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The Effect of Tamoxifen on Plasma Growth Hormone and Prolactin in Postmenopausal Women with Advanced Breast Cancer*

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Abstract—*The effect of tamoxifen on serum levels of basal prolactin and basal and stimulated growth hormone was assessed in* 10 *women with advanced breast cancer prior to and after* 1 *and* 8 weeks *of treatment. Tamoxifen had no effect on basal levels of either hormone or on insulin-stimulated growth hormone. Two of* 4 *patients undergoing arginine provocation testing had a partial response to tamoxifen and both exhibited marked diminution of growth hormone stimulation which was not seen in the non-responders.*

INTRODUCTION

OESTROGENS deplete the pituitary of growth hormone [1] while they seem to increase the sensitivity of the gland to growth hormone-releasing effects such as physical activity [2] and arginine [1]. The response to insulin appears to be less oestrogen-dependent than that to arginine and exercise [1], indicating that insulin and arginine have different mechanisms of releasing growth hormone. This is further supported by the fact that corticosteroids suppress insulin stimulation of growth hormone whilst not affecting arginine-induced secretion [1].

The growth hormone rsponse to arginine in women is reduced by prior administration of the anti-oestrogen clomiphene citrate [3]. Arafah *et al.* [4] have reported that the anti-oestrogen trioxifene mesylate can reduce basal growth hormone levels in rats, but in 4 female patients with advanced breast cancer there was no significant effect on the basal or sleep-related rise in growth hormone, although arginine-stimulated growth hormone release was decreased.

There are two reports on the effect of tamoxifen on basal growth hormone in humans. It has been reported to have no effect [5] or no consistent effect [6] on basal growth hormone secretion, but its effect on stimulated secretion has not been reported.

Lamberts *et al.* [7] reported that the addition of tamoxifen to bromocriptine had a beneficial clinical effect and normalised circulating growth hormone levels in a patient with a pituitary tumour that had escaped control by bromocriptine alone. In this patient, the sensitivity of the pituitary tumour to bromocriptine appeared to be oestrogen-dependent as it decreased with rising oestradiol-17 levels around ovulation. However, the short-term administration of tamoxifen to 4 further patients with pituitary adenomas and low oestrogen levels was found to be ineffective in influencing growth hormone levels.

Suppression of growth hormone or other pituitary hormones would be an attractive additional quality of an anti-oestrogen as it would go one step further towards achieving a complete medical hypophysectomy. The effect of tamoxifen on basal prolactin, basal growth hormone and stimulated growth hormone secretion is further investigated here.

MATERIALS AND METHODS

Patients

Ten female patients, all more than 2 yr post-menopausal and with a median age of 62 yr (range 48–80 yr), with advanced breast cancer and a performance status better than 2 on the ECOG scale, were tested prior to treatment with

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tamoxifen 20 mg twice daily and then 1 and 8 weeks later. None had evidence of cerebral metastases, or pituitary or other endocrine abnormalities and none had experienced recent surgery or severe stress. No other form of therapy was used and none of the patients were given any additional medication over the period of investigation. Informed consent was obtained from all.

Serum samples for basal prolactin and basal growth hormone assay were obtained from the 10 patients. Four patients underwent the arginine provocation test as described by Parker *et al.* [8] and 6 patients underwent the insulin provocation test. The patients for both tests were fasted overnight and a venous cannula was placed in each forearm for blood sampling and infusion at least 30 min before starting the active infusion. Testing began between 9.00 and 10.00 a.m., blood samples being taken over the ensuing 2 hr. The samples were allowed to clot at room temperature, were centrifuged at 500 *g* for 10 min and the serum stored at −70°C until assayed.

The arginine provocation test was performed by infusion with 0.5 g/kg body wt of L-arginine hydrochloride over 30 min. Those undergoing the insulin provocation test were injected with 0.1 U/kg body wt of insulin, blood being collected in tubes containing fluoride oxalate over the period of the procedure for glucose estimation by the glucose oxidase method.

Growth hormone and prolactin measurements were carried out by double antibody radioimmunoassays (RIA) as previously described [9].

Growth hormone RIA employed a rabbit anti-growth hormone serum (R16, Burrough Wellcombe Ltd.) and calibrated standards against the reference preparation of MRC 66/217 (National Institute for Biological Standards and Control, NIBSC, London). The purified growth hormone (MRC 69/46) for labelling was also provided by NIBSC and iodinated with chloramine-T after the method of Greenwood *et al.* [10], with subsequent purification on PD-10 columns (Pharmacia Fine Chemicals, Uppsala). Prolactin RIA was also employed on antiserum (PR_1b_2 raised in rabbits against a highly purified human pituitary preparation, kindly donated by Professor W. Butt, Birmingham, and a commercial label, Netria, London). Standards were calibrated against the reference preparation WHO 75/504 and provided by NIBSC. In both assays antibody-bound tracer was precipitated by sheep anti-rabbit IgG and the counts associated with the antibody-bound fraction were determined in a γ-counter. The concentrations of growth hormone and prolactin in serum samples were calculated from the dose–response curve using a Commodore (3032 series) desk-top computer and a log–logit program.

Response to treatment was assessed using UICC criteria as described by Hayward *et al.* [11].

RESULTS

One patient had complete remission, 2 partial remission, 4 no change and 3 progression of disease as assessed using UICC criteria.

No complications occurred in patients undergoing the arginine provocation test. However, one of the patients on whom the insulin provocation test was performed required injection of glucose midway through her second test to counteract severe hypoglycaemia. Adequate hypoglycaemia (<2 mmol/l) was obtained during each insulin provocation test.

Basal prolactin and basal growth hormone levels did not change significantly with tamoxifen (Table 1), and there was no clinical response-associated trend.

Table 1. Hormone levels related to treatment

	Pretreatment	After 1 week of treatment	After 8 weeks of treatment
Basal prolactin ($n = 10$)	309 (111–412)	292 (123–510)	232 (162–525)
Basal growth hormone ($n = 10$)	1.7 (0.7–8.1)	1.4 (0.8–33.9)	2.9 (1.1–12.7)
Maximal growth hormone —insulin-stimulated ($n = 6$)	40.4 (16.2–77.6)	29.2 (18.9–68.7)	44.4 (13.1–100)

Figures are median values and ranges (mU/l).

Maximal growth hormone stimulation occurred between 60 and 75 min after insulin provocation. There was no significant change in maximal stimulated levels following treatment with tamoxifen (Table 1) and no trend was noted associated with the clinical response to tamoxifen therapy.

Arginine caused maximal growth hormone stimulation 60 min after administration. Two patients who responded to treatment exhibited more than a 50% decrease in the maximal stimulated level of growth hormone within a week of starting tamoxifen, maximal stimulation remaining diminished in one and being totally suppressed in the other at 8 weeks (Fig. 1a, b). The two patients who showed no decrease in disease burden displayed no such trend (Fig. 1c, d).

DISCUSSION

Manni *et al.* [12] showed that significant palliation with tamoxifen could be obtained in a proportion of patients who had undergone complete surgical hypophysectomy. Serum levels of growth hormone and prolactin were not measurable in these patients but measurable levels of oestrogens were present, suggesting that oestrogens played an important part in the growth of hormone-responsive cancers in the absence of pituitary hormones. He also showed [13] that surgical hypophysectomy could induce further remissions in two-thirds of patients whose response to tamoxifen had relapsed and in one-quarter of patients who failed on antioestrogen therapy, suggesting that pituitary hormones such as growth hormone or prolactin might be implicated in stimulating tumour growth in some patients with breast cancer.

This study supports the findings of Manni *et al.* [5] and Golder *et al.* [6] that basal growth hormone levels are not altered by tamoxifen.

Similarly, insulin-induced growth hormone stimulation is not affected by tamoxifen, and these observations confirm that the response to insulin is not strongly oestrogen-dependent.

Like McFadyen *et al.* [14] we have found no change in basal plasma prolactin levels in postmenopausal women following administration of tamoxifen.

In our study the 2 patients who responded to tamoxifen exhibited decreased arginine-induced growth hormone stimulation following treatment, showing that tamoxifen, like trioxifene mesylate and clomiphene, is capable of suppressing arginine stimulation. Arafah *et al.* [4] noted arginine-stimulated growth hormone release was decreased in three of four patients with advanced

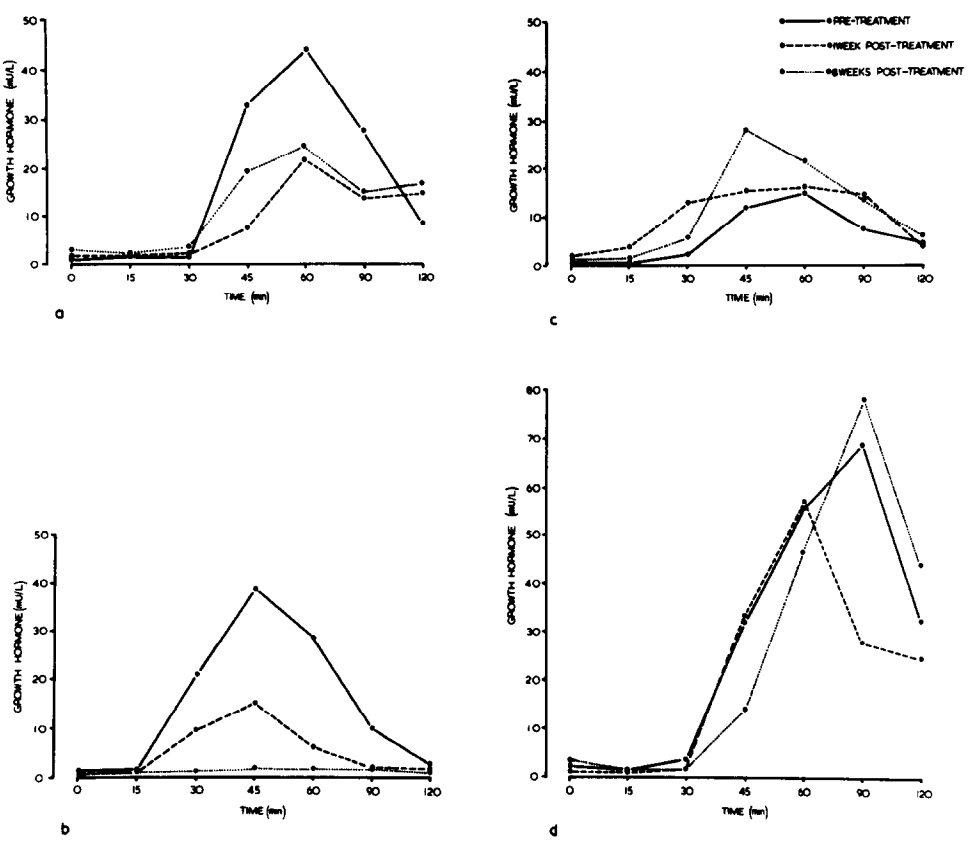

Fig. 1. Arginine-provoked growth hormone stimulation curves in 4 individual patients before and on treatment. (a,b) Partial remissions; (c) disease progression; (d) no change.

breast cancer 1 week after starting the anti-oestrogen trioxifene mesylate. Two of these patients responded to this drug, but it is not stated whether both of these showed diminished arginine-induced stimulation of growth hormone. Why growth hormone suppression should occur only in the clinical responders to tamoxifen is not clear. It is possible that suppression of high plasma levels of growth hormone is important in the therapeutic response to tamoxifen, in addition to the direct effect of the drug on the tumour cells.

Normal breast development requires oestrogens and a functioning pituitary [15], and hormonally dependent breast cancers may also grow most rapidly under these conditions. Conceivably, patients who undergo remission of disease on anti-oestrogens are those more susceptible to competitive inhibition of oestrogen at the receptor sites on the hypothalamus responsible for the release of growth hormone. Clearly this hypothesis must be evaluated, and further patients are being studied.

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