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Research Article

Effects of Megestrol Acetate on Adrenal Function and Survival in Cancer Patients

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Abstract

Objectives: Megestrol acetate (MA) can induce significant secondary adrenal suppression. We designed this study to determine the extent of adrenal insufficiency in cancer patients receiving MA and whether ther was any predictive factor for this.

Methods: Thirty-one patients (aged 48–83 years) who were receiving MA took part in this study. Serum concentrations of TSH, ACTH, free T4, cortisol were measuresd in samples obtained at 7 AM, at baseline and 1st month. Standart ACTH (250 mg) stimulation test was performed if cortisol levels were below 18 µg/dl at any time.

Results: 1 month after drug initiation, 32% of patients were accepted as adrenal insufficient. There wasn't any correlation between the basal cortisol, ACTH levels, any biochemical parameter and overall survival. There was negative correlation between 1 month cortisol levels and survival time (p=0.04) If cortisol levels were lower at month of theraphy survival time was longer. Cox regression analysis showed that patients having lower cortisol levels at first month had 98% lower risk of death compared to patients having higher cortisol levels (p=0.02: OR 0.12 (0.02-0.75)).

Conclusion: It is important to evaluate adrenal functions especially during episodes of infection or after withdrawal of MA therapy since this may require prompt corticosteroid treatment.

Keywords: Adrenal function, cortisol, megestrol acetate, overall survival

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Megestrol acetate (MA) is a progesteron-like compound that has been used in various cancers as a palliative agent to treat cancer cachexia, and systematic reviews have concluded that MA improves appetite and results in weight gain in cancer patients.[1, 2] MA displayed considerable affinity towards the glucocorticoid receptor in various cells, as well as glucocorticoid-like activity both in vitro and in vivo.[3–5] MA therapy may cause suppression of hypothalamic-pituitary-adrenal (HPA) axis and subsequent adrenal insufficiency.[3–7] Weakness, fatigue, hypotension and vomiting which are common in patients with adrenal insufficiency are also common in patients with metastatic cancer. Furthermore, patients receiving MA who develop asymptomatic adrenal insufficiency might have inadequate adrenal function if they become acutely ill. We designed this study to determine the extent of adrenal insufficiency in cancer patients receiving MA and find out if any predictive factor for this.

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Methods

Thirty-one patients (11 females and 20 males, aged 48–83 years) who were receiving MA took part in this study. One of the patients was receiving MA for 48 months, one of them was receiving it for 12 months. The others were not taking MA and evaluated for HPA axis; before the initiation and 1 month later. Patients who had been treated with oral corticosteroids during the 6 months preceding the study were excluded. They were evaluated at the Pamukkale University oncology and endocrinology outpatient clinic.

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 Pamukkale University and informed consent was obtained from the patients.

Serum concentrations of thyroid stimulating hormone (TSH), ACTH, free T4, cortisol were measuresd in samples obtained at 7 AM, at baseline and 1st month. Standart ACTH (250 mg) (81-24) stimulation test was performed if cortisol levels were below 18 µg/dl at any time. After cosynotropin injection blood samples were obtained at 30 and 60 min for the measurement of serum cortisol concentrations.

Statistical Analysis

Associations between overall survival and cortisol levels were estimated using Kaplan-Meier method with log-rank test. Cox regression model was used to calculate the hazard ratio (HR) of survival time among patients with, adjusted for histopathological type and cortisol levels at initiation and first month. Student's t-test and the $\chi 2$-test were used. All statistical analyses were performed using SPSS 17.0.

Results

17 of patients were died during follow up. Mean survival time was 14±2.3 months and mean follow up time was 22.16±22.1 months.

Patients and tumour characteristics were shown in Table 1, biochemical and hormonal variables of patients at initiation were shown in Table 2. 1 month after drug initiation, in 10 of 31patients (32%) basal serum cortisol levels were below 3 µg/dl and so they were accepted as adrenal insufficient. In 10 of them basal serum cortisol levels were above 18 µg/dl and so they were accepted as adrenal sufficient. In11 of them basal serum cortisol levels were between 3-18 µg/dl and ACTH stimulation was performed. Peak serum cortisol levels following stimulation with ACTH were above 18 µg/dl for all of them.

There wasn't any correlation between the basal cortisol, ACTH levels and overall survival. There wasn't any correlation between any biochemical parameter and survival time, eitheir. There was negative correlation between 1 month cortisol levels and survival time (p=0.04) If cortisol levels were lower at first month of theraphy, survival was longer. Cox regression analysis showed that patients having lower cortisol levels at first month had 98% lower risk of death compared to patients having higher cortisol level (p=0.02: OR 0.12 (0.02-0.75)). Patients in group 2 had lower cortisol levels at first month.

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.[3, 4, 6] We also found 32% adrenal insuffiency in patients on MA theraphy even at the first month.

The mechanism by which MA causes adrenal insufficiency is likely related to MA's glucocorticoid-like action and suppression of the endogenous HPA axis.[8] It has been proposed that MA binds to glucocorticoid receptors in a dual agonist-antagonist fashion, acting as a weak agonist initially, and then acting as an antagonist by blocking more potent glucocorticoids.[9, 10] MA has been reported to bind to the glucocorticoid receptor with approximately half the banding affinity of dexamethasone and twice the affinity of cortisol.[10]

MA-associated adrenal insufficiency has been reported both in patients currently taking MA and in patients abruptly taken off MA after prolonged use.[6, 11] In a case series by Naing et al. 9 in 10 postmenopausal women with metastatic breast and ovarian cancer who were receiving chronic MA therapy, 9 patients developed adrenal insufficiency, as indicated by synacthen test results and low basal cortisol levels.[12] Ron et al.[13] also found 53% adrenal insufficiency in cancer patients receiving MA. Symptoms of adrenal insufficiency are more likely to develop in hospitalized patients with clinical disease, as they may have a blunted stress response. This is supported by the results of a case-control study by Chidakel et al.[14] in hospitalized patients receiving MA, in which the incidence of clinical symptoms and adrenal insufficiency was 43% in patients receiving MA compared with controls (10%). We also found 32% adrenal insuffiency in patients on MA theraphy. Different from other studies, we also looked for the factors to predict the patients who will develop adrenal insufficiency. Basal cortisol, ACTH levels and biochemical paramaters were not predictive of adrenal insufficiency. We also tried to find out whether devoloping adrenal insufficiency may

Table 1. Patients and tumour characteristics

Number	Age (years)	Gender	Groups of patients	Duration of Treatment (months)	Baseline serum ACTH Levels (mg/dl)	Baseline serum cortisol levels (µg/dl)	ACTH levels at first month (µg/dl)	Cortisol levels at first month (µg/dl)
1	48	F	1	1	46	26	5	0,5
2	72	M	3	1			5	1
3	53	M	2	1	58	22		18
4	73	M	4	2	253	20		9
5	49	M	2	3		32		3
6	65	M	3	2	31	15	45	20
7	55	F	3	48			8	0
8	69	M	3	2	25	14	15	30
9	61	M	2	1			26	13
10	58	M	2	1				12
11	68	M	3	2	30	18	18	15
12	83	M	2	2	25	31	37	18
13	52	F	4	1			22	23
14	74	M	4	2	29	15		13
15	80	F	2	1			74	19
16	68	M	3	1			5	1,5
17	57	M	3	1	23	22	20	23
18	54	F	2	2	28	26		16
19	51	F	4	1			28	17
20	61	F	3	2	51	13		17
21	73	M	3	1			6	2.5
22	58	M	3	1			20	17
23	58	M	2	1			9	3
24	80	F	3	12			5	3
25	64	M	3	1	93	35		
26	75	F	2	1	11	25		28
27	69	F	3	1				
28	58	M	2	1	28	10		
29	61	M	2	1	9	10		27.3
30	74	F	4	1	163	17		1
31	34	M	3	1	19	22		26

Groups of patients; 1: Head and and Neck tumors; 2: Tumors of Respiratory System; 3: Tumors of Gastrointestinal System; 4: Others.

Table 2. Biochemical and hormonal variables of patients

Fasting blood glucose (mg/dl)	114±37
ALT (IU/L)	32.9±52
Creatinin (mg/dl)	0.78±0.3
Sodium (mmol/L)	137±6.9
Potasium (mmol/L)	4.4±0.4
Calcium (mg/dl)	9.2±0.5
TSH (uIU/mL)	3.1±6.8
Ft4 (ng/dL)	1.4±0.5

have any effecet on survival. Basal cortisol, ACTH levels and biochemical paramaters had not any effect on survival time also. But interestingly, if cortisol levels were lower at first month of theraphy, survival time was longer. This may be due to the fact that patients with more advanced disease may have higher counterregulatory stress response so higher cortisol levels and lower survival time.

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.[15] None of our patients have electrolyte disturbances, hypotension suggesting adrenal insufficiency. But it is important to be aware of the effects of MA on adrenal functions and evaluate adrenal functions especially during episodes of infection or after

withdrawal of MA therapy since this may require prompt corticosteroid treatment.

Conclusion

It is important to be aware of the effects of MA on adrenal functions and evaluate adrenal functions especially during episodes of infection or after withdrawal of MA therapy since this may require prompt corticosteroid treatment.

Disclosures

Ethics Committee Approval: Pamukkale University, 16.08.2013 60116787/020/28845.

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