SHORT COMMUNICATION

Effect of acute and chronic administration of tamoxifen on GH response to GHRH and on IGF-I serum levels in women with breast cancer

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Abstract

Tamoxifen, an estrogen antagonist, is usually employed in the treatment of breast cancer. Its mechanism of action is not well known because an antiproliferative effect of the drug has been shown also in estrogen receptor negative tumors, most likely mediated by the inhibition of local growth factors and particularly IGF-I. However, the action of tamoxifen on the GH–IGF-I axis is still open to investigation. We have investigated the influence of acute and chronic treatment with tamoxifen on GH response to GHRH and IGF-I serum levels in six postmenopausal women with metastatic breast cancer.

A GHRH test (50 μg i.v. at time 0, GH determinations at 0, 15, 30, 60, 90 and 120 min) was performed (a) basally, (b) 3 h after 40 mg oral administration of tamoxifen and (c) after 8 weeks of 20 mg twice a day oral tamoxifen treatment. IGF-I was measured basally and after chronic tamoxifen therapy.

No significant modifications in GH response to GHRH were observed after acute or chronic treatment with tamoxifen vs the basal test. On the contrary, chronic tamoxifen treatment induced a significant decrease in serum IGF-I levels. Basal pretreatment levels of 123 ± 6 μg/l were suppressed to 65 ± 11 μg/l (mean suppression 47%, P<0.001).

These preliminary data confirm the inhibitory effect of tamoxifen on IGF-I production but seem to exclude the possibility that this effect may be due to an inhibition of GH secretion.

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Introduction

Tamoxifen, a nonsteroidal partial competitive antagonist to the estrogen receptor, is usually employed in the adjuvant and palliative treatment of breast cancer. However, its mechanism of action is not well known because an antiproliferative effect of the drug has been demonstrated also in estrogen receptor negative tumors (1), thus suggesting mechanisms of action alternative to the ‘classical’ antiestrogen model.

Insulin-like growth factor-I (IGF-I) is a potent mitogen for breast cancer cells in vitro (2). Furthermore the majority of human breast cancers contain receptors for IGF-I (2). In vitro studies have shown that antibodies against IGF-I receptors inhibit the growth of breast cancer cells (3). In vivo studies demonstrated that the IGF-I plasma concentration is significantly higher in the breast cancer patient population than in the control population (4). All these data suggest that IGF-I may play a key role in the development of breast cancer in humans, and emphasize the potential use of IGF-I-lowering drugs in the treatment of this disease.

A tamoxifen effect mediated by the inhibition of local growth factors and particularly IGF-I has been postulated. However, the action of tamoxifen on the growth hormone (GH)–IGF-I axis is still open to investigation. While several studies have shown that tamoxifen is able to suppress plasma levels of IGF-I in humans, few and conflicting results have been obtained in animals and humans concerning the involvement of the hypothalamo–pituitary axis in this action (5, 6).

The present investigation was, therefore, undertaken to give further insight into this topic by evaluating the effect of acute and chronic tamoxifen treatment on GH response to growth hormone-releasing hormone (GHRH), as well as on IGF-I serum levels, in six postmenopausal women affected by metastatic breast cancer.
Subjects and methods
We evaluated the effect of acute and chronic tamoxifen treatment on GH response to GHRH as well as on IGF-I serum levels in six postmenopausal women affected by metastatic breast cancer. All patients were over 65 years old (65–82 years, mean 75 years). All had undergone mastectomy for stage III or IV breast cancer. Three patients had lung or liver metastases while three had axillary node metastases only. The course of the disease was stable during the length of the study and in particular no differences in metastases were observed. All the tumors were estrogen receptor positive (>30 fmol). Exclusion criteria were: chemotherapy, previous tamoxifen therapy, endocrine diseases and drugs interfering with GH or IGF-I secretion. The study protocol was approved by the Local Ethical Committee. Informed consent was obtained from all participants.

A GHRH test (50 μg i.v., blood samples for GH determinations at 0, 15, 30, 60, 90 and 120 min) was performed: (a) basally, before tamoxifen treatment; (b) 3 h after 40 mg oral administration of tamoxifen (acute); and (c) after 8 weeks of 20 mg twice a day oral tamoxifen treatment (chronic).

In all the tests GHRH was injected at time 0 (1000 h), in recumbent subjects after overnight fasting. An indwelling cannula was inserted in an antecubital vein at 0930 h. It was used for blood sampling and GHRH injection. In individual subjects tests (a) and (b) were performed at least at a 72 h interval. Test (c) was performed during chronic tamoxifen treatment, administering the 20 mg morning dose of the drug 3 h before GHRH injection.

IGF-I was measured at time 0 basally and after chronic tamoxifen therapy.

GHRH (1–44) was furnished by Serono (Milan, Italy). Vials containing 0.1 mg were diluted in 0.9% saline solution giving a final concentration of 50 μg/ml. Serum GH concentrations were measured in duplicate by an IRMA kit (hGH-IRMA-CT, Radim, Rome, Italy). One nanogram of GH corresponded to 2 μU/ml WHO 66/217 standard. The sensitivity of the assay was 0.04 ng/ml. The intra-assay and interassay coefficients of variation were 3.4 and 4.6% respectively. IGF-I in serum was measured using an RIA kit (Medgenix Diagnostics, Fleurus, Belgium). The procedure included an acid–ethanol extraction in order to decrease artifacts induced by quantitative and qualitative variations in the IGF-I binding protein complex. The detection limit was 0.25 ± 0.10 μg/l and intra-assay and interassay coefficients of variation were 4.9 and 9.6% respectively.

All samples from a given study were measured in the same assay.

The results are given as mean ± S.E.M. The area under the curve (AUC) was calculated by a trapezoidal method. Both analysis of variance and a paired t-test with Bonferroni correction were used for statistical evaluation. The significance level was established at P < 0.05.

Results
Before tamoxifen treatment, 50 μg GHRH administration induced a clearcut although slight increase in GH levels in all our patients (mean peak 4.3 ± 0.8 μg/l, AUC 344 ± 55 μg/l/min). A single 40 mg tamoxifen oral dose administered 3 h before GHRH injection induced a slight and not significant increase in GH response to GHRH (mean peak 5.7 ± 0.9 μg/l, AUC 427 ± 67 μg/l/min). After 8 weeks of 20 mg twice a day oral tamoxifen treatment the GH response to GHRH was slightly but not significantly reduced (mean peak 3.5 ± 0.6 μg/l, AUC 279 ± 50 μg/l/min) (Figs 1 and 2). On the contrary chronic tamoxifen treatment induced a significant decrease in serum IGF-I levels. Basal pretreatment levels of 123 ± 18 μg/l were suppressed to 65 ± 11 μg/l (mean suppression 47%, P < 0.001) (Fig. 3).

Discussion
Clinical and experimental research has shown that tamoxifen has a suppressive effect on IGF-I secretion. Several authors have demonstrated that plasma IGF-I levels are significantly lower among breast cancer patients receiving tamoxifen than in patients not treated with the drug (7, 8). Furthermore, when IGF-I has been measured in samples obtained from the same patients before and during tamoxifen therapy at variable dosages and for different periods of time, a significant reduction has always been found in the various series (9, 10). Considering that GH is the major hormone implicated in the control of IGF-I secretion, the question arises as to whether tamoxifen suppresses IGF-I peripherally or by acting at the pituitary level to inhibit GH release. In vitro studies using primary cultures of ovine pituitary cells demonstrated that tamoxifen has a direct, dose-related, inhibitory effect on GH release by somatotropes during acute as well as chronic treatment (5). These data supported the hypothesis of a direct inhibition by tamoxifen of pituitary GH output possibly by a mechanism involving pituitary estrogen receptors. According to this hypothesis, data in vivo demonstrated that tamoxifen has a potent inhibitory effect on pulsatile GH secretion in free-moving adult male and female rats. This action could be attenuated by an antisomatostatin antiserum, thus suggesting that the inhibitory effect of tamoxifen on GH output may be mediated, at least in part, by an increased release of endogenous somatostatin (6). Although these in vitro and animal studies seem to provide evidence that tamoxifen has an inhibitory effect on the whole GH–IGF-I axis, studies in humans are much more conflicting and less conclusive.

Several studies have shown that in breast cancer patients there is no difference in basal plasma GH levels before and after tamoxifen therapy (11, 12). Furthermore, no change in GH concentrations with tamoxifen added to previously unopposed estrogen therapy has been reported (13). A trend towards an increase in the
basal levels of GH has also been found after 3 months of adjuvant tamoxifen treatment of 40 mg daily, while IGF-I was significantly suppressed (9).

On the contrary, by using frequent blood sampling in male adolescents, Metzger & Kerrigan (14) demonstrated that short-term tamoxifen treatment leads to a significant decrease in mean 24 h serum GH concentrations. Our data confirm previous reports that chronic treatment with tamoxifen (40 mg for 2 months) in postmenopausal breast cancer patients is able to induce a significant inhibition of IGF-I serum levels. No significant modifications in GH response to an acute bolus of GHRH were observed after both acute and chronic tamoxifen treatment in the same patients. It has

![Graph of GH responses to GHRH in six postmenopausal women before tamoxifen treatment (basal), 3 h after 40 mg oral administration of tamoxifen (TMX acute) and after 8 weeks of 20 mg twice a day tamoxifen treatment (TMX chronic).]

**Figure 1** Mean (± S.E.M.) GH responses to GHRH 50 μg i.v. in six postmenopausal women before tamoxifen treatment (basal), 3 h after 40 mg oral administration of tamoxifen (TMX acute) and after 8 weeks of 20 mg twice a day tamoxifen treatment (TMX chronic).

![Graph of GH AUC after GHRH in six postmenopausal women before tamoxifen treatment (basal), 3 h after 40 mg oral administration of tamoxifen (TMX acute) and after 8 weeks of 20 mg twice a day tamoxifen treatment (TMX chronic).]

**Figure 2** Mean (± S.E.M.) GH AUC after GHRH 50 μg i.v. in six postmenopausal women before tamoxifen treatment (basal), 3 h after 40 mg oral administration of tamoxifen (TMX acute) and after 8 weeks of 20 mg twice a day tamoxifen treatment (TMX chronic).
to be noted that the old age of our female patients may explain the low mean response of GH to GHRH encountered. These data represent the first demonstration that the reduction in IGF-I levels in breast cancer patients treated with tamoxifen is not associated with a reduced response of GH to its physiological secretagogue. Accordingly, a previous report has demonstrated that a short-term estrogen receptor blockade with tamoxifen (30 mg for 2 days) does not alter the GH response to GHRH in young normal women (15). Furthermore, it has been demonstrated that acute hypoestrogenism due to ovarian blockade by a gonadotropin-releasing hormone agonist or chronic hypoestrogenism, as in anorectic women, does not modify GH responsiveness to GHRH (15).

Our preliminary data therefore suggest that tamoxifen suppresses plasma IGF-I levels by mechanisms not involving GH secretion, or at least that it does not exert any effect on GH secretion at the pituitary level.

However, it cannot be excluded that tamoxifen could have some negative influence on GH secretion and/or positive influence on somatostatin secretion at the hypothalamic level.

Further studies are needed for a better understanding of the tamoxifen influence on the GH–IGF-I axis. These experiments might be performed in stage I or II breast cancer patients in whom more extensive testing and sampling could be performed.

References
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