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Adrenal suppression by oral high-dose medroxyprogesterone acetate in breast cancer patients

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Summary. *The effects of oral MPA, 300 mg t.i.d., on adrenal function in postmenopausal patients with disseminated breast cancer were evaluated. The levels of serum cortisol, ACTH, androstenedione, DHEA-S, LH, FSH, GH, and prolactin in 22 patients receiving MPA were compared with those in another group of 28 postmenopausal patients in whom levels were measured before treatment.*

The median morning cortisol level was 70, range 10–465 nmol/l (controls 395, range 155–785 nmol/l), median androstenedione 1.09, range 0.55–3.10 nmol/l (controls 3.75, range 1.23–9.81 nmol/l), and median DHEA-S 555, range 55–1,300 nmol/l (controls 2,440, range 1,015–6,340 nmol/l).

No appreciable change in ACTH levels was found.

Gonadotropins were also markedly suppressed. The median LH level was 4.3 (range 0.8–18) U/l, as against 83 (range 19–116) U/l in controls. The median FSH level was 7.2 (range 0.5–27) U/l, as against 71 (range 12–262) U/l in controls. Prolactin and GH levels remained largely unchanged.

The suppression of androstenedione synthesis, the main precursor of postmenopausal estrogens, may represent the major therapeutic effect of high-dose MPA in postmenopausal patients with breast cancer.

Introduction

Recently there has been renewed interest in the use of progestational compounds in the treatment of patients with disseminated breast cancer. Data from Sweden and Italy have shown 30% remission rates with parenteral high-dose medroxyprogesterone acetate (MPA), which is similar to that achieved with tamoxifen [4, 6, 13, 14]. Although in most cases MPA has been administered IM, high oral doses result in comparable serum levels measured by radioimmunoassay [18]. We preferred to use oral administration for its convenience, since we anticipated the same tumor response.

Suppression of adrenal function by MPA has been demonstrated before [12, 16, 21], but has not been widely recognized as a possible mode of its therapeutic action in breast cancer patients. On the other hand, MPA has a corticosteroid effect of its own, as shown by the Cushingoid appearance of patients treated with high-dose MPA [7]. These facts prompted us to investigate the possible mechanism of the pituitary-adrenal axis disturbance.

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Patients and methods

Twenty-two postmenopausal patients (age range 52–76 years, mean age 64 years) with inoperable or disseminated breast cancer were treated with oral MPA, 300 mg t.i.d. In view of the cumulation of MPA, treatment was continued for at least 6 weeks before any serum samples were taken.

Twenty-eight postmenopausal women with advanced breast cancer (age range 54–72, mean age 62 years) were selected before hormonal or cytostatic treatment was instituted to act as controls. Apart from their breast cancer, all these patients were free of other endocrine diseases known to affect pituitary or adrenal function.

In all patients and controls, serum levels of cortisol, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), LH, FSH, prolactin, GH, and plasma ACTH were sampled between 8.00 and 10.00 a.m. to detect an effect of MPA on adrenal or pituitary function.

Plasma cortisol levels were measured by radioimmunoassay (RIA) without prior extraction, with antibodies against cortisol-3-0-carboxymethyloxime-BSA and with 3H cortisol as a tracer. The coefficients of variation are lower than 6% for inter- and below 5% for intra-assay comparisons at 100 nmol/l. The sensitivity is 10 nmol/l. Androstenedione was measured by an RIA procedure [5] after extraction with 5% ethylacetate in pentane. The antisera were raised in rabbits against an androstenedione-7-carboxyethyl-thioether-bovine thyroglobulin conjugate.

DHEA-S levels were determined by RIA without prior extraction, with antibodies against androst-5-en-3-β-ol, 17-one, 3-β-hemisuccinate, covalently bound to bovine thyroglobulin. Tritium-labeled DHEA sulfate was used as a tracer. The cross-reactivity with DHEA is almost 100%. However, this effect is negligible in the face of the 100-fold lower levels of DHEA in serum in vivo. The assay fulfills the usual criteria for inter- and intra-assay variability, i.e., coefficients of variation below 15% and 10%, respectively, at 1.0 µmol/l.

Plasma ACTH was determined in unextracted plasma using a commercially available radioimmunoassay kit (CIS, Italy). Levels are expressed in CIS standard: 1 ng MRC 74/555 is equal to 3.0 ± 0.3 ng CIS standard. Assay sensitivity is 10 ng/l, and the interassay coefficient of variation 15% at 100 ng/l.

LH and FSH were assayed by a double-antibody solid-phase RIA as described previously [22]. WHO reference preparations IRP 68/40 and 69/104 were used as standards. The interassay coefficient of variation for LH and FSH lies below

Table 1. Median values of serum cortisol, ACTH, androstenedione, DHEA-S, LH, FSH, prolactin, and growth hormone (GH) in 22 postmenopausal breast cancer patients treated with MPA and 28 postmenopausal breast cancer controls without treatment

	Control (n = 28)	MPA (n = 22)	% Control	P value
Cortisol (nmol/l) Median (range)	395 (155–785)	70 (10–465)	18	< 0.01
ACTH (ng/l) Median (range)	63 (16–154)	78 (10–641)	124	NS
Androstenedione (nmol/l) Median (range)	3.75 (1.23–9.81)	1.09 (0.55–3.10)	29	< 0.01
DHEA-S (μmol/l) Median (range)	2440 (1,015–6,340)	555 (55–1,300)	23	< 0.01
LH (U/l) Median (range)	83 (19–116)	4.3 (0.8–18)	5	< 0.01
FSH (U/l) Median (range)	71 (12–162)	7.2 (0.5–27)	10	< 0.01
Prolactin (mU/l) Median (range)	289 (80–708)	314 (146–996)	105	NS
GH (μg/l) Median (range)	3.5 (1.1–9.5)	2.3 (1.1–11.0)	66	NS

NS, Not significant

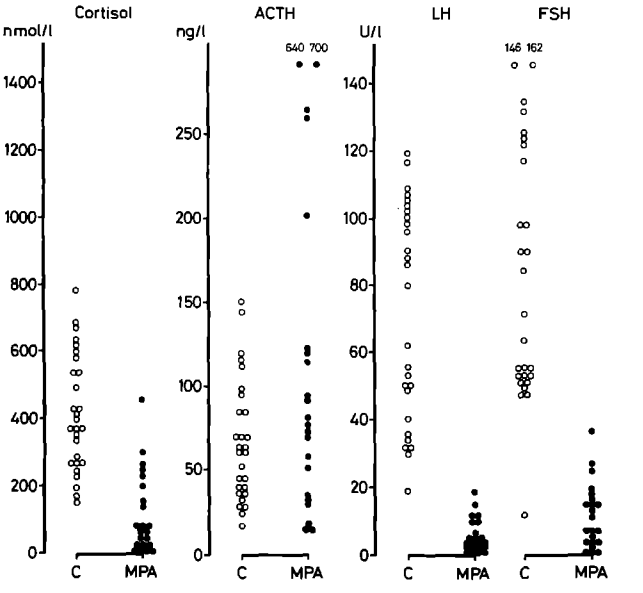

Fig. 1. Serum levels of cortisol, ACTH, LH, and FSH in postmenopausal breast cancer patients treated with MPA and in postmenopausal breast cancer controls (C) without treatment

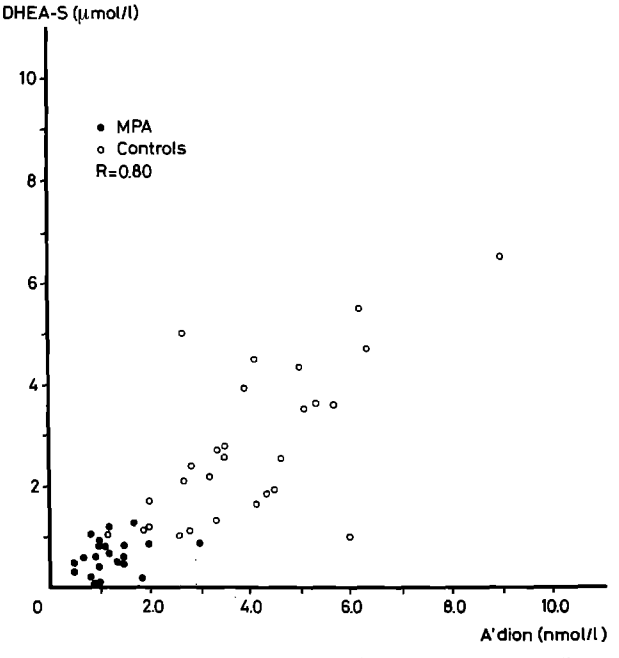

Fig. 2. Rank correlation of serum levels of androstenedione and DHEA-S in postmenopausal breast cancer patients treated with MPA and in postmenopausal breast cancer controls without treatment

5% and the intraassay reproducibility is 9% for LH and 11.5% for FSH, at 10 U/l. The sensitivity for both methods is 0.5 U/l.

Prolactin levels were assayed with a commercially available kit (CIS), using reference preparation MRC 71/222 as a standard. GH levels were measured by an RIA from IRE, using the standard IRP 66/217. One microgram is equal to 2 mIU.

The groups were compared using Wilcoxon's test. Rank correlations were calculated according to Spearman's method.

Results

In patients treated with MPA, median cortisol levels were 18% of control values (Table 1, Fig. 1), but some overlap with the control group remained. However, a significant decrease in ACTH levels could not be found during MPA treatment, nor could a negative correlation between cortisol and ACTH values in the treatment or control groups be established.

All patients receiving MPA exhibited low adrenal androgens. Median androstenedione levels were 29% and DHEA-S levels 23% of control values (Table 1, Fig. 2). A close

correlation between the levels of both steroids was established in the treated patients ($r = 0.85$), in the controls ($r = 0.59$), and in both groups together ($r = 0.80$). Good correlations between the levels of cortisol and androstenedione ($r = 0.74$) and of cortisol and DHEA-S ($r = 0.66$) were also found.

Gonadotropins (LH and FSH) were suppressed markedly and to the same extent ($r = 0.88$ for all patients together; Table 1, Fig. 1).

Prolactin and GH levels showed no difference between the treated and nontreated groups (Table 1).

Discussion

In this study we found markedly suppressed levels of adrenal androgens and cortisol, whereas ACTH levels varied widely. These data are difficult to explain as the result of only one mode of action of MPA on the pituitary-adrenal axis. If MPA had a direct inhibitory effect on adrenal steroid synthesis, low cortisol, low androgen, and clearly elevated ACTH levels would be expected. On the other hand, if MPA had an inhibitory effect on ACTH release, low ACTH levels should be found. Indeed, low ACTH levels during oral high-dose MPA administration are described by some investigators [1, 10]. These ACTH levels must be caused by a direct effect on ACTH release by MPA itself or a metabolite. The formation of a cortisol-like 21-hydroxylated MPA metabolite has been described by other authors [3, 8]. Our finding that ACTH levels were not uniformly suppressed might be explained by our use of a lower dose schedule (900 mg MPA daily) than in the studies cited above. When ACTH levels are completely suppressed, e.g., during treatment with dexamethasone, serum cortisol levels are below detection limits and androstenedione levels are suppressed to 38%–47% of baseline values, but never disappear completely [2, 20].

To explain the contradictory effects of MPA on cortisol and ACTH levels in our study, we have to assume that our dosage of MPA induces a direct, but partial, inhibition of adrenal steroidogenesis, leading to an incomplete decrease of cortisol and the androgens DHEA-S and androstenedione. Such an effect of progesterone has been described in vitro [15], indicating the probability of a direct interaction of high-dose MPA with adrenal function. This, however, would lead to uniformly high ACTH levels. Our finding of varying ACTH levels must be attributable to a simultaneous inhibition of ACTH release by MPA.

Moreover, the fact that during treatment with aminoglutethimide the patients' adrenal function can be substituted by MPA also suggests an intrinsic corticoid effect of MPA [1]. The absence of a negative correlation between ACTH and cortisol levels in this study also implies that a direct effect of MPA on the adrenals is not the only mechanism of action.

The suppression of LH and FSH levels is not surprising, as MPA is used with this intention as a contraceptive. This mechanism is probably not of therapeutic importance in postmenopausal breast cancer patients, as gonadotropin levels themselves do not seem to influence prognosis.

Prolactin and growth hormone levels remain unchanged during high-dose MPA treatment, in accordance with the findings of other authors [10, 17].

The suppression of adrenal androgens may be an important issue in the understanding of the therapeutic potential of MPA, as androstenedione is known to be the most important precursor of estrone in postmenopausal women [11].

The extent to which adrenal androgens are suppressed by MPA in our patients is comparable to the effect of dexamethasone, which as a rule lowers cortisol more markedly than adrenal androgens. During MPA treatment, however, the overlap of androstenedione and DHEA-S levels between MPA-treated and control patients seems to be less than that seen with cortisol.

The therapeutic effects of MPA in breast cancer patients cannot be based on the effects on adrenal androgens only, as the remission rate for prednisone treatment mentioned in the literature is lower than that for MPA [19]. The difference in remission rate suggests the probability of a direct cytotoxic effect of MPA, as has been demonstrated in vitro [9].

In conclusion, we found that oral high-dose MPA in postmenopausal women suppresses adrenal function incompletely, probably by a direct inhibitory action on adrenal steroidogenesis, combined with a negative effect on ACTH release. This leads to lower androstenedione levels and probably to diminished production of estrone, which may be mainly responsible for the tumor-reducing effect of MPA in human breast cancer patients.

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