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Effect of letrozole on the lipid profile in postmenopausal women with breast cancer

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Abstract

Hormonal therapy plays a central role in the overall treatment of breast cancer. Aromatase inhibitors can inhibit the aromatase enzyme system resulting in a reduction of oestrogens. Letrozole is a non-steroidal aromatase inhibitor that effectively blocks aromatase activity without interfering with adrenal steroid biosynthesis. The drug can significantly reduce the levels of plasma oestrogens, which remain suppressed throughout the treatment. Data are scarce concerning the influence of these drugs on serum lipid levels. In the present study, we evaluated the effects of letrozole on the serum lipid profile in postmenopausal women with breast cancer. A total of 20 patients with breast cancer were treated with letrozole, 2.5 mg once daily. After an overnight fast, serum lipid parameters (total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, apolipoproteins A1, B and E and lipoprotein (a)) were measured before treatment and at 8 and 16 weeks afterwards. A significant increase in total cholesterol ($P=0.05$), LDL cholesterol ($P<0.01$) and apolipoprotein B levels ($P=0.05$) in the serum, as well as in the atherogenic risk ratios total cholesterol/HDL cholesterol ($P<0.005$) and LDL cholesterol/HDL cholesterol ($P<0.005$) was noticed after letrozole treatment. We conclude that letrozole administration in postmenopausal women with breast cancer has an unfavourable effect on the serum lipid profile.

Keywords: Aromatase inhibitor; Cholesterol; Letrozole; Lipid parameters; Triglycerides

1. Introduction

Hormonal therapy plays a prominent role in the overall treatment of breast cancer [1]. Aromatase inhibitors can inhibit the aromatase enzyme system leading to a reduction of oestrogens, as a result of blocking the conversion of androgens to oestrogens [2–4]. Letrozole is a non-steroidal aromatase inhibitor that is more specific and better tolerated than aminoglutethimide, which was originally introduced as the first clinically useful aromatase inhibitor [5–7]. In doses of 0.5–2.5 mg/day the drug effectively blocks aromatase activity without interfering with adrenal steroid biosynthesis. It can substantially reduce the levels of plasma and urinary oestrogens, which remain suppressed throughout treatment [5–7]. This letrozole-induced decrease in plasma oestrogens could result in a deterioration of the lipid profile in women with breast cancer treated with the drug. There is no adequate information in the literature concerning the influence of this group of drugs on the serum lipid profile. Corta and colleagues studied the effect of fadrozole on routine lipid parameters in 14 postmenopausal women with breast cancer [8]. A comparable study between letrozole and aminoglutethimide showed that hypercholesteroaemia developed in 3.8% of the patients receiving letrozole (2.5 mg/day). However, no detailed evaluation of lipid parameters was carried out in this report [9]. Thus, we undertook the present study to evaluate the effects of letrozole on serum lipid parameters, including apolipoproteins and Lipoprotein (a) (Lp(a)), in postmenopausal women with metastatic breast cancer.

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2. Patients and methods

2.1. Patient population

The study group consisted of 20 fully ambulatory postmenopausal women aged 46–68 years with advanced breast cancer who were allocated to receive hormonal treatment with letrozole (2.5 mg once daily), and had no evidence of liver metastases. Patients' characteristics are shown in Table 1. Patients with diabetes mellitus, hypothyroidism (thyroid stimulating hormone (TSH) >4.8 mU/ml), liver or renal failure, proteinuria, alcoholism, or primary hyperlipidaemia were excluded. Moreover, no subject in the study was administered drugs known to affect lipid metabolism, such as diuretics, beta-blockers, corticosteroids, cyclosporin, etc. For patients receiving tamoxifen, the median time between the end of tamoxifen treatment and the initiation of letrozole was 11 months (range 2–72 months). The mean pretreatment body weight was 61 kg (range 51–73 kg), which did not alter significantly during the study. Patients were instructed to follow their usual diet. Prior to treatment with letrozole, as well as at 8 and 16 weeks afterwards, venous blood was obtained after an overnight fast for the determination of lipid parameters. Blood samples were centrifuged for 15 min (3000*g*) and then the serum was separated and stored at 4°C for less than 48 h for analysis of lipid parameters. Serum for the assay of Lp(a) was frozen and stored at −70°C. Written informed consent was obtained from all subjects. The study was approved by the Scientific Committee of our hospital.

2.2. Laboratory determinations

Concentrations of total cholesterol and triglycerides were determined enzymatically on the Olympus AU600 Clinical Chemistry analyser (Olympus Diagnostica, Hamburg, Germany). High density lipoprotein (HDL) cholesterol was determined in the supernatant, after precipitation of the ApoB-containing lipoproteins with dextran sulphate-Mg^{++} (Sigma Diagnostics, St. Louis, MO, USA). Low density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula. Apolipoproteins A1, B and E were measured with a Behring Nephelometer BN100, and reagents (antibodies and calibrators) from Dade Behring Holding GmbH (Liederbach, Germany). The ApoA1 and ApoB assays were calibrated according to the International Federation of Clinical Chemistry (IFCC) standards. Lp(a) levels were determined by the enzyme immunoassay Macra Lp(a) (Trinity Biotech, Jamestown, NY, USA). The lower limit of detectability was 0.8 mg/dl.

Table 1
Clinical characteristics of the study population

Number	20
Mean age (range)	54 (46–68) years
Body mass index[a] (kg/mÇ)	23.4±1.8 (21–27)
Prior adjuvant chemotherapy (*n*)	13
Prior adjuvant hormonotherapy (*n*)	9
Prior hormonal treatment for metastatic disease (*n*)	11
Metastatic sites (*n*)	
Skin	5
Pleura	2
Bone	13
Lymph nodes	4

[a] Mean±standard deviation (S.D.) (range).

3. Statistical analysis

Values of all parameters were expressed as means ±standard deviations (S.D.). A repeated measures analysis of variance (ANOVA) was applied to each variable to assess changes in response over time. Linear regression analysis was performed for correlations between parameters. For variables with a non-normal distribution, logarithmic transformation was applied before the statistical analysis. A P of <0.05 was considered statistically significant.

4. Results

As shown in Table 2, letrozole administration was followed by a deterioration of the serum lipid profile; specifically, a significant increase in serum total and LDL cholesterol, as well as in ApoB levels was noticed. No significant changes in serum triglyceride, Lp(a), ApoE, HDL cholesterol and ApoA1 levels were observed. However, there was a trend towards a decrease in HDL cholesterol and ApoA1 levels. Consequently, a significant increase in the atherogenic risk ratios total cholesterol/HDL cholesterol, LDL cholesterol/HDL cholesterol and a significant decrease in the anti-atherogenic risk ratio ApoA1/ApoB was found. Similar results were obtained in both hypercholesteroaemic (total cholesterol >200 mg/dl, $n=13$) and normocholesteroaemic patients ($n=7$) participating in the study. There were no significant differences in the serum lipid levels between patients with metastatic disease ($n=13$) and those without ($n=7$) nor was there any significant difference in their percentage changes after letrozole therapy between the two groups (data not shown).

5. Discussion

Our study showed for the first time that letrozole administered at a dose of 2.5 mg once daily significantly influenced serum lipid parameters, including apolipo-

Table 2
Effects of letrozole on serum lipid parameters

Parameter	Before treatment ($n=20$)	After 8 weeks (n = 20)	After 16 weeks ($n=20$)	P value[a]
T CHOL (mg/dl)	239±56	259±58	258±53	0.05
HDL CHOL (mg/dl)	65.3±17.9	60.8±14.5	60.4±13.5	NS
LDL CHOL (mg/dl)	148±50	169±55	170±53	<0.01
TRG (mg/dl)	130±69	148±73	128±56	NS
ApoA1 (mg/dl)	185±29	177±21	172±22	NS
ApoB (mg/dl)	109±36	120±37	117±32	0.05
ApoE (mg/dl)	42.1±14.9	52.8±15.6	49.9±9.5	NS
Lipoprotein (a) (mg/dl)	13.0±11.0	13.8±10.5	14.0±9.0	NS
T CHOL/HDL CHOL	3.94±1.46	4.53±1.53	4.48±1.40	0.005
LDL CHOL/HDL CHOL	2.46±1.13	2.97±1.24	3.00±1.18	<0.005
ApoA1/ApoB	1.91±0.85	1.62±0.65	1.62±0.69	0.005

T CHOL, total cholesterol; HDL CHOL, high density lipoprotein cholesterol; LDL CHOL, low density lipoprotein cholesterol; TRG, triglycerides; Apo, apolipoprotein; NS, non significant.
[a] By repeated measures analysis of variance.

proteins, over a treatment period of 16 weeks. This effect was independent of the baseline cholesterol levels, as well as the presence of metastatic disease. These data contradict those of a previously published study which showed that fadrozole, a second generation aromatase inhibitor, was not associated with a significant alteration of lipid parameters [8]. In that study, only the classic lipid parameters were included, while there were no data on apolipoproteins and Lp(a), which are known to be affected by oestrogens or tamoxifen [10]. Furthermore, it is worth mentioning that letrozole is a third generation aromatase inhibitor and thus exhibits a substantially greater potency in suppression of aromatase than fadrozole [11,12]. Our results suggest that the third generation aromatase inhibitors, unlike other hormonal treatments, such as tamoxifen, which has been found to have a favourable effect on lipid metabolism [10,13], compromise the lipid profile of postmenopausal women with breast cancer and induce a substantial increase in LDL cholesterol and ApoB levels. Furthermore, a considerable increase in the atherogenic risk ratios known to significantly increase the cardiovascular risk in the general population was noticed [14,15]. Since letrozole treatment was initiated, in most cases, at a considerable time after tamoxifen discontinuation, tamoxifen has a long half-life, the unfavourable changes in the lipid profile observed do not reflect the tamoxifen cessation, but rather are a true effect of letrozole. It is tempting to suggest that these effects on serum lipid parameters may be related to the drug's oestrogen lowering activity, as oestrogens may still play a role in lipid metabolism in postmenopausal women [16]. Alternatively, or synergically, the aromatase inhibitors, may interfere with enzymatic pathways in the liver or with bile acid secretion, as is the case with tamoxifen, which has been found to inhibit the conversion of delta-8 cholesterol to lathosterol leading to a downregulation of cholesterol synthesis [17,18].

Considering the potential future of aromatase inhibitors, their unfavourable effect on the serum lipid profile could substantially increase cardiovascular morbidity and mortality. However, further studies with a larger number of participants are needed to investigate the long-term effects of aromatase inhibitors on lipid metabolism and their consequences.

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