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Pharmacokinetics of Tamoxifen in Premenopausal and Postmenopausal Women with Breast Cancer

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We measured the serum levels of tamoxifen and 5 of its metabolites in serum from 7 premenopausal and 9 postmenopausal women during the first 56 days of treatment. The serum levels of *N*-desdimethyltamoxifen were higher in postmenopausal women compared to premenopausal women ($P < 0.02$). A similar trend was observed for *N*-desmethyltamoxifen ($P = 0.06$).

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INTRODUCTION

Tamoxifen is a first line drug in the treatment of breast cancer [1, 2]. Up to now more than 3 million women with breast cancer have been treated with tamoxifen. The drug seems to be less effective in premenopausal women [1, 2]. Ongoing trials are evaluating the drug as a chemopreventive agent in pre- and postmenopausal women at high risk of developing breast cancer [3–5].

Tamoxifen is extensively metabolized, mainly through demethylation and hydroxylation. The serum levels of the demethylated metabolites are of the same magnitude as the parent drug whereas concentrations of the hydroxylated metabolites are low [6]. The hydroxylated metabolites may, however, be of pharmacological importance since their affinity towards the oestrogen receptor far exceeds that of the demethylated metabolites and the parent drug [7].

Most pharmacokinetic studies on tamoxifen have been performed on postmenopausal women [8]. Since tamoxifen seems to be more effective in postmenopausal women [1, 2] and an increasing number of premenopausal women are treated with tamoxifen, knowledge of the pharmacokinetics of tamoxifen in premenopausal women is also needed. We have compared the serum levels of tamoxifen and five metabolites in pre- and postmenopausal women during the first 56 days of treatment.

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PATIENTS AND METHODS

All patients attended the Department of Oncology at the Bergen University hospital. The mean age of the premenopausal women ($n = 7$) was 43.9 y (range 36–49) and of the postmenopausal women ($n = 9$) 60.9 y (range 51–74).

The premenopausal patients had no known diseases other than breast cancer. Two of the postmenopausal women had ischemic heart disease; two had diabetes and one used thyroxin for hypothyroidism.

Three of the premenopausal patients received 20 mg tamoxifen once daily. The other patients were treated with a standard dose of 30mg once daily. Blood was drawn just before intake of the first dose, and then non-fasting on days 1, 2, 3, 4, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, 30, 32, 36, 39, 43, 46, 49, 52 and 56 after start of treatment.

We used a liquid chromatography method which was developed for the determination of tamoxifen and metabolites in serum [9].

We adjusted for serum concentrations of the three premenopausal women who used the dose of 20 mg tamoxifen daily to a daily dose of 30 mg. Due to small numbers of patients and patient drop outs at sampling time, we estimated the mean concentrations for each patient in four time intervals, i.e. day 0–5, day 8–19, day 22–36, and day 39–56. The serum concentrations of pre- and postmenopausal women were compared using analysis of variance for repeated measures. *P*-values below 0.05 were regarded as significant. Analyses were carried out with program 2 V in the BMDP Statistical Package which is a parametric method [10]. As the study variables followed a normal

distribution the analysis was performed on untransformed data.

RESULTS

During the first 56 days of treatment, the mean serum concentrations of *N*-desdimethyltamoxifen and *N*-desmethyltamoxifen were higher in postmenopausal than in premenopausal women. After adjusting for dose, there was still a difference in mean values between the two patient groups for *N*-desdimethyltamoxifen ($P < 0.02$, Fig. 1), and a trend was observed for *N*-desmethyltamoxifen ($P = 0.06$). For tamoxifen and several hydroxylated metabolites no significant difference was detected ($0.2 \geqslant P \geqslant 0.1$).

DISCUSSION

In this preliminary study the serum concentrations of *N*-desdimethyltamoxifen were higher in postmenopausal than in premenopausal patients during the first eight weeks of treatment ($P < 0.02$), whereas a trend was observed for *N*-desmethyltamoxifen ($P = 0.06$). Because tamoxifen and its demethylated metabolites may reach concentrations in tissues, which have been shown to be cytotoxic in experimental studies with human breast cancer cells [11, 12], this finding may be of importance.

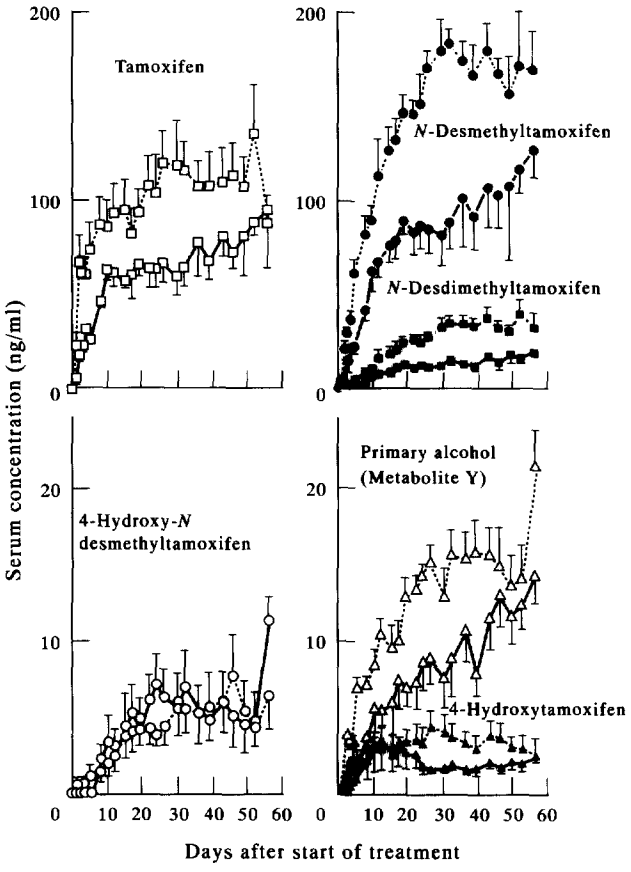

Fig. 1. Serum concentrations of tamoxifen and its metabolites during the 56 first days of tamoxifen treatment of premenopausal (solid lines) and postmenopausal (broken lines) breast cancer patients. Vertical bars represent standard error of the means.

The design of the present study does not allow delineation of the kinetic parameters, and mechanism(s) behind the reported difference would be conjectural. Differences in absorption, distribution, or metabolism should be considered as possible causes.

Older women may have a better compliance to tamoxifen therapy than younger women [13], and some drugs are more completely absorbed in older than in younger patients [14]. Tamoxifen and its metabolites are lipophilic compounds with a large distribution volume and extensive binding in tissues including bone [11]. A higher distribution volume in premenopausal women may partly explain our findings. Weight gain, which is a side effect of tamoxifen, is more common in premenopausal women than in postmenopausal women [15, 16].

Finally, decreased tamoxifen metabolism and low tamoxifen clearance in postmenopausal compared to premenopausal women are unlikely for several reasons. Such pharmacokinetic alterations would increase rather than reduce (Fig. 1) the time required to obtain steady state. In addition, age-related decrease in hepatic metabolism [17] is expected to alter the ratio between serum levels of metabolites and the parent drug, and this was not observed in the present study (data not shown). Furthermore, *N*-demethylation of tamoxifen in the microsome fraction of human liver has been found to be independent of age of the tissue donor [18].

Tamoxifen treatment causes pronounced elevation in serum oestradiol levels in premenopausal women. This effect increases the difference in serum oestradiol levels between premenopausal and postmenopausal women. Experimental studies with mice [19] suggest that a high level of oestradiol may antagonize the receptor blocking effect of tamoxifen. Thus, pharmacodynamic, besides pharmacokinetic properties of tamoxifen may explain the clinical observation that the benefit from adjuvant tamoxifen treatment of breast cancer is considerably less in patients below 50 years of age compared to older women [1, 2].

In conclusion, the results of this preliminary study suggest different tamoxifen pharmacokinetics in premenopausal and postmenopausal women. Thus, less favourable clinical effects from tamoxifen treatment in premenopausal women may be explained by pharmacokinetics as well as pharmacodynamic factors including different oestrogen status. Optimal tamoxifen dosing in future clinical trials has a bearing on knowledge on pharmacokinetics in these two patient categories, and should be investigated further.

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