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Mechanism of adrenal suppression by high-dose medroxyprogesterone acetate in breast cancer patients

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Summary. To investigate the mechanism of adrenal suppression by high-dose MPA, we performed direct and indirect stimulation tests in postmenopausal women with disseminated breast cancer who were receiving MPA and in a postmenopausal breast cancer control group.

A partial adrenal insufficiency was found during Synacthen stimulation, confirmed by a slight increase of 11-desoxycortisol after metyrapone, despite a sufficient rise in ACTH levels. Peak levels of androstenedione and 17-OH progesterone after Synacthen correlated with those after metyrapone. Peak cortisol levels after Synacthen also correlated with the sum of cortisol and 11-desoxycortisol values after metyrapone, indicating the presence of a maximum adrenal response and a sufficient rise of endogenous ACTH after metyrapone.

As the peak levels of cortisol and androstenedione were highly correlated with baseline values, a short Synacthen stimulation test may give a good indication as to whether adrenal suppression by MPA is adequate. The adrenal androgen androstenedione is the precursor of the main postmenopausal oestrogen, oestrone. In this way, adrenal suppression may constitute an important therapeutic effect of high-dose MPA.

Introduction

Progestins are being used with increasing frequency as treatment for patients with disseminated breast cancer [5]. Higher dosages of these compounds appear to be more effective than lower ones [8]. Suppression of adrenal function by larger amounts of medroxyprogesterone acetate (MPA) in a majority of patients has been described [2, 9, 17, 20, 23]. In a former study, we postulated a dual mode of action by MPA on the pituitary adrenal axis: a direct inhibitory effect on adrenal steroidogenesis and a diminished pituitary ACTH release simultaneously [22]. To differentiate between these two effects of MPA, direct (Synacthen) and indirect (metyrapone) stimulation tests were performed in MPA-treated postmenopausal patients with disseminated breast cancer and the results were compared with those obtained in a control group.

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Patients and methods

Two groups of postmenopausal women with inoperable or disseminated breast cancer were studied, one group during treatment with MPA and one group before any hormonal or cytostatic treatment.

Patients in both groups were subjected to ACTH stimulation, followed after 1 week by metyrapone administration.

The MPA-treated group comprised eight women with a mean age of 62 years (range 55–75 years), without endocrine diseases and not taking any other medication, who were treated with MPA, 300 mg t.i.d. PO for at least 6 weeks in view of its cumulative properties. The control group comprised nine breast cancer patients with a mean age of 63 years (range 56–69 years), also without endocrine disease or medication.

ACTH stimulation was achieved in the fasting subject by injecting tetracosactide (Synacthen, 0.25 mg IM at 9.00 a.m.). Blood samples were taken immediately before injection and 60 min later, for measurements of cortisol, androstenedione, and 17-OH progesterone.

Metyrapone was given PO 1 week after Synacthen stimulation, at 9.00 a.m. after a light meal (milk and toast), the dose depending on body weight (below 60 kg: 2 g, 60–70 kg: 2.5 g; above 70 kg: 3 g metyrapone). The subjects lay supine; blood samples were taken just before drug administration and at 1.00 p.m. for determination of cortisol, 11-desoxycortisol, androstenedione, 17-OH progesterone, and ACTH levels. Serum steroids and ACTH were measured by radioimmunoassays, as described earlier [4, 26]. Cross-reaction with MPA is negligible in these assays.

For statistical analysis, Wilcoxon's test was used, and correlations were calculated according to the Spearman method.

Results

Synacthen tests

Median baseline and stimulated plasma cortisol levels in patients on MPA were lower than in the control group (Table 1). Only in one patient did they fall within the normal range for this test (Fig. 1). The percentage increase in cortisol did not differ between the MPA-treated and control groups, however. Maximum cortisol levels correlated with baseline levels in the MPA group ($R=0.95$, $P<0.001$) and for all patients together ($R=0.86$, $P<0.001$).

Table 1. Results of Synacthen tests (median and range)

		MPA	Control	P-value
Cortisol nMol/l	Baseline	125 35–675	560 420–815	< 0.02
	Peak	485 220–1200	1470 1055–1630	< 0.01
Androstenedione nMol/l	Baseline	1.6 0.6–4.4	3.5 2.7–5.7	n.s.
	Peak	4.3 1.3–8.1	6.7 3.7–8.6	< 0.05
17-OH progesterone nMol/l	Baseline	1.9 0.5–4.3	1.5 1.1–3.0	n.s.
	Peak	5.3 3.5–6.0	8.0 6.2–12	< 0.01

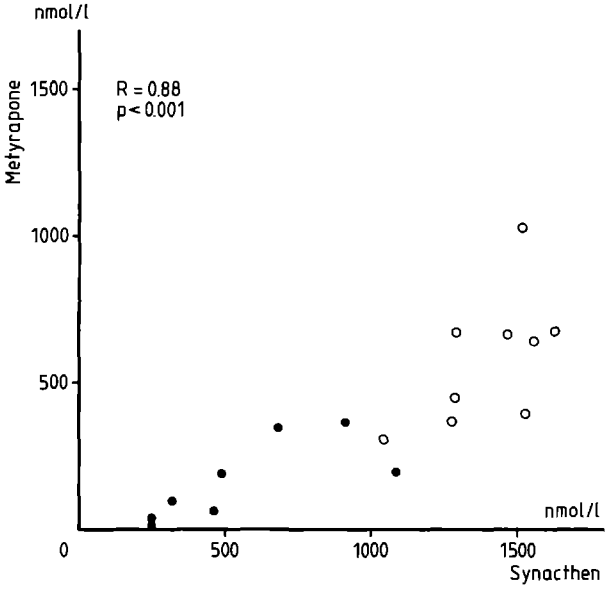

Fig. 1. Relation between peak levels of plasma cortisol after Synacthen and the sum of peak cortisol (*E*) and peak 11-desoxycortisol (*S*) after Metyrapone in patients receiving MPA (●) and in postmenopausal controls (○)

The value for median stimulated androstenedione was somewhat lower than that found in the control group (Table 1, Fig. 2). Baseline and peak levels did not correlate in the MPA group, but they correlated for all patients ($R=0.62$, $P<0.02$).

The median stimulated 17-OH progesterone level was lower than in the control group. No correlation was found between baseline and peak levels of 17-OH progesterone in the MPA group or for all patients together.

Metyrapone tests

After metyrapone administration, the median cortisol value fell to lower levels in the MPA-treated patients than in controls (Table 2).

In contrast to controls, however, the median value of 11-desoxycortisol increased slightly above its baseline concentration; only in one patient did it reach a level that might be considered a normal response (Table 2). Baseline

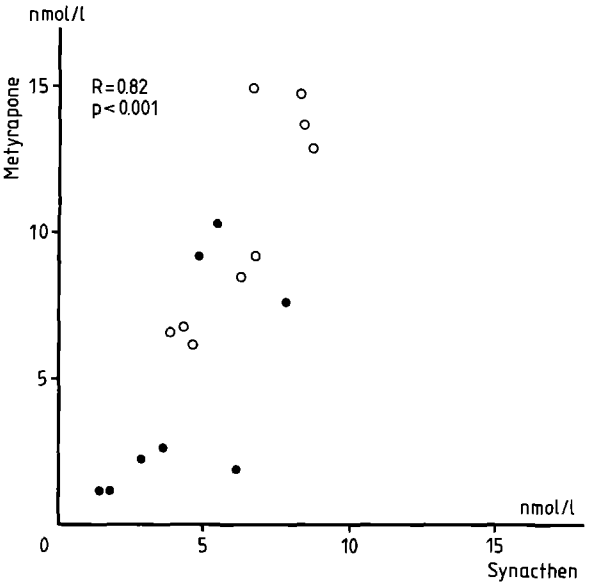

Fig. 2. Relation between peak levels of plasma androstenedione after Synacthen and peak levels after metyrapone in patients receiving MPA (●) and in postmenopausal controls (○)

cortisol levels were individually correlated with the total adrenal response to metyrapone-induced ACTH release, expressed as the sum of cortisol and 11-desoxycortisol ($R=0.78$, $P<0.05$ in MPA treated patients and $R=0.90$, $P<0.001$ in the whole group). Baseline ACTH concentrations did not differ between the two groups; the median ACTH concentration after metyrapone, however, was higher than the peak ACTH levels found in controls (Table 2), as a result of the lower cortisol levels reached in the former group.

The median peak level of androstenedione was lower than that found in the control group. Individual peak le-

Table 2. Results of metyrapone tests (median and range)

		MPA	Control	P-value
Cortisol nMol/l	Baseline	165 25–600	675 535–915	< 0.01
	Nadir	55 5–330	320 175–540	< 0.01
11-desoxycortisol nMol/l	Baseline	21 5–30	77 19–91	n.s.
	Peak	27 10–166	192 77–570	< 0.01
ACTH µg/l	Baseline	74 37–228	40 10–72	n.s.
	Peak	114 54–203	53 37–122	< 0.02
Androstenedione nMol/l	Baseline	2.1 0.9–3.9	2.4 1.7–5.6	n.s.
	Peak	2.5 1.2–10.2	9.4 6.1–15	< 0.05
17-OH progesterone nMol/l	Baseline	1.5 1.4–3.6	1.3 0.9–3.6	n.s.
	Peak	3.0 1.6–8.1	9.0 7.0–22	< 0.001

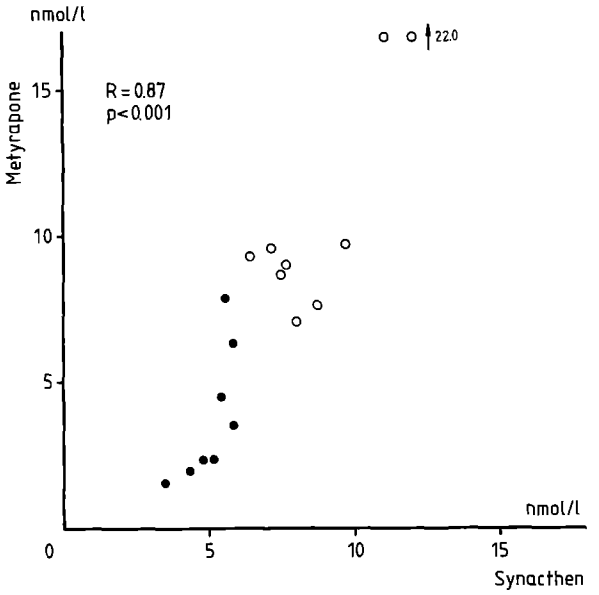

Fig. 3. Relation between peak levels of plasma 17-hydroxyprogesterone after Synacthen and peak levels after metyrapone in patients receiving MPA (●) and in postmenopausal controls (○)

vels were correlated with basal androstenedione levels in the MPA-treated group ($R=0.98$, $P<0.001$) and for all patients ($R=0.71$, $P<0.01$).

Peak 17-OH progesterone levels after metyrapone were also lower than the levels found in the control group, but individual maxima did not correlate with the basal levels.

Correlations between peak levels after Synacthen and metyrapone

The individual peak levels of cortisol after Synacthen correlated with the sum of cortisol and 11-desoxycortisol after metyrapone in all patients together ($R=0.88$, $P<0.001$) (Fig. 1).

Individual peak levels of androstenedione after Synacthen correlated with those after metyrapone in all patients ($R=0.82$, $P<0.001$) (Fig. 2).

The individual peak levels of 17-OH progesterone after Synacthen correlated with those after metyrapone in all patients ($R=0.87$, $P<0.001$) (Fig. 3).

Discussion

During treatment with oral doses of 900 mg MPA in postmenopausal patients with disseminated breast cancer, we found depressed levels of adrenal steroids, which confirms previous results [23]. After direct stimulation of the adrenals with Synacthen, the response of cortisol, 4-androstenedione, and 17-OH progesterone in the control group was comparable to the results described in healthy postmenopausal women [24, 25] and in younger persons [14]. In MPA-treated patients the same amount of Synacthen induced an inadequate adrenal response.

Indirect stimulation of endogenous ACTH by metyrapone resulted in a slight increase of 11-desoxycortisol, androstenedione, and 17-OH progesterone, while in the control group metyrapone stimulation induced an adrenal response comparable to those reported by other authors [6, 7, 10, 14, 18, 21, 22].

Thus, adrenal responses were inadequate after direct or indirect stimulation in MPA-treated patients. The marked difference in peak cortisol or desoxycortisol levels between MPA-treated and control patients suggests that this partial adrenal insufficiency is primarily of adrenal origin. This suggestion is further supported by the higher post-metyrapone ACTH levels in the MPA-treated patients despite the existence of lower cortisol levels, negating a direct suppression of ACTH by MPA as the sole cause of adrenal blockade. However, MPA must exert some inhibitory influence on ACTH release, as the baseline ACTH levels in the MPA-treated group were not significantly higher despite lower cortisol in this group of patients.

These findings are not quite in accordance with the data of others. Blossey and Izuo found complete suppression of ACTH and cortisol during oral MPA, which may be explained by their use of higher MPA dosages [2, 9].

We could find no marked difference between the effects of Synacthen and metyrapone in peak levels of androstenedione and 17-OH progesterone in the MPA-treated group. The same applies for peak androstenedione and 17-OH progesterone in controls. Indeed, the individual peak levels in both tests are correlated for both steroids. In addition, peak cortisol after Synacthen and the sum of cortisol and desoxycortisol after metyrapone were also correlated in all patients together.

A narrow correlation of maximal cortisol levels after direct (Synacthen) or indirect stimulation (with insulin) has been described in normal controls [15], but also in patients with a partial ACTH insufficiency [11]. The same correlation has been described between peak cortisol (after Synacthen) and the sum of cortisol and desoxycortisol (after metyrapone) in similar patients [1]. These observations have led to the supposition that the magnitude of the adrenal response depends more on their baseline function at the time of stimulation and not so much on the existence of sufficient ACTH reserve. As a matter of fact, the amount of Synacthen and the endogenous amounts of ACTH released after metyrapone both represent a massive overstimulation of the adrenals. Indeed, after stimulation of ACTH by insulin, the maximum rise in cortisol is limited after a certain ACTH increment [16]. Other workers have demonstrated a log-ACTH dose – response correlation, where a maximum increase of cortisol has been found after as little as 0.5 μg ACTH [12, 13].

However, our finding of an impaired adrenal response to metyrapone despite a sufficient rise in endogenous ACTH indicates a direct inhibiting effect of MPA on adrenal steroidogenesis. This conclusion is confirmed by the insufficient steroid response after direct stimulation with ACTH, although the percentage increase of cortisol after Synacthen did not differ significantly in the two groups. A direct inhibiting influence of progestins on the adrenals has indeed been described in vitro [19]. In addition, a simultaneous, although partial, inhibition of ACTH release is suggested by the normal baseline ACTH levels in the face of markedly suppressed cortisol. This may be brought about by MPA itself or one of its 21-hydroxylated metabolites [3].

The correlation between peak steroid levels after direct or indirect stimulation thus indicates that the adrenals respond maximally to this overstimulation by both exogenous and endogenous ACTH.

In conclusion, the results of both stimulation tests point to a direct inhibitory effect of MPA on the adrenals, possibly combined with a partial inhibition of ACTH release by MPA itself or one of its metabolites.

The inhibition of adrenal steroidogenesis, that is of adrenal androgens, the precursors of postmenopausal estrogens such as estrone, may explain the greater efficacy and higher response rate found during the use of progestins at a higher dosage.

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