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Endocrine Effects of the Combination of Megestrol Acetate and Tamoxifen in the Treatment of Metastatic Breast Cancer

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Abstract—*Six postmenopausal patients with metastatic breast cancer, who responded to megestrol acetate after* 6 weeks *of treatment, were treated with the combination of megestrol acetate and tamoxifen during the next* 6 weeks. *The study was oriented towards the endocrine effects of this combination since it was known from our previous studies that megestrol acetate induces suppression of serum gonadotropins and of the pituitary-adrenal axis, a decrease of peripheral concentration of SHBG and of estradiol, and an increase of basal and TRH-stimulated plasma prolactin concentration. Tamoxifen, on the other hand, produces a decrease of prolactin and gonadotropins, whilst estradiol remains unaffected. Although the role of prolactin in the growth of human breast cancer has not been elucidated yet and there is no unequivocal evidence that a decrease in plasma prolactin could be of benefit for treatment of metastatic breast cancer, we tested whether addition of tamoxifen to the treatment regimen eliminated megestrol acetate-induced hyperprolactinaemia. The results show that addition of tamoxifen to megestrol acetate treatment annihilated the hyper-response of prolactin to TRH stimulation, while basal prolactin levels remained unaffected. The negative effect on plasma gonadotropin concentration appeared to be amplified, while estradiol and cortisol were not affected and SHBG increased. The results of these endocrine investigations merit a further study, directed to antitumor effects of this combination modality.*

INTRODUCTION

APPROXIMATELY 30% of patients with metastatic breast cancer will respond to a single-agent endocrine therapy. The mechanism through which tumor regression is achieved has not been completely resolved for any modality of endocrine treatment. Anti-estrogens are thought to act mainly by interference of the action of estrogens on estrogen target cells [1, 2]. Progestins, on the other hand, may act through their progestagenic but also through glucocorticoid and/or (anti-) androgenic properties [3]. Based on these differences in the presumed mechanism of action of anti-estrogens and progestins, an additional benefit might be expected from a combination of these two modalities.

Iacobelli *et al.* [4] studied the interaction of the progestin medroxyprogesterone acetate (MPA) and the anti-estrogen tamoxifen (TAM) on the growth of the human breast cancer cell line CG-5 (an estrogen-supersensitive variant of the MCF-7 cell line). They observed that addition of MPA and TAM together caused a stronger inhibition of cell growth than either agent alone. This potentiating effect might be achieved through steroid receptors. The biosynthesis of the progestin receptor is known to be under estrogenic control. Anti-estrogens deplete cytoplasmic estrogen receptor sites but also stimulate the synthesis of cytoplasmic progesterone receptors [5, 6]. In addition, for the action of synthetic progestins with androgenic and glucocorticoid properties the presence of other than estrogen and

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progestin receptors could be important [7, 8]. Alternatively, the potentiating effect of progestin and anti-estrogen treatment might be attributed to differences in their influences on the endocrine system. Both agents induce a decrease in the circulating concentrations of gonadotropins. Megestrol acetate (MA) induces a suppression of the pituitary–adrenal axis, a decrease in the circulating levels of sex-hormone-binding globulin (SHBG) and estradiol and an increase in the plasma concentration of prolactin (PRL), both under basal conditions and after TRH stimulation [3]. Tamoxifen (TAM) has been reported to cause an increase of plasma SHBG and a decrease of PRL while circulating estradiol levels remain unaffected in postmenopausal women [9–11].

Therefore it may be expected that a combination of progestin and anti-estrogenic drugs further suppresses the level of circulating gonadotropins, whereas the effects of progestins on SHBG and PRL are partly eliminated by antiestrogens. The present study was undertaken to evaluate this possibility.

MATERIALS AND METHODS

Seven patients with evaluable and measurable metastatic breast cancer, who were not yet treated otherwise for their metastatic disease, were selected for this study. All patients gave informed consent before participating in the study. They all were more than 4 yr post-menopausal (two of them after adjuvant ovariectomy) and between 43 and 76 yr of age. All patients were in good general condition, without gastrointestinal, hepatic or renal disease, diabetes mellitus or malabsorption. Five patients had bone metastases and lung metastases were observed in two patients. None of the patients had soft tissue metastases only. The patients received a 6-week treatment with megestrol acetate (MA) 180 mg daily orally, and after the clinical assessment of the response [12] only the six responders continued the treatment with MA in combination with tamoxifen (TAM) 40 mg daily orally during the next period of 6 weeks.

Routine clinical and biochemical investigations were performed at the start of the study, after 6 weeks of treatment with MA and after 6 weeks of treatment with the combination of MA + TAM. In addition, blood was collected for the estimation of estradiol, SHBG, cortisol, LH and FSH. PRL and TSH were estimated before and after administration of 200 μg TRH intravenously. PRL, TSH and estradiol were measured with commercial radioimmunoassay kits and SHBG by agar gel electrophoresis as described before [3]. Normal values: PRL, <15 ng/ml; TSH, <5 μU/ml. Cortisol was measured by RIA, using the gammacoat kit from Clinical Assays (Cambridge, MA, U.S.A.); normal values at 9.00 a.m. were >220 nmol/l. LH and FSH levels were estimated using the Coat RIA solid phase radioimmunoassays from Biomerieux (Marcy l'Etoile, France). Results of these assays are expressed as ng/ml; 1 ng LH corresponds to 5 mIU (MRC 68/40) and 1 ng FSH corresponds to 2.7 mIU (MRC 78/579). The plasma level of tamoxifen was measured by thin-layer densitometry before and 6 weeks after the addition of TAM to MA [13].

During the whole period of 12 weeks there was no change in other medications in order to avoid any influence on the endocrine parameters.

RESULTS

The results obtained are summarized in Table 1 and indicate that the addition of tamoxifen to megestrol acetate annihilated the effects of MA on TRH-induced prolactin release and on SHBG. The effects of MA on basal PRL and cortisol levels appeared to be unaffected by addition of TAM, whereas the suppressive effect of MA on gonadotropins appeared to be amplified. Estradiol values were not affected by addition of TAM to MA. Because of a large heterogeneity observed in the magnitude of the parameters studied, the results were expressed not only in absolute values, but also as a percentage of the pretreatment values (Table 1). In addition, results of individual patients are shown in Figs 1 and 2. Sera, obtained after 6 weeks of MA treatment, served as blanks for estimation of TAM serum levels since it was not known whether MA or its metabolites are capable of interfering with the TAM assay. These blanks were essentially zero and thus the possibility of interference was ruled out. The combination was excellently tolerated without any signs of side-effects, e.g. glucose tolerance deterioration, fluid retention or increase in blood pressure.

DISCUSSION

The present study confirms the results obtained in a previous series of breast cancer patients in which the endocrine effects of MA treatment were studied [3]. The hyper-response of prolactin to TRH stimulation on MA treatment was eliminated by addition of TAM to MA, while basal PRL level tended to be lower in patients receiving the combination of both drugs (Table 1, Fig. 1). There is no unequivocal evidence, however, that lowering of plasma PRL concentrations in itself is of benefit in the treatment of metastatic breast cancer. PRL could be involved, at least in a supportive role, in the development and growth of breast cancer, not only in animal models but also in humans [14, 15]. Even though conflicting

Table 1. *Effect of administration of megestrol acetate (MA) alone and in combination with tamoxifen (MA + TAM) on endocrine parameters in postmenopausal patients with metastatic breast cancer (results are given as means ± S.D.,* n = 6)

Parameter	Before treatment Absolute	Before treatment % of pretreatment value	After 6 weeks MA Absolute	After 6 weeks MA % of pretreatment value	After 6 weeks MA + 6 weeks MA + TAM Absolute	After 6 weeks MA + 6 weeks MA + TAM % of pretreatment value
Basal PRL (ng/ml)	6.6 ± 3.5	100	10.0 ± 4.3	165 ± 79*	10.0 ± 7.3	153 ± 74
PRL (ng/ml) (20′ after TRH)	44.9 ± 16.7	100	66.9 ± 29.1	147 ± 21*	40.3 ± 15.2†	96 ± 36†
LH (ng/ml)	6.9 ± 2.4	100	3.3 ± 1.6*‡	49 ± 26*‡	1.5 ± 0.7*	22 ± 11*
FSH (ng/ml)	18.9 ± 6.2	100	7.8 ± 4.7*	41 ± 20*	3.4 ± 1.8*	19 ± 8†
Estradiol (pmol/l)	53 ± 21	100	41 ± 10	90 ± 43	40 ± 24	75 ± 22
SHBG (nmol/l)	19 ± 14	100	14 ± 16	66 ± 15*	23 ± 15	141 ± 99†
Cortisol (nmol/l)	431 ± 159	100	97 ± 141*	19 ± 26*	125 ± 138*	35 ± 45
Tamoxifen (nmol/l)	N.D.		0	N.D.§	610 ± 125†	N.D.

*$P < 0.05$ vs pretreatment value (Wilcoxon's test).
†$P < 0.05$ vs value obtained after MA alone (Wilcoxon's test).
‡$n = 4$.
§N.D. = not determined.

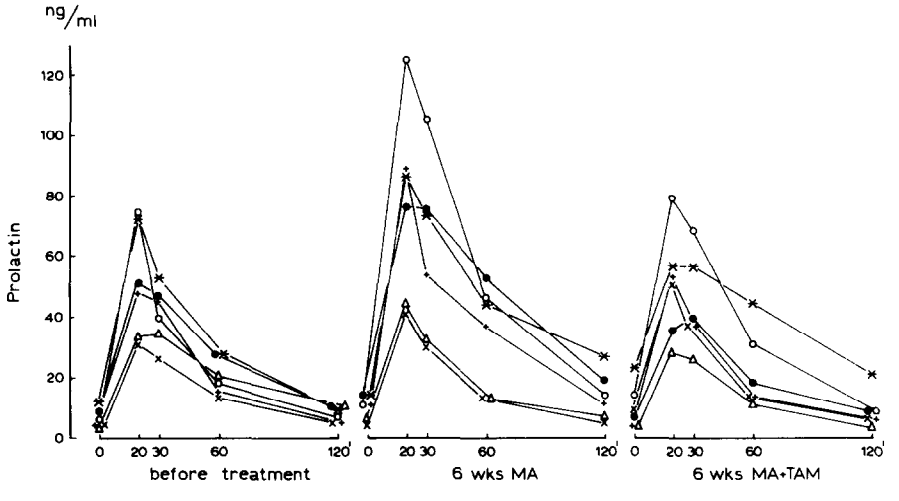

Fig. 1. *The concentration of prolactin in plasma before and after administration of* 200 μg *TRH in six breast cancer patients before therapy, after* 6 weeks *of megesterol acetate therapy (MA) and after* 6 weeks *of the combination of megestrol acetate and tamoxifen (MA + TAM). Different symbols have consequently been used for the same patient in Figs* 1 *and* 2.

data exist about the involvement of prolactin in malignant breast tumor growth in humans, the presence of prolactin receptors in human breast tumors and the relation between prolactin and steroid hormone receptors indirectly supports an importance of this hormone as a growth factor in malignant neoplasia [16–20]. The inhibition of PRL secretion with the PRL-release inhibitor bromocriptine has recently been reported as a prophylaxis for spontaneous mammary tumorigenesis in rats [21] and of DMBA-induced mammary tumors in rats and mice [22]. TAM produced the same inhibition of tumor growth, while a further inhibition occurred when both TAM and bromocriptine were combined [23]. In human breast cancer bromocriptine as a single drug was ineffective [24] while after the addition of bromocriptine to medroxyprogesterone acetate a better response was suggested [25]. The influence of combination treatment of a steroid hormone and a prolactin inhibitor demands further investigation.

A further lowering of gonadotropins elicited by TAM could have an additional inhibitory effect to that of MA. All six patients showed a decrease during MA therapy in plasma SHBG concentra-

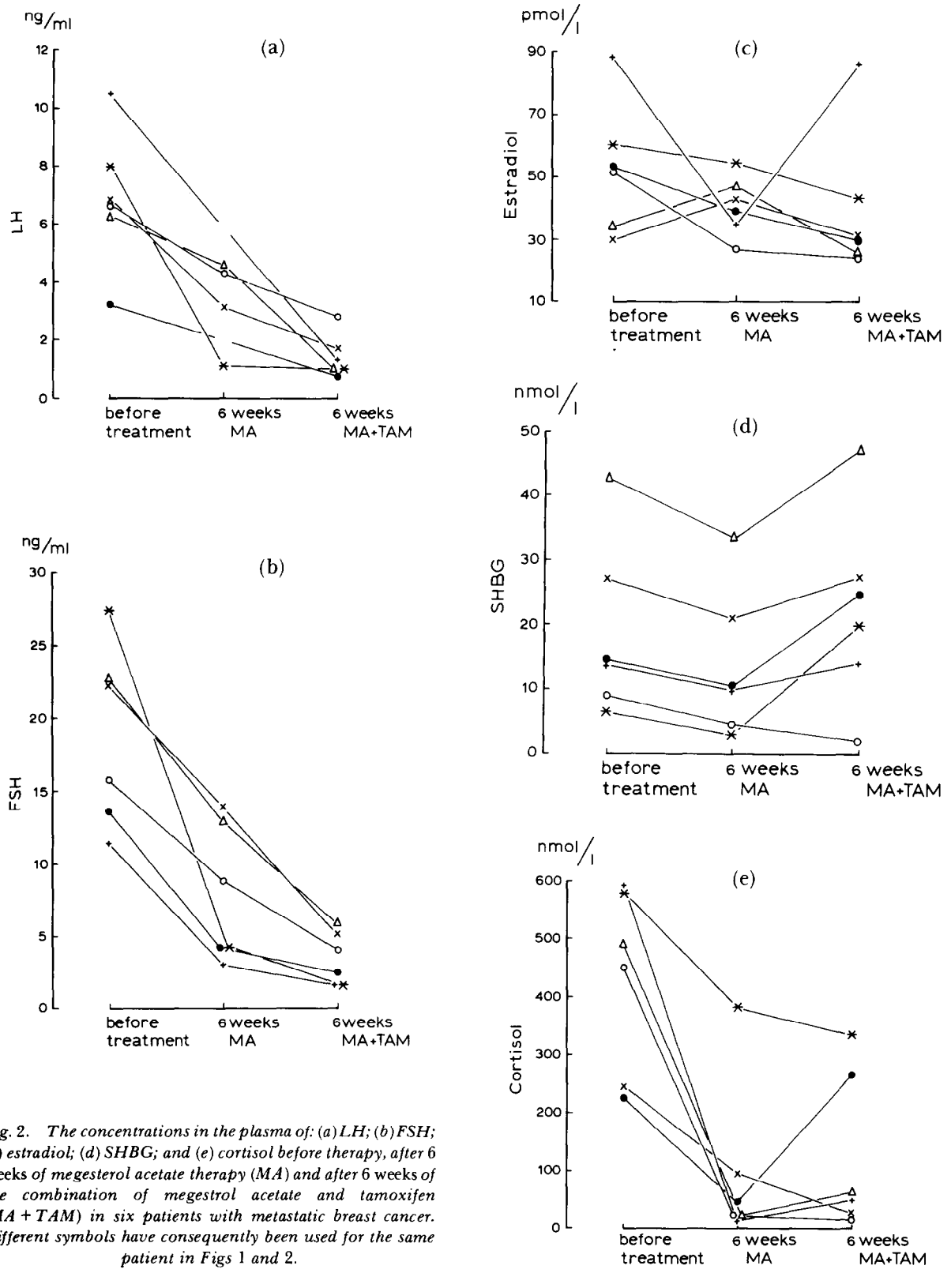

Fig. 2. The concentrations in the plasma of: (a) LH; (b) FSH; (c) estradiol; (d) SHBG; and (e) cortisol before therapy, after 6 weeks of megesterol acetate therapy (MA) and after 6 weeks of the combination of megestrol acetate and tamoxifen (MA + TAM) in six patients with metastatic breast cancer. Different symbols have consequently been used for the same patient in Figs 1 and 2.

tions, while in only one of them was no increase observed after addition of TAM to the regimen. To assure that this could not be due to protocol violation or poor absorption, the serum levels of TAM were estimated. The patient whose SHBG did not increase after addition of TAM had a plasma tamoxifen level comparable to that found in the other patients. The TAM levels observed (Table 1) agree with those reported [13].

The glucocorticoid effect of MA seemed to be unaffected by addition of TAM. Cortisol levels remained very low in four patients; in one patient

the suppression was very slow and in one patient plasma cortisol recovered (Fig. 2e). However, no data on MA levels were collected in this particular study and therefore a possible inadequately low level of MA, allowing an escape of suppression of the adrenal axis, cannot be ruled out.

Tumor response of this combination of drugs could not be considered in this study, which was directed to the endocrine effects, since only the responders to MA were treated with a combination of both drugs. It can be mentioned, however, that all six patients are still in remission at the present moment (with a follow-up of 6–12 months). The fact that six out of seven patients (an extremely high 'percentage' of ±85%) responded beneficially to MA simply demonstrates again that trials in small numbers of patients may be very useful for endocrine studies to indicate outlines for further research but cannot be used for demonstration of the effectiveness of drugs.

This combination treatment could become a new therapeutic approach, and therefore a large study directed to its tumor effects has to be done. Also, the possibility of dose reduction of both drugs, when given simultaneously, should be investigated.

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