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EFFECT OF TOREMIFENE ON CLINICAL CHEMISTRY, HEMATOLOGY AND HORMONE LEVELS AT DIFFERENT DOSES IN HEALTHY POSTMENOPAUSAL VOLUNTEERS: PHASE I STUDY

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Summary—Toremifene was given within the dose range of 3–680 mg as a single dose or on five consecutive days to 72 postmenopausal volunteers. Blood samples for clinical chemistry were taken hourly up to 7 h and 1, 2, 3, 7, 10 and 15 days after the last dose of toremifene. The concentrations of serum bilirubin, creatinine, amylase, free thyroxine, cortisol, prolactin, electrolytes and blood glucose remained unchanged at all dose levels. A statistically significant decrease was observed in liver enzymes (ASAT, ALAT, ALP) at the dose levels of 220–680 mg, whereas γ-GT remained unchanged. A decrease in the concentration of LH and FSH was observed at the dose levels of 46 mg or higher and 220 mg or higher, respectively. These hormonal changes including the increase of SHBG at the dose levels of 220–680 mg and the decrease of antithrombin III (220–680 mg) may be attributed to a weak estrogen-like effect of toremifene. Side effects were minimal: pulse rate, blood pressure and ECG remained unchanged during the test period. Only two patients on 680 mg dose suffered from nausea and vertigo, and one of them discontinued the medication.

SUBJECTS AND METHODS

The study was undertaken to evaluate the tolerance, and the hemodynamic, biochemical and hormonal effects of toremifene. Increasing doses (3–680 mg) were administered as a single administration or daily for five consecutive days to 72 healthy postmenopausal volunteers [mean (±SD) age = 54 (±8.3) yr; mean (±SD) time elapsed after menopause = 8.7 (±4.7) yr]. All were gynecological outpatients and none suffered from active malignant disease, severe endocrinological, heart, pulmonary or other disease. There were three patients in the dose groups of 3, 10 and 22 mg, and five patients in other groups.

Toremifene citrate, containing 3, 10, 22, 46, 68, 100, 220, 460 and 680 mg of toremifene, was given in soft gelatine capsules. Each capsule was ingested on an empty stomach at 0800 with 200 ml of water.

Blood samples were taken immediately before toremifene administration and, in the single dose study, at 1, 2, 3, 4, 5, 6 and 7 h and 1, 2, 3, 7, 10 and 15 days after administration. In the 5-day study, samples were taken each day just before toremifene administration as well as 1, 3, 7, 10 and 15 days after the last dose of toremifene. Serum was separated by centrifugation and stored at −20°C until assayed. The following analyses were performed in both groups: red blood cell count (RBC), differential white blood cell count (WBC), serum direct and indirect bilirubins (S-Bil dir and S-Bil indir), antithrombin III (AT III, in dose groups of 220–680 mg), ASAT (SGPT), ALAT (SGOT), alkaline phosphatase (ALP), gammaglutamyl transpeptidase (γ-GT), potassium (S-K), sodium (S-Na), calcium (S-Ca), phosphate (S-PO_4), creatinine (Fs-Crea), fasting blood glucose (Fb-gluc), LH, FSH, sex hormone-binding globulin (SHBG), cortisol (Cor), thyroxine (T_4), thyroid-stimulating hormone (TSH) and prolactin (PRL). The analyses were carried out by standard procedures of the hospital laboratories. Hormones were measured by RIA kits (Farmos Diagnostica, Turku, Finland). The measured hemodynamic parameters were pulse rate, systolic and diastolic blood pressure as well as ECG which was taken before and after the study.

Urine samples were collected for glucose and protein determinations on the day before the toremifene administration and on days 1, 2, 3, 7, 10 and 15 in the single-dose study and on days 1, 3, 7, 10 and 15 after the last toremifene dose in the 5-day study. Paired t-test was used for statistical evaluation.

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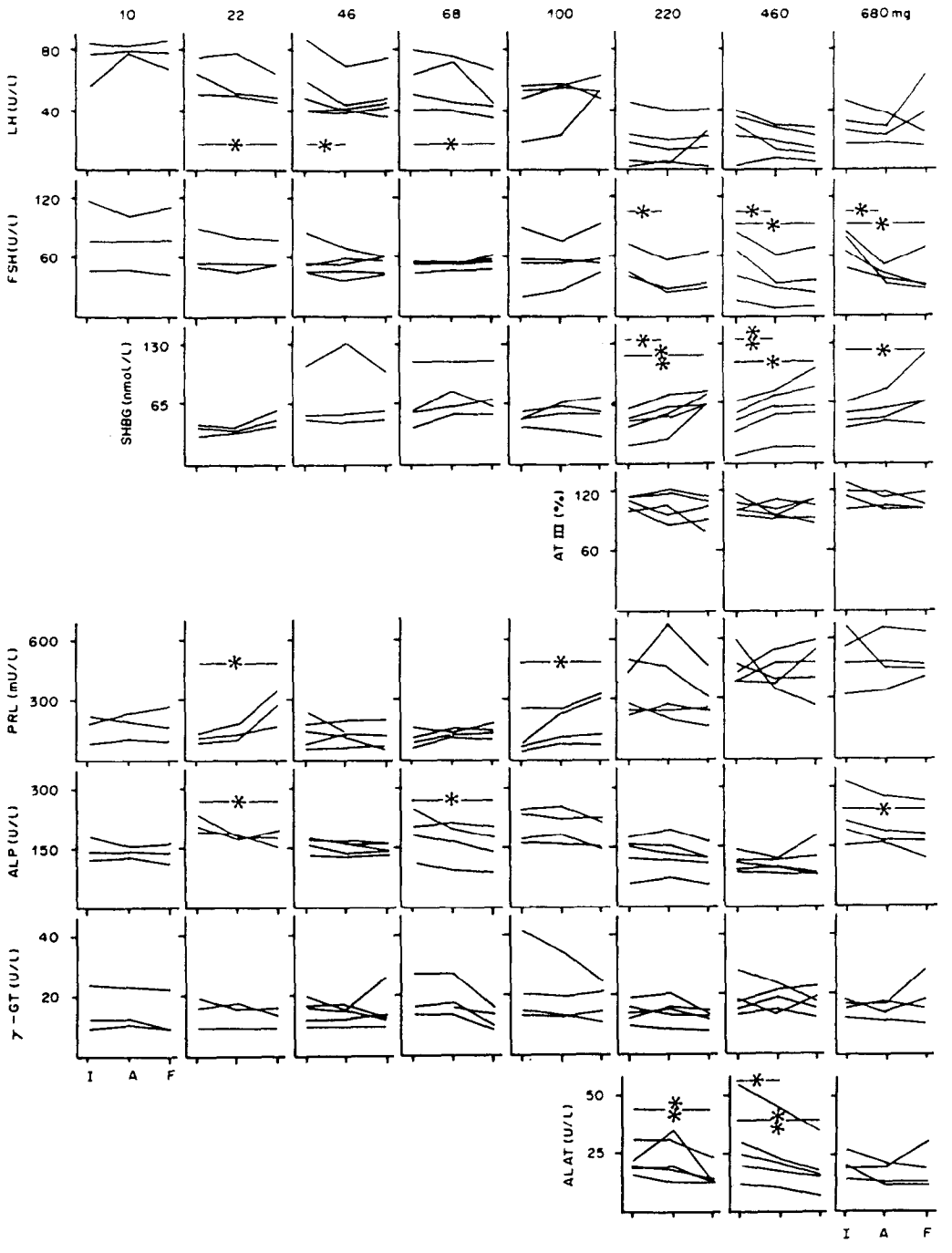

Fig. 1. Effect of 5-day high-dose toremifene administration on LH, FSH, SHBG, AT III, prolactin (PRL), ALP, γ-GT and ALAT in healthy postmenopausal volunteers. Statistically significant changes from initial (I, immediately before the first dose) to the after the fifth dose (A) or to final (F, 15 days after the last dose) values have been indicated by (* = $P < 0.05$ or ** = $P < 0.01$ by paired t-test.

RESULTS

In the single-dose group there were no statistically significant deviations from the normal range in any measured biochemical, hematological or hormonal values at any dose level except a decrease in hemoglobin and increase in WBC concentrations. These changes were due to abundant blood sampling.

Effect of toremifene on biochemistry and hematology

The results of the biochemical and hematological determinations in the 5-day administration group showed increases in WBC and decreases in ASAT, ALAT and ALP at doses above 220 mg. The decrease in ALAT and ALP was statistically significant at the three highest dose levels (220–680 mg) in 13 out of 14

Table 1. Effect of 5-day toremifene administration at different dose levels on clinical chemistry and hematology

Dose	3	10	22	46	68	100	220	460	680
LH	±	±	±	↓	↓	±	↓	↓	↓
FSH	±	±	±	±	±	±	↓	↓	↓
SHBG	±	±	↑	±	↑	↑	↑	↑	↑
Cortisol	ND	ND	ND	ND	ND	ND	↑	↑	↑
T_4	±	±	±	±	±	±	±	±	±

Changes of the measured values have been indicated. ± = no statistically significant changes, ↑ increase ($P < 0.05$), ↓ decrease ($P < 0.05$).
ND = not determined.

patients (Fig. 1), whereas the serum values of γ-GT were not changed.

The changes in the concentrations of bilirubins, potassium, sodium, calcium, phosphate, creatinine, amylase and Fb-glucose were not statistically significant. The changes in the pulse rate, blood pressure and ECG during the test period were negligible. Traces of albumin in the urine—obviously not drug related—were observed temporarily in four subjects.

Twelve out of 14 patients at the dose levels 220–680 mg showed decreased hemoglobin ($P < 0.05$) and increased WBC. This was apparently due to abundant blood sampling. The alterations in the AT III concentration were inconsistent and statistically not significant in individual test groups (Fig. 1). However, in 12 of 14 patients there was a significant decrease of AT III as early as one day after the last dose ($P < 0.05$), lasting up to 15 days ($P < 0.001$).

Effect of toremifene on serum hormones

In the single dose study no statistically significant changes were recorded. In the 5-day study no statistically significant changes were observed in the serum values of T_4, TSH and prolactin. LH concentrations were decreased (Table 1), and the decrease was most significant 1 week after the last dose. At the three highest doses the decrease was still significant ($P < 0.01$) 15 days after the last dose. The decrease of FSH was statistically significant only at doses of 220 mg or more ($P < 0.05$) (Fig. 1). Serum cortisol tended to increase at the dose levels of 220–680 mg (all values were morning values). In the 460 mg dose group cortisol was still elevated ($P < 0.05$) after 15 days. Slight elevation of SHBG was a consistent finding at almost all doses. At the two highest dose levels the SHBG increase ($P < 0.05$) persisted to the end of the test period (Fig. 1).

General tolerance and side effects

None of the subjects reported any immediate or late side effects at any dose level in the single-dose study. The following side effects and symptoms were recorded in the 5-day study: fatigue in connection with fasting and sampling in the women receiving 46 mg or less. Insomnia in one subject at the dose of 100 mg as from the third day of the test. Fits of perspiration at the dose of 100 mg in two women. One of them complained of pain in the lower abdomen on the first day after completion of the study. One volunteer on 680 mg suffered from slight vertigo on the third medication day. The symptoms aggravated on the following day, were very intense on the next day (i.e. the last medication day) but disappeared late in the evening. Another subject on the same dose was uncapacitated by severe heart burn and nausea which started about 6 h after the first dose and persisted until the fourth day when the investigator discontinued the drug. The symptoms, which also included vertigo, disappeared slowly during the next 36 h.

DISCUSSION

Toremifene is a new antiestrogenic compound but it has also a slight intrinsic estrogen-like effect. The first signs of hormonal activity, a decrease in LH and an increase in SHBG, were already seen at the daily dose of 22 mg. The significant decrease, although within normal limits, of AT III resembles that of combined oral contraceptives [1], where the reduction appears to be correlated with estrogen dose. There is no evidence that low serum concentrations of AT III would increase thrombotic risk [2]. The decrease in LH and FSH concentrations induced by even a single dose of toremifene resembles that of tamoxifen when given 40 mg daily for 2 weeks [3]. The statistically significant increase in SHBG and cortisol values also reflect a direct estrogen-like activity of toremifene. A similar effect has been described by other synthetic anti-estrogens, clomiphene [4] and tamoxifen [5]. The decreasing tendency of the four analyzed liver enzymes, ASAT, ALAT, ALP and γ-GT, indicate, however, that toremifene does not have harmful effects on liver function.

Nausea, vomiting and dizziness have been reported in 10% of patients on low-dose tamoxifen (60 mg or less daily) [3] whereas none of the patients in this study reported such side effects at the dose levels of 460 mg or less daily. Fatigue, weakness, sweating and insomnia, which were observed at lower dose levels i.e. 100 mg daily or less, can be attributed to the daily fasting and blood sampling. Nausea and heartburn in one subject on the 680 mg dose can be attributed to the direct irritative effect of toremifene on the mucous membrane of the stomach whereas vertigo in another

subject on the same may be due to a direct effect of toremifene on the central nervous system. The pharmacokinetic studies—performed within this study—indicated that these two women with side effects did not have higher serum concentrations of toremifene than two women who received the same dose without side effects. Thus, serum concentrations of toremifene did not predict the side effects.

Conclusion

These preliminary results indicate that toremifene is well tolerated up to 460 mg daily administered orally and its hormonal effects resemble those of tamoxifen.

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