*Eur J Cancer Clin Oncol*, Vol. 20, No. 1, pp. 33–40, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00


# Treatment of Metastatic Breast Cancer Patients with Different Dosages of Megestrol Acetate; Dose Relations, Metabolic and Endocrine Effects*

J. ALEXIEVA-FIGUSCH,† M. A. BLANKENSTEIN,† W. C. J. HOP,† J. G. M. KLIJN,† S. W. J. LAMBERTS,‡ F. H. DE JONG,‡ R. DOCTER,‡ H. ADLERCREUTZ§ and H. A. VAN GILSE†

†*Department of Internal Medicine and Clinical Endocrinology, Biochemistry and Biostatistics, Rotterdamsch Radio-Therapeutisch Instituut, Groene Hilledijk* 301, 3075 *EA Rotterdam, The Netherlands,* ‡*Department of Internal Medicine III and Clinical Endocrinology, Erasmus University, Rotterdam, The Netherlands and* §*Department of Clinical Chemistry, University of Helsinki, Finland*

**Abstract**—*Megestrol acetate (MA) is of therapeutic value in breast cancer patients. This study was designed to evaluate the effects of different dosages of MA on endocrine events potentially influenced by the drug in relation to plasma level of MA and clinical effects in patients with advanced breast cancer. Eighteen postmenopausal patients were randomly distributed over six groups to receive daily* 90, 180 *or* 270 mg *of MA (Niagestin®) orally in a cross-over study consisting of* 3 *periods of* 6 weeks. *Complete remission was observed in* 1 *patient, partial remission in* 9, *no change in* 4 *and failure in* 4 *patients. During the* 18 weeks *of treatment plasma levels of MA gradually increased, irrespective of the dose administered. Significant rises of the basal and TRH-stimulated plasma PRL and basal insulin levels were observed, whereas LH and FSH, estradiol, SHBG and the pituitary–adrenal axis were suppressed. None of these metabolic effects showed a correlation with the clinical response. We concluded that treatment of metastatic breast cancer with* 180 mg *MA/*day *is effective and causes minimal adverse effects.*

## INTRODUCTION

THE SYNTHETIC progestin megestrol acetate (MA) (17α-acetoxy-6α-methyl-pregna-4,6-diene-3,20-dione) is effective in the treatment of patients with advanced breast cancer [1, 2]. The mechanism through which MA exerts its effects on mammary tumors is unclear. The drug has been reported to display progestin-, glucocorticoid-like and androgenic properties [3, 4]. An attempt to explain the action of MA through a progesterone-receptor-mediated increase in estradiol dehydrogenase activity in the tumor specimens of postmenopausal breast cancer patients was unsuccessful. Only a very low affinity of MA to estrogen receptors was observed, but the drug bound relatively well to progesterone, androgen and glucocorticoid receptors [5]. This study was designed to evaluate the effect of oral administration of 3 different dosages of MA on the plasma concentrations of gonadotropins, prolactin (PRL), growth hormone, estradiol, sex hormone binding globulin (SHBG), insulin and glucose, on adrenocortical function and to investigate relationships between plasma levels of MA and clinical responses during the treatment of metastatic breast cancer.

Accepted 11 June 1983.
*Partly presented at VIII[th] Dutch-British Endocrine Meeting 25th–27th August 1982, Noordwijkerhout, The Netherlands.

## MATERIALS AND METHODS

*Patients*

Eighteen patients with evaluable and measurable advanced breast cancer, who had not yet otherwise been treated, were selected for this study. Informed consent to participate in this study was obtained from all patients. All were more than 2 yr after their natural menopause and between 54 and 75 yr of age. All patients except one (ascites with gastrointestinal discomfort) were in good general condition, without gastrointestinal-, hepatic- or renal disease, diabetes mellitus or malabsorption. The patients received three 6-week treatments with daily doses of 90, 180 and 270 mg of megestrol acetate (Niagestin®,

supplied by NOVO, Denmark) in a cross-over regimen. Medication was taken orally with 8-hr intervals (07.00–15.00–23.00). When definite progression of metastatic cancer occurred, the drug was withdrawn. At the start and end of each treatment period, routine clinical and biochemical investigations were performed. In addition, blood was collected for the estimation of the plasma concentration of MA (at 14.30), basal gonadotropins, growth hormone, estradiol, SHBG, prolactin (PRL) and TSH before and after administration of 200 μg of TRH intravenously, 11-deoxycortisol before and after 6 × 750 mg of metyrapone and insulin and glucose during a glucose tolerance test (100 g of glucose orally). Fifteen fully evaluable patients completed the study, which allowed statistical analysis with respect to the endocrine parameters. Clinical evaluation was done after each period of 6 weeks based on UICC criteria of response with regard to visceral, osseous and soft tissue metastases [6].

*Laboratory methods*

For the radioimmunological assay of MA in plasma, an anti-MPA-3-(*o*-carboxymethyl)oxime–bovine serum albumin serum, which cross-reacts extensively with MA, was used [7, 8]. Blood samples were taken before and at the end of each treatment period just before the administration of the drug. LH and FSH were measured by specific radioimmunoassay, using materials from KABI (Stockholm, Sweden). Results were expressed as U/l; normal values for postmenopausal women were for LH more than 21.0 and FSH more than 5.0 U/l respectively. Plasma PRL levels were determined by a double-antibody radioimmunoassay method using the kit from IRE (Antwerp, Belgium). One nanogram of the standard employed is equivalent to 1 ng of the standard VLS/1 of the NIH. The upper limit of normal in women is 15 ng/ml. Blood samples were taken at 0, 20, 30, 60 and 120 min after 200 μg of TRH given i.v. before and at the end of each treatment period (at 09.00–11.00 a.m.). In addition, TSH estimation was performed. TSH was determined by radioimmunoassay, using the kit from DPC (U.S.A.). Normal values are lower than 10 μU/ml. Plasma levels of growth hormone were determined by a double-antibody radioimmunoassay using the CEA kit (Paris, France). Normal basal fasting levels are 1–5 ng/ml. Estradiol was measured by radioimmunoassay [9]. 11-Deoxycortisol (compound S) was estimated in plasma by a competitive protein binding assay following a simple solvent extraction before and 24 hr after 6 × 750 mg metyrapone given orally. The normal value after metyrapone exceeds 15 μg/100 ml [10]. The capacity of the serum to bind [$^3$H]-dihydrotestosterone was used as a measure for the concentration of SHBG and was determined by agar gel electrophoresis [11]. Total immunoreactive insulin was determined using ethanol extraction, whereby antibody-bound immunoreactive insulin is dissociated and separated together with the free insulin from the serum proteins and antibodies [12]. Glucose was estimated enzymatically.

*Statistics*

Dose-effects for the various parameters were in the first instance investigated by multivariate methods appropriate for change-over designs [13]. These methods, in addition to dose-effects, allow for individual differences, differences between the 3 treatment periods and residual effects from the treatment with a particular dose in the previous period for periods 2 and 3. These analyses were supplemented by standard non-parametric tests (the Friedman test, the signed rank test and the rank sum test). *P* values given in the text and figures arose from these non-parametric tests.

## RESULTS

*Clinical response*

Complete remission after 18 weeks was achieved in 1/18, partial remission in 9/18 and stable disease in 4/18 patients while progression occurred in 4/18 patients. Favourable effects of MA have been found in all types of metastases, e.g. in soft tissue, bone and viscera. No patient had liver metastases. During the study period no

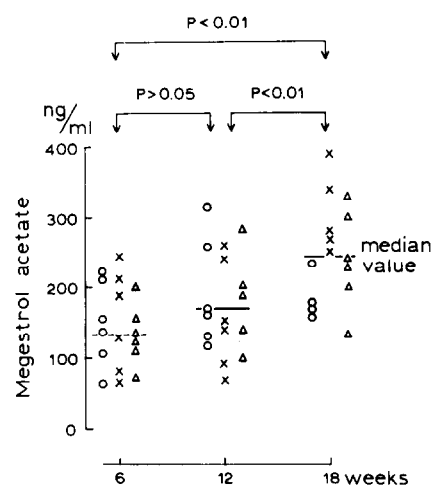


*Fig. 1. Concentration of megestrol acetate (MA) in plasma of breast cancer patients treated with different daily doses of MA for 3 periods of 6 weeks. Individual values are given as a function of the time after the start of the experiment, and with respect to the dosage of MA received during the 6 weeks immediately preceding the blood sampling.* O : 90 mg/day; × : 180 mg/day; Δ 270 mg/day.

*Table 1. Plasma concentrations of megestrol acetate and endocrine parameters in patients with metastatic breast cancer responsive (CR+PR) or refractory (NCH+F) to treatment with megestrol acetate*

| Mean value of plasma concentration at 6 weeks | Responders ($n=10$) | Non-responders ($n=8$) | $P$ |
|---|---|---|---|
| Megestrol acetate (ng/ml) | 125 | 174 | 0.1 |
| Basal prolactin (ng/ml) | 10.7 | 18.6 | 0.1 |
| Basal TSH (μU/ml) | 7.1 | 5.1 | 0.2 |
| Basal growth hormone (μg/l) | 4.4 | 9.3 | 0.4 |
| LH (U/l) | 20.8 | 15.0 | 0.8 |
| FSH (U/l) | 15.9 | 10.0 | 0.9 |
| Estradiol (pmol/l) | 57.8 | 67.0 | 0.06 |
| 11-Deoxycortisol (μg/100 ml) after metyrapone | 1.9 | 2.8 | 0.9 |
| SHBG (nmol/l) | 57.8 | 52 | 0.5 |
| Basal insulin (μU/ml) | 23.1 | 20 | 0.4 |
| Basal glucose (mmol/l) | 5.1 | 4.8 | 0.4 |

adverse effects of the drug have been observed; MA was tolerated excellently at all 3 dosages.

*Megestrol acetate concentration in plasma*

The concentrations of MA in plasma increased with time during the treatment (Fig. 1, $P<0.01$). No relation could be demonstrated between dose and plasma level, even if corrected for body surface. Therefore the results for the different dosages were combined to give median values of 134, 170 and 243 ng/ml after 6, 12 and 18 weeks respectively. No relation to the clinical response has been found; plasma levels of failures did not differ from those in responders (Table 1).

In 5 other patients who gradually discontinued long-term treatment with 180 mg MA (within 18 days), plasma levels of MA 3 days after complete cessation appeared decreased from 243 ± 25 (S.E.M.) during the steady state to 17 ± 7 ng/ml.

*Endocrine effects*

*Prolactin.* Before the start of the treatment basal plasma PRL levels were normal in all patients, while there was a normal reaction of PRL to TRH (Fig. 2). During treatment with MA the mean basal PRL levels increased significantly from 7.1 ± 0.8 to 13.9 ± 2.2 ng/ml (Table 2, $P<0.001$). There was also a hyper-response of PRL to TRH during treatment with MA. The range of the response of plasma PRL to TRH varied widely (Fig. 2).

*TSH and growth hormone.* Plasma levels of TSH were measured before and after TRH stimulation. There was no change in the basal and stimulated TSH levels during MA treatment. Basal mean TSH level was 6.6 ± 1.8 μU/ml before treatment and 6.2 ± 0.6 μU/ml after 6 weeks of treatment. In addition, TSH response to TRH was not altered during MA treatment. Basal

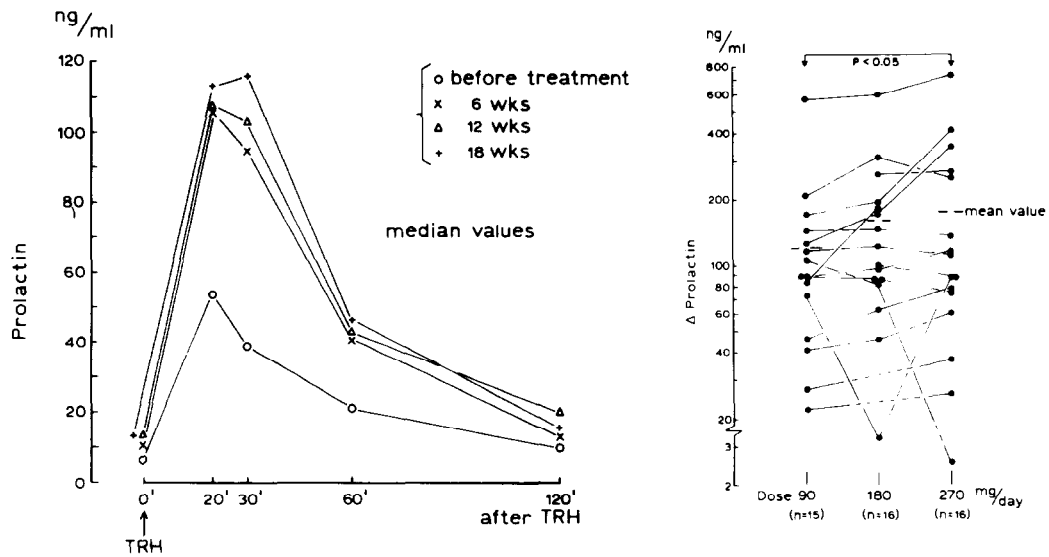


*Fig. 2. Concentration of prolactin (PRL) in plasma of breast cancer patients treated with different dosages of megestrol acetate (MA) before and after injection of 200 μg TRH as a function of time after administration of TRH (left) and dosage of MA received during 6 weeks prior to the test (right). Δ prolactin: increase in PRL 20 min after injection of TRH.*

*Table 2. Response of plasma prolactin to TRH administration (200 μg i.v.) in patients with metastatic breast cancer before and after a 6-week treatment with megestrol acetate*

| Time after TRH (min) | Prolactin (ng/ml) (mean ± S.E.M. $n = 18$) Before treatment | After treatment | $P$ |
|---|---|---|---|
| 0 | 7.1 ± 0.8 | 13.9 ± 2.2 | 0.001 |
| 20 | 78.9 ± 15.2 | 157.2 ± 41.1 | NS |
| 30 | 60.5 ± 11.0 | 128.4 ± 29.4 | NS |
| 60 | 28.4 ± 4.2 | 51.5 ± 9.3 | NS |
| 120 | 12.1 ± 2.4 | 17.0 ± 2.3 | 0.005 |

plasma growth hormone was not influenced by the use of MA. The mean value before the treatment was 5.8 ± 1.2 μg/l; after a 6-week period the plasma concentration of growth hormone was 6.4 ± 1.8 μg/l.

*Gonadotropins.* All doses of MA used caused a significant decrease ($P < 0.001$) of the basal plasma concentrations of LH and FSH after 6 weeks (Fig. 3). Before treatment the mean concentrations of LH and FSH were 46.6 ± 4.5 and 28.0 + 3.0 U/l respectively. After 6 weeks of treatment these mean values were 18.4 ± 2.9 and 13.4 ± 2.6 U/l respectively. The inhibition of gonadotropin levels was identical with all three doses of MA without exception during the whole period.

*Estradiol and SHBG.* All doses of MA caused a significant decrease ($P < 0.001$) of plasma estradiol concentrations after 6 weeks of treatment (Fig. 3), which persisted throughout the whole treatment period. The mean concentration was 79 ± 6.3 pmol/l before and 62 ± 2.5 pmol/l after the 6-week period. This inhibition did not differ in the three dose-groups.

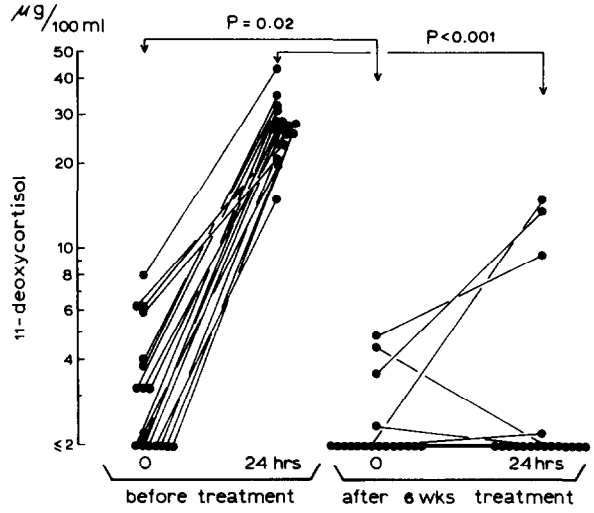


*Fig. 4. Concentration of 11-deoxycortisol (compound S) before and 24 hr after the start of oral administration of 6 × 750 mg of metyrapone in patients with advanced breast cancer. The metyrapone test was performed before and after a 6-week treatment course with megestrol acetate.*

A significant decrease ($P < 0.001$) in the concentration of SHBG was found after 6 weeks (Fig. 3). During the study periods a weak correlation ($P < 0.02$) between SHBG concentration and the dose administered appeared to be present.

*11-Deoxycortisol (compound S).* Plasma levels of 11-deoxycortisol before as well as after 6 × 750 mg metyrapone orally showed a significant decrease during MA therapy (Fig. 4). During treatment with 90 mg daily 3 out of 6 patients still showed a detectable increase of plasma compound S (to 9.0, 14.9 and 13.6 μg/100 ml), while these levels remained completely suppressed after metyrapone administration during treatment with 180 and 270 mg MA/day.

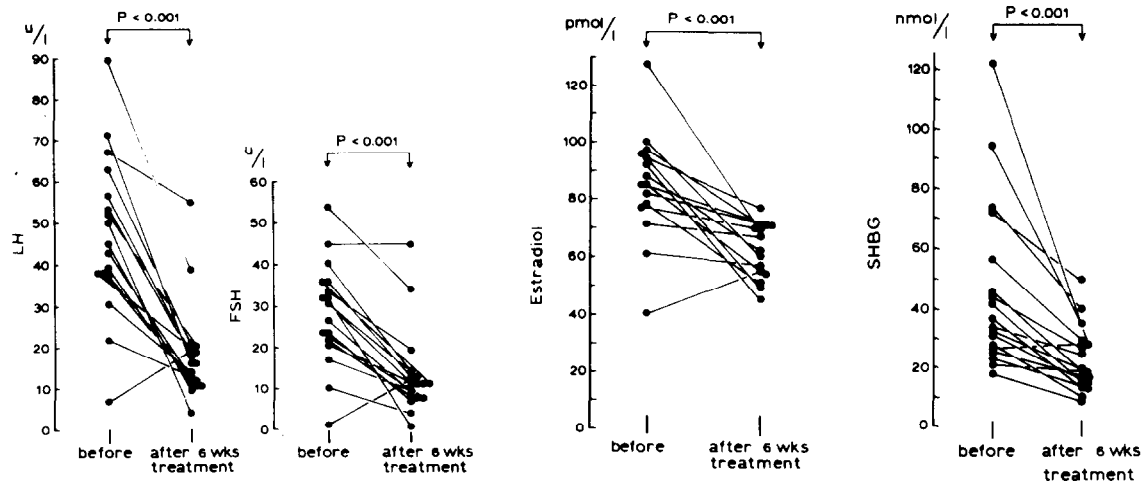


*Fig. 3. Concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol ($E_2$) and sex hormone binding globulin (SHBG) in plasma of patients with advanced breast cancer before and after a 6-week treatment course with megestrol acetate.*

*Table 3. Results of a prolonged glucose tolerance test in patients with metastatic breast cancer before and after a 6-week treatment course with megestrol acetate (MA)*

| | Glucose (mmol/l) | | | | Insulin (μU/ml) | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 hr | 1 hr | 2 hr | 5 hr | 0 hr | 1 hr | 2 hr | 5 hr |
| Before treatment | 5.5 | 9.7 | 8.4 | 4.3 | 17 | 122 | 147 | 20 |
| | (0.2) | (0.6) | (0.7) | (0.2) | (1.6) | (21.4) | (23.7) | (2.7) |
| After 6 weeks of MA | 4.9 | 9.7 | 8.8 | 4.4 | 22 | 162 | 203 | 32 |
| | (0.1) | (0.8) | (0.5) | (0.2) | (1.7) | (30.3) | (27.2) | (6.4) |
| *P* | 0.002 | | | | 0.01 | | | 0.04 |
| After 6 weeks of: | | | | | | | | |
| 90 mg of MA | 5.0 | 9.7 | 8.6 | 4.8 | 18 | 127 | 155 | 19 |
| | (0.1) | (2.1) | (0.9) | (0.3) | (2.8) | (45.7) | (36.6) | (4.2) |
| 180 mg of MA | 4.7 | 8.8 | 8.7 | 4.4 | 22 | 96 | 151 | 54 |
| | (0.2) | (0.7) | (0.7) | (0.6) | (3.4) | (11.7) | (18.1) | (24.3) |
| 270 mg of MA | 5.2 | 10.5 | 9.1 | 4.2 | 26 | 256 | 305 | 34 |
| | (0.2) | (1.1) | (0.9) | (0.3) | (3.3) | (72.8) | (58.8) | (7.4) |

Results are expressed as means ($n = 18$).
Standard errors of the mean (S.E.M.) are given in parentheses.

*Insulin and glucose*

Insulin and glucose in plasma were estimated before and at 1, 2 and 5 hr after oral administration of 100 g of glucose. Mean basal plasma glucose and insulin levels before the treatment were 5.5 mmol/l and 17 μU/ml respectively (Table 3). After 6 weeks of MA treatment the mean basal glucose was significantly decreased ($P < 0.002$), whereas the concentration of insulin before ($P < 0.01$) and 5 hr after ($P < 0.04$) glucose administration was significantly increased. The increase of basal plasma insulin appeared dose dependent ($r_s = 0.71$, $P = 0.002$).

## DISCUSSION

The results of this study demonstrate that treatment of metastatic breast cancer with megestrol acetate (MA) induces multiple changes in the hormonal environment of the tumor. The drug caused significant increases in basal plasma prolactin and insulin and decreases in basal plasma LH, FSH, estradiol and SHBG, and a suppression of the pituitary-adrenal axis. Some of these parameters changed slightly in a dose-dependent way. There was no relation between these changes and the clinical response.

The study was designed as a cross-over regimen in order to obtain extensive information from a limited number of patients. Treatment periods of six weeks were chosen since this period is the minimum time span required for the evaluation of the clinical reponse. Based on data from the available literature obtained after administration of a single dose of 60 mg of MA [14–16], it was anticipated that steady-state plasma levels of MA would be achieved very soon after initiation of treatment or cross-over to a different dose. The excretion of a single dose of MA has been reported to be essentially complete within 4–7 days [17]. Our observation that plasma MA 3 days after complete withdrawal was decreased by 93 ± 2% of the steady-state level further justified the choice of a 6-week cross-over interval. In contrast to our expectation, however, we found an accumulation of MA in the plasma of the patients, irrespective of the order in which the different dosages were administered (Fig. 1). Moreover, for the doses used, no relation was found between the plasma concentration of MA and the clinical response (Table 1). Based on these observations, an exact therapeutic level for MA cannot be derived from plasma levels of MA alone. The lowest plasma level of MA associated with an objective response was 65 ng/ml. When the observed metabolic and endocrine effects are taken into account an optimal dose with minimal adverse effects can be defined. Treatment with a daily dose of 270 mg of MA caused an undesirably high basal concentration of insulin, whereas treatment with 90 mg daily was not sufficient to completely suppress the pituitary-adrenal axis. Such a suppression seems to be desirable, because a glucocorticoid effect may be important for the mechanism of action. Therefore, we advocate the use of 180 mg of MA/day. This dose is in agreement with the doses reported by other investigators [2, 18, 19]. Our results are the first to provide a rationale for this dose. When compared to the structurally related progestin medroxyprogesterone acetate (MPA), which is also frequently used, MA has several

advantages. Firstly, much lower oral doses of MA than of MPA are required [20, 21] to reach therapeutic levels of the drugs (roughly, above 100 ng/ml). This is probably due to the presence of a C-6,7 double bond in the MA molecule, which prevents it from breakdown by the intestinal bacterial enzymes [22, 23]. A second advantage of MA is the oral way of application in contrast to MPA, which is routinely administered intramuscularly and thus may cause local irritation. Thirdly, the intramuscular administration of MPA leads to the formation of a depot which may interfere with the next kind of treatment at the time of progression [24–26].

The metabolic effects of MA observed in this study are similar to those reported for high-dose progesterone and MPA [27–34]. Our results are in agreement with a hypothesis in which the primary effect of MA would be an effect on hypothalamic-pituitary function resulting in decreased secretion of ACTH, LH, FSH and estradiol and increased secretion of prolactin. Animal experiments, however, were not unequivocal since administration of MPA or MA to rats bearing DMBA-induced mammary tumors [35] or estrogen-induced prolactinomas [36] caused a decrease in the circulating prolactin. Atrophy of pituitary adrenocorticotrophs after administration of progestins [35] is probably the explanation for the suppression of the pituitary-adrenal axis, as found during long-term treatment with pharmacological doses of corticosteroids. The observed decrease in the plasma concentration of SHBG may be attributed to the (anti-) androgenic properties of MA [37, 38].

The observed increase in basal plasma insulin levels was not unexpected since progestins have been reported to induce hyperinsulinaemia [39–42]. This is possibly a direct action on pancreatic islets [43], whereas an additional glucocorticoid-like effect on gluconeogenesis cannot be excluded. Progestins promote glycogen storage in the liver and stimulate deposition of body fat. Paradoxically, they antagonize the effects of insulin on glucose metabolism in adipose tissue and skeletal muscle [44–46]. The most relevant expression of these actions appears to reside in the physiology of normal pregnancy. Based on our observations, it is difficult to identify the increase of insulin as a primary or secondary effect. In conclusion, megestrol acetate induced multiple endocrine and metabolic changes, which could be attributed to the progestational, (anti-)androgenic and glucocorticoid properties of the drug. None of these changes, nor the plasma concentration of MA, were related to the clinical response. This may be explained by the occurrence of hormone-resistant tumor. Decrement of plasma estradiol may be important for hormone-dependent tumors, but we found no clear relationship between response of the tumors and the presence of the estrogen rceptors [5]. Also, estrogen-receptor-negative tumors can respond to MA. Besides an indirect effect, MA may have a direct cytotoxic effect because of glucocorticosteroid properties of the drug. On the other hand, high doses of progestins cause at least twice as many regressions as comparable doses of glucocorticoids (roughly, 35 vs 15%). So a glucocorticoid-like anti-tumor effect cannot be the sole mechanism of action. On the basis of a relation with the androgen receptor [5, 38], an extra anti-tumor effect may be attributed to the (anti-)androgenic effect of MA.

**Acknowledgements**—The authors thank Mrs. M. S. Christensen, NOVO, Copenhagen, Denmark for support, Mr. P. van Assendelft and Mrs. A. Sugiarsi for their assistance, and the members of the Breast Cancer Group for contributing their patients.

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