Medroxyprogesterone Acetate Lowers Plasma Corticotropin and Cortisol but Does Not Suppress Anterior Pituitary Responsiveness to Human Corticotropin Releasing Factor

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The endocrine action of medroxyprogesterone acetate (MPA) has been claimed to be of a glucocorticoid-like nature. Upon clinical observation, MPA has been shown to improve life quality and overall well-being in patients with advanced breast cancer, renal carcinoma, prostatic carcinoma, and uterine adenocarcinoma. The authors have evaluated MPA endocrine action by the administration of human corticotropin releasing factor (hCRF) in a 90-minute assay in 15 patients with advanced breast cancer or renal cell carcinoma both, before the initiation of oral high-dose MPA treatment (1000 mg MPA) as well as after at least 10 days of therapy. The curves for corticotropin, β-endorphin, and cortisol responses to hCRF of tumor patients who were tested before the initiation of MPA treatment were parallel to the curves of a healthy control group of probands tested under equal conditions, although at significantly higher respective hormone levels. In patients with malignant disorders assayed after MPA administration, both basal and peak hormone levels were found to be comparable with values obtained in healthy controls. In conclusion, MPA appeared to act at a suprapituitary level since pituitary responsiveness to hCRF was preserved under MPA treatment. Moreover, it appeared that MPA brought the hormonal stress state found in patients with malignant tumors back to normal. *Cancer* 66:1949–1953, 1990.

EVER SINCE THE SYNTHESIS of medroxyprogesterone acetate (MPA) by Babcock and Sala in 1958 and its subsequent wider therapeutic use, many investigators have taken interest in MPA as a potent progestational agent with additional endocrine activities.[1–6] Corticotropin (ACTH) tests and assays of insulin-induced hypoglycemia have been reported for the evaluation of endocrine effects, cortisol plasma profiles, and the assessment of 17-hydroxysteroids and 17-ketosteroids in plasma and urine.[7,8] Thus, similar results have been obtained after low-dose as well as high-dose (up to 1500 mg) MPA intake per day. During the administration of MPA, a marked decline of basal and ACTH-stimulated cortisol and of corticotropin was observed, thus encouraging the idea of a glucocorticoid-like MPA action on the hypothalamic–hypophysary–adrenal axis (HHA axis).[7–9]

In the current study, we have studied this supposed glucocorticoid action of MPA on the HHA axis using human corticotropin releasing factor (hCRF), an endogenous releaser of anterior pituitary ACTH, and investigating the levels of ACTH, β-endorphin (β-E), and cortisol in 15 patients with malignant disease both before and after at least 10 days of a daily oral administration of 1000 mg MPA.

Materials and Methods

Patients and Treatment

Fifteen patients (four men, 11 women; mean age, 56 years; age range, 33–73) with advanced malignant diseases

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(nine with advanced breast cancer and six with metastatic renal carcinoma) gave informed consent to the study. Pituitary and cerebral metastatic disease were excluded by confirmation of normal endocrine function. There was no acute problem due to tumor progression during the entire time of observation.

High-dose MPA therapy was initiated on clinical grounds since beneficial effects have been reported in similar clinical settings.[9,10] Eight weeks before MPA therapy, any kind of cytostatic or hormone treatment had been discontinued for reasons not related to the study. After at least 10 days of therapy with 1000 mg MPA, 13 patients reported significant subjective improvement, whereas the remaining two patients did not feel any benefit. There were no side effects of MPA during the observation period. Individual MPA plasma levels were determined by a radioimmunoassay (RIA) method as previously described by other authors.[11]

Controls

In addition to the patients with metastatic tumors, 27 normal controls without MPA medication were submitted to a single test after the same test procedure.

Corticotropin releasing factor tests and hormonal workup: Each patient was tested twice by a CRF test conducted at 10 AM: one test was done immediately before the initiation of MPA treatment, whereas the second test was performed after at least 10 days of daily oral therapy with 1000 mg MPA (5 × 200 mg/day; Farmitalia-Carlo Erba, Italy).[12] Each test was performed within 90 minutes, starting with plasma sampling at −30 minutes (9:30 AM). Further samples were drawn immediately before and at 10, 20, 30, and 60 minutes after an intravenous bolus injection of 100 μg hCRF (Bachem, Bubendorf, Switzerland). Plasma samples for the determination of ACTH, β-E, and cortisol were collected in prechilled tubes and centrifuged within 10 minutes after sampling.

Commercially available RIA kits were used for hormone measurements: cortisol, Clinical Assays (Cambridge, MA; interassay variation: 4.8%, intraassay variation: 1.4%); ACTH, Nichols Institute (Los Angeles, CA; interassay variation: 7.4%, intraassay variation: 5.5%); β-E, Immuno Nuclear Corp. (Stillwater, MN; interassay variation: 10.7%, intraassay variation: 5.0%).

Statistics

Statistical analysis of the obtained data included paired and one-tailed *t* test and correlation analysis as well as variant analysis of both, individual hormone levels, and respective areas under the curves.

Results

Patients with advanced malignant tumors showed higher basal and hCRF-stimulated values for ACTH, β-E, and cortisol in the control test performed before the initiation of MPA therapy (Fig. 1), as compared with 27 healthy control persons tested under equal conditions. Variant analysis showed significantly higher curves for ACTH ($P < 0.03$) and cortisol ($P < 0.001$) which persisted during the entire test of 90 minutes' duration. When tested after at least 10 days of therapy with MPA, ACTH and cortisol basal levels were significantly suppressed ($P < 0.03$ for ACTH and $P < 0.0001$ for cortisol), as compared with pretreatment levels.

When the entire curves of a 90-minute assay obtained before and after MPA administration were compared with each other, a significant decline of hormone levels was found ($P < 0.03$ for ACTH, $P < 0.004$ for cortisol), whereas no significant difference was seen in β-E concentrations. Moreover, there was no significant difference in delta values (= increase in levels after stimulation with hCRF) before and after MPA administration (Fig. 2) for either parameter tested which resulted in curves that were virtually identical with those obtained in healthy controls.

When analyzing the respective areas under the curves before and after MPA treatment (mean areas under the hormone curve ± standard error of the mean: ACTH before MPA, 144.3 + 22.0 pg/ml, after MPA therapy, 104.4 + 26.6 pg/ml; β-E before MPA, 90.3 + 15.3 pg/ml, after MPA therapy, 66.7 + 14.7 pg/ml [dQ10 minutes]; cortisol before MPA therapy, 46.2 + 5.9 pg/100 ml, after MPA therapy, 30.5 + 9.0 pg/100 ml) no significant differences were found between the corresponding values of ACTH ($P > 0.4$), β-E ($P > 0.2$), and cortisol ($P > 0.06$), respectively.

Individual MPA levels varied from 20×10^3 to 700×10^3 pg/ml. The MPA levels correlated with ACTH, β-E, and cortisol values throughout the 90-minute test performed after MPA administration ($P < 0.05$).

Discussion

Our results do not support the concept of glucocorticoid-like action of MPA in so far as by acute hCRF administration an adequate pituitary responsiveness was demonstrated. These results are in disagreement with previous findings of Leis *et al.*[13] who reported a marked reduction of an increase in cortisol after ACTH administration in the presence of preserved basal cortisol levels. These patients were on an even lower MPA dose of 300 mg/day. The marked ACTH suppressive effect of MPA has also been claimed by Blossey *et al.*[10] In all of these

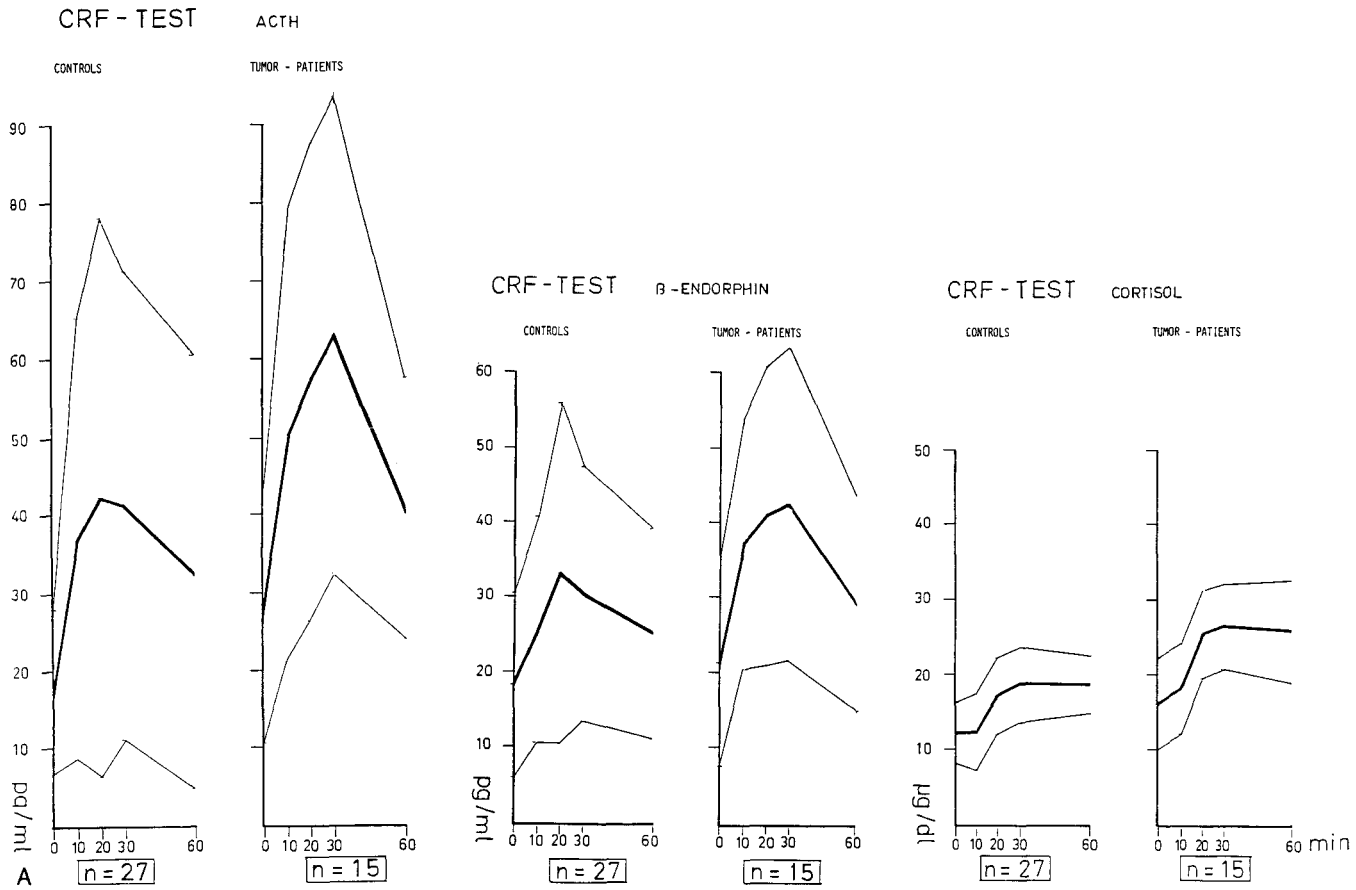

FIG. 1. Results of hCRF tests (ACTH, β-endorphin, and cortisol after administration of 100 µg hCRF as an intravenous bolus) over 90 minutes in 27 normal volunteers and in 15 patients with advanced-stage tumors.

studies, however, functional testing was confined to the adrenal gland only. We hypothesize on the grounds of our data that MPA could have an intrinsic suprapituitary feedback effect, as reflected by a decline of ACTH in the presence of a preserved ACTH response to CRF. Rapid resumption of normal HHA function after discontinuation of MPA treatment[6] would support such a concept which has already been considered by Hellman previously.[5] In this respect, we share the idea of a glucocorticoid property of MPA, even more so as it has been shown that MPA weakly binds to a glucocorticoid receptor *in vitro*.[14] In comparison, glucocorticoid administration classically affects both basal and stimulated ACTH and cortisol values in a dose-dependent manner.[15]

All hCRF tests were carried out at the same time of day since marked circadian fluctuations of both basal and stimulated ACTH, β-E, and cortisol have been reported.[16] Basal ACTH, β-E, and cortisol tend to be lower in the evening, yet at the same time HHA responsiveness as assessed by hCRF-induced maximal hormone increments is enhanced. Similarly, low basal hormone levels under MPA administration do not necessarily indicate a suppressed functional state. Medroxyprogesterone acetate lowers sex hormone binding globulin,[3] luteinizing hormone (LH), and testosterone.[17,18] The concept that MPA competes with cortisol for cortisol binding protein binding sites and that subsequently free cortisol rises and exerts a negative feedback inhibition on the HHA seems unlikely in the presence of a normal HHA response to hCRF. Furthermore, in order to exert a suppressive effect on the HHA in spite of low total cortisol, free cortisol would have had to rise very high. Although these considerations would warrant free cortisol determination, this was not done because of expected low total cortisol. Whether the reported suppression of LH[3] is an unspecific effect remains to be clarified.

Acute and chronic stress was noted to increase the CRF-stimulated ACTH and β-E release.[19] In the current investigation, tumor patients were found to have elevated basal ACTH, β-E, and cortisol serum levels. In addition, increased CRF stimulated ACTH and cortisol levels were significantly higher than the corresponding values for the

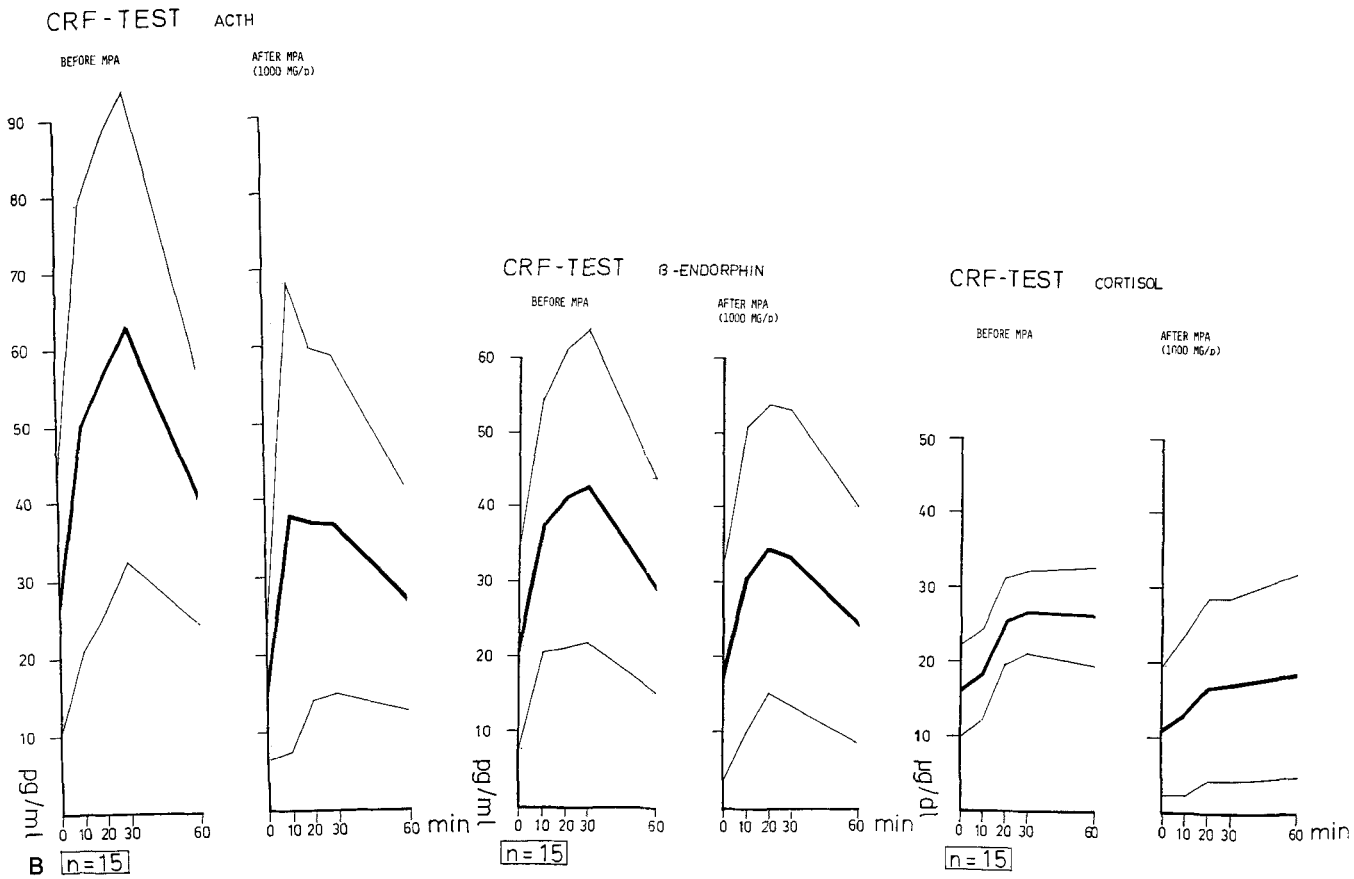

FIG. 2. Results of hCRF tests (ACTH, β-endorphin, and cortisol after administration of 100 μg hCRF as an intravenous bolus) over 90 minutes in 15 patients with advanced-stage tumors before and after at least 10 days of oral treatment with high dose medroxyprogesterone acetate.

control group. Although delta values of the tumor patients were not significantly greater than those of healthy control subjects, our data support the notion of a clinically chronic stress condition in patients with advanced malignant diseases. Furthermore, MPA decreased both basal as well as CRF stimulated serum levels of ACTH and cortisol resulting in serum levels comparable with those of the control group. Thus, MPA restored increased pituitary function of tumor patients resulting in a pituitary function seen in normal subjects. This effect relates to the relief and improvement of life quality seen in patients during high-dose MPA therapy.

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