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Tamoxifen Protects Against Steroid-induced Bone Loss

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As part of a clinical trial of adjuvant endocrine treatment in postmenopausal women with operable breast cancer serial bone density measurements have been performed by dual photon absorptiometry. Tamoxifen alone was given to 26 women, and 20 received additional prednisolone. By 24 months after entry there was no significant difference between mean bone density of the two groups, nor any significant change from baseline levels. There was a mean gain of 0.46% in the tamoxifen group and 1.95% in those given additional prednisolone. Thus the predicted steroid-induced bone loss was inhibited by tamoxifen. This may be of more general use in prevention of osteoporosis in patients requiring long-term steroid treatment.
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INTRODUCTION

TAMOXIFEN IS widely used as adjuvant treatment for postmenopausal women with early breast cancer since it reduces significantly the risk of dying from the disease [1]. The addition of prednisolone to tamoxifen in patients with advanced disease leads to an increase in response rate and duration of remission [2]. Because of this an adjuvant trial has been underway since 1985 to determine the benefits and risks of tamoxifen treatment for 5 years, with or without prednisolone. Since it was known that this dosage of steroids can accelerate bone loss and cause severe osteoporosis, particularly in postmenopausal women [3] serial bone measurements were conducted to determine whether the combination of tamoxifen and prednisolone had a negative, positive or neutral effect. Despite the oestrogen-receptor blocking action of tamoxifen [4] previous studies of bone density in both pre- and postmenopausal women receiving the agent had shown no measurable bone loss [5, 6], suggesting a partial oestrogen agonist effect.

PATIENTS AND METHODS

46 postmenopausal women with breast cancer were included and none had evidence of metastatic disease before either mastectomy or breast conservation treatment. They were randomised to receive either tamoxifen 20 mg daily for 5 years (T) or tamoxifen 20 mg with prednisolone 7.5 mg daily for 5 years (T + P). Mean follow-up was 26 months for the T group and 28 months in the T + P group.

Bone mineral content (BMC) of lumbar spine (L2-4) and femoral neck were measured by dual-photon absorptiometry (DPA) using a Novo BMC-LAB 22A system and a ^{153}Gd source. BMC was expressed as grams of hydroxyapatite per unit projected area of bone (gHA/cm^2). Precision data have been previously reported as 2% for BMC of lumbar spine and 2.2% for femoral neck [7].

DPA measurements were performed before entry to the study and thereafter every 6 months. Blood was also taken at the same time intervals and calcium, phosphate, albumin and alkaline phosphatase measured using a Vickers autoanalyser.

RESULTS

The mean age of the T group was 60.7 years and that of the T + P group was 59.3 years. Mean follow-up was 27 months. Lumbar spine BMC measurements during the first 24 months of adjuvant treatment are shown in Table 1. The mean baseline BMC of the T group was greater than that of the T + P group (0.868 versus 0.787 gHA/cm^2) but this difference was not

Table 1. Sequential bone density, gHA/cm^2 in patients receiving tamoxifen (T) or tamoxifen and prednisolone (T + P)

	Baseline	6 months	1 year	18 months	2 years
Lumbar spine					
T	0.868(0.14)	0.850(0.14)	0.858(0.16)	0.847(0.16)	0.872(0.16)
T + P	0.787(0.11)	0.804(0.10)	0.782(0.10)	0.798(0.1)	0.809(0.12)
Femoral neck					
T	0.745(0.1)	0.725(0.09)	0.741(0.10)	0.744(0.1)	0.719(0.09)
T + P	0.687(0.1)	0.719(0.1)	0.727(0.09)	0.688(0.1)	0.688(0.12)

Mean (S.D.).

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statistically significant. When the baseline mean was compared with that at 24 months there was no significant change (T group, $t = 0.06$ n.s. T + P group, $t = 0.68$ not significant).

Thus there was no measurable bone loss in the group given tamoxifen and prednisolone, indeed a slight gain of 1.95%. Similar results were seen in serial femoral BMC measurements, also given in Table 1. No significant changes in blood levels of calcium, phosphate or alkaline phosphatase were seen in either group.

DISCUSSION

These preliminary data support the safety of tamoxifen and prednisolone given together for up to 2 years. This is of particular interest since it has been shown that bone loss in response to glucocorticoid therapy generally occurs within 6 months of starting treatment and that the majority of bone loss is seen within this time [8]. Prednisolone at a dosage of more than 7 mg per day has been shown to consistently induce bone loss, particularly in postmenopausal women [3].

The aim of adding prednisolone to tamoxifen was to determine whether a greater reduction in odds of dying from breast cancer could be achieved. This has yet to be determined. It was assumed that this might be achieved at the expense of some toxicity, particularly in relation to bone loss. This has not been observed in the present study, which suggests that tamoxifen can prevent bone resorption, that is, be bone-sparing even in the presence of steroid therapy. This raises the exciting possibility that tamoxifen might have wider therapeutic value in terms of skeletal protection in individuals needing long term glucocorticoids for a variety of potentially life-threatening conditions.

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