Profound Suppression of Plasma Estrogens by Megestrol Acetate in Postmenopausal Breast Cancer Patients

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ABSTRACT

Twelve postmenopausal women suffering from advanced breast cancer had plasma estrogens, androgens, cortisol, and gonadotropins determined before therapy and during treatment with megestrol acetate (MA) in oral doses escalated from 40 to 160 mg. The plasma clearance and production rate of estrone and estrone sulfate were determined before treatment and after 4 weeks of therapy with 160 mg MA. Treatment with MA suppressed plasma levels of dehydroepiandrosterone sulfate, androstenedione, and cortisol in a dose-dependent manner to <10% of pretreatment levels. Plasma testosterone, estradiol, estrone, and estrone sulfate were suppressed to 18–29% of pretreatment values, whereas the gonadotropins were suppressed to 35–52%. The plasma clearance rates of estrone and estrone sulfate were increased by a mean value of 23.7% (P < 0.01) and 23.5% (P < 0.025), whereas the production rates were reduced by 76.7% (P < 0.0005) and 76.1% (P < 0.00005), respectively. Our findings indicate that MA causes profound suppression of adrenal steroid production but in addition suppresses ovarian secretion of androgens in postmenopausal breast cancer patients. The reduction in plasma estrogens is comparable to values obtained with commonly used aromatase inhibitors and may be responsible for its antitumor effects in breast cancer.

INTRODUCTION

Endocrine therapy plays a pivotal role in the treatment of breast cancer. Currently, several treatment options, including antiestrogens, estrogen deprivation (castration in premenopausal women or aromatase inhibitors in postmenopausal ones), or progestins are available.

Synthetic progestins given in high-dose regimens (MPA in a dose of ≥1000 mg or MA in a dose of ≥160 mg daily) have been shown to induce tumor regression in postmenopausal women with hormone-sensitive breast cancers (1). Randomized studies have revealed similar response rates to progestins and other contemporary treatment modalities like tamoxifen (2, 3) and the aromatase inhibitor aminoglutethimide (4).

Despite the fact that progestins are shown to be effective against breast cancer, the exact mechanism(s) of their antitumor action is not known. Several mechanisms, like down-regulation of the concentration of the estrogen receptor (5), alterations in tissue metabolism of estrogens (6), suppression of plasma estrogens (7), interactions with growth factors (8), and a direct cytostatic influence on tumor cells (9) have all been proposed.

Progestins are known to suppress adrenal steroid synthesis, reducing the secretion of cortisol and also the secretion of androstenedione and testosterone (10). Estrogen production in postmenopausal women occurs by conversion of circulating androgens into estrogens in peripheral tissue (11). MPA and MA have been reported to suppress plasma E1 and E2 by 20–40% (7, 10, 12). However, in two previous studies, we found MA to suppress plasma E1S to less than 50% of its pretreatment value (10, 13), suggesting MA could have a selective influence on the metabolism or PR of this estrogen conjugate. E1S is synthesized from circulating E1 and E2 (14, 15). Plasma levels of E1S are about 5- and 20-fold higher than plasma levels of E1 and E2, respectively, in postmenopausal women (16, 17). Although E1S is not biologically active on its own, breast cancer tissue contains the enzymes required to convert E1S into the biologically active E1 (18, 19). Because circulating E1S may be an important estrogen reservoir in postmenopausal women, suppression of the plasma level of this estrogen conjugate may be of importance to the antitumor effect of progestins.

The aim of this study was to evaluate the influence of treatment with MA in different doses on the plasma concentration, metabolic clearance rate, and PRs of estrogens in postmenopausal breast cancer patients. Thus, we measured plasma levels of E1, E2, and E1S together with their precursors, androstenedione and testosterone. Because both these androgens have an adrenal and also an ovarian origin in postmenopausal women, we measured plasma DHEAS, cortisol, and gonadotropins to address the influence of MA on each glandular system. To evaluate the influence of MA treatment on the pharmacokinetics of E1 and E1S, we measured the Cl of E1 and E1S and the fraction of E1 transferred into E1S after injection of [15]C]E1 and [1]H]E1S before treatment and after 4 weeks of therapy with MA (160 mg o.d.). From these data we calculated the PR of E1 and E1S before and during treatment.

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3The abbreviations used are MPA, medroxyprogesterone acetate; AUC, area under plasma concentration curve; Cl, plasma clearance rate; DHEAS, dehydroepiandrosterone sulfate; E1, estrone; E2, estradiol; E1S, estrone sulfate; fm, fraction of a compound metabolized into another compound (also termed "transfer factor"); MA, megestrol acetate; o.d., once daily; PR, production rate.
PATIENTS, MATERIALS, AND METHODS

Patients. Twelve patients suffering from advanced breast cancer who were to receive MA treatment for progressive disease took part in the investigation. The protocol was approved by the regional ethical committee. All patients gave their written informed consent. Their median age was 67 years (range 60–78 years), median body weight was 71 kg (range 55–83 kg), and median height was 1.62 m (range 1.53–1.67 m). Two of the patients were moderate smokers who did not change their smoking habits during the last months before the investigation or during the investigation period; the other 10 patients were nonsmokers. None of the patients received any other forms of endocrine therapy, anticancer treatment, or drugs known to enhance or inhibit drug-metabolizing enzymes during the investigation period. Previous anticancer therapy was terminated ≥4 weeks before commencing treatment with MA.

Study Protocol. The treatment schedule was as follows: each patient commenced on MA at a dose of 40 mg o.d. (Megestrol® 40 mg tablets; Bristol Arzneimittel GmbH, Munich, Germany). The dose was subsequently escalated every fourth week to 80 mg o.d., 120 mg o.d., and, finally, 160 mg o.d. After the study period was completed, each patient continued treatment with MA 160 mg o.d. until evidence of disease progression (none of the patients had progressive disease during the study period).

Blood samples for plasma hormone measurement were obtained before initiating therapy and subsequently at the end of each 4-week treatment interval. In addition, each patient had Cls of E1 and E1S determined before initiating therapy and after 4 weeks of treatment with MA 160 mg o.d.

Materials. [6,7,3H]E1S (60 Ci/mmol), [2,4,6,7,3H]E1 (85–105 Ci/mmol), and [4,14C]E1 (50–60 Ci/mol) were obtained from DuPont New England Nuclear (Drerich, Germany). E2-6-carboxymethylxoxime-[2-125I]iodohistamine (~2000 Ci/ml) was obtained from Amersham International (U.K.). Sephadex LH-20 was obtained from Pharmacia (Uppsala, Sweden), and sulfatase (S-9754) was obtained from Sigma (United Kingdom). All solvents were of analytical or spectrophotometric grade and were obtained from Merck (Darmstadt, Germany) except for ethanol, which was obtained from A/S Vinmonopolet (Oslo, Norway).

Plasma Hormone Measurements. Plasma estrogens (E2, E1, and E1S) were determined as reported elsewhere (16, 20). Briefly, [3H]E1S (~400 cpm) was evaporated to dryness in test tubes. Plasma (2 ml) was added, and the samples were allowed to equilibrate overnight. Unconjugated estrogens were extracted with diethyl ether, were purified on a Sephadex LH-20 column using benzene:methanol (90:10, v/v) as eluent, and were measured by RIA. E1S was hydrolyzed by sulfatase [S-9754; 1.5 mg dissolved in 2 ml 0.2 M sodium acetate buffer (pH 5)], and the unconjugated E1S was extracted and purified on Sephadex LH-20 columns using dichloromethane. E1S was subsequently reduced into E1 by sodium borohydride in methanol. The sample was neutralized with sodium acetate, and E2 was extracted with diethyl ether, was purified on a LH-20 column, and was measured with RIA. The sensitivity limit of the assay was 2.1 pmol/liter, 6.3 pmol/liter, and 2.7 pmol/liter for E2, E1, and E1S, respectively, and the intra-assay coefficient of variation was 4.4%, 3.9%, and 5.9%, respectively.

Plasma androstenedione, testosterone, DHEAS, and cortisol were determined by commercial RIA, and the gonadotropins were determined by commercial IRMA kits (Orion Diagnostica, Diagnostic Products Corp., and Diagnostic System Laboratories). The intra-assay coefficient of variation was <7% for all analyses. All samples obtained from each patient were analyzed in the same batch.

Measurement of the Cl of E1 and E1S by Isotope Injections. The Cl of E1 and E1S was determined by administering a mixture of [3H]E1S and [14C]E1 as a bolus injection followed by determination of the concentration of radioactive E1 and E1S in the plasma after certain time intervals as described previously (15, 21). Briefly, each patient received 25 μCi of [4,14C]E1 and 75 μCi of [6,7-3H]E1S dissolved in 20 ml of ethanol:saline 0.9% (8:92, v/v) as a 1-min bolus injection. The midpoint of the injection was taken as time zero. Blood samples were drawn from an indwelling needle in the opposite arm immediately before injection of the tracers and after 5, 10, 15, 22.5, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 480, 600, 720, and 900 min.

Cl for E1 and E1S was calculated from the equation: Cl = Dose/AUC, where AUC is the area under the elimination curve. In previous studies, we have shown that the concentration of radioactive E1S over time after a bolus injection of tracer E1S may not be described by a simple mathematical function (15, 21), probably due to enterohepatic cycling of estrogens with a substantial amount of the material reabsorbed entering the plasma as conjugates due to sulfatation or glucuronidation in the splanchnic and liver (22, 23). Thus, the area under the [3H]E1S concentration curve was determined by the trapezoid rule, adding the residual by extrapolating to infinity.

Plasma concentration of [14C]E1 as a function of time was tested for goodness of fit to a multicompartmental exponential function using Kaleidograph software on an Apple Macintosh LC computer. Although the elimination curves for E1 were found to be well fitted to a three-compartmental model in several instances, in 8 of 12 patients the elimination curve for E1 did not fit to a three-compartmental model in one or both of the test situations (one or more of the parameters gave a negative value). In these patients, the curves were described by a two-compartmental model in both of the test situations. Therefore, to handle all cases in a uniform way, the AUC for E1 was calculated by use of the trapezoid rule in all patients. In addition, the AUC was calculated by integrating the multicompartmental function (three-compartmental model in four patients, two-compartmental in eight patients).

The fraction of E1 metabolized to E1S (fm) was calculated from the equation (24):

\[
fm = \left( \frac{AUC[14C]E,S \times Cl_{E,S}}{AUC[14C]E, \times Cl_{E}} \right)
\]

and the PR for plasma E1 and E1S from the equations:

\[
PR_{E1} = Cl \times E1 \times \text{Plasma concentration E1}
\]

and

\[
PR_{E1S} = Cl \times E1S \times \text{Plasma concentration E1S}
\]
Fig. 1  Plasma levels of cortisol (top), androstenedione (middle), and DHEAS (bottom) in patients before and during treatment with MA at different doses. Geometrical mean values with 95% confidence intervals of the mean.

Fig. 2  Plasma levels of luteinizing hormone (top), follicle-stimulating hormone (middle), and testosterone (bottom) before and during treatment with MA at different doses. Geometrical mean values with 95% confidence intervals of the mean.

Statistics. In a previous study, we reported plasma estrogen and androgen levels in postmenopausal breast cancer patients to be best fitted to a lognormal distribution (16). Thus, plasma hormone concentrations expressed as absolute values and values obtained during treatment with MA expressed as percentage of pretreatment values are given as their geometrical mean values with 95% confidence intervals of the mean. In addition, plasma hormone levels obtained in different situations were compared using the Friedman test (two-way nonparametrical analysis of variance), and the clearance rates and PRs for E1 and E2S before and during treatment with 160 mg o.d. MA were compared by the Wilcoxon matched pair sign rank test.

RESULTS

Plasma Hormone Levels. Plasma hormone levels before and during treatment with MA at different doses are depicted in Figs. 1–3. Values obtained during treatment, expressed as percentage of pretreatment levels, are shown in Table 1. Treatment with MA in doses from 40 mg o.d. to 160 mg o.d. caused a dose-dependent suppression of plasma androstenedione, DHEAS, and cortisol to a mean value of less than 10% of
pretreatment levels, whereas plasma testosterone was suppressed to 20% of its pretreatment level. Similarly, plasma levels of E₂, E₁, and E₁S were suppressed in a dose-dependent manner to 29%, 16%, and 18% of pretreatment levels, respectively. Although treatment with MA suppressed plasma levels of luteinizing hormone and follicle-stimulating hormone by 48–65%, this suppression was fully developed at a dose of MA 80 mg o.d. MA and Plasma Estrogen Levels

Treatment with MA was found to have no influence on the ratio of plasma E₁:S:E₁. Contrariwise, the E₁:S:E₁ and the E₁:E₂ ratios were both reduced during treatment with MA (Friedman

\[
P < 0.0025 \text{ and } P < 0.025, \text{ respectively). Considering the } E₁:A \text{ ratio, the } 95\% \text{ confidence interval for the values obtained during treatment expressed as percentage of pretreatment values spanned the 100} \% \text{ value at treatment with all doses of MA. However, a Friedman test revealed a significant difference between the different test situations (} P < 0.025\text{), caused mainly by an increase in the ratio during treatment with 160 mg o.d. MA.}

**Table 1.** Plasma hormone values and hormone ratios during treatment with escalating doses of MA given as percentage of pretreatment level. Geometrical mean values with 95% confidence intervals of the mean

<table>
<thead>
<tr>
<th>Steroid*</th>
<th>40 mg</th>
<th>80 mg</th>
<th>120 mg</th>
<th>160 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>E₁</td>
<td>69(49–96)</td>
<td>47(33–57)</td>
<td>31(21–47)</td>
<td>29(18–47)</td>
</tr>
<tr>
<td>E₂</td>
<td>54(33–88)</td>
<td>40(22–70)</td>
<td>19(12–32)</td>
<td>16(10–32)</td>
</tr>
<tr>
<td>E₁S</td>
<td>66(43–100)</td>
<td>50(34–73)</td>
<td>25(17–35)</td>
<td>18(13–25)</td>
</tr>
<tr>
<td>C</td>
<td>75(53–96)</td>
<td>54(34–86)</td>
<td>26(15–45)</td>
<td>9(6–13)</td>
</tr>
<tr>
<td>DHEAS</td>
<td>59(45–78)</td>
<td>39(25–60)</td>
<td>21(14–32)</td>
<td>9(5–14)</td>
</tr>
<tr>
<td>A</td>
<td>84(79–104)</td>
<td>51(28–93)</td>
<td>22(10–46)</td>
<td>8(4–13)</td>
</tr>
<tr>
<td>T</td>
<td>44(29–67)</td>
<td>20(14–31)</td>
<td>35(18–66)</td>
<td>52(38–71)</td>
</tr>
<tr>
<td>LH</td>
<td>40(27–60)</td>
<td>35(18–66)</td>
<td>52(38–71)</td>
<td>52(38–71)</td>
</tr>
<tr>
<td>FSH</td>
<td>51(39–66)</td>
<td>52(38–71)</td>
<td>52(38–71)</td>
<td>52(38–71)</td>
</tr>
<tr>
<td>E₁/E₂</td>
<td>78(59–104)</td>
<td>85(65–112)</td>
<td>62(46–84)</td>
<td>63(45–87)</td>
</tr>
<tr>
<td>E₁S/E₂</td>
<td>96(64–144)</td>
<td>107(76–149)</td>
<td>79(58–107)</td>
<td>62(47–81)</td>
</tr>
<tr>
<td>E₁S/E₁</td>
<td>122(81–184)</td>
<td>125(80–194)</td>
<td>126(78–203)</td>
<td>98(64–150)</td>
</tr>
<tr>
<td>E₁/A</td>
<td>64(35–114)</td>
<td>78(32–189)</td>
<td>99(32–309)</td>
<td>237(93–608)</td>
</tr>
</tbody>
</table>

*Abbreviations: C, cortisol; A, androstenedione; T, testosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

**DISCUSSION**

Plasma levels of androgens, estrogens, and gonadotropins before treatment were in the same range as reported previously for postmenopausal women from our group as well as by others.
Whereas plasma concentrations of estrogens are considerably lower in postmenopausal women compared to premenopausal ones, estrogen ablation (through surgical procedures as adrenalectomy or hypophysectomy or medical treatment with aromatase inhibitors) is well documented to cause tumor regression in postmenopausal patients (30). Thus, any influence of progestins on plasma estrogen concentrations may be of importance to the antitumor effects of these drugs.

Improvement of the RIAs may explain the difference in plasma estrogen levels in postmenopausal women (30). However, the observation that all adrenal steroids were suppressed to a similar extent suggests that MA suppresses adrenal steroid synthesis by a glucocorticoid-agonistic suppression of adrenocorticotropic hormone secretion (35).

The discrepancy between the suppression of testosterone and steroids of adrenal origin (androstenedione, cortisol, and DHEAS) could be due to a significant contribution from ovarian synthesis of testosterone (28, 29). The finding that MA (160 mg o.d.) suppresses plasma levels of gonadotropins by 48–65% indicates that treatment with MA suppresses ovarian steroid synthesis, albeit to a somewhat smaller extent compared to suppression of the adrenals.

For unexplained reasons, treatment with MA caused a more pronounced suppression of plasma androgens than estrogens. This occurred despite the fact that MA treatment enhanced the CI of E1. However, this difference occurred during treatment with MA 160 mg o.d. only, as doses of 40–120 mg o.d. suppressed plasma levels of E1 and E1S by the same percentage as the adrenal steroids. Progestins are known to express glucocorticoid agonistic effects (34), and the observation that all adrenal steroids were suppressed to a similar extent suggests that MA suppresses adrenal steroid synthesis by a glucocorticoid-agonistic suppression of adrenocorticotropic hormone secretion (35).

Despite well-documented clinical effects, the mechanism causing the antitumor effects of progestins in postmenopausal breast cancer patients is not known. However, the observation that the expression of estrogen and progesterone receptors predicts a response to treatment with progestin therapy (27) suggests endocrine mechanisms to be involved. Estradiol is a most potent mitogen to estrogen receptor-positive breast cancer cells. Although ovarian estrogen synthesis ceases at menopause, estrogens are synthesized by peripheral aromatization of circulating androgens. The major pathway is aromatization of androstenedione into E1, with a minor contribution from aromatization of testosterone into E2 (11). The main source of these androgens is the adrenal gland, but the postmenopausal ovary contributes significantly to circulating testosterone (28, 29). Whereas plasma concentrations of estrogens are considerably lower in postmenopausal women compared to premenopausal ones, estrogen ablation (through surgical procedures as adrenalectomy or hypophysectomy or medical treatment with aromatase inhibitors) is well documented to cause tumor regression in postmenopausal patients (30). Thus, any influence of progestins on plasma estrogen concentrations may be of importance to the antitumor effects of these drugs.

Improvement of the RIAs may explain the difference in plasma androgen and estrogen suppression by MPA and MA in previous studies compared to the results of this investigation. Similar to our findings, a recent investigation by Pommier et al. (31) found MA (160 mg daily) to suppress plasma levels of DHEA and gonadotrophins. In contrast to our findings, these authors reported MA to increase plasma levels of E2 by 91%. However, the RIA used to determine plasma E2 in that investigation had a sensitivity limit of about 80 pmol/liter, which is about 4-fold the mean pretreatment concentration of E2 measured in this study. Earlier studies by us (13) and others (12, 32, 33) have shown treatment with MA and MPA to suppress plasma E1 and E2 by 20–40%, although one study reported plasma E2 to be suppressed by 65–70% (33). This differs from the findings of this study, in which MA (160 mg o.d.) was found to suppress all plasma estrogens by 71–82%. Accordingly, the results presented here show treatment with MA 160 mg o.d. to be as effective as many aromatase inhibitors in suppressing plasma estrogen levels in postmenopausal women (30).

Treatment with MA suppressed plasma levels of androstenedione and testosterone to less than 10% and 20% of pretreatment levels, respectively. Progestins in high doses are known to express glucocorticoid agonistic effects (34), and the observation that all adrenal steroids were suppressed to a similar extent suggests that MA suppresses adrenal steroid synthesis by a glucocorticoid-agonistic suppression of adrenocorticotropic hormone secretion (35).

The discrepancy between the suppression of testosterone and steroids of adrenal origin (androstenedione, cortisol, and DHEAS) could be due to a significant contribution from ovarian synthesis of testosterone (28, 29). The finding that MA (160 mg o.d.) suppresses plasma levels of gonadotropins by 48–65% indicates that treatment with MA suppresses ovarian steroid synthesis, albeit to a somewhat smaller extent compared to suppression of the adrenals.

Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment</th>
<th>During treatment</th>
<th>Percentage change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR E1a</td>
<td>1.89 (1.15–3.11)</td>
<td>0.44 (0.33–0.59)</td>
<td>−76.7 (−87.4–56.8)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>PR E1Sb</td>
<td>2.02 (1.32–3.08)</td>
<td>0.48 (0.37–0.62)</td>
<td>−76.1 (−83.5–65.3)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Cl E1c</td>
<td>24.6 (22.0–27.5)</td>
<td>30.5 (26.3–35.2)</td>
<td>+23.7 (+8.5+1.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cl E1Sd</td>
<td>3.8 (3.0–4.8)</td>
<td>4.7 (3.6–6.1)</td>
<td>+23.5 (+7.5+41.9)</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>fmf</td>
<td>76.9 (65.2–90.6)</td>
<td>72.5 (59.9–87.8)</td>
<td>−6.0 (−10.4–0.6)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

a nmol/h.

b liter/h.

c %.

d %.

Fig. 4 Elimination curves for [3H]E1S (●), [14C]E1S (Δ), and [14C]E1 (○) after administration of [14C]E1 and [3H]E1S to a representative patient before treatment with MA (160 mg o.d.).

Table 2

Cl and PR for E1 and E1S and the fraction of E1 converted into E1S before and during treatment with MA (160 mg o.d.).

Geometrical mean values (with 95% confidence intervals).

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a nmol/h.

b liter/h.

c %.

d %.
term treatment with dexamethasone has been reported not to influence aromatization in vivo (39). It is noteworthy that in this study treatment with MA 40 or 80 mg o.d. both caused a nonsignificant reduction in the ratio of plasma E₁ to androstenedione, whereas 160 mg caused a nonsignificant increase in this ratio. Although the 95% confidence interval spanned the 100% level in every test situation, a Friedman test revealed a significant difference in the ratio of plasma E₁ to androstenedione in the different test situations (P < 0.025). Thus, the possibility exists that treatment with MA at a dose of 160 mg o.d. may enhance in vivo aromatization.

In contrast to our previous investigations (10, 13), we found no evidence for a selective suppression of plasma E₁S compared to E₁. On the other hand, the finding that plasma E₂ was suppressed to a smaller extent compared with plasma E₁ and E₁S is interesting. Plasma E₂ in postmenopausal women is partly synthesized by aromatization of testosterone but also arises by the reduction of plasma E₁ (11). In this study, we found plasma testosterone to be suppressed to a smaller extent than plasma androstenedione, and sustained plasma levels of E₂ may reflect a higher concentration of its precursor. An alternative explanation could be a differential effect of MA treatment on the Cl of E₁ and E₂. Although we found MA 160 mg o.d. to enhance the clearance rate of E₁ and E₁S by 23–24%, the possibility exists that MA may not have a similar influence on the clearance rate of E₂.

The findings that treatment with MA 160 mg o.d. suppresses plasma estrogens with an efficacy comparable to most aromatase inhibitors suggests MA may exert its antitumor effect through estrogen suppression. An objection to such a hypothesis would be the lack of cross-resistance to treatment with progestins and aromatase inhibitors. Although some authors have reported a low response rate to aminoglutethimide in patients previously exposed to progestins (40), others (41, 42) have shown that a limited number of patients may respond to both treatment options in sequence. On the other hand, recent data suggest a lack of cross-resistance between different aromatase inhibitors (43), possibly caused by a differential effect on intratumor estrogen synthesis. Accordingly, a lack of cross-resistance to an aromatase inhibitor and progestins does not refute a hypothesis that progestins may act by suppressing plasma estrogen levels.

An interesting option for future studies could be to combine treatment with a potent aromatase inhibitor with MA to achieve maximal estrogen suppression. Although studies have reported administration of progestins in concert with the aromatase inhibitor aminoglutethimide (44) as well as progestins in concert with aminoglutethimide and tamoxifen (45) not to improve response rates compared to single-drug therapy, these studies are confounded by severe drug interactions, inasmuch as aminoglutethimide significantly enhances the metabolism of progestins (46, 47) as well as tamoxifen (48). In addition, aminoglutethimide inhibits the 11β-hydroxylase in the adrenal gland, causing substrate accumulation and enhanced secretion of androstenedione (49). With the introduction of selective aromatase inhibitors, an interesting option is to evaluate the endocrine and clinical effects of such drugs and MA in concert in patients suffering from advanced breast cancer.

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