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HORMONAL EFFECTS OF TOREMIFENE IN BREAST CANCER PATIENTS

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Summary—The effect of toremifene treatment on the serum levels of sex steroids (estradiol, progesterone, testosterone), FSH, LH, prolactin, TSH, T3, T4 and SHBG was investigated. Basal prolactin level and the "prolactin reserve capacity" of the hypophysis was also studied by the TRH functional test. Steroid hormone receptors were detected in the patients where a tumor biopsy could be obtained. In a randomized trial patients were treated by 60 and 300 mg of toremifene per os, daily. Hormone levels were assayed prior to treatment and at the 2nd, 6th, 8th and 12th week of toremifene therapy. The hormonal effects of toremifene were the most marked at the 2nd and at the 8th week. Estradiol decreased continuously, SHBG increased slightly and the high initial value of basal prolactin level decreased. The TRH-induced prolactin release was suppressed by toremifene after an 8-week period. No clinical response-related tendency was found.

INTRODUCTION

A new antiestrogen, toremifene (Fc-1157a) was developed by Farmos Group Research Center. The antitumor effects of the drug are due mainly to the antiestrogenic activity [1], but a weak estrogen agonistic, as well as oncolytic effect, especially at high dose level, has also been observed [1, 2].

In general, the influence of antiestrogens on hormone profiles of breast cancer patients is neither simple nor easy to interpret. These drugs exert pronounced and very different endocrine influences in human. The nature of these effects is related to various factors, mainly to age, to menopausal status and to the target tissue [3].

There are several studies dealing with the hormonal effects produced by the antiestrogens in breast cancer patients. Especially the endocrine effects of tamoxifen, which have been investigated by many research groups [4–11].

In this study, the hormonal changes during prolonged treatment with toremifene were investigated in 14 breast cancer patients at two dose levels: 60 and 300 mg.

Serum levels of estradiol-17β (E_2), progesterone (PROG), testosterone (TE), prolactin (PRL), growth hormone (GH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and sexual hormone-binding globulin (SHBG) were monitored for 12 weeks during toremifene therapy. The effect of toremifene on the hypothalamo–hypophyseal axis was also studied by a functional test with thyrotrophin-releasing hormone (TRH).

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MATERIALS AND METHODS

Patients

Fourteen postmenopausal women suffering from advanced breast cancer with bone metastases were treated with toremifene. None of the patients had evidence of cerebral metastasis, pituitary or other endocrine abnormalities and they had no hormonal treatment for 6 months prior to toremifene administration. Psychotropic drugs, dopamine and morphine derivatives were not administered during the period of endocrine investigation. The dose of toremifene was 60 mg/day in 8 and 300 mg/day in 6 patients for a period of at least 3 months.

Hormone assays

Serum samples for basal hormone assays were taken prior to toremifene treatment and then 2, 6, 8 and 12 weeks later. Hormones were measured by radioimmunoassays, SHBG was determined by IRMA method (Farmos Diagnostica, Turku, Finland).

Functional PRL test

Blood samples were taken at 0, 15, 30 and 120 min after the injection of 400 μg TRH (Ferring AB, Malmö, Sweden). This test was done before toremifene treatment and at the 2nd, 8th and 12th week after the initiation of therapy. PRL release of 8 menopausal healthy women served as normal control.

Patient's response to the treatment

Clinical response of the patients investigated was assessed using WHO criteria [12].

RESULTS

Serum hormones

Among the endocrine parameters there were only four hormones: E_2, basal PRL, FSH and LH which showed considerable changes during the treatment period. In addition, the changes of SHBG and TRH-induced PRL release were also notable. At 60 mg dose level the initial value of E_2 was above the normal postmenopausal range in all patients (Fig. 1). The E_2 level continuously decreased for 6 weeks, when its concentration dropped suddenly to the normal range. Later, there was no change during the whole treatment period. That phenomenon is very similar to our findings obtained by tamoxifen, however, 60 mg of tamoxifen did not normalize the E_2 level [11]. At 300 mg dose level the high initial E_2 value was also intensively suppressed by toremifene in spite of the temporary peak appearing at the 8th week. After 12 weeks E_2 level was very near to the upper limit of the normal value (Fig. 1). The level of SHBG increased slightly compared to the initial value, at both dose levels (Fig. 2). It is interesting to note that at 300 mg, similarly to the E_2, a transient peak in SHBG level could be observed at the 8th week.

The most marked hormonal changes could be observed in the basal PRL levels of the patients at both dose levels (Fig. 3). The pretreatment PRL level was double that of the normal value. It decreased markedly within 2 weeks of treatment, and by the 6th week it has reached the normal level. In the case of the high dose, the normalization of PRL appeared as early as the 2nd week. It seems that one of the important effects of toremifene is that the drug is able to suppress the high initial value of PRL. The degree of suppression was more pronounced in women having higher pretreatment PRL levels. The FSH and LH levels decreased slightly during the treatment, but the changes remained within the normal postmenopausal range.

TRH functional test

The secretion of PRL is regulated mainly by the inhibitory effect of hypothalamus, which secretes prolactin-inhibiting factor (PIF) via the hypophyseal portal circulation. PIF is supposed to be dopamine [13]. The PIF secretion is under dopaminergic

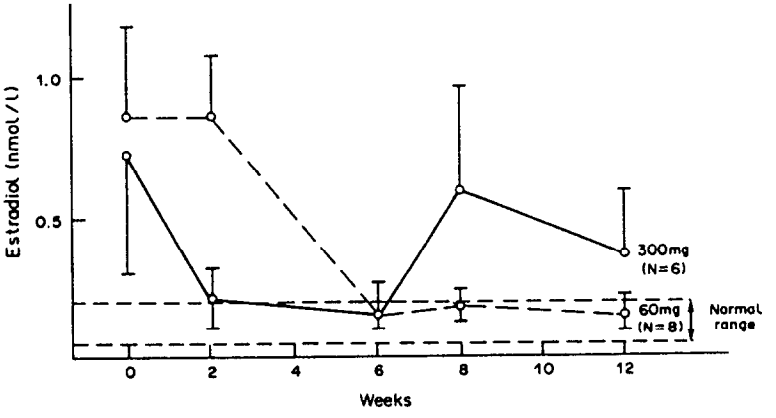

Fig. 1. Changes of estradiol levels (mean ± SE) in patients treated with toremifene.

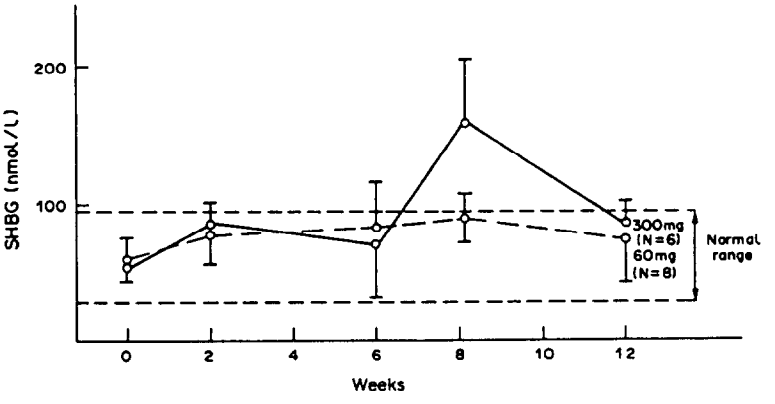

Fig. 2. Changes of sex hormone binding globulin (SHBG) levels (mean ± SE) in patients treated with toremifene.

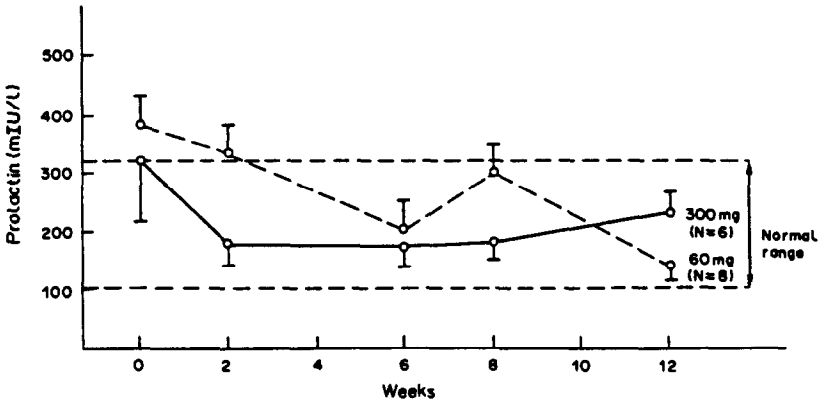

Fig. 3. Changes of basal prolactin levels (mean ± SE) in patients treated with toremifene.

control. Most of the PRL-stimulating agents act by blocking dopamine synthesis or dopamine receptors. A single i.v. injection of 400 μg TRH elevates PRL with peak values recorded at 15 min. Therefore TRH seems to be suitable for measuring the "prolactin reserve capacity" of the adenohypophysis. At the same time, measurement of the TRH-induced PRL release during the administration of different anti-tumor agents, can give information about the PRL synthetic capacity of the pituitary gland under the influence of these drugs. The TRH-induced PRL release of the patients was compared to the secretion profile of 8 healthy postmenopausal women. There was no difference between the PRL release of the breast cancer patients and the normal control group (Table 1).

The suppression of the TRH-induced PRL release by toremifene was expressed at the 8th week of the therapy. At that time the suppression of the releasable PRL was similar at both dose levels (Figs 4 and 5). This finding indicates that the 60 mg dose is able to decrease the inducible PRL to the same level as did the 300 mg. In the case of tamoxifen the degree of suppression was as high as 57%, but only in patients responding to therapy [11]. Because of the small number of cases investigated, the hormonal changes cannot be reliably compared to the clinical response of the patients. However, there is an interesting case in the high dose group. A woman responded well to the treatment. Her TRH-induced PRL release was extremely low before and after the therapy (Fig. 6). Toremifene did not cause a further suppression of PRL level supposedly due to the normal initial value. This finding is similar to that published by Nagy *et al.*[14] who observed the same phenomenon when investigating tamoxifen.

Table 1. Thyrotropin-releasing hormone (TRH)-induced prolactin release (mean ± SE) in healthy women ($n = 8$) and in patients with breast cancer ($n = 14$)

	TRH-induced prolactin release (mean ± SE) (mIU/l)			
	0 (min)	15 (min)	30 (min)	120 (min)
Healthy women ($n = 8$)	344 ± 54	1151 ± 144	1151 ± 148	160 ± 15
Breast cancer patients ($n = 15$)	316 ± 55	1173 ± 176	1143 ± 237	431 ± 77

DISCUSSION

This study has shown that toremifene can produce some changes in the hormone profile of breast cancer patients. Despite the considerable modulation of the endocrine milieau efficacy cannot be predicted early on the basis of these changes.

The effect of 60 mg and 300 mg of toremifene on the circulating E_2 level was considerable resulting in a continuous decrease in both groups. Similarly to tamoxifen, toremifene produced an increase in SHBG, proving the weak estrogen-like effect of the drug, which is probably due to a direct effect on the liver [11, 15–18]. One may emphasize that the partial estrogenicity of toremifene plays a role in the anti-tumor effect, which may be mediated through the "antiestrogen receptor" or some other novel

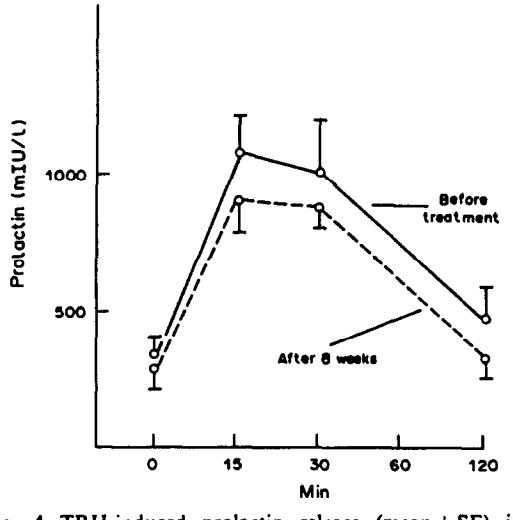

Fig. 4. TRH-induced prolactin release (mean ± SE) in patients treated with 60 mg of toremifene.

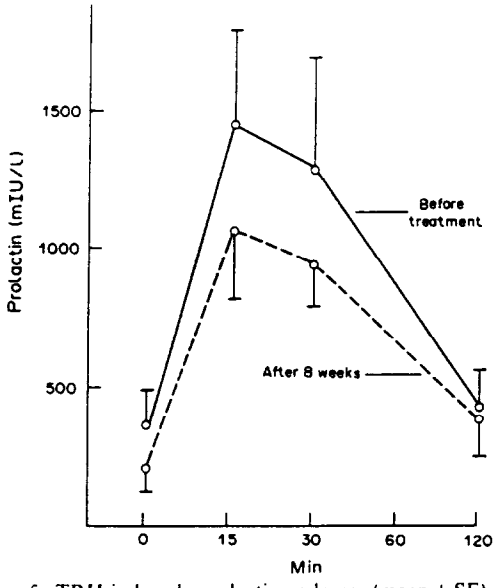

Fig. 5. TRH-induced prolactin release (mean ± SE) in patients treated with 300 mg of toremifene.

mechanism [16]. The agonistic and antagonistic properties of toremifene were investigated by Kangas *et al.*[1] and Kallio *et al.*[2] in rats and mice and their findings are consistent with our human data. The fall of FSH and LH might confirm the antiestrogenic character of toremifene at the level of the hypothalamo–hypophyseal axis. In most of the studies on tamoxifen a similar phenomenon was observed [18–21]. The effects of antiestrogenic drugs on gonadotropins are rather complex. This is due to the opposing estrogen effects of the pituitary gland and the hypothalamus. Whereas high physiologic concentrations of E_2 inhibit secretion of LH-RH, resulting in a decrease in FSH and LH, exogenous

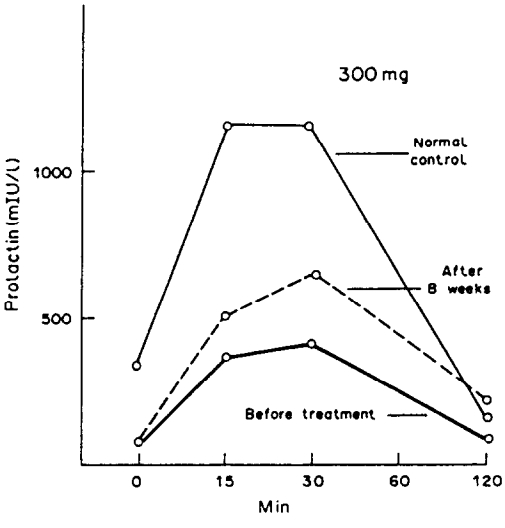

Fig. 6. TRH-induced prolactin release in patients responding well to 300 mg of toremifene after an 8-week treatment period.

and endogenous estrogens sensitize the pituitary gland to the action of LH-RH, which tends to increase serum gonadotropin levels. The net effect of estrogen or antiestrogen treatment therefore depends on the balance between these two opposing actions. The fall in FSH and LH in postmenopausal patients during toremifene treatment may be due to a partial agonistic activity on the hypothalamus or the antiestrogenic activity on the pituitary gland [18]. Our study did not assess the LH-RH stimulated release of gonadotropins, but the decrease of the basal levels of FSH and LH, and the changes of basal PRL suggest that an antiestrogenic activity at the level of the hypophysis could have occurred. We speculate that toremifene affects the PRL synthesis at the level of PRL secreting cells. A similar opinion was published by Nagy *et al.*[14] concerning tamoxifen which caused a 45% reduction in [^{3}H]PRL synthesis and release *in vitro*.

The reduction of basal PRL level by toremifene could be an important aspect of the mechanism of action of the drug, since PRL may be one of the factors controlling tumor growth. So, it might be postulated that one of the actions of toremifene may involve its antiprolactinic property in the treatment of breast cancer. According to the TRH functional test, toremifene is able to suppress the PRL reserve of the pituitary gland by blocking the PRL secretion. This observation correlates well with the findings of Lamberts *et al.*[22] who noted a similar suppression with tamoxifen. According to our finding the degree of suppression was greater in patients with high pretreatment PRL values. Normal PRL release was not affected by toremifene suggesting that PRL synthesis is predominantly inhibited by the drug. Similarly to the findings of Boccardo *et al.*[18] obtained with tamoxifen, patients with higher basal PRL levels were more affected by toremifene than patients with lower levels.

In conclusion, toremifene has variable endocrine effects in humans. The drug produces agonistic effects on some targets and antagonistic effects on the others. In particular, a weak estrogenic action occurred in the liver. In contrast, the fall of FSH, LH and PRL may indicate an antiestrogenic action at the level of the hypophysis. A possible dopamine agonistic effect of toremifene might also be postulated, but for clarifying the exact biochemical mechanism of action of the drug further investigations are needed.

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