Effects of hormones on the plasma levels of the atherogenic amino acid homocysteine

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Introduction

Growing evidence suggests that elevated plasma levels of total homocysteine (tHcy) are associated not only with arterial thrombosis and atherosclerosis but also with venous thrombosis [1,2].

tHcy levels appear to be related to oestrogen status. Premenopausal women have lower levels than postmenopausal women and men. In addition, plasma tHcy has been reported to decrease in pregnancy, in postmenopausal women on hormone-replacement therapy and during the high hormone phase in women taking oestrogen-containing contraceptives (for references see [3]).

Cardioprotective action of tamoxifen

The antioestrogen tamoxifen is the drug most commonly used for endocrine treatment of breast cancer. Initially, the drug was used for treatment of advanced disease. It is now widely used for adjuvant therapy and is explored as a chemopreventive agent in women at high risk for developing breast cancer [4].

Tamoxifen also has oestrogen agonistic effects. Thus it acts as an oestrogen agonist on plasma proteins [5,6] as well as on blood lipids [7,8]. This may in turn result in a reduction in cardiovascular disease during tamoxifen treatment. Clinical studies support this suggestion.

In a Scottish trial on adjuvant tamoxifen, patients who received the drug for a 5-year period experienced a reduction in fatal myocardial infarctions of more than 50% compared with placebo-treated controls [9]. In a Swedish study, tamoxifen treatment was associated with a reduced incidence of hospital admissions because of cardiac disease [10]. The cardioprotective effect of tamoxifen may be due to a moderate reduction in plasma cholesterol [7,8,11], but it is not known whether this is the only explanation.

Tamoxifen suppresses serum cholesterol by a mean value of 10–15% [7,11]. In an analysis of 19 randomized trials, a 1% reduction in cholesterol was associated with 2.5% reduction in cardiovascular mortality rate. Accordingly, a 10–15% reduction in plasma cholesterol may account for a reduction in cardiovascular mortality of about 25–35% (for references see [3]). This suggests that additional factors may contribute to the effect during tamoxifen treatment.

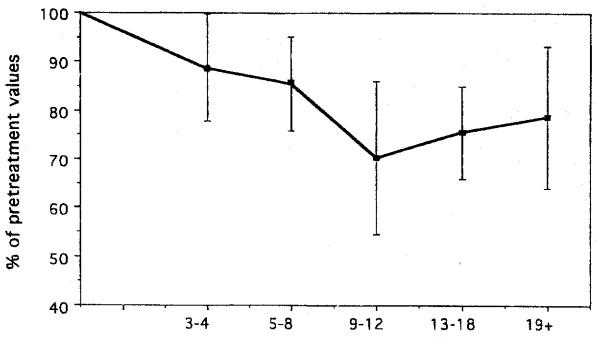
Influence of tamoxifen on plasma tHcy levels

We have studied the effect of tamoxifen on tHcy in postmenopausal patients with breast cancer [3]. Plasma tHcy levels were determined by a modification of an automated procedure developed for the determination of tHcy in plasma [12].

Plasma tHcy decreased by a mean of 30% after 9–12 months of tamoxifen treatment (Figure 1). The decrease in plasma tHcy was correlated with the pretreatment tHcy levels, so that the patients with the highest pretreatment tHcy level showed the largest absolute decrease in plasma tHcy. Thus the patients that may be at high risk of developing coronary heart disease because of elevated plasma tHcy levels are those who may benefit most from tamoxifen treatment. This may, together with a favourable effect of tamoxifen on the serum lipid profile, contribute to the observed decrease in coronary heart disease in patients with breast cancer taking tamoxifen. Furthermore the effect of tamoxifen treatment on tHcy may be lower in populations

Figure 1

Mean plasma tHcy levels with 95% confidence intervals before and during tamoxifen treatment expressed as percentage of pretreatment values



Abbreviation used: tHcy, total homocysteine.
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with lower tHcy levels, for instance in premenopausal women.

The average reduction in plasma tHcy induced by tamoxifen equals the difference in plasma tHcy between a population with vascular disease compared with healthy controls [13,14]. A recent prospective analysis including both men and women indicates that the relative risk for coronary heart disease may be increased by 40% for each 4 μmol/l increase in plasma tHcy, and somewhat higher for women than for men [15]. Thus a reduction in plasma tHcy level as observed during tamoxifen treatment in this study may correspond to a reduction in cardiovascular disease of about 20–30%.

There was no correlation between plasma tHcy and the tumour burden before tamoxifen treatment, and we did not find any difference in tHcy response to tamoxifen treatment between patients with and without macroscopic disease. Therefore a reduced tumour burden in patients responding to tamoxifen is not a likely mechanism behind the decrease in plasma tHcy.

Tamoxifen acts as an oestrogen agonist or an antagonist, depending on species, target organ studied and the end point measured [16]. Similar effects of tamoxifen and oestrogens on plasma tHcy suggest that the tHcy-lowering effect of tamoxifen may be due to oestrogen-agonistic properties. Other mechanisms may be involved as well. Plasma tHcy has been established as an indicator of intracellular folate functions, and has been negatively correlated to folate in serum in a large series of hospitalized subjects [17]. We found a negative correlation ($P < 0.02$) between pretreatment values of plasma tHcy and erythrocyte folate in our patient group, even though 30 of 31 patients had plasma and erythrocyte folate levels in the normal range.

Tamoxifen treatment tended to elevate plasma as well as erythrocyte folate concentrations, but the 95% confidence intervals of the mean values spanned the 100% control values. Nonetheless, tamoxifen may also exert its influence on tHcy disposition, at least partly, by interacting with folate disposition. This hypothesis deserves further investigation.

Influence of other hormone-modulating drugs on plasma tHcy levels

Recent preliminary results from studies on tHcy before and during treatment with other hormone-modulating drugs indicate that the mechanisms involved are complex. Aminoglutethimide, an aromatase inhibitor that blocks the conversion of androgens into oestradiol in postmenopausal women, causes a marked increase in plasma tHcy (G. Anker, E. A. Lien, H. Refsum, P. M. Ueland, D. C. Johannessen and P. E. Lønning, unpublished work). However, aminoglutethimide is also an efficient inducer of mixed-function oxidase, and may possibly enhance folate turnover, which may result in an increase in plasma tHcy. This is in keeping with the finding that some new steroidal aromatase inhibitors, examestane and formestane, seem not to have any influence on plasma tHcy during the first 5 months of treatment (G. Anker, E. A. Lien, H. Refsum, P. M. Ueland, D. C. Johannessen and P. E. Lønning, unpublished work). In addition, treatment in six premenopausal breast cancer patients for up to 8 weeks with a luteinizing hormone-releasing hormone analogue, goserelin, which causes medical castration and oestradiol reduction to postmenopausal level, did not significantly affect plasma tHcy (E. A. Lien, unpublished work).

Influence of disease states on plasma tHcy levels

The plasma levels of tHcy have also been studied during hyperthyroidism, hypothyroidism and diabetes. During hypothyroidism and diabetes the levels of tHcy were increased compared with controls whereas the levels tend to be low during hyperthyroidism [18,19]. The mechanisms of action of thyroid hormones and insulin have not been further examined.

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