Long-Term Adjuvant Therapy with Tamoxifen: Effects on Sex Hormone Binding Globulin and Antithrombin III

V. Craig Jordan,^2 Nancy F. Fritz, and Douglass C. Tormey

Department of Human Oncology, University of Wisconsin Clinical Cancer Center, Madison, Wisconsin 53792

ABSTRACT

Plasma levels of luteinizing hormone, sex hormone binding globulin, and antithrombin III were measured in pre- and postmenopausal breast cancer patients receiving adjuvant combination chemotherapy or combination chemotherapy and long-term tamoxifen therapy. The aim was to determine the estrogen-like effects of tamoxifen. The premenopausal patients had received tamoxifen for between 434 and 2592 days and postmenopausal patients between 91 and 1560 days. Tamoxifen caused a consistent rise in sex hormone binding globulin in premenopausal (P < 0.03) and postmenopausal (P < 0.01) patients compared to chemotherapy controls. Luteinizing hormone levels were only significantly lowered (P < 0.008) in premenopausal patients compared to chemotherapy controls. Antithrombin III levels were significantly depressed (P < 0.001) in postmenopausal patients compared with chemotherapy controls. However, none of the patients had a value that was depressed by more than 30% of the laboratory control (the level of clinical significance). The mean for the group was 90% ± 4 (mean ± SD, N = 11).

The estrogen-like rise in sex hormone binding globulin produced by adjuvant tamoxifen therapy could be advantageous for maintaining the antiestrogenic action of the drug. A decrease in antithrombin III occurred in premenopausal (P < 0.008) and postmenopausal patients between 91 and 1560 days. Tamoxifen caused a partial reduction in gonadotrophin levels in postmenopausal patients (8) and produces an estrogen-like effect on vaginal cytology (9).

The partial estrogenicity of tamoxifen has been implicated in the potential to cause thromboembolic disorders in patients. However the incidence is extremely low (10) and there is no direct correlation between thromboembolism and tamoxifen therapy alone has been established.

Estrogen-induced thromboembolism has been associated with a decrease in plasma antithrombin III levels (11). Tamoxifen causes a decrease in the plasma antithrombin levels in some patients being treated for advanced breast cancer (12). The purpose of the present study was to determine whether prolonged adjuvant therapy with tamoxifen resulted in a clinically significant decrease in antithrombin III levels. Clearly if the patients are placed at extreme risk from thromboembolism by prolonged tamoxifen therapy this must be weighed against any potential therapeutic benefits.

Short-term therapy with tamoxifen for advanced breast cancer results in a rise in the circulating level of SHBG^3 (13, 14). This again is considered to be an estrogen-like effect of tamoxifen on liver protein synthesis. However, alterations in the amount of SHBG in the plasma will affect the amount of free estradiol that can localize in a breast tumor. Since tamoxifen is considered to be a competitive inhibitor of estrogen action (15), a low steroid environment may be an advantage for the long-term control of breast cancer. Our patients have been monitored for changes in SHBG as well as antithrombin III during long-term tamoxifen adjuvant therapy.

PATIENTS AND METHODS

Patients

All patients attended the clinics of the University of Wisconsin Clinical Cancer Center. Patients were accepted for study based upon their routine attendance at the clinics during 1984–1985. There were 25 women (29–51 years old; mean, 43 years old) who were premenopausal at the time of their mastectomy and 22 women (43–64 years old; mean, 57 years old) who were postmenopausal. All women received adjuvant therapy. The premenopausal women formed two groups: those who received combination chemotherapy (CMFP, N = 15) alone, or those who received combination chemotherapy plus tamoxifen but then the tamoxifen therapy was continued alone (N = 10). The length of time that the patients had been taking tamoxifen alone was between 434 and 2592 days with a mean for the group of 1254 days. The patients ranged between 40 and 58 years old (mean 48.3 years old) at the time the blood samples were drawn. The postmenopausal women formed three groups: those who received combination chemotherapy alone (N = 3), those who received combination chemotherapy plus tamoxifen (N = 8) but had, at the time of study, not taken tamoxifen for at least the past 100 days and those who received chemotherapy plus tamoxifen but who continued to take tamoxifen (N = 11). The length of time tamoxifen alone was taken was at the time of study ranged between 91 and 1560 days with a mean for the group of 734 days. The patients ranged between 48 and 66 years old (mean 60 years old) at the time the blood samples were drawn.

Citrated blood was drawn, centrifuged, and plasma was stored at −70°C in the facilities of the University of Wisconsin Clinical Cancer Center. All plasma samples were coded and assayed as a group for antithrombin III, SHBG, or LH.

Laboratory Assays

Antithrombin III. Antithrombin III was determined by a fluorometric assay using a synthetic substrate d-phenylalanine proline-arginine-S-amido isophthalic acid, dimethylster. The assay kits were purchased from American Dade, Miami, FL. The patient plasma is incubated with thrombin, heparin, and the synthetic substrate. Thrombin causes the release of the fluorescent molecule 5-aminoisophthalic acid dimethyl ester. Residual thrombin activity was calculated as % thrombin inhibited which was computed as a percentage of the value of normal pooled plasma.

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2 To whom requests for reprints should be addressed, at Department of Human Oncology, University of Wisconsin Clinical Cancer Center, 600 Highland Avenue, Madison, WI 53792.
3 The abbreviations used are: SHBG, sex hormone binding globulin; CMFP, cyclophosphamide, methotrexate, 5-fluouracil, and prednisone; LH, luteinizing hormone.
SHBG. SHBG was measured by an immunoradiometric assay purchased from Nuclear Diagnostics Inc., Troy, MI, a supplier for Farmos Diagnostics (Oulu, Finland). Plasma samples were diluted and incubated (1 h) with a monoclonal $^{125}$I-SHBG antibody and anti-SHBG antiserum. A solid phase donkey antirabbit IgE antiserum was added and then 15 m later this was diluted with saline. Tubes were centrifuged and the supernatant decanted for $\gamma$ counting. The normal SHBG value for postmenopausal women (55–82 years old; mean, 68 years old) for the laboratory was 30.8 ± 4.2 nmol/liter ($N = 8$).

LH. LH was measured by a radioimmunoassay kit purchased from Sterne Diagnostics (Braintree, MA). The normal LH values for postmenopausal women (55–82 years old) for the laboratory was 38.8 ± 4.2 mIU/ml ($N = 8$).

RESULTS

The assay of LH (Fig. 1), SHBG (Fig. 2), and antithrombin III (Fig. 3) in the pre- and postmenopausal patients during long-term tamoxifen therapy demonstrate the estrogen-like actions of the drug.

Tamoxifen reduced the level of LH but the effect was the most pronounced in premenopausal patients; in postmenopausal patients there was a reduction in LH levels but this was not statistically significant (Fig. 1).

In contrast, the level of SHBG was increased significantly by tamoxifen in both pre- and postmenopausal patients (Fig. 2). The level of SHBG was doubled by long-term tamoxifen treatment. SHBG and antithrombin III are both produced by the liver but tamoxifen therapy did not appear to produce a dramatic decrease on antithrombin III. In premenopausal patients, the antithrombin III levels were depressed slightly (Fig. 3) but this was not significantly different from control. There was a highly significant difference in the antithrombin III levels between the postmenopausal women treated with tamoxifen compared with those who stopped the drug more than 100 days earlier. In part this result was caused by the increased level of antithrombin III in the patients not taking tamoxifen compared to the normal plasma laboratory control. Nevertheless tamoxifen did depress the antithrombin III level in postmenopausal patients. However none of the patients had a antithrombin III below 70% (the level of clinical significance) of the laboratory control plasma pool.

We obtained plasma from three postmenopausal patients who received adjuvant chemotherapy alone. The values for LH (28.7 ± 13 mIU/ml), SHBG (33.3 ± 3 nmol/liter), and antithrombin III (110 ± 2% compared with laboratory plasma control) were similar to the postmenopausal patients who had stopped tamoxifen but we did not include them in the analysis.

DISCUSSION

The aim of this study was to evaluate the contribution of the estrogen-like effects of tamoxifen upon antithrombin III, LH, and SHBG levels of patients during long-term adjuvant therapy. An earlier report (12) suggested that the estrogenicity of tamoxifen may cause a depression of antithrombin III to place some patients at risk for thromboembolic disorders (10). This present study showed that arbitrarily obtained blood samples...
In summary, tamoxifen has an intriguing pharmacology with a spectrum of estrogenic and antiestrogenic actions. The depression of antithrombin III is not clinically significant but we believe that patients should be monitored to ensure that a clinically significant depression does not occur during therapy. Furthermore, we recommend that women with a history of thromboembolic disorders are considered very carefully for long-term adjuvant therapy with tamoxifen. Finally, the fact that there is a general increase in SHBG should provide additional benefit for the majority of patients with hormone-dependent disease.

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REFERENCES

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