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INFLUENCE OF PROGESTINS ON SERUM HORMONE LEVELS IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER—II. A DIFFERENTIAL EFFECT OF MEGESTROL ACETATE AND MEDROXYPROGESTERONE ACETATE ON SERUM ESTRONE SULFATE AND SEX HORMONE BINDING GLOBULIN

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Summary—Serum estradiol, estrone, estrone sulfate and sex hormone binding globulin were measured in 10 postmenopausal patients with advanced breast cancer receiving sequential treatment with medroxyprogesterone acetate and megestrol acetate. Treatment with megestrol acetate caused a non-significant reduction in serum estradiol (mean reduction of 19%, $0.05 < P < 0.1$) but significant reductions in serum estrone (mean reduction of 20%, $P < 0.02$) and serum estrone sulfate (mean reduction of 54%, $P < 0.005$) compared to treatment with medroxyprogesterone acetate. In contrast, treatment with medroxyprogesterone acetate reduced serum sex hormone binding globulin more compared to treatment with megestrol acetate (mean reduction of 69%, $P < 0.01$). These findings suggest that the two progestins have differential effects on serum hormone levels. The finding that treatment with megestrol acetate causes a significant reduction in serum estrone sulfate level warrants further investigations of this potentially important mechanism of action of this drug in advanced breast cancer.

INTRODUCTION

Administration of synthetic progestins as medroxyprogesterone acetate (MPA) and megestrol acetate (MA) in "high dose drug schedules" are efficient endocrine treatments of advanced breast cancer [1–5]. Given as first line treatment, MPA, given orally at a dose of 500 mg b.i.d., or MA, given orally, at a dose of 160 mg o.d., induce response rates similar to tamoxifen (TAM) treatment [6–8]. Randomized trials have suggested both drugs to have a response rate similar to aminoglutethimide when given as second line treatment [9, 10]. The mechanism(s) of action of progestins on breast cancer are not clear. Suppression of adrenal steroid hormone synthesis [11, 12], alterations in steroid metabolism [13–15], suppression of tumour cell estradiol receptor (ER) content [16] or a direct cytostatic/cytotoxic effect upon tumour cells [17] have all been suggested.

In a previous study [18] we found serum levels of estrone sulfate (E_1S) to be reduced in patients receiving oral high dose progestin treatment. The results of this study also suggested a possible different effect of MPA given as 500 mg b.i.d. in comparison with MA given as 160 mg o.d. on serum E_1S. The MA drug schedule seemed more potent than MPA in suppressing serum E_1S, whereas treatment with MPA seemed to suppress serum SHBG more strongly than with MA treatment. Therefore, this cross-over study was designed to evaluate differential effects of MA and MPA treatment on serum estrogens and SHBG in patients with advanced breast cancer.

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EXPERIMENTAL

Patients, drug schedules and blood sampling

Ten postmenopausal patients receiving oral high dose progestin treatment with MPA (Farlutal®, Farmitalia) 500 mg b.i.d. or MA (Megace®, Bristol-Myers) 160 mg o.d. for advanced breast cancer were enrolled in this study. Their mean age was 67.3 years (range 53–80 yr), and their body weight stayed unchanged during the study. None of the patients were smokers. Drugs known to be enzyme inducers or inhibitors were not ingested, and other drugs (analgetics, etc.) were kept constant during the study.

All patients gave their verbal informed consent to participate in the study. After 4–12 weeks of

treatment with either MA (5 patients) or MPA (5 patients) blood samples (20 ml) were collected on two consecutive days at 8 a.m. after an overnight fast. The patients were then crossed over to receive the alternative drug schedule for a period of 4–6 weeks, whereafter blood samplings were repeated as mentioned above.

Each blood sample was allowed to clot for 1 hr, centrifuged, and the serum was stored at −20°C until analysis.

Hormone analyses

Serum estrogens were measured by RIA methods described elsewhere [19, 20]. All analyses were performed in duplicate, and samples from each patient were analyzed in the same run. SHBG was measured by a commercially available RIA kit (Farmos, Turku, Finland) as described elsewhere [18].

Serum level of MPA and MA were determined as described by us elsewhere [18, 21].

Statistical analysis

Hormone levels obtained in the two different test-situations were compared by the Wilcoxon Matched Pair Sign Rank Test, to provide two-tailed P-values.

RESULTS

Mean serum levels of estrogens, SHBG and progestin during steady-state treatment with MA and MPA are shown in Table 1. Individual serum levels of estrogens are given in Fig. 1, and SHBG and progestins are given in Fig. 2. Serum levels of MA (mean 315 ng/ml) were 3 times greater than serum levels of MPA (mean 108 ng/ml).

Treatment with MA caused slight reduction of serum E_2 and E_1 levels compared to treatment with MPA (mean reduction of 19 and 20%, $0.05 < P < 0.1$ and $P < 0.02$, respectively), and a substantial suppression of serum E_1S compared to treatment with MPA (mean suppression of 54%, $P < 0.005$). In contrast, the treatment with MPA caused a significant mean reduction of 69% in serum SHBG compared to MA treatment ($P = 0.009$).

DISCUSSION

The two oral drug schedules compared in this study (MA 160 mg o.d. and MPA 500 mg b.i.d.) are progestin schedule doses recommended for clinical use [1–10], although the need for such high doses has been challenged [22]. The only randomized study comparing MA 160 mg and MPA 500 mg × 2 found an identical response rate on the two drug schedules [23].

Table 1. Mean ± SD serum levels of estradiol, estrone, estrone sulfate, SHBG, MPA and MA in ten postmenopausal advanced breast cancer patients during sequential therapy with MPA and MA

Analysis	During MPA treatment	During MA treatment	P
Estradiol ($n = 10$) pmol/l	42.0 ± 11.4	33.3 ± 13.8	0.08
Estrone ($n = 10$) pmol/l	68.6 ± 13.1	54.9 ± 10.1	0.01
Estrone sulfate ($n = 10$) pmol/l	687.2 ± 548.7	318.4 ± 266.9	0.003
SHBG ($n = 7$) pmol/l	5.9 ± 1.8	19.0 ± 9.1	0.009
Progestin ($n = 8$) ng/ml	108 ± 63	315 ± 140	

Abbreviations used: SHBG = sex hormone binding globulin, MPA = medroxyprogesterone acetate, MA = megestrol acetate.

Serum levels of MPA and MA could be measured by the same RIA method since the antiserum raised against MPA-3-CMO-BSA crossreacts with MA [21]. The finding that MA 160 mg o.d. caused a 2–3-fold higher serum level than MPA levels following a 500 mg b.d. schedule, (Fig. 1, Table 1), is consistent with our previous findings [3, 18]. This difference in bioavailability could be the result of lower absorption possibly due to a more pronounced deactivation of MPA in the intestine [24], possibly by the intestinal bacterial flora.

In a previous study we reported that oral treatment with MA 160 mg o.d. or MPA 500 mg b.i.d. for advanced breast cancer could possibly influence serum levels of E_1S and SHBG to a different extent [18]. The present study was designed to explore this hypothesis further. Accordingly, serum hormones were measured in patients receiving both drug schedules sequentially. As both progestins given in this study may influence serum estrogens and SHBG [12, 18, 25], serum hormone levels found in this study cannot be compared to values in patients not receiving progestin treatment. However, serum levels of estrogens as well as SHBG found in this study are similar to values previously reported by us [18] and others [12, 25] in breast cancer patients receiving similar doses of progestin treatment.

This investigation confirms that oral treatment with MA in a dose of 160 mg o.d. causes a slight suppression of serum E_1 and possibly E_2, and a pronounced suppression of serum E_1S levels compared to oral treatment with MPA 500 mg b.i.d. In contrast, MPA treatment causes a selective reduction in the serum SHBG level compared to MA treatment. Such effects may have important clinical implications.

Evidence indicates that serum E_1S may be an important source of estrogens for the breast cancer cell [26, 27]. While this conjugate is considered to be biologically inactive *per se*, there is evidence that E_1S is taken up and metabolized to E_1 and E_2 inside the tumour cell [26, 27]. As MA treatment causes a selective suppression of serum levels of this steroid, such an effect could reduce estrogen supply to the breast tumour cells. The mechanism behind this alteration remains obscure, and further investigations are needed to confirm whether MA reduces the serum E_1S level by stimulating its metabolism or reducing its production rate.

While MA causes a minor suppression of serum E_2 compared to MPA, MPA treatment causes a pronounced suppression of serum SHBG. As E_2 is bound to SHBG, free serum E_2 could be higher on MPA than on MA treatment.

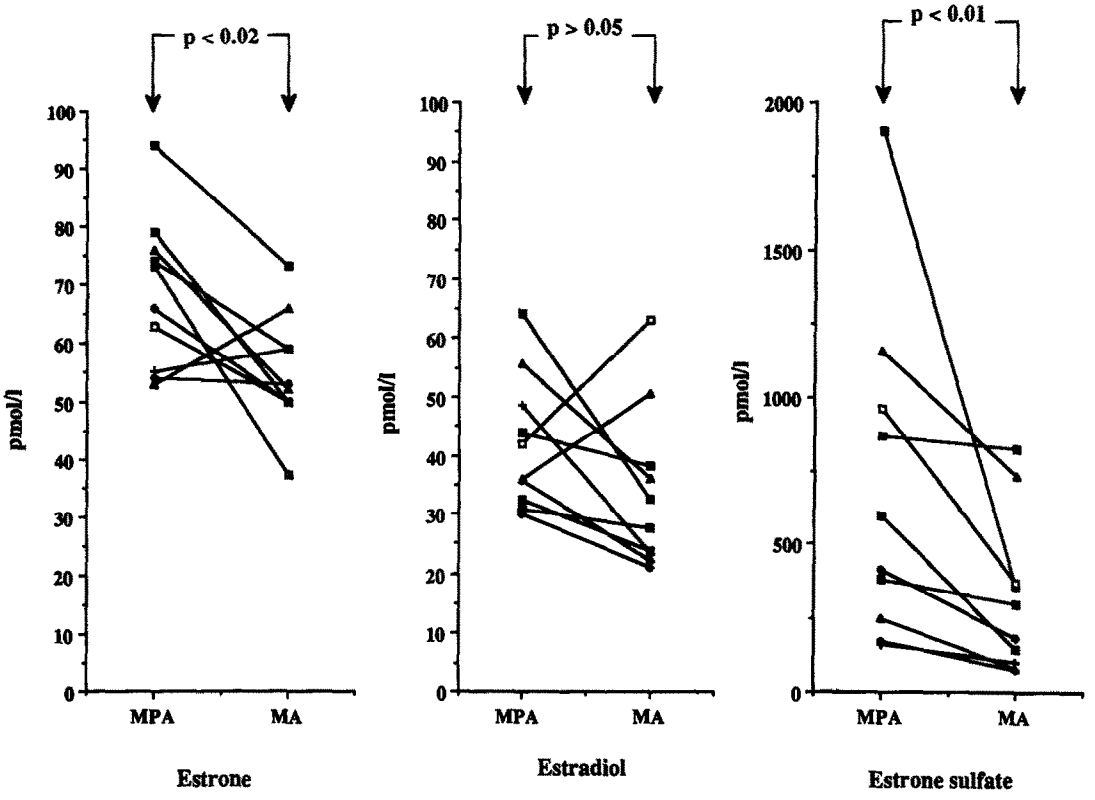

Fig. 1. Individual serum levels of estradiol ($n = 10$), estrone ($n = 10$) and estrone sulfate ($n = 10$) during sequential treatment with medroxyprogesterone acetate (MPA) and megestrol acetate (MA).

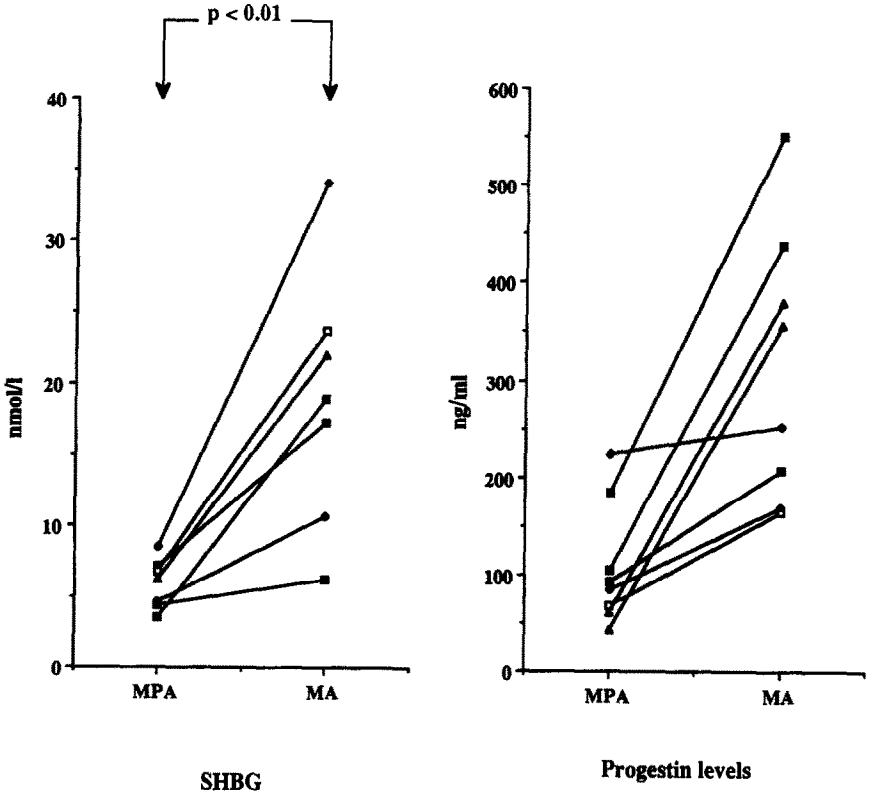

Fig. 2. Individual serum levels of progestins (MPA and MA) ($n = 8$) and SHBG (sex hormone binding globuline) ($n = 7$) during sequential treatment with medroxyprogesterone acetate (MPA) and megestrol acetate (MA)

SHBG synthesis is suppressed by androgens and stimulated by estrogens [28]. In a previous study [18] we found no great difference in serum testosterone and androstendione levels in patients during treatment with MA 160 mg o.d. or MPA 500 mg b.i.d. In this study we found MA to suppress serum estrogens more than treatment with MPA. Accordingly, the suppression of serum SHBG after changing drug schedule from MA to MPA cannot be secondary to any alteration in serum androgen or estrogen levels. Possibly, MA and MPA may have different direct influence on hepatic SHBG synthesis.

An important question is whether the influence of MA and MPA on serum estrogens may be part of their mechanism of action. Assuming serum E_1S to be a major prohormone for active estrogens to the tumour cell [26, 27], any suppressing effect on this estrogen could be beneficial. Findings that some patients may respond to one drug following relapse on the other drug, suggest that different biochemical mechanisms of action are involved [2, 3]. Randomized trials comparing the response rate to MPA and MA treatment with a crossover design may be warranted.

The two drugs were administered in markedly different doses, but due to a possibly better bioavailability of MA a higher serum level is achieved. This can probably partly explain the different levels of E_1S, but not the effect on SHBG during MPA and MPA treatment. Studies with dose escalating treatment with the two progestins is warranted.

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