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# A low-dose adrenocorticotropin test reveals impaired adrenal function in cancer patients receiving megestrol acetate therapy

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**Abstract**

Megestrol acetate (MA) has glucocorticoid activity and can induce significant secondary adrenal suppression. We designed this study to determine the extent of adrenal insufficiency in cancer patients receiving MA by utilising a sensitive low-dose adrenocorticotropin (ACTH) stimulation test. Adrenal function was assessed by a low-dose (0.625 μg) ACTH (1-24) stimulation test in 30 patients receiving MA for metastatic cancer. 10 of the patients who failed this test underwent a standard (250 μg) test on another day. Adrenal function was also evaluated in 15 of the patients by measuring the excretion of free cortisol in 24-h urine samples. Peak serum cortisol levels following stimulation with low-dose (0.625 μg) ACTH (1-24) were $<18$ μg/dl in 16 of 30 (53%) patients, of whom 9 had a basal serum cortisol level of $<5$ μg/dl. Five of 16 poor responders to the low-dose test showed normal stimulation with the standard (250 μg) ACTH (1-24) test. Thus, adrenal insufficiency would fail to be detected by the standard high dose test in these patients. Patients who failed the low-dose ACTH (1-24) test had lower 24-h urinary free cortisol excretion ($8.7\pm10.3$ μg/24 h) than normal responders ($35\pm12.7$ μg/24 h). Impaired adrenal function is common in cancer patients receiving MA. The low-dose ACTH (1-24) test is apparently capable of revealing adrenal insufficiency undetected by the standard high-dose ACTH test. Patients receiving MA might have inadequate adrenal function during episodes of infection or after withdrawal of MA therapy and this may require prompt corticosteroid treatment. © 2002 Published by Elsevier Science Ltd.

*Keywords:* Megestrol acetate; Adrenal insufficiency; ACTH test; Cortisol; Metastatic cancer

## 1. Introduction

Megestrol acetate (MA) is a synthetic progestational agent that has been used in the treatment of advanced breast and endometrial cancer since the mid-1970s [1,2]. Since MA therapy can induce weight gain, it is also used for the management of AIDS-related cachexia [3]. An increasing number of reports have suggested that MA also has glucocorticosteroid activity. MA displayed considerable affinity towards the glucocorticoid receptor in various cells, as well as glucocorticoid-like activity both *in vitro* and *in vivo* [4–6]. The latter studies demonstrated that MA therapy may cause suppression of plasma adrenocorticotropin (ACTH) and cortisol levels which may lead to clinically significant adrenal insufficiency and, in some patients new-onset diabetes mellitus. Larger doses, longer durations or both of MA therapy may cause Cushingoid symptoms [4–8].

For over three decades, the intravenous (i.v.) injection of a pharmacological dose (250 μg) of ACTH (1-24) has been used as a standard test in the initial assessment of adrenal function. However, studies in healthy volunteers demonstrated that low doses (0.5–1 μg) of ACTH (1–24) are sufficient to stimulate release of cortisol from the adrenal gland that will meet the standard criteria for a satisfactory ACTH test result [9-13]. Indeed, it has been suggested that the low-dose ACTH test could be a sensitive method to detect subtle primary or secondary adrenal insufficiency that would be masked when the standard test is used [11–13].

Weakness, fatigue, hypotension and vomiting which are common in patients with adrenal insufficiency are also common in patients with metastatic cancer or with AIDS. Furthermore, patients receiving MA who

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develop asymptomatic adrenal insufficiency might have inadequate adrenal function if they become acutely ill.

We conducted this study in order to delineate the extent of asymptomatic adrenal insufficiency in cancer patients receiving MA therapy, and to evaluate the possibility of its being a more sensitive method than the standard one for the detection of impaired adrenal function in these patients.

## 2. Patients and methods

### 2.1. Patients

30 patients (22 females and 8 males, aged 54–86 years) who were receiving MA for metastatic cancer took part in this study. Their characteristics are described in Table 1. They were evaluated at the oncology outpatient service of the Tel Aviv Sourasky Medical Center. Patients who had been treated with oral corticosteroids during the 6 months preceding the study were excluded. None of our patients had metastatic involvement or destruction of the adrenal glands. The study protocol was approved by the ethics committee of the Tel Aviv Sourasky Medical Center and informed consent was obtained from the patients.

### 2.2. Study protocol

The low-dose ACTH (1–24) test was performed in all patients. A vial of 250 μg ACTH (1–24) (Cortrosyn, Orgenon International Oss, The Netherlands) was diluted in sterile saline solution to a concentration of 0.625 μg/ml. The solution was used immediately. An indwelling heparinized i.v. cannula was inserted into the forearm at 09.30 h. After a resting period of 60 min, 0.625 μg/1.73 $m^2$ ACTH (1–24) was administered as an i.v. bolus injection, and blood samples were obtained at 0, 20, 30 and 45 min for the measurement of serum cortisol concentrations. The low-dose ACTH (1-24) test has been established in many laboratories, and its sensitivity, specificity, accuracy and reproducibility have been

Table 1
Patients and tumour characteristics

| *N* | Diagnosis | Age (years) | Gender | Dose (mg/day) | Duration of treatment (months) | Response to low-dose ACTH[a] | Baseline cortisol serum levels μg/dl | Maximum cortisol serum levels μg/dl |
|---|---|---|---|---|---|---|---|---|
| 1 | Ca of unknown origin | 86 | m | 160 | 3 | – | 5.8 | 12.0 |
| 2 | Ca of breast | 67 | f | 160 | 48 | – | 8.2 | 14.8 |
| 3 | Ca of endometrium | 65 | f | 160 | 12 | – | 3.9 | 11.8 |
| 4 | Ca of lung | 76 | f | 160 | >6 | – | 6.9 | 8.8 |
| 5 | Ca of breast | 54 | f | 160 | >6 | – | 2.0 | 11.0 |
| 6 | Ca of unknown origin | 55 | f | 160 | >6 | – | 5.0 | 11.0 |
| 7 | Ca of colon | 62 | m | 160 | >6 | – | 1.0 | 3.0 |
| 8 | Ca of breast | 62 | f | 160 | 5 | – | 2.0 | 11.0 |
| 9 | Ca of endometrium | 67 | f | 160 | 7 | – | 5.0 | 7.0 |
| 10 | Ca of breast | 63 | f | 160 | 6 | – | 2.4 | 11.4 |
| 11 | Ca of breast | 53 | f | 160 | 8 | – | 3.6 | 7.5 |
| 12 | Ca of breast | 81 | f | 160 | 6 | – | 7.0 | 15.4 |
| 13 | Ca of stomach | 73 | f | 320 | 5 | – | 0.3 | 3.0 |
| 14 | Ca of breast | 61 | f | 160 | 2 | – | 7.3 | 13.2 |
| 15 | Ca of stomach | 66 | m | 320 | 6 | – | 7.4 | 13.7 |
| 16 | Ca of pancreas | 54 | m | 320 | 6 | – | 0.7 | 9.1 |
| 17 | Ca of breast | 60 | f | 320 | 12 | + | 10.6 | 18.5 |
| 18 | Ca of rectum | 84 | f | 160 | 4 | + | 16.1 | 19.5 |
| 19 | Ca of breast | 64 | f | 160 | 12 | + | 5.5 | 20.7 |
| 20 | Ca of pancreas | 70 | m | 160 | 3 | + | 10.5 | 18.6 |
| 21 | Ca of breast | 72 | f | 320 | 3 | + | 11.7 | 20.8 |
| 22 | Ca of breast | 65 | f | 160 | 3 | + | 17.1 | 26.0 |
| 23 | Ca of breast | 58 | f | 240 | 6 | + | 12.6 | 19.1 |
| 24 | Ca of breast | 76 | f | 160 | >6 | + | 17.8 | 27.8 |
| 25 | Ca of breast | 54 | f | 160 | >6 | + | 12.4 | 23.1 |
| 26 | Ca of pancreas | 81 | m | 160 | 8 | + | 15.6 | 21.9 |
| 27 | Ca of lung | 73 | m | 160 | 3 | + | 25.4 | 31.4 |
| 28 | Ca of breast | 61 | m | 160 | 2 | + | 22.1 | 28.3 |
| 29 | Ca of breast | 57 | f | 320 | 6 | + | 27.2 | 29.4 |
| 30 | Ca of stomach | 72 | f | 160 | 3 | + | 13.9 | 23.0 |

Ca, cancer.
[a] Normal response to low-dose ACTH (+). Abnormal response to low-dose ACTH (−).

determined and compared with those of the previous gold standard high dose (250 μg) test. These data were published by various research groups [10,14], including four papers originating in our medical centre [11–13,15]. These studies demonstrate that, in healthy people, doses of ACTH (1–24) of 0.5 to 1.0 mcg are sufficient to stimulate the release of cortisol from the adrenal gland that will meet the criterion for a satisfactory short ACTH test: when the highest serum cortisol recorded (peak value) during the test equalled or exceeded 18 mcg/dl (500 nmol/l). This criterion is commonly advocated [9], was recently validated, and is the same as that used for many years as the high-dose (250 mcg) ACTH test.

10 of the patients who failed to meet this criterion of a normal ACTH (1-24) test, underwent a standard (250 μg) test 1–3 weeks later. Adrenal function was also evaluated in 15 patients by measuring the excretion of free cortisol in 24-h urine samples.

### 2.3. Cortisol measurement

Serum- and urinary-free cortisol concentrations were measured using a commercially available radioimmunoassay kit (coat-A-count, Diagnostic Products, Los Angeles, CA, USA), with intra-assay coefficients of variation of 3.2 and 7.2% for cortisol measurements in the serum and urine, respectively, and inter-assay coefficients of variation of 4.8 and 7.5%, respectively.

### 2.4. Statistical analysis

Data are expressed as means ± standard deviations (S.D.). The results were analysed using an unpaired two-tailed Student's test. Pearson's correlation coefficient and linear regression were used to evaluate the relationship between peak serum cortisol after injection of ACTH (1-24) and 24-h urinary excretion.

## 3. Results

### 3.1. ACTH test

In 16 of 30 patients (53%), peak serum cortisol levels following stimulation with low-dose ACTH (1-24) (0.625 μg/1.73 $m^2$ were less than 18 μg/dl and, of these, 11 (37%) also had an incremental rise in cortisol of $<7.2$ μg/dl ($<200$ nmol/l). Serum cortisol responses at 20, 30 and 45 min to low-dose ACTH (1-24) were significantly lower in these 16 patients than in 14 patients who attained a normal peak cortisol level of $>18$ μg/dl. Interestingly, treatment with the higher dose (320 mg) did not increase the suppression of the hypothalamic–pituitary–adrenal axis. Specifically, 14 of 23 patients who received 160 mg/day failed the low-dose ACTH test compared with 2 of 7 patients who received 320 or 240 mg/day. 9 of these 16 patients had basal serum cortisol levels of $<5$ μg/dl (138 nmol/l) (Fig. 1). All 14 patients who responded normally to the low-dose ACTH test had basal cortisol levels of $>5$ μg/dl.

10 of the patients who failed to meet the criteria of a normal response to the low-dose ACTH (1-24) test (peak cortisol concentration $<18$ μg/dl) underwent a standard 250 μg ACTH (1-24) test 1–3 weeks later: the responses were normal in 5 and abnormal in the other 5 (Fig. 2). Thus, it appears that the low-dose ACTH (1-24) test is capable of revealing mild adrenal insufficiency that would fail to be detected by the standard high-dose test.

### 3.2. Urine free cortisol

There was a positive correlation between the peak cortisol response to the low-dose ACTH (1-24) test and the urinary cortisol excretion ($r=0.68$; $P<0.0053$)

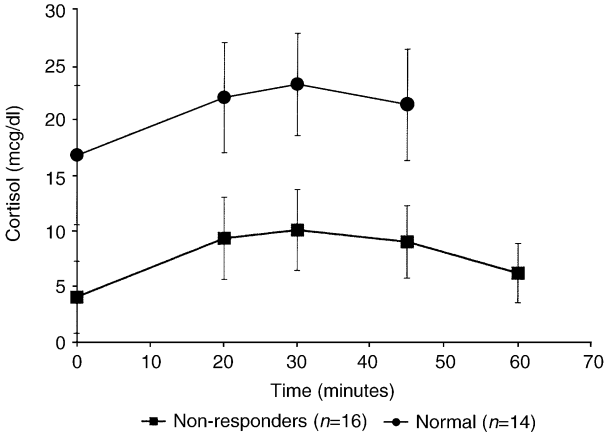


Fig. 1. Low-dose (0.625 mcg) ACTH (1-24) stimulation test in 30 cancer patients receiving megestrol acetate (MA) therapy. ● normal vs. ■ non-responders.

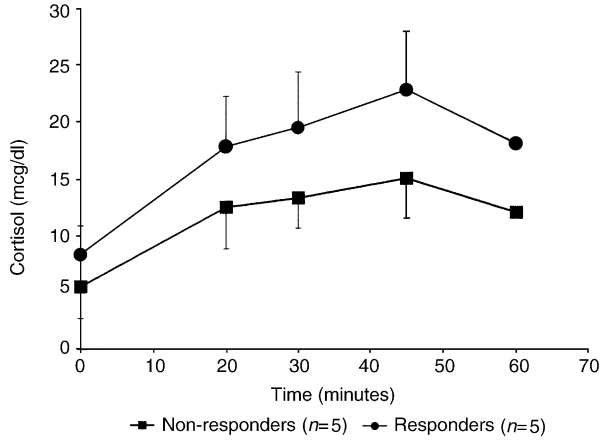


Fig. 2. Standard (250 mcg) ACTH (1-24) stimulation test in 10 patients who failed the low-dose ACTH test. ● normal vs. ■ non-responders.

(Fig. 3). Furthermore, those patients who failed to pass the low-dose ACTH (1-24) test had lower 24-h urinary-free cortisol concentrations (8.7±10.3 μg/24 h) than the patients who responded normally (35±12.7 μg/24 h) ($p<0.001$).

## 4. Discussion

Several recent reports have demonstrated that MA therapy in cancer and AIDS patients may cause suppression of the hypothalamic–pituitary–adrenal axis, which results in low-serum ACTH and cortisol levels followed by an inadequate or lack of a rise of serum control after a rapid corticotropin stimulation test [4,5,7]. However, low basal cortisol concentration tests and standard high-dose corticotropin stimulation tests are not sensitive enough to detect subtle or partial adrenal insufficiency in patients on MA therapy. Indeed, this study demonstrates that only 9 out of 16 patients who failed to pass the low-dose ACTH (1-24) test and who had abnormal low 24-h urinary free cortisol excretion had basal serum cortisol concentrations of <5 μg/dl [16,17]. Furthermore, the standard (250 μg) ACTH (1-24) test provides information only about the ability of the adrenals to respond to unusual stimuli, but may not detect partial adrenal insufficiency. We used the low-dose (0.625 μg) ACTH (1-24) stimulation test in our current study and demonstrated that 5 of 16 of the patients on MA therapy who failed to meet the criteria of a satisfactory low-dose ACTH (1-24) test had a normal response to the standard high dose test. This would indicate that the low-dose ACTH (1-24) test is capable of revealing mild adrenal insufficiency that would fail to be detected by the standard high-dose test. It should be noted that metastases to the adrenals may occur in cases of breast cancer, but the likelihood that it may cause adrenal insufficiency is rather remote because the process would have to severely affect both adrenals.

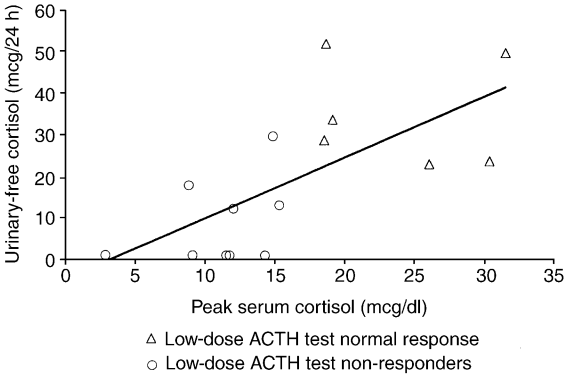


Fig. 3. Relationship between the peak serum cortisol concentration following low-dose ACTH (1-24) stimulation and 24 h urinary-free cortisol. △ Patients who reached a serum cortisol peak of more than 18 μg/dl after stimulation with 0.625 μg ACTH (1-24) and ○ poor responders.

Although the suppression of the pituitary–adrenal–axis appears to be asymptomatic in most patients receiving MA, there are several reported cases of clinically symptomatic adrenal insufficiency [6,7]. Weakness, fatigue, hypotension and vomiting, which are common complaints and symptoms in patients with adrenal insufficiency, are also common in patients with metastatic cancer or with AIDS, thus the diagnosis of adrenal insufficiency in patients receiving MA is frequently delayed unless there is a high degree of clinical suspicion or adrenal function tests are performed. Furthermore, patients receiving MA who develop mild asymptomatic adrenal insufficiency might have inadequate adrenal function during episodes of infection and, consequently, an increased likelihood of septic death [18]. The clinical significance of the low-dose ACTH test, therefore, appears to be early recognition of mild adrenal insufficiency that might pose a danger in the presence of even mild stress. We conclude that patients taking MA should be followed carefully: those who respond poorly to low-dose ACTH stimulation during or after the withdrawal of MA therapy may require prompt treatment with corticosteroids when under stressful conditions.

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