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ORIGINAL ARTICLE

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Acute effects of megestrol on the hypothalamic–pituitary–adrenal axis

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Abstract *Background*: Clinical observations suggest that prolonged treatment with megestrol can lead to Cushing-like symptoms, while withdrawal of prolonged treatment with megestrol may result in adrenal insufficiency. However, only little is known about the acute effects of megestrol on the hypothalamic–pituitary–adrenal (HPA) axis. As part of an endocrine study, we evaluated the acute effects of megestrol, hydrocortisone and placebo on morning cortisol and ACTH levels. *Method*: Using a balanced double-blind design, ten healthy male subjects were treated at 11:00 P.M. and 8:00 A.M. with megestrol (total dose 320 mg), hydrocortisone (total dose 30 mg) or placebo. After 1 h of rest, blood was drawn at 10:00 A.M. and 10:30 A.M. for determination of cortisol and ACTH levels. *Results*: Compared to placebo, acute administration of megestrol resulted in a significant decrease in morning ACTH and cortisol levels. The suppression of ACTH after pretreatment with megestrol was less pronounced than after pretreatment with hydrocortisone. *Conclusions*: Our results suggest that megestrol exerts glucocorticoid-like effects and has an acute depressing effect on the HPA axis. Therefore alterations in the steroid system should be included in the differential diagnosis of all subjects under treatment with megestrol.

Keywords Megestrol · Hydrocortisone · Cortisol · ACTH · Cancer

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Introduction

Megestrol (17-hydroxy-6-methylpregna-3,6-diene-3,20-dione) is a synthetic derivative with agonist activity of the naturally occurring hormone progesterone. Megestrol has been widely used for the treatment of advanced breast [17] and ovarian cancer [14] as well as metastatic prostate cancer [3]. Additional indications for megestrol include cachexia and wasting associated with HIV infection [19]. Clinical observations suggest that megestrol has glucocorticoid-like activity and that prolonged treatment with megestrol may occasionally result in Cushing syndrome [10]. Similarly, cases of adrenal insufficiency have been described after prolonged treatment with megestrol [10, 11].

While these observations were obtained in patients under long-term treatment with megestrol, little is known about the acute effects of megestrol on the hypothalamic–pituitary–adrenal (HPA) axis. As part of a neuroendocrine challenge study (data not presented), we pretreated ten healthy male volunteers in a balanced and blinded fashion with megestrol, hydrocortisone and placebo and determined resting cortisol and ACTH plasma levels the next morning.

Subjects and methods

Subjects

A group of 14 healthy male volunteers were screened for the study. All were free of known psychiatric and medical disorders, and were not substance abusers. At the time of the study, the subjects were not taking any prescription or over-the-counter medication. Subjects were excluded if they had undergone major life events during the month prior to the study. All subjects underwent a physical examination, an EKG, routine blood tests and a urinary toxicology screen. The German version of the Mini-International Neuropsychiatric Interview [13], a standardized psychiatric screening interview, was administered by an experienced psychiatrist (T.J.R.) to rule out psychiatric disorders. Ten of the subjects were cleared for participation in the study. The other four subjects were excluded for the following reasons:

diagnosis of a previously unknown chronic hepatitis B infection, diagnosis of a tic disorder, urinary toxicology screen positive for cannabis, and inability to establish a peripheral venous access.

Ethics approval

The study was approved by the Ethics Board of the Board of Medicine in Hamburg, Germany. All subjects gave written informed consent prior to inclusion in the study.

Study procedure

The study was performed in a balanced double-blind and placebo-controlled fashion. The randomization was done by one investigator (K.W.) and the study was not unblinded until after the last subject had completed all study arms. Subjects were studied on three occasions separated by at least 1 week. On the day prior to each study, subjects received two pills of the study medication and were told to take one dose at 11:00 P.M. and one dose at 8:00 A.M. The premedication consisted of either megestrol (160 mg at 11:00 P.M. and 8:00 A.M.) (Megestat 160; Bristol Pharmaceutics, Munich, Germany), hydrocortisone (20 mg at 11:00 P.M. and 10 mg at 8:00 A.M.) (Hydrocortison Hoechst; Hoechst, Frankfurt, Germany) or placebo (at 11:00 P.M. and 8:00 A.M.). Subjects were instructed to abstain from alcohol and to maintain their normal activities including their sleeping habits prior to the study.

After a light breakfast, subjects presented to the laboratory at 8:45 A.M. They were instructed to void before being comfortably placed in a supine position. At 9:00 A.M., a venous access was established and a continuous infusion of normal saline was administered at a rate of 50 ml/h. Subjects were not allowed to eat or drink until after the completion of the study. They were allowed to read or write non-stimulating material and were instructed to stay alert throughout the entire study. The level of alertness was continuously assessed by the examiner (B.G.).

Collection kits using 1 mg EDTA for anticoagulation (Titriplex III; Merck, Darmstadt, Germany) were used for all blood draws. After 1 h of rest, two blood samples of 10 ml each were drawn from the intravenous access at 10:00 A.M. The first blood sample was rejected for potential contamination with the infusion fluid. The second was used for the determination of the levels of cortisol and ACTH. An additional blood sample of 20 ml was drawn at 10:30 A.M. As the first psychological examination was performed after the 10:30 A.M. blood draw, we discontinued the baseline evaluation at this point. The blood samples were immediately transferred into sterile vials and packed in dry ice. The blood samples were centrifuged at 4000 *g* after the termination of the entire study at 1:00 P.M. and the plasma was immediately stored at −80°C until analysis.

Determination of ACTH and cortisol levels

ACTH and cortisol were determined using commercially available immunoradiometric and radioimmunoassays (Nichols Institute, San Juan Capistrano, Calif.; ICN Biomedicals, Carson, Calif.). Intra- and interassay coefficients of variation were below 8%.

Statistical analysis

Statistical analysis was performed with Microsoft Excel 2002 and Statistica 6.1 (StatSoft, Tulsa, Okla.). Group comparisons of ACTH and cortisol levels were performed using ANOVA with pretreatment as the grouping factor. As the same subjects were tested on several occasions under identical conditions, paired *t*-test was used to compare the different pretreatments.

Results

Subjects

Ten healthy male subjects with a mean age of 32.6 ± 6.9 years (range 21 to 41 years) participated in this study. All subjects were able to finish all three arms of the study. One subject reported pruritus without rash after premedication with megestrol that did not limit him in his daily activities. All other subjects were free of side effects after the premedication. All subjects reported being comfortable during the study and denied any stressful events prior to the study. Subjects also denied any changes in their daily activities during the days prior to each study.

ACTH levels

After 1 h of rest (10:00 A.M.), the mean baseline level of ACTH after pretreatment with placebo was 18.9 ± 9.1 pg/ml. At 10:30 A.M., the mean ACTH level remained unchanged at 19.2 ± 7.6 pg/ml. The respective ACTH levels after pretreatment with megestrol were 11.3 ± 4.1 pg/ml (10:00 A.M.) and 9.6 ± 4.5 pg/ml (10:30 A.M.). After pretreatment with hydrocortisone, the ACTH levels were 5.8 ± 3.2 pg/ml at 10:00 A.M. and 4.8 ± 3.2 pg/ml at 10:30 A.M. The ACTH levels for the different pretreatments are shown in Fig. 1.

ANOVA with pretreatment as a grouping factor and time (10:00 A.M. and 10:30 A.M.) as a dependent factor showed a significant effect of pretreatment ($df = 2$, $F = 13.4$, $P < 0.001$) but neither the effect of time ($df = 1$, $t = 3.0$, $P < 0.10$) nor the interaction between pretreatment and time ($df = 2$, $F = 1.3$, $P < 0.30$) were significant. Comparison of the ACTH levels between subjects pretreated with megestrol and those pretreated with placebo showed significantly lower ACTH levels after megestrol treatment for both the 10:00 A.M. measurement ($df = 9$, $t = -2.68$, $P < 0.03$) and the 10:30 A.M. measurement ($df = 9$, $t = -3.4$, $P < 0.001$). Comparing megestrol with hydrocortisone, the 10:00 A.M. ACTH levels were significantly decreased after pretreatment with hydrocortisone ($n = 10$, $t = -2.69$, $P < 0.03$). After pretreatment

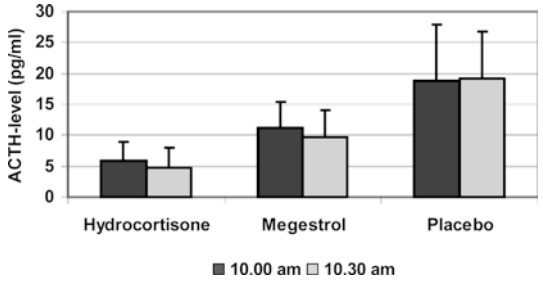

Fig. 1 ACTH levels at 10:00 A.M. (*black columns*) and 10:30 A.M. (*grey columns*) after pretreatment with megestrol, hydrocortisone and placebo

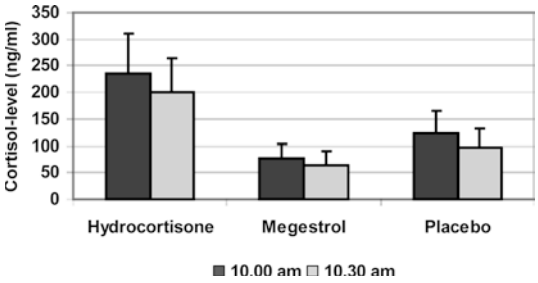

Fig. 2 Cortisol levels at 10:00 A.M. (*black columns*) and 10:30 A.M. (*grey columns*) after pretreatment with megestrol, hydrocortisone and placebo

with hydrocortisone, 10:00 A.M. ACTH levels were significantly lower than after pretreatment with placebo ($df = 9$, $t = -4.73$, $P < 0.01$). Similar results were found for the ACTH levels at 10:30 A.M. (data not shown).

Cortisol levels

After 1 h of rest (10:00 A.M.), the mean baseline cortisol level after pretreatment with placebo was 122.9 ± 42.8 ng/ml. At 10:30 A.M., the mean cortisol level decreased to 95.9 ± 35.3 ng/ml. The respective cortisol levels after pretreatment with megestrol were 76.2 ± 27.0 ng/ml (10:00 A.M.) and 63.3 ± 27.7 ng/ml (10:30 A.M.). After pretreatment with hydrocortisone, the cortisol levels were 235.9 ± 74.7 ng/ml at 10:00 A.M. and 200.4 ± 63.0 ng/ml at 10:30 A.M. The cortisol levels after the different pretreatments are shown in Fig. 2.

ANOVA with pretreatment as a grouping factor and time (10:00 A.M. and 10:30 A.M.) as a dependent factor showed a significant effect of pretreatment ($df = 2$, $F = 28.1$, $P < 0.001$) and time ($df = 1$, $t = 33.4$, $P < 0.001$), but not for the interaction between treatment and time ($df = 2$, $F = 2.9$, $P < 0.08$). The comparison of the cortisol levels between subjects pretreated with megestrol and those pretreated with placebo showed significant differences for both the 10:00 A.M. measurement ($df = 9$, $t = -2.90$, $P < 0.02$) and the 10:30 A.M. measurement ($df = 9$, $t = -2.48$, $P < 0.05$). Cortisol levels at 10:00 A.M. were significantly lower after pretreatment with megestrol than after pretreatment with hydrocortisone ($df = 9$, $t = -6.04$, $P < 0.01$). Cortisol levels at 10:00 A.M. were also significantly lower after pretreatment with placebo than after pretreatment with hydrocortisone ($df = 9$, $t = 4.12$, $P < 0.01$). Similar results were found for the cortisol levels at 10:30 A.M. (data not shown).

Discussion

Megestrol is a widely used synthetic progestational hormone. This is the first study in which the acute effects of megestrol on mid-morning HPA axis activity have been assessed. Compared to placebo pretreatment, pretreatment with megestrol significantly reduced both resting ACTH and cortisol mid-morning levels. Reflecting the exogenous hydrocortisone, cortisol levels were increased after pretreatment with hydrocortisone while ACTH levels were strongly decreased. Pretreatment with megestrol resulted in a weaker suppression of ACTH than pretreatment with hydrocortisone. Our results therefore suggest that megestrol has glucocorticoid-like activity that may be clinically relevant even after only a few doses.

Previous studies of the effects of megestrol on the HPA axis have focused on long-term treatment. In a summary of adverse drug reports to the FDA as well as published case reports, Mann et al. reported 5 cases of Cushing syndrome, 12 cases of new-onset diabetes and 16 cases of adrenal insufficiency in association with treatment with megestrol for the time period from 1984–1996. While Cushing syndrome occurred after at least 9 months of megestrol treatment, new-onset hyperglycemia occurred as soon as 3 weeks after the onset of treatment with megestrol. Adrenal insufficiency was noted as early as 6 weeks after the onset of treatment with megestrol. Adrenal insufficiency occurred in 5 subjects after discontinuation of megestrol, while 11 subjects continued treatment with megestrol [10]. Since the publication of this review, additional clinical reports of adrenal insufficiency after treatment with megestrol have been published [2]. Adrenal insufficiency after prolonged treatment with megestrol has been described in HIV-infected patients [8]. Adrenal insufficiency has also been reported in a male with tetraparesis who received prolonged treatment with megestrol for cachexia [7]. Overall, the risk of a pharmacologically induced Cushing syndrome seems to be higher with megestrol than with medroxyprogesterone, another progestational hormone [15].

Shifting from clinical observation to the measurement of hormone levels, a suppression of serum cortisol levels has been noted in different clinical studies after prolonged treatment with megestrol [1, 9]. CRF and ACTH stimulation tests can help to identify early alterations in the steroid system. Impaired ACTH and CRH stimulation after treatment with megestrol have been found in different studies. Subramanian et al. found abnormal corticotropin tests in patients with advanced breast cancer, suggestive of adrenal insufficiency [18]. In another study, nine out of ten subjects under prolonged treatment with megestrol showed an impaired response to ACTH stimulation, while eight out of ten subjects also had an abnormal CRH stimulation test [11]. Adrenal suppression has also been observed in HIV-infected children treated with megestrol [16]. Comparing different challenge tests, a low-dose ACTH test has been shown to be best suited to reveal adrenal insufficiency in subjects under treatment with megestrol [12].

Corticosteroid feedback is the term used to describe the different mechanisms that are responsible for the inhibitory activity of corticosteroids on the HPA axis. Three different time-frames play a role in corticosteroid feedback: fast feedback (within 2 h), intermediate

feedback (2 to approximately 10 h) and slow feedback (more than 10 h). These time-frames result from different physiological regulatory mechanisms. While the fast and intermediate corticosteroid feedback are mainly due to membranous steroid binding sites, slow feedback results from binding to nuclear steroid receptors [4, 6]. Since the effects of megestrol on the HPA axis occurred in this study within 2 to 11 h after administration, it can be assumed that intermediate feedback mechanisms underlie the acute effects of megestrol on the HPA axis. The long-term effects of megestrol on the HPA axis after multiple dosing may also result from binding to the nuclear steroid receptors.

While in the present study the focus was on the effects of megestrol and hydrocortisone on morning hormone levels, Wiedemann et al. studied the effects of progesterone agonists and antagonists on nocturnal ACTH and cortisol levels [20, 21]. In both studies megestrol was given at 2:00 P.M. and 7:00 P.M. during the beginning of the physiological cortisol trough before the nadir of glucocorticoid receptor occupation. Mifepristone, a progesterone antagonist, enhanced early morning ACTH and cortisol levels. On the other hand, in both studies megestrol suppressed the physiological early morning surge in ACTH and cortisol levels. In contrast to the findings of the present study, the suppression of ACTH and cortisol levels after megestrol treatment were only shown until 07:00 A.M. Wiedemann et al. explained the suppression of ACTH and cortisol levels as an agonistic effect of megestrol on the glucocorticoid receptor [21].

In the present study, megestrol was administered before and after the maximum activity of the HPA axis in the morning corresponding to the maximum glucocorticoid receptor occupation. Megestrol suppressed ACTH and cortisol secretion from 10:00 A.M. until 1:00 P.M. In addition, the effects of megestrol on the HPA axis were assessed in comparison with those of hydrocortisone, a steroid with known activity on the HPA axis. Thus this study extends our understanding of the effects of megestrol on the HPA axis.

However, the mechanism of action responsible for the glucocorticoid-like activity of megestrol remains unclear. In vitro, megestrol displays considerable affinity to the glucocorticoid receptor [5]. Using cells transfected with human steroid receptors, megestrol has been shown to have a strong agonist effect on the glucocorticoid receptor, while no effect was seen on the mineralocorticoid receptor [20]. The results of our study are compatible with a glucocorticoid-like activity of megestrol on central elements of the feedback mechanism of the HPA axis. As both ACTH and cortisol levels were reduced after the acute administration of megestrol, it seems plausible that megestrol exerts its effects above the level of ACTH regulation. Further studies are needed to clarify the mechanism responsible for the suppression of ACTH and cortisol levels.

Summarizing the results of our study, we were able to show that the acute administration of rather small doses of megestrol resulted in a significant and rapid decrease in both cortisol and ACTH levels in normal male volunteers. Females were excluded from this study as the female reproductive cycle may have effects on the regulation of the HPA axis. Males have progesterone levels comparable to females during the first period of the menstrual cycle. Therefore the effects of megestrol in males observed in our study should be applicable to females during the first period of the menstrual cycle. However, it is unclear how the effects of megestrol on the HPA axis would apply to females in the luteal phase of the menstrual cycle or during menopause.

Despite these limitations, our results add further evidence to the notion that subjects treated with megestrol should be screened for possible changes in the HPA axis in the presence of relevant clinical symptoms. Based on our results as well as the findings reported in the literature, adrenal insufficiency and Cushing syndrome should be included in the differential diagnosis of all subjects under treatment with megestrol. This is of particular importance as some of the symptoms (e.g. anergia, weight loss) of a pharmacologically induced alteration in the steroid system are nonspecific and could wrongly be attributed to the primary illness.

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