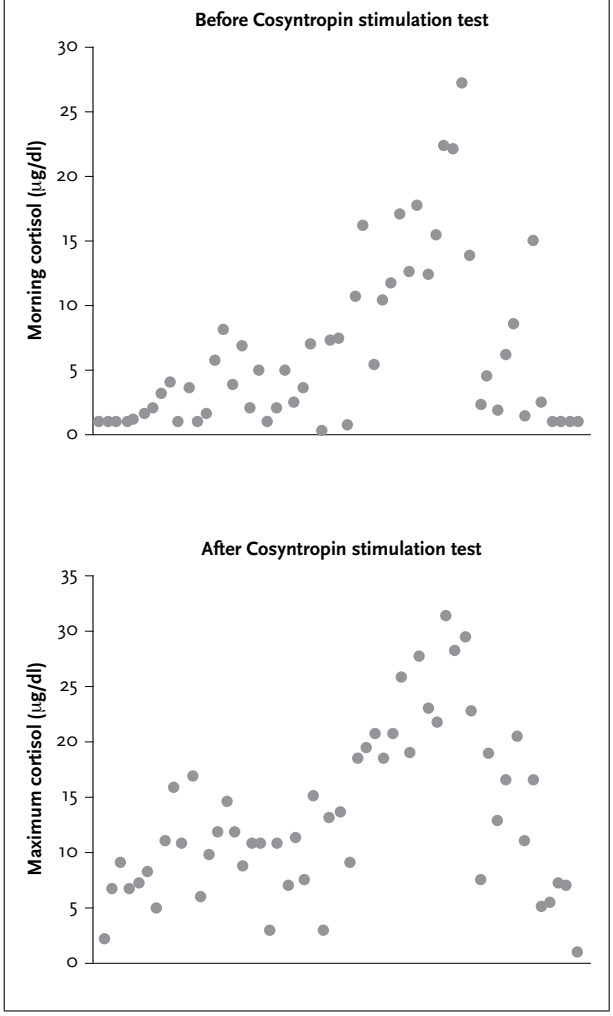
The effect of MA on cortisol secretion in humans was first demonstrated by Alexieva-Figusch *et al*.[4]. Some years later, Loprinzi *et al*. reported that patients taking MA at doses of 160 mg or 800 mg daily had low blood cortisol and ACTH levels.[13] Leinung *et al*. confirmed these data and demonstrated that before starting MA therapy patients had normal ACTH and cortisol values, both basal and after low-dose cosyntropin stimulation test. After at least a month of therapy (240 mg/day), plasma ACTH and cortisol levels showed a decrease together with a reduced adrenal response to cosyntropin stimulation.[14] Naing *et al*.[15] performed three different tests in ten post-menopausal women receiving MA in order to investigate the hypothalamic or pituitary site of MA action. Most patients had a normal response to the cortisol-releasing hormone test, demonstrating a possible suppression of the axis at the hypothalamic level, although a small number of patients showed no response. So there is still some doubt as to whether MA-induced suppression occurs at the level of the hypothalamus and/or at the pituitary gland. The clinical impact of the pharmacological effect of MA is still unknown since these patients may have no symptoms in baseline conditions, although they are known to have an abnormal activation of adrenal secretion under stressful situations. Moreover, cortisol suppression may well occur during both chronic and acute administration.[16] The suppression of the HPA axis induced by MA is not sex and age dependent.[14,17,18] It has been postulated that MA could have two different activities on glucocorticoid receptors: weak agonist initially, and then acting as an antagonist by blocking more potent glucocorticoid. Consistent with this hypothesis, adrenal insufficiency was described in patients currently taking MA and in those who abruptly discontinued it after prolonged use. This evidence, taken together, clearly suggests that the endocrine effects observed *in vivo* during MA therapy are caused by the glucocorticoid-like activity of the compound.

In our cases, all the patients were being treated with MA. ACTH and cortisol levels were below the reference range, and the corticotropin-stimulation test confirmed

the presence of adrenal insufficiency, probably caused by chronic ACTH suppression. We could not perform further dynamic endocrine tests in these patients owing to the severity of their clinical conditions. However, MRI studies excluded adrenal insufficiency secondary to pituitary abnormalities in Patient 1 as well as in Patient 2. Moreover, in Patients 2 and 3 a normal adrenal function after discontinued MA was documented. Therefore, the clinical and biochemical data of our report clearly suggest that the HPA insufficiency was likely caused by MA therapy. Our case series also raises the additional question as to whether the glucocorticoid activity of MA can provide adequate protection to prevent the symptoms of adrenal insufficiency, particularly in stressful conditions.

Previously published data and a MEDLINE search (1980-2012) performed by us, demonstrated that in patients taking MA morning cortisol levels can be suppressed, defined by a morning cortisol level of <5 μg/ dl, with a prevalence ranging from 33% to 90%. Cortisol levels are always low with MA 800 mg/daily dosing and they may even be lower with a 160 mg/ daily dose. From a clinical standpoint, few patients were reported to be overtly symptomatic. However, the symptoms of hypoadrenalism (anorexia, nausea, fatigue) have low specificity since they are commonly reported by cachetic patients with cancer and/or AIDS, meaning that adrenal insufficiency is often overlooked, left undiagnosed, and might be fatal in compromised patients. Furthermore, patients who are biochemically hypoadrenal during MA-induced suppression of the HPA axis might, although clinically asymptomatic, have relative adrenal insufficiency in the presence of stressful conditions, such as sepsis, burns, and major surgery. ACTH and cortisol level in the morning should be checked together with 24-hour urinary free cortisol value in all patients taking MA, even if asymptomatic, and a corticotrophin-stimulating test performed, since using only the morning cortisol value may underestimate the frequency of hypoadrenalism (*figure 2*). The diagnostic use of low-dose ACTH stimulation may reveal mild adrenal insufficiency that would be missed with the standard high-dose pharmacological test.[19] Although not universally accepted, the low-dose corticotropin test seems to be superior to the standard-dose test for diagnosing chronic HPA insufficiency.[20]

Figure 2. *Overview of reported cases of Cosyntropin stimulation test in patients taking MA. The overall frequency of hypoadrenalism was 58% before and 73% after the test*



MEGESTROL ACETATE AND OTHER ENDOCRINE COMPLICATIONS

MA can also alter the secretion of other pituitary hormones, including a decrease in gonadotropin, testosterone and oestrogen secretion and a mild elevation in plasma prolactin levels. The low testosterone plasma level observed in Patient 1 confirms previously published data. This additional action of MA leading to androgen deficiency in males may represent a real clinical problem, particularly when MA is mainly prescribed to treat anorexia and weight loss.

MA can adversely affect bone metabolism. Well-documented cases of osteoporosis probably induced by MA chronic therapy have been reported.[21] The glucocorticoid activity of MA was probably the causative factor although the reduction of oestradiol and testosterone production induced by a MA-mediated gonadotropin suppression may represent an additional variable.

As for its glucocorticoid-like activity, MA could eventually result in the other typical complications of corticosteroids therapy. In the literature, some cases of Cushing's syndrome in association with the use of MA have been reported.[22] They were correlated with high doses and

long-lasting duration of the therapy. Hyperglycaemia and diabetes mellitus could occur as well, but their clinical appearances were usually precocious and often manifest with doses of MA that were lower than those causing Cushing's syndrome.

In conclusion, recognising MA activity on the HPA axis is clinically important for the diagnosis of subclinical hypoadrenalism or overt adrenal insufficiency, particularly when the therapy is discontinued. Moreover, symptomatic adrenal failure can occur during MA administration, as documented by published case reports and by our additional patients, suggesting that supplementation of hydrocortisone seems to be empirically indicated for major surgery or stressful situations. Finally, the glucocorticoid-like activity of MA should be kept in mind during chronic therapy, since hyperglycaemia, clotting disorders, osteoporosis, hypogonadism as well as Cushing's syndrome have been clearly documented in clinical practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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