Effects of Megestrol Acetate on Pituitary Function and End-Organ Hormone Secretion: A Post Hoc Analysis of Serum Samples from a 12-Week Study in Healthy Older Men

Donald L. Bodenner, MD, PhD; Monisha Medhi, MD; William J. Evans, PhD; Dennis H. Sullivan, MD; Hui Liu, MS; and Charles P. Lambert, PhD

Department of Geriatrics, Donald W Reynolds Center on Aging, The University of Arkansas for Medical Sciences and the Geriatric Research, Education and Clinical Center, Central Arkansas Veterans Healthcare System, Little Rock, Arkansas

ABSTRACT

Background: Megestrol acetate (MA) is a synthetic progestin commonly used to promote weight gain in malnourished older individuals. In small studies, MA administration has been associated with reduced serum cortisol concentrations in patients with cancer or AIDS. The impact of MA on the pituitary secretion of adrenocorticotropic hormone (ACTH) and other hormones is unclear, and the prevalence and extent of hypocortisolemia in older individuals after MA treatment is unknown. A randomized, placebo-controlled study of the effects of testosterone (T) and resistance training (RT) on body composition after MA administration in older men has been reported previously.

Objective: The purpose of this post hoc analysis was to examine the effect of 12 weeks of MA on pituitary function and end-organ hormone secretion in healthy older individuals using frozen serum samples from that study.

Methods: The previous study was conducted at the Department of Geriatrics, Donald W. Reynolds Center on Aging and the General Clinical Research Center at The University of Arkansas for Medical Sciences, Little Rock, Arkansas. Healthy male volunteers aged 60 to 85 years were recruited from the center and were randomly assigned to 1 of 4 study groups: RT + T, T, RT + placebo (P), or P. Subjects enrolled in the RT groups underwent supervised upper- and lower-body strength-training exercises 3 d/wk at 80% of 1 repetition maximum. Subjects in the groups to receive T received injections of testosterone enanthate 100 mg IM QW for 12 weeks. Subjects receiving P were given 1-mL saline injections IM QW for 12 weeks. All subjects received MA 800 mg PO QD concurrently for 12 weeks. For the present analysis, serum concentrations of the pituitary hormones follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), ACTH, prolactin (PRL), and luteinizing hormone (LH), as well as the end-organ hormones estradiol (E_2), cortisol, free T4, and T, were measured in samples obtained at baseline (week 0) and after 12 weeks of MA treatment.

Results: Serum samples from 21 men (mean [SD] age, 67.0 [7.3] years; mean [SD] body mass index, 23.1 [10.4] kg/m^2; mean [SD] percentage of body fat, 22.5% [8.8%]; RT + T, T, RT + P, and P groups, n = 4, 5, 6, and 6 subjects, respectively) were available from the original study. The mean percentage changes from baseline in serum pituitary hormone concentrations after 12 weeks of MA administration were as follows: TSH, –14.7%; ACTH, –89.5%; PRL, 162.2%; and LH, –49.0%; (P = 0.03, <0.001, <0.001, and <0.001, respectively). The mean (SD) percentage changes from baseline in serum end-organ hormone concentrations with MA at 12 weeks were as follows: E_2, 181.6%; and cortisol, –90.8% (both, P < 0.001). In the P and RT + P groups, the mean percentage changes from baseline in T were –84% and –85%, respectively (both, P < 0.001). FSH and free T4 concentrations were not significantly changed.

Conclusions: This analysis of serum samples from healthy older men suggests that MA administration significantly affected the secretion of several pituitary hormones and end-organ hormone synthesis. Most notably, ACTH secretion and serum cortisol levels were statistically significantly suppressed in 20 of 21 subjects, without the develop-

Accepted for publication June 15, 2005

doi 10.1016/j.amjopharm.2005.09.007
1543-5946/05/$19.00

ment of clinically significant adrenal suppression. (*Am J Geriatr Pharmacother*. 2005;3:160–167) Copyright © 2005 Excerpta Medica, Inc.

Key words: megestrol acetate, adrenal insufficiency, cortisol, pituitary, older patients.

INTRODUCTION

Megestrol acetate (MA) is a progesterone-like compound used to combat malnutrition associated with AIDS[1] and cancer.[2] Long-term MA treatment is frequently prescribed to prevent or reverse weight loss in residents of long-term care facilities and in anorexic older patients.[3–6] However, based on a MEDLINE search (key terms: *megestrol acetate, adrenal insufficiency,* and *adrenal suppression*; years: 1965–2005), few studies have examined the efficacy and tolerability of MA in this patient population.

MA, similar to progesterone, functions as a glucocorticoid agonist. Several case series have shown that MA significantly suppresses serum cortisol levels.[7–15] However, generalization of these observations, particularly to the geriatric population, is hampered by the small numbers of subjects enrolled in available studies, the absence of an untreated control group, and extremely few older subjects enrolled. Moreover, the majority of these reports have involved children or patients with AIDS.[8,10,11,14,16–18]

MA has been shown to markedly reduce serum estrogen concentrations in women[19] and to suppress serum testosterone (T) concentrations to castrate levels in men.[20] However, the mechanism of these effects and the impact of MA on the secretion of other pituitary hormones are poorly understood. In 1 series of patients with breast cancer, MA increased basal and stimulated prolactin (PRL) levels, decreased estrogen level, and suppressed luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[21]

The purpose of this post hoc analysis was to examine the effect of MA on pituitary function and end-organ hormone secretion in healthy older individuals using frozen serum samples from a previously reported investigation examining the effect of T and progressive-resistance muscle strength training (RT) on body composition in healthy older men receiving MA to induce weight gain.[22]

MATERIALS AND METHODS

Study Design and Population

The previous study was conducted at the Department of Geriatrics, Donald W. Reynolds Center on Aging and the General Clinical Research Center at The University of Arkansas for Medical Sciences, Little Rock, Arkansas. The study protocol was approved by the Human Research Advisory Committee at the university. Details of the original study design were reported previously.[22]

In brief, healthy men aged 60 to 85 years and with a body mass index (BMI) ≤25 kg/m^2 were recruited from the center. Subjects were randomly assigned to 1 of 4 groups: RT + T, T, RT + placebo (P), or P. Subjects enrolled in the RT groups underwent supervised upper- and lower-body strength-training exercises 3 d/wk at 80% of 1 repetition maximum. Group T was administered replacement with testosterone enanthate 100 mg IM QW for 12 weeks; group RT + P received RT and saline injections IM QW for 12 weeks; and group P received 1-mL saline injections IM QW for 12 weeks. All subjects received MA 800 mg PO QD concurrently for 12 weeks.[22]

Venous blood was sampled from an antecubital vein at 7:00 AM before the start of the study and at study end, 8 days after the final injection, 3 days after the final RT session, and 1 day after the last dose of MA. Blood samples were obtained after subjects had been in the supine position for at least 15 minutes.[22] Serum concentrations of the pituitary hormones FSH, thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), PRL, and LH, as well as the end-organ hormones estradiol (E_2), cortisol, free T4, and T, were measured in the pretreatment (baseline) and posttreatment (12-week) samples. The hormones were assayed using enzyme-linked immunosorbent assay kits according to manufacturer's instructions.[23] The interassay coefficients of variation for the kits were as follows: FSH, 4.8%; TSH, 8.9%; ACTH, 6.2%; PRL, 7.4%; LH, 8.1%; E_2, 3.7%; cortisol, 6.9%; free T4, 5.7%; and T, 7.6%.

Statistical Analysis

Three-factor repeated measures analysis of variance (RT × T × time [d]) was performed, followed by a Tukey post hoc analysis where appropriate. Results were considered significant at $P < 0.05$. A power analysis for this study was not performed.

RESULTS

Serum samples from 21 subjects in the original study were available for analysis (RT + T, n = 4; T, n = 5; RT + P, n = 6; P, n = 6). The mean (SD) age, BMI, and percentage of body fat of the participants were 67.0 (7.3) years, 23.1 (10.4) kg/m^2, and 22.5% (8.8%), respectively. No significant differences in age or BMI were found between the 4 groups.

The serum concentrations of several pituitary hormones and the hormone levels associated with their respective target organs were significantly changed from baseline after 12 weeks of MA administration in all 4 groups combined (**Table**).

Pituitary Hormones

MA had little effect on FSH levels. In contrast, the mean percentage decrease from baseline in LH levels was 49.0% ($P < 0.001$), with no significant group-by-time effects. TSH was significantly decreased (by 14.7%) after MA administration ($P = 0.03$), but the changes were within the normal range. The mean percentage decrease from baseline in ACTH was 89.5% (from 20.9 [6.2] to 2.2 [2.3] pg/mL; $P < 0.001$). This change is illustrated by the significant time effect as shown in **Figure 1**. Although ACTH was significantly higher in the RT + T group compared with those in the other groups at baseline, there was no RT-by-time interaction, indicating differences between groups at baseline. PRL levels were significantly increased at 12 weeks; the mean percentage change was 162.2% (range, 118%–1300%; $P < 0.002$), with levels detected outside the normal range in 19 of 21 subjects.

End-Organ Hormones

As previously reported, the percentage decreases from baseline in T levels at 12 weeks were 84% in the P group and 85% in the RT + P group (both, $P < 0.001$).[22] Conversely, E_2 levels increased from baseline by 181.6% after MA administration (from 9.7 [16.4] to 27.4 [24.1] pg/mL; $P < 0.001$). The change in ACTH was reflected by a similarly significant mean percentage decrease from baseline of 90.8% in the serum cortisol levels in all 4 groups combined (from 424.8 [127.2] to 38.9 [112.5] nmol/L; $P < 0.001$), with no significant group-by-time effect (**Figure 2**). Free T4 was not significantly affected.

DISCUSSION

Hypothalamic-Pituitary-Adrenal Axis

MA treatment was associated with ~90% decreases in ACTH and cortisol, representing a profound suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Importantly, this extent of suppression was almost universal, with cortisol and ACTH reduced to less than the lower limits of normal (LLNs) in 20 of 21 subjects, without the development of clinically significant adrenal insufficiency.

MA binds to the glucocorticoid receptor, with approximately half the binding affinity of dexamethasone and twice the affinity of cortisol.[24] Several relatively small case series have shown that the glucocorticoid activity of MA might induce adrenal suppression.[8,10–12,14,16–18,25,26] However, symptomatic adrenal insufficiency appears to be uncommon: in a review of US Food and Drug Administration records from 1984 to 1996,[27] only 17 cases of adrenal insufficiency possibly associated with MA were reported. Since 1996, despite widespread MA use in patients with AIDS or cancer, few cases of clinically significant adrenal insufficiency have been reported.[14] However, adrenal insufficiency often has a protean presentation and frequently is underdiagnosed.[28] Thus, whether the presumed incidence of adrenal insufficiency is a reflection of inadequate reporting of an unrecognized adverse effect remains unclear. For example, in a study of 13 patients with breast cancer receiving MA,[15] all 13 experienced fatigue and weakness while receiving the drug. Eight patients were hypotensive, and 3 experienced nausea and vomiting. In another study,[29] 12 of 13 children had adrenal suppression while being treated with MA for weight loss from malignant disease, with 1 patient experiencing a circulatory collapse requiring inotropic support.

The glucocorticoid activity of MA might be sufficient to provide adequate basal physiologic glucocorticoid activity in most individuals, which might explain the common finding of adrenal suppression but the low incidence of adrenal insufficiency noted during treatment with MA. Similarly, in the previous study,[22] deep venous thrombosis was noted in 1 subject, but no signs or symptoms consistent with adrenal insufficiency were reported.

In the present study, the extent of adrenal axis suppression was similar to or greater than that seen in a study in 75 patients of similar age (mean, 66 years) administered glucocorticoids bioequivalent to at least 25 mg/d of prednisolone for 5 to 30 days.[30] Recovery of adrenal function after discontinuation of treatment with these relatively high doses of prednisone occurred within weeks in most patients but varied considerably, and might require >1 year.[30] Similarly, the function of the HPA axis might recover within weeks after discontinuation of MA therapy[31]; however, in cats administered MA at a dose of 5 mg/d,[32] only 3 of 7 animals had regained adrenal function within weeks after discontinuation of the drug. Although recovery of adrenal function was not assessed in the present study, suppression was virtually universal, with ACTH and cortisol reduced to less than LLN in 20 of 21 healthy subjects. Even mild adrenal insufficiency can be harmful in critical illness,[33] which might explain the increased mortality reported with MA treatment in patients with AIDS[34] or can-

Table. Serum pituitary and end-organ hormone concentrations before and after 12 weeks of treatment with megestrol acetate 800 mg/d in healthy older men. Values are presented as mean (SD).

Hormone (Normal Range)	RT + T (n = 4)		T (n = 5)		RT + P (n = 6)		P (n = 6)		All (N = 21)			
	Before	After	Before	After	Before	After	Before	After	Before	After	%Δ	*P*
Pituitary hormones												
FSH, mIU/mL (1.4–18.1)	7.3 (1.4)	6.5 (1.5)	10.2 (1.6)	8.3 (1.2)	6.8 (0.7)	6.9 (0.6)	12.1 (4.3)	8.0 (1.1)	9.2 (6.0)	7.5 (2.3)	−18.6	0.075
TSH, μIU/mL (0.1–6.0)	10.7 (2.8)	8.5 (1.4)	15.3 (4.8)	14.5 (3.9)	12.2 (3.1)	11.0 (3.0)	14.4 (3.2)	10.9 (2.0)	13.7 (8.5)	11.7 (6.8)	−14.7	0.03
ACTH, pg/mL (8.3–57.8)	24.7 (6.9)	4.3 (3.6)	20.0 (4.2)	1.6 (1.2)	22.3 (6.4)	1.7 (1.8)	17.9 (5.2)	1.8 (1.2)	20.9 (6.2)	2.2 (2.3)	−89.5	<0.001
PRL, ng/mL (6–30)	15.6 (6.2)	48.1 (10.4)	15.3 (4.8)	41.7 (9.0)	12.2 (3.1)	18.4 (7.9)	20.6 (28.9)	53.6 (31.0)	13.7 (8.5)	11.7 (6.8)	162.2	<0.002
LH, mIU/mL (1.9–5.3)	9.0 (3.3)	3.3 (2.3)	7.5 (2.7)	5.1 (4.5)	8.5 (2.7)	5.4 (3.3)	11.6 (9.1)	4.6 (2.5)	9.7 (16.4)	27.4 (24.1)	−49.0	<0.001
End-organ hormones												
E_2, pg/mL (15–60)	3.1 (10.3)	31.6 (25.2)	8.5 (11.3)	25.5 (11.2)	8.1 (5.3)	19.9 (17.6)	16.9 (29.6)	33.6 (36.5)	9.2 (5.6)	4.7 (3.4)	181.6	<0.001
Cortisol, nmol/L (138–690)	502.5 (118.6)	147.2 (227.0)	393.2 (160.2)	38.9 (112.0)	394.3 (119.6)	21.9 (8.5)	429.5 (75.8)	7.7 (2.5)	424.8 (127.2)	38.9 (112.5)	−90.8	<0.001
Free T4, ng/dL (0.8–2)	1.3 (0.1)	1.2 (0.1)	1.2 (0.2)	1.2 (0.2)	1.2 (0.1)	1.2 (0.3)	1.2 (0.1)	1.2 (0.1)	9.2 (6.0)	7.5 (2.3)	0.9	0.38

RT = resistance training, T = testosterone, P = placebo, FSH = follicle-stimulating hormone, TSH = thyroid-stimulating hormone, ACTH = adrenocorticotropic hormone, PRL = prolactin, LH = luteinizing hormone, E_2 = estradiol

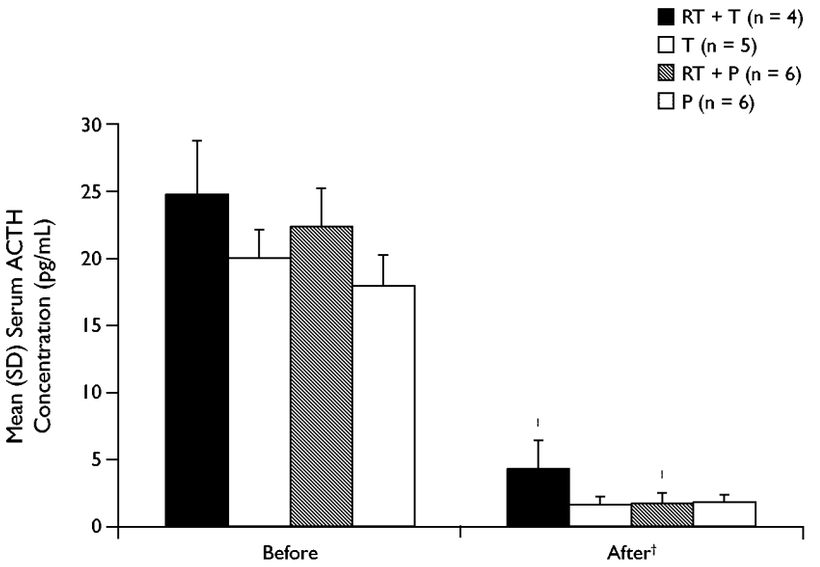

Figure 1. Effect of 12 weeks of treatment with megestrol acetate 800 mg/d on serum adrenocorticotropic hormone (ACTH) concentrations in healthy older men. RT = resistance training; T = testosterone; P = placebo. *$P < 0.05$ versus T and P groups; †$P < 0.05$ versus before treatment (all 4 groups).

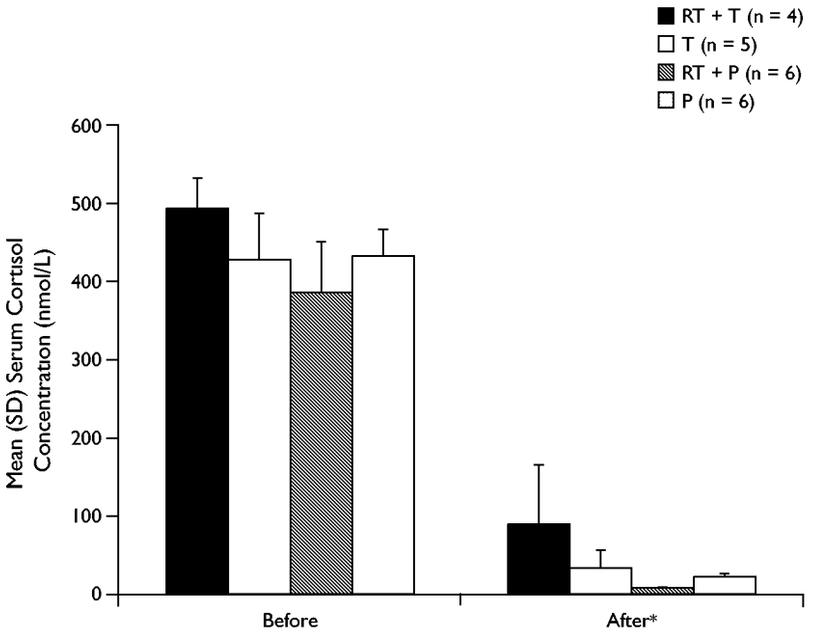

Figure 2. Effect of 12 weeks of treatment with megestrol acetate 800 mg/d on serum cortisol concentrations in healthy older men. RT = resistance training; T = testosterone; P = placebo. *$P < 0.05$ versus before treatment (all 4 groups).

cer.[35,36] In the elderly, if weight gain is not observed after 3 months of MA treatment, the drug is often discontinued without taper. The development of clinically significant adrenal insufficiency in frail, older individuals after such abrupt discontinuation of MA might be associated with similar serious outcomes.

MA has been shown to affect the adrenal axis at several levels. It has been found to directly inhibit cortisol production by adrenal cells in vitro by 85%.[37] However, the results of the present study and others[11,12] showed a marked decrease in ACTH after MA treatment, suggesting that the predominant effect of MA on the HPA axis might occur at the hypothalamic-pituitary level.

Gonadal Axis

In the previously reported study,[22] MA markedly reduced serum total T and free T to near-castrate levels in 20 of 21 subjects studied. The precise mechanism of T reduction is unclear. In a study of prostate tissue examined after the administration of MA 80 mg/d for up to 25 days in males with benign prostatic hypertrophy, testicular production of T was significantly reduced, and the conversion of T to dihydrotestosterone was reduced 31% presumably by the inhibition of 5α-reductase activity.[38] MA also competes with androgens for the androgen receptor[39] and is associated with a decreased number of androgen receptors.[40] The effect of MA on pituitary hormones might also play a significant role in the observed reduction in serum T. In the present study, MA was associated with 50% decreases in serum LH levels, similar to the decreases reported during antiandrogen therapy in patients with advanced prostate cancer[20] and in females receiving therapy for breast cancer.[41]

Hyperprolactinemia is also associated with low T levels. We observed that MA increased PRL levels by 150% in 19 of 21 subjects. However, although the reduction in LH and elevation in PRL might have contributed to the decline in serum T levels, near-castrate levels of T with normal PRL and LH levels have been noted in patients treated with lower doses of MA.[17,38] Loss of libido and impotence occurs in up to 18% of patients when MA doses exceed 120 mg/d,[42,43] presumably due to reduced T levels; this loss has not been observed at lower doses.[44] Patients should be advised of the possibility of loss of libido and/or impotence, and T replacement should be considered when androgen suppression is not a primary goal.

Based on our literature search, this is the first study of MA on E_2 levels in males. In postmenopausal women with breast cancer, MA has been found to suppress the level of estrone and E_2 to between 18% and 29% of pretreatment values.[19] The mechanism behind the highly significant, paradoxical increase in E_2 levels found in men in the present study was unclear. MA administration has been found to decrease sex hormone binding globulin levels,[45,46] which would result in decreased, not increased, total E_2 levels. These results suggest that defects in the adrenal production of E_2 or enhanced aromatization of T might be responsible. An increased E_2 level with MA treatment in males might alleviate some of the concern regarding the effect of T at levels of castrate on bone mineral density (BMD) and risk for fracture. In men, the E_2 level has a more significant role in maintaining BMD compared with the role of T.[47]

Other Axes

In the present study, TSH levels were modestly decreased, but free T4 levels were unchanged. Similarly, normal TSH and free T4 levels during MA treatment have been reported.[12]

Study Limitations

The present study was limited in several respects. The analysis was performed post hoc on samples from a study in which the population was comprised only of healthy older men, and that was not designed to assess the effects of MA on pituitary function. As a result, the changes in hormone levels were not correlated with symptoms, and the clinical significance of the changes was uncertain. Although the changes from baseline in the adrenal axis and several other pituitary hormones were significant, there was no true control group: all subjects were treated with MA.

CONCLUSIONS

In this post hoc analysis of serum samples from healthy older men, MA significantly affected the secretion of several pituitary hormones and end-organ hormone synthesis. Significant adrenal suppression was observed in 20 of 21 subjects, without the development of clinically significant adrenal insufficiency. These findings suggest that the inherent glucocorticoid activity of MA was sufficient to fulfill basal glucocorticoid requirements. However, whether this degree of glucocorticoid activity is adequate in critical illness or after abrupt discontinuation of MA is unknown. Even partial adrenal insufficiency in malnourished, frail older patients might have serious consequences. Until additional research establishes the adrenal status after discontinuation of MA treatment, we recommend that oral glucocorticoid

administration or tapering of MA be strongly considered in these patients.

ACKNOWLEDGMENTS

This study was supported by grants from Bristol-Myers Squibb Company, Princeton, New Jersey; General Clinical Research Center at The University of Arkansas for Medical Sciences (no. M01-RR-12488); the National Institutes of Health, Bethesda, Maryland (nos. R01-AG-15385 [W.J.E.] and F32-AG-05873 [C.P.L.]); and the Veterans Health Administration (merit review grant [D.L.B.]).

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Address correspondence to: Donald L. Bodenner, MD, PhD, Department of Geriatrics, The University of Arkansas for Medical Sciences, Box 806, 4301 West Markham Street, Little Rock, AR 72205. E-mail: bodennerdonald@uams.edu