Pharmacokinetic and Pharmacodynamic Basis for the Treatment of Metastatic Breast Cancer With High-Dose Medroxyprogesterone Acetate

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Postmenopausal patients with metastatic breast cancer were treated with medroxyprogesterone acetate (MPA) (Clinovir) in dosages between 500 and 1500 mg orally per day. The relation of MPA plasma concentrations and endocrine effects were studied in a longitudinal fashion. MPA exerted suppressive effects on the basal and gonadotropin-releasing hormone (GnRH) stimulated gonadotropin secretion, cortisol, dehydroepiandrosterone (DHEA), and estradiol (E_2) in a dose-dependent manner leading to a complete suppression with 1500 mg orally per day. The depression of thyroid hormones (T_3 and T_4) coincided with a depression of the thyroxine-binding index (TBI). MPA did not affect human growth hormone (hGH), basal and thyrotropin-releasing hormone (TRH) stimulated thyroid-stimulating hormone (TSH) and aldosterone. Basal and TRH-stimulated prolactin (PRL) secretion showed a slight but distinct elevation. From these data it is concluded that in postmenopausal patients MPA exerts its antitumor activity by an interference with the hypothalamo–pituitary adrenal axis in the sense of a selective pharmacologic hypophysectomy leading to complete suppression of adrenal steroid secretion. Additionally, MPA inhibits tumor cell growth through the progesterone receptor. A dual mechanism for the antitumor activity of high dose is postulated MPA: ablative through suppression of the hypothalamo–pituitary–adrenal axis and subsequent estrogen deprivation, and additive via the progesterone receptor directly on the tumor cell. The significance of gonadotropin suppression in the postmenopause for breast cancer growth is unclear. The depression of T_3 and T_4 is due to a depression of thyroid hormone-binding proteins. The elevation of PRL secretion may be explained by a slight estrogenic activity of MPA metabolites.

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THE SYNTHETIC PROGESTIN 17α-acetoxy-6α-methyl-4-pregnene-3,20-dione (medroxyprogesterone acetate, MPA) (Provera; Upjohn, Kalamazoo, MI; Clinovir; Upjohn, Heppenheim, FRG) is an effective drug in the hormonal therapy of breast cancer. One of the characteristic features of this drug is that its antitumor activity shows two levels of therapeutic efficiency: the response rates with low or moderate dosages were reported to be approximately 25%,[1] whereas with high dosages response rates of 40% and more were observed.[1,2] The mechanism of the antitumor activity is not known. The dose-related difference in the therapeutic efficiency suggests that MPA may act through two mechanisms, and that one of them is related to the high dosage.[3]

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Pharmacokinetically, MPA in plasma rises rapidly after a single dose administered orally or intramuscularly (IM) with peak concentrations after about 2 hours. After oral administration peak concentrations are 10 to 15 times higher than after IM administration.[4–7] The half times of MPA in plasma after a single oral or IM dose are about 12 hours and 6 weeks, respectively.[4,6,8] These kinetic characteristics determine the strategies for high-dose therapy. With IM administration the accumulation of the drug is slow but due to the long half-time doses given repetitively within a short period exert almost additive effects on the plateau state. In oral therapy, accumulation of MPA in plasma is rapid, reaching the plateau state within about 4 days, but due to the short half-time plasma levels remain sensitive against dose modifications, and for maintenance of a high level of plasma concentrations a continuous administration of the drug is mandatory.[9] The minimum required level of the plateau state to achieve high therapeutic efficiency is still a matter of discussion.[10,11]

Endocrinologically, MPA exerts suppressive effects on the hypothalamo–pituitary–gonadal axis in women[12,13] and men,[14] on the hypothalamo–pituitary–adrenal axis,[15] and on the thyroid hormones (T_3, T_4) in plasma.[16] MPA

did not affect plasma concentrations of human growth hormone (hGH),[17] prolactin (PRL),[13] and aldosterone.[18] A stimulatory effect of MPA has been observed on thyroid-stimulating hormone (TSH) secretion.[6] Not all endocrine actions of MPA were reported unequivocally, in particular those on the hypothalamo-pituitary-adrenal axis.[19,20] This may be related to the fact that the experimental and therapeutic conditions varied considerably among these investigations. MPA was administered IM or orally, and various dosages were used for single or continuous administrations.

The significance of the MPA-related endocrine actions for the therapeutic effects on breast cancer has not yet been evaluated. In order to assess the relation between MPA dose, plasma concentrations and endocrine effects, we investigated postmenopausal patients with metastatic breast cancer during oral therapy with a high and a low dose of MPA in a longitudinal fashion.

Materials and Methods

Within a clinical Phase II trial postmenopausal patients with metastatic breast cancer were treated with MPA in dosages between 500 and 1500 mg orally/day as specified in the figures. The design and modalities of the clinical trial have been described elsewhere.[21]

MPA in plasma was determined with a radioimmunoassay (RIA)[4] modified as described.[9] The antibody (goat no. 16, reference 9980-ICC-112) was kindly provided by the Upjohn Company, Kalamazoo, MI.

Cortisol in plasma was determined with a protein-binding method.[22] Other hormones were measured with commercial RIAs according to the specifications of the respective companies; RIAs were purchased from: (1) follicle stimulated hormone (FSH) and luteinizing hormone (LH), Behringwerke; (2) hGH and PRL, Serono; (3) dehydroepiandrosterone (DHEA), Panchem; (4) aldosterone, Isotopendienst West; (5) estradiol (E_2), Steranti; (6) T_3 and T_4, Corning; (7) TSH, Bio-Rad; (8) the TBI was determined with the T_3-uptake test from Byk-Malinckrodt.

The gonadotropin releasing hormone (GnRH)-induced gonadotropin secretion was determined in blood samples taken before and 30 minutes after intravenous injection of 100 μg GnRH (Hoechst). The TSH-releasing hormone (TRH)-induced secretion of TSH and PRL was determined in the same manner after intravenous injection of 200 μg TRH (Hoechst). The Student's *t* Test was used to calculate *P* values.

Results

The relation between oral MPA dosage and plasma concentrations in the plateau state was almost linear (Fig. 1). The interindividual variability of the level of the plateau state increased considerably with the dosage.

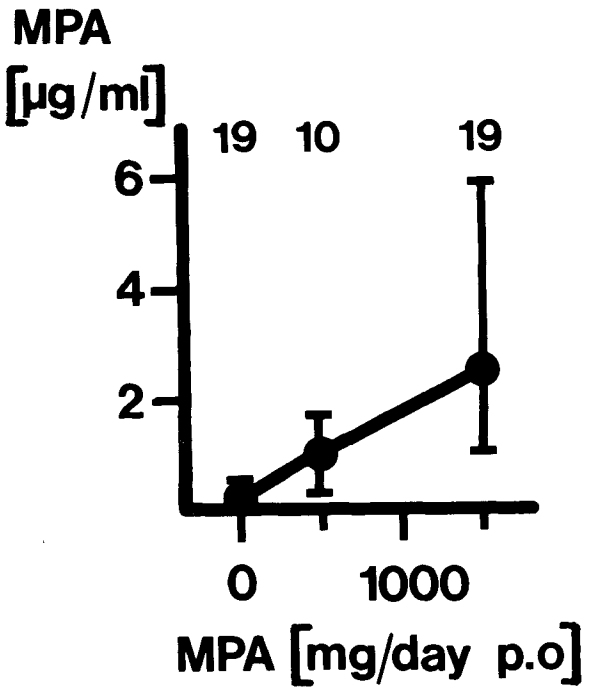
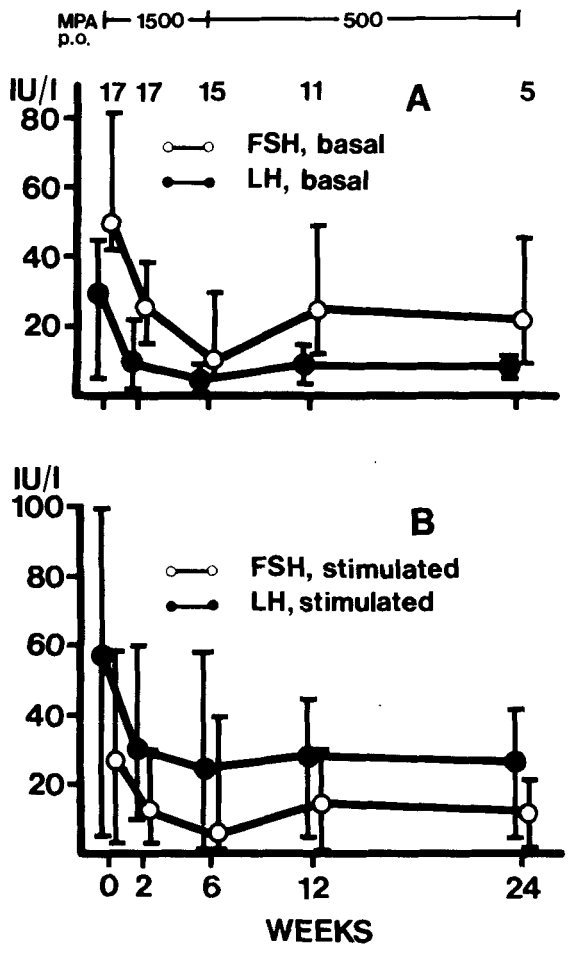


FIG. 1. MPA plasma concentrations as a function of daily oral dosage. In this and the following figures the bars and circles represent range and median, respectively. The numerals within the panel reflect the number of patients. The median of each patient was determined with three to seven MPA plasma concentrations in the plateau state. *P* values: 0–500, 1500, $P < 0.001$; 500–1500, $P < 0.002$.

MPA suppressed the high basal gonadotropin secretion in postmenopausal patients (Fig. 2A). The hypophyseal reaction was very slow and a complete suppression was observed after approximately 12 weeks of therapy with 1500 mg/day continuously. The action of MPA was dose dependent, and after dose reduction the gonadotropin levels increased and remained constant on a level lower than the initial level. The GnRH-induced gonadotropin release was affected in a comparable manner (Fig. 2B). In terms of range and median, a preferential LH release was observed.

Figure 3 shows the initial kinetics of MPA and cortisol in plasma during the first 10 days of therapy. The plateau state of MPA plasma concentrations was reached after 2 days. In terms of range and median the sensitivity of endogenous cortisol secretion against the MPA-induced suppression was different, but after 8 days of therapy no significant cortisol concentrations in plasma could be observed. Figure 4 shows that this effect is dose dependent. A complete suppression of endogenous cortisol secretion was observed with MPA doses equal to or higher than 1000 mg/day. MPA also suppressed the secretion of DHEA (Fig. 5). Basal estradiol was very low, and a further reduction could be observed to a certain extent (Fig. 6). MPA did not affect aldosterone secretion (Fig. 7). MPA



FIGS. 2A AND 2B. Time course of basal and GnRH-stimulated FSH and LH in plasma. In this and the following figures the MPA dosage is given in mg/day. Δ FSH and Δ LH are defined by the difference of basal and GnRH stimulated plasma concentrations of the hormones. *P* values: (A) 0–6 LH, FSH, $P < 0.001$; 0–24 LH, $P < 0.01$; FSH, $P < 0.001$. (B) 0–6 LH, $P < 0.05$; FSH, NS; 0–24 LH, FSH, $P < 0.05$.

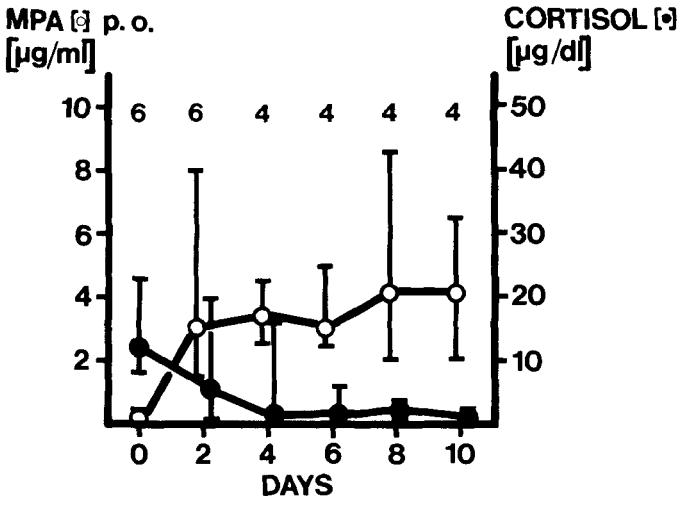


FIG. 3. Time course of MPA and cortisol in plasma. *P* values: 0–10 MPA, cortisol $P < 0.001$.

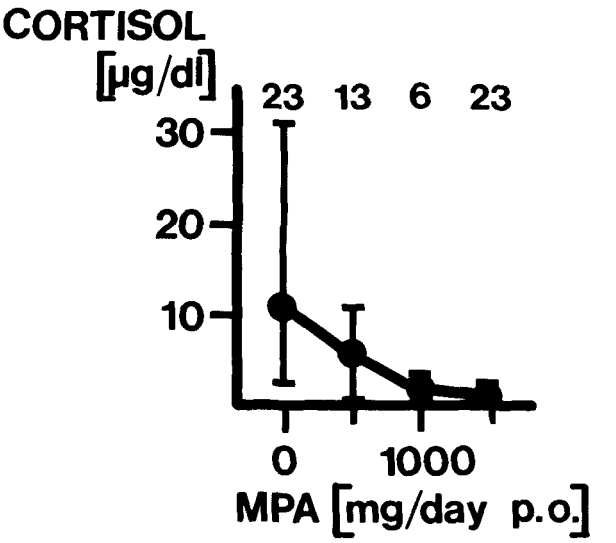


FIG. 4. Plasma cortisol as a function of MPA dosage. The median of each patient was determined with 3 to 10 cortisol concentrations. The duration of therapy was at least 2 weeks. *P* values: 0–500 cortisol, $P < 0.001$; 500–1000, $P < 0.02$; 500–1500, $P < 0.001$; 1000–1500, NS.

reduced the thyroid hormones T_3 and T_4 in plasma (Fig. 8), and concomitantly the TBI. Basal and TRH-stimulated TSH secretion remained normal (Fig. 9). MPA had no effect on basal hGH concentrations. MPA moderately induced basal, and TRH stimulated PRL secretion (Fig. 10). The medians of basal PRL concentrations showed a dose relationship, whereas the TRH-stimulated PRL release remained on constant level under 500 and 1500 mg MPA, respectively.

Discussion

Using a high and a low dose of MPA in one regimen we have demonstrated that the crucial difference between these two forms of therapy is the complete suppression of the ACTH-dependent adrenal steroid secretion. This effect occurs only in, and is typical for, high-dose therapy.

In the postmenopause period, estrogen production is dependent on the hypothalamo–pituitary–adrenal axis rather than the hypothalamo–pituitary–gonadal axis.[23] The main, if not the only, source of estrogen production consists of the aromatization of adrenal androgens in peripheral tissues like fat and muscle.[24] This is the rationale for therapeutic approaches like surgical adrenalectomy[25] or the use of aromatase inhibitors for the endocrine therapy of metastatic breast cancer.[26]

The intrinsic glucocorticoid activity of MPA in man has not been unequivocally reported.[20] Partially suppressive effects on ACTH and cortisol secretion were observed.[15,16] More convincingly, it was shown that MPA abolished the diurnal rhythm of cortisol secretion.[27] We have recently reported the complete abolition of the diur-

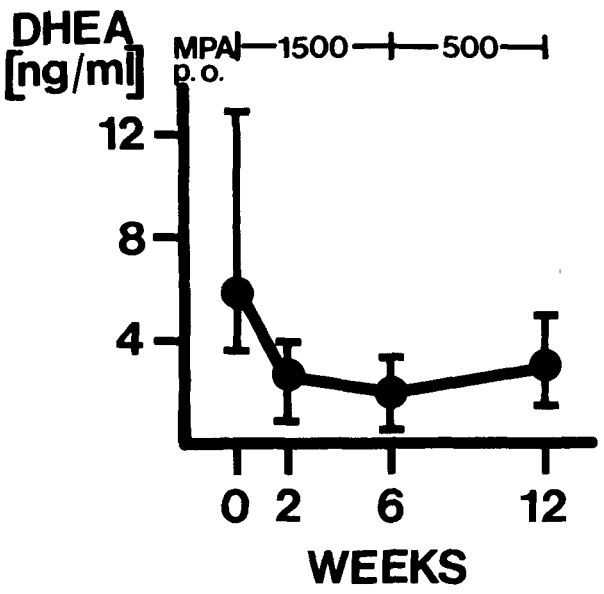


FIG. 5. Time course of DHEA in plasma. All determinations were done in nine patients. *P* values: 0–6, $P < 0.001$; 0–12, $P < 0.01$; 6–12, NS.

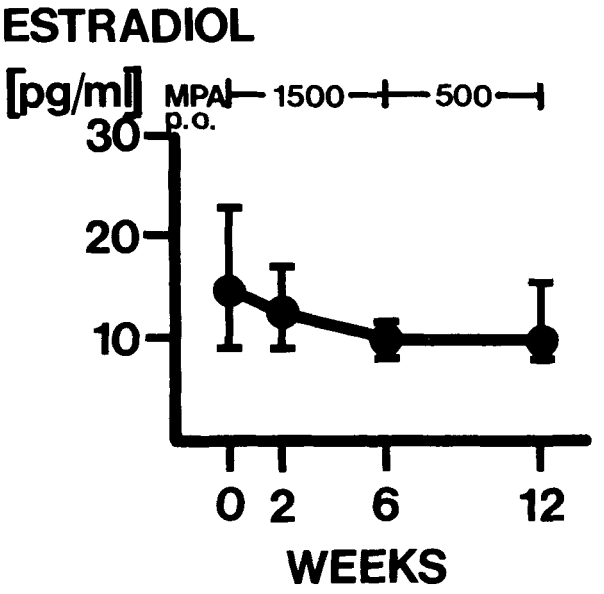


FIG. 6. Time course of estradiol in plasma. All determinations were done in six patients. The lower borderline of detectability was 10 pg/ml. *P* values: 0–6, 12, $P < 0.05$; 6–12, NS.

nal rhythm of ACTH and cortisol secretion in the presence of high MPA plasma concentrations.[28] Here we have shown that MPA is a weak glucocorticoid in man, and that the oral dose equipotent to the daily endogenous cortisol production is about 1000 mg/day. Consequently, high-dose MPA has successfully been used as a glucocorticoid substitute in patients undergoing medical adrenalectomy with aminoglutethimide.[29] A reduction of adrenal androgens in postmenopausal patients is consistent with an estrogen reduction. The high dose is necessary because otherwise the adrenal steroid synthesis will not be sufficiently suppressed. In synopsis of MPA pharmacokinetics, pharmacodynamics, and clinical efficiency we directly observed patients where the antitumor activity coincided with the extent of endogenous cortisol suppression.[30] In this context the term "high dosage" is not related to the absolute quantity but to the endocrine function of the drug. We have shown that the sensitivity of the hypothalamo–pituitary–adrenal axis is not necessarily identical in different patients. This implies that for a given pharmakodynamic effect the MPA dosage may be adjusted to the individual sensitivity of the patient.

In addition to the endocrine systemic effects, MPA may act directly on breast cancer. As the drug is a progestin this action should be mediated by the progesterone receptor (PR). *In vitro,* MPA inhibited growth of human breast and endometrium cancer cells only in the presence of the PR.[31,32] *In vivo,* the therapeutic effect on endometrium carcinomas was positively correlated to PR-positive tumor.[33] In breast cancer the situation is less clear. Sixty percent of estrogen-receptor (ER)-positive tumors also contain the PR.[33a] Not all PRs are therapeutically active. *In vitro,* some PR-positive endometrium cancer cells did not respond to MPA,[32] and we have observed a PR-positive but MPA-resistant breast cancer *in vivo.* The percentage of inactive PR in breast cancer is unknown, but it is reasonable to assume that the rate may be in the same order of magnitude as there are inactive ERs. This would mean that approximately 25% of all breast cancers have an active PR which corresponds to a 25% remission rate in breast cancer patients treated

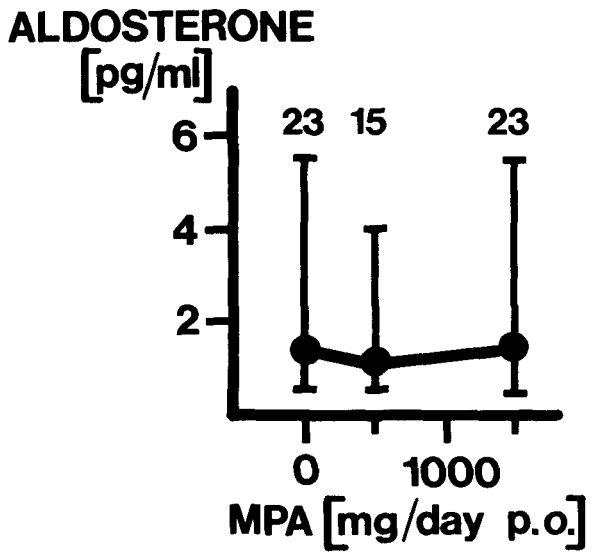
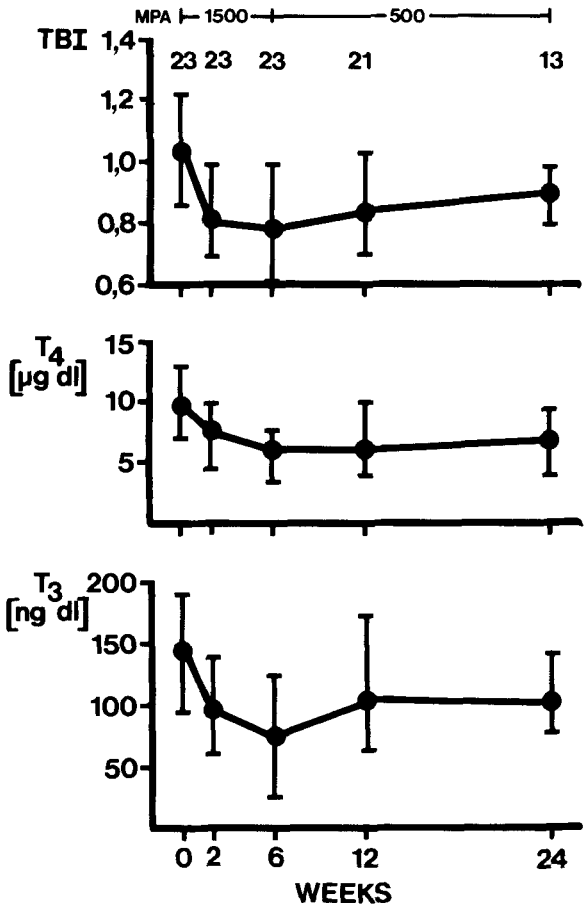


FIG. 7. Plasma aldosterone as a function of MPA dosage. The duration of therapy for each dosage was at least 6 weeks. *P* value: NS.



FIGS. 8A–8C. Time course of (A, top) TBI, (B, center) T_4, and (C, bottom) T_3 in plasma. *P* values: 0–6 T_3, T_4, TBI, $P < 0.001$; 0–24 T_3, $P < 0.02$; T_4, $P < 0.01$; TBI, $P < 0.05$.

with low-dose MPA.[1] The efficiency of high dose MPA which appears superior to low dose in the therapy of metastatic breast cancer may be explained by a dual mechanism of the drug: (1) additive by the direct action of MPA on the tumor cell through the progesterone receptor; and (2) ablative through the suppression of the hypothalamo–pituitary adrenal axis and subsequent estrogen deprivation. According to this model the two basic principles in endocrine tumor therapy, deprivation and interference,[34] are fulfilled in the mechanisms of one drug.

In premenopausal patients the interference of MPA with the hypothalamo–pituitary–gonadal rather than adrenal axis may play a predominant role. In contrast to progesterone, MPA has a pronounced suppressive activity on gonadotropin secretion.[35] According to the experience with MPA as a contraceptive, ovarian estrogen secretion is suppressed for at least 2 months after a single injection of 150 mg IM.[8] This suggests that the gonadotropic function of the pituitary is more sensitive against MPA than the adrenotropic. The adequate oral dose to suppress ovarian steroid secretion is unknown. After dose reduction from 1500 to 500 mg/day, we have not observed any difference in the extent of estradiol suppression.

The principle of therapy in the premenopause again is ablative in the sense of a selective pharmacologic hypophysectomy,[3] but it is questionable whether the high dose is necessary in the premenopause. The treatment of premenopausal patients with MPA in high dosage implies that ovarian and adrenal steroid secretion is blocked simultaneously. As patients with relapse after surgical oophorectomy may respond to a subsequent adrenalectomy in 10% to 20%[36] a differentiated therapy with MPA seems to be possible, suppressing the ovarian and adrenal steroid secretion sequentially according to the development of the disease.

We have shown that in postmenopausal patients the adrenal steroid secretion is completely suppressed with MPA 1500 mg/day within 10 days. Continuation of this dosage longer than 6 weeks led to clinical signs of glucocorticoid overdosage in about 30%.[37] Therefore, we used a regimen with dose reduction after 6 weeks. However, a dosage of 500 mg/day turned out not to be sufficient to suppress adrenal steroid secretion which is why a maintenance dose of 1000 mg/day is suggested.

The adequate dose schedule for IM therapy is still un-

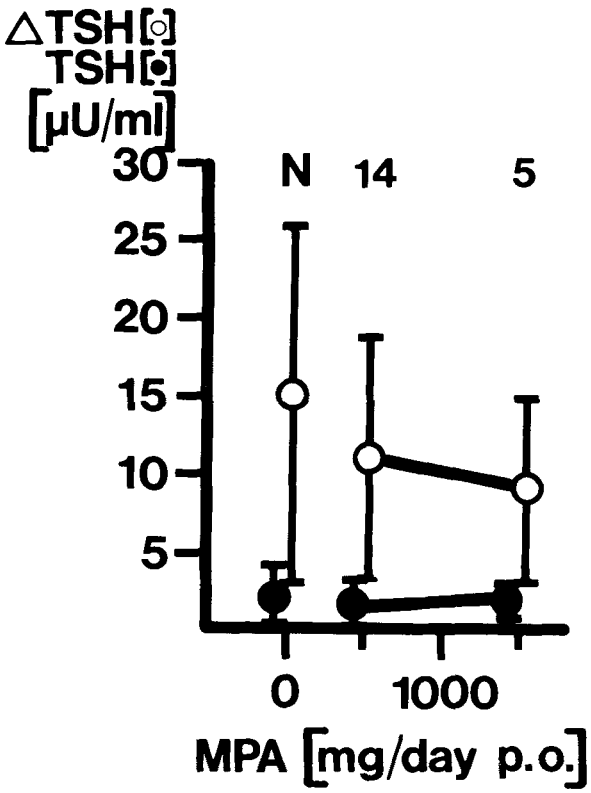


FIG. 9. Basal and TRH-stimulated TSH in plasma as a function of MPA dosage. N represents the normal range and median. Δ TSH reflects the difference between basal and TRH stimulated TSH concentrations. The duration of therapy was between 6 and 24 weeks. *P* value: NS.

known. With reference to the pharmacokinetic characteristics, a biphasic regimen has been recommended using an initial dose of 500 to 1000 mg/day for 4 weeks and a maintenance dose of 1000 mg/week.[37] The corresponding endocrine basis for this schedule has not yet been established.

In a recently published review[2] covering 19 clinical trials, the response rates were about 41% with dosages between 500 and 1500 mg IM per day for about 30 days. After this induction period, the maintenance therapy was performed with slightly different schedules. These clinical results indicate that in the initial phase 500 mg IM per day may be sufficient, and that due to the long half-time of MPA differences in the maintenance therapy are of minor importance.

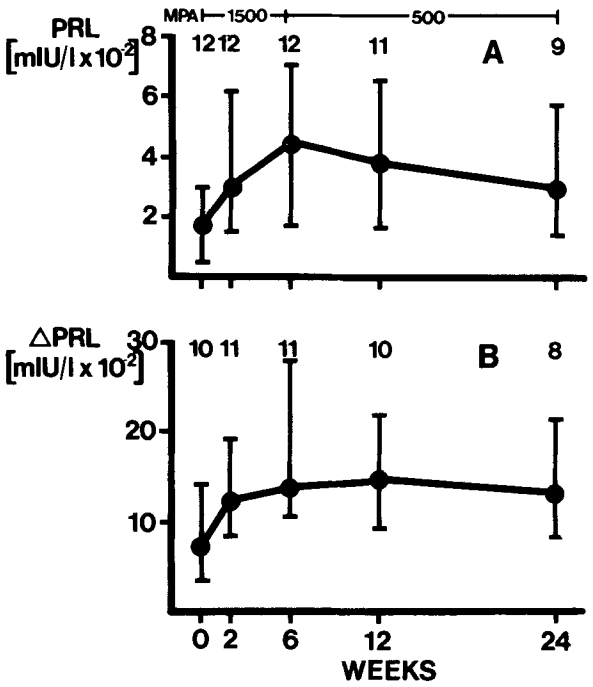
The significance of endogenous cortisol depletion after high-dose MPA application for the tumor growth *in vivo* is unknown. *In vitro* cortisol and dexamethason inhibit the growth of human breast cancer cell lines.[38] As the glucocorticoid activity of MPA is low in man, the significance of this activity for the inhibition of tumor growth *in vivo* is difficult to evaluate.

After surgical oophorectomy gonadotropin secretion rises immediately to postmenopausal levels.[39] Nevertheless, the ablation is effective in 30% to 45% of all patients.[40] Up to now there is no evidence for a direct action of gonadotropins on breast cancer growth. In this context the therapeutic significance of the MPA-induced suppression of gonadotropin secretion in postmenopausal or oophorectomized patients is unknown.

MPA did not interfere with the hypothalamo–pituitary–thyroid axis, and this observation was substantiated by a normal TSH secretion after TRH stimulation. This contradicts earlier reports where an increase of TSH in plasma was observed.[6,18] However, in those reports only basal TSH was determined, and the original data show that TSH remained within the normal range. We could confirm a decrease of the thyroid hormones T_3 and T_4 in plasma,[16,18] but in addition we show that this effect is due to MPA-induced reduction of thyroid hormone-binding proteins, probably thyroglobulin. This effect can also be observed during therapy with other glucocorticoids[41] or androgens.[42] With respect to the thyroid, the metabolic situation of the patients remains normal during MPA therapy.

Depending on the severity of the tumor disease, patients may develop a low T_3 or even low T_4 syndrome, and the thyroid hormones in plasma may be uncommonly reduced. In these cases a TRH test may help to clarify the state of thyroid function.

MPA did not interfere with aldosterone secretion, which confirmed earlier observations.[18] The regulation of aldosterone secretions appears to be essentially ACTH independent. MPA reduced hGH secretion in acromegalics,



FIGS. 10A AND 10B. Time course of basal (A) and TRH stimulated (B) PRL in plasma. Δ PRL reflects the difference between basal and TRH stimulated plasma PRL concentrations. P values: 0–6 PRL, $P < 0.01$; Δ PRL, $P < 0.02$; 0–24 PRL, $P < 0.05$, Δ PRL, NS.

but not in normal volunteers.[17] In patients with metastatic breast cancer the authors and others[13] have not observed any effect of MPA on hGH secretion.

The MPA-induced elevation of basal and TRH-stimulated PRL secretion is not well understood. MPA metabolites rather than MPA itself may have a weak intrinsic estrogenic activity or may be partially converted to estrogens.[16] This elevation of PRL secretion was regularly observed, and is apparently not related to certain forms of hyperprolactinemia that coincide with progression of the tumor disease.[43] Other authors could not find an influence of MPA on PRL secretion.[13,44,45] This may be explained by the fact that we uniformly used a massive oral dose at the beginning of therapy. Due to the rapid increase in MPA plasma concentrations, weak endocrine effects can be detected more easily.

The discussion of the MPA-induced endocrine and antitumor activities has to include the question whether MPA itself is the biologically active substance. MPA plasma concentrations determined with gas liquid chromatography were found to be 5 to 10 times lower than those measured with the RIA.[46] The time courses of MPA in both methods were parallel and, therefore, the kinetic characteristics identical. We have discussed earlier that the antibody may recognize MPA metabolites modified at C_3 and C_6 of the steroid molecule.[9] As the endocrine reactions, especially the suppression of endogenous cor-

tisol secretion, were exactly reflected by the MPA–RIA-determined plasma concentrations, we suggest that the antibody recognizes MPA and a biologically active group of MPA metabolites. Whether the biological activities of these metabolites are only restricted to endocrine actions or whether these metabolites participate in the antitumor activity of MPA is still unknown. It would be interesting to know how endocrine and antitumor activities are related to MPA itself.

In summary, we have demonstrated the pharmacokinetic and endocrine background of high-dose and low-dose MPA therapy, and we have generated hypotheses for the mechanisms of action of the drug in metastatic breast cancer. These hypotheses now have to be proven in extended endocrine and steroid hormone-receptor-oriented trials.

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