Megestrol-induced clinical adrenal insufficiency

A. Goodman[1], *M.D.*; **E. Cagliero**[2], *M.D.*

[1]*Assistant Professor of Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School Massachusetts General Hospital*
[2]*Assistant Professor of Medicine, Harvard Medical School, Boston (USA)*

Summary

Objective: To describe a case of megestrol-induced adrenal insufficiency.
Methods: A patient who received megestrol and then developed pituitary-adrenal axis abnormalities is described. The literature is reviewed.
Results: The patient developed megestrol-induced Cushingoid features. She developed adrenal insufficiency when megestrol was stopped.
Conclusion: Megestrol can induce alterations of the pituitary-adrenal axis in some patients. It is important to consider a diagnosis of adrenal insufficiency in patients with symptoms of fatigue, hypotension, and asthenia who have been treated with megestrol.

Key words: Megestrol; Adrenal insufficiency; Cushingoid Features.

Introduction

Megestrol acetate (Megace) is used extensively in gynecologic oncology. This progestational agent has demonstrated cytostatic activities in advanced and recurrent endometrial cancer [1]. It has also been used to treat cancerous cachexia [2].

Several authors have reported that prolonged use can lead to clinically significant secondary adrenal suppression [3, 4]. This paper describes a patient who developed clinical adrenal insufficiency after megestrol acetate administration. The patient presented with Cushingoid features and adrenal insufficiency upon stopping the drug.

Case Report

A 40-year-old Caucasian woman with a family history of familial nonpolyposis colon cancer developed Stage IV endometrial cancer. Her past history was significant for a right colectomy due to colon cancer in December 1995. An endometrial biopsy performed for menorrhagia revealed endometrioid adenocarcinoma. In April 1997 she underwent an exploratory laparotomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy. Omentectomy and transverse colon resection with reanastomosis were performed because of a metastatic nodule to the mesentery of her transverse colon. Pathologic analysis demonstrated a non-invasive grade II endometrioid adenocarcinoma with squamous differentiation of the endometrium with identical histology in the metastatic colon nodule.

After consideration of various treatment options, the patient opted for adjuvant progesterone therapy. In June 1997, she started Megace 40 mg po BID. Because of a 30 pound weight gain, she stopped the megace after two months. One month later she returned complaining of profound fatigue. On examination she had a Cushingoid appearance with a rounded face and fat deposition between her shoulders.

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There was no evidence of recurrent disease. Table 1 shows the adrenal axis evaluation. She was started on prednisone 7.5 mg po daily with resolution of her fatigue. She remained on this regimen for six months and then was tapered off without difficulty.

As of August 1999, she remains free of recurrence and has had no further problems with her adrenal-pituitary axis.

Discussion

Megestrol acetate is commonly used in gynecologic malignancies for therapy, palliation, and stimulation of appetite. Progesterones are also commonly used in gynecology for the control of irregular menses, induction of menses in anovulatory cycles, and treatment of endometrial hyperplasia [5]. Recently, there has been increasing interest in the use of high dose progesterones for the non-surgical treatment of early endometrial cancer in young women [6].

Several reports have shown that prolonged administration of megestrol can induce clinically significant secondary adrenal suppression [3, 4]. In this setting, abrupt withdrawal can cause adrenal insufficiency as was seen in this report. Our patient was taking a smaller dose of Megace than other patients reported in the literature. Secondary adrenal insufficiency in patients with acquired immunodeficiency syndrome (AIDS) on long term megestrol has been reported [7]. Nathwani *et al.* described a

Table 1. — *Megestrol induced Cushing's syndrome.*

Test	Result	Reference range
AM cortisol	<1.0 ug/dl	7-25 ug/dl
24-hour urine		
Free cortisol	5.0 ug/dl	
Cortrosyn stimulation		
Baseline	<1.0 ug/dl	7-25 ug/dl
Response	3.2 ug/dl	2-9 ug/dl

patient with AIDS-related cachexia on megestrol who developed adrenal insufficiency upon abrupt withdrawal of therapy [2].

Suramanian *et al.* reported on 13 patients with advanced breast cancer who were treated with 160 mg per day of megestrol acetate [3]. Clinical adrenal insufficiency was proven by a rapid corticotropin test. A mean of 16.8 months of therapy was noted before onset of symptoms. The symptoms appeared when the patients generally showed subjective and objective clinical improvement from their cancers. Another study reported 16 cases of adrenal insufficiency in association with megestrol [4]. All patients had clinical complaints characteristic of adrenal suppression such as nausea, vomiting, dizziness, hypotension, weight loss, or profound fatigue. Five patients developed symptoms while tapering therapy but 11 cases occurred while patients were still receiving treatment.

Steer *et al.* reported a patient with an early endometrial cancer who developed megestrol-induced Cushing's syndrome [8]. She required maintenance on hydrocortisone after cessation of the progesterone. Five cases of Cushing's syndrome in association with the use of megestrol are described by Mann *et al.* [4]. All had received at least 9 months of this therapy. Doses ranged from 160 mg per day to daily doses of 800 mg. Two patients improved clinically and one patient had no change on cessation of megestrol. The patient described in this report rapidly developed symptoms suggestive of Cushing's syndrome while on megestrol and then adrenal insufficiency upon cessation of the drug.

Megestrol acetate appears to have glucocorticoid-like activity in some patients. High pharmacological concentrations of megestrol causes in-vitro glucocorticoid activity in human breast cancer cells [9]. Some reports suggest that megestrol might suppress serum cortisol levels in humans to about 10 to 20% of normal values [10]. Serum cortisol levels were universally decreased in patients receiving 800 mg per day and often reduced in those receiving 160 mg per day [11].

Conclusion

Megestrol is an effective and useful drug in cancer care. It is important to be aware of possible suppression of the adrenal-pituitary axis in patients on megestrol. Any symptoms suggestive of adrenal insufficiency need to be evaluated. There are important implications of possible subclinical adrenal insufficiency. Patients on megestrol who are facing surgery may need stress dose steroids or should be evaluated by corticotropin stimulation testing.

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Address reprint requests to:
ANNEKATHRYN GOODMAN, M.D.
Massachusetts General Hospital
Department of Obstetrics and Gynecology
WACC 231
Boston, MA 02114 (USA)