INTRODUCTION

Breast cancer is one of the commonest causes of cancer mortality in females. Treatment of breast cancer is complex and involves surgery, radiotherapy, chemotherapy and hormonal therapy depending on the stage and estrogen receptor status of the disease in the individual patient. Tamoxifen, has been the main stay of hormonal treatment of all phases of breast cancer and represents a major therapeutic advance for clinical practice.  

Originally it has been classified as anti-estrogen but subsequent experience has shown that it has agonistic activity on bone, liver and endometrium and hence now classified as selective estrogen receptor modulator. It shares the beneficial effects of estrogens on cardiovascular risk factors by decreasing total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) both in pre-menopausal and postmenopausal women.  

Whereas, it produces no significant change in triglyceride (TG), high density lipoprotein cholesterol (HDL-c) and very low-density lipoprotein cholesterol (VLDL-c) levels in pre-menopausal and postmenopausal women.  

Contrary results are also available in this regards as, many authors failed to show any change in TG, VLDL-c and HDL-c after tamoxifen therapy. Similarly, Sharma, Miyauchi, et al and Atalay, et al contrary to above findings have reported tamoxifen to increases the levels of TG. As well as, Bruning showed increase in HDL levels contrary to above mentioned reports in both pre-menopausal and postmenopausal patients.

Most of the reports regarding the effects of tamoxifen on lipid profile originate from outside India and there is paucity of data regarding these effects in India and the data whatsoever available is controversial. Thus, in view of these contrary and varying reports it becomes even more important to evaluate the effect of tamoxifen therapy on lipid profile in patients of breast cancer. Moreover, knowing its relationship with cardiovascular risk factors will lead to better clinical understanding. Therefore, the present study has been undertaken to assess the effect of tamoxifen therapy on plasma lipid profile in pre-menopausal and postmenopausal patients of breast cancer.

MATERIAL AND METHODS

A prospective, non-randomized study over a period of one year was conducted in the Post Graduate Department of Pharmacology and Therapeutics in collaboration with Department of Radiotherapy and Oncology and the Postgraduate Department of Radiodiagnosis and Imaging, Government Medical College, Jammu in postoperative patients of breast cancer. A total
of 55 pre-menopausal and postmenopausal patients of breast cancer (35 to 75 years) participated in this study. The study was approved by institutional ethics committee. Written informed consent was obtained from all patients after explaining the nature and purpose of study. All patients were subjected to a detailed history, clinical and gynecological examination. Patients with normal routine laboratory tests, urine test, biochemical tests like (LFT, RFT, and blood sugar) and ECG were included in the study.

Any patient with unexplained uterine bleeding, preexisting endometrial cancer, diabetes mellitus, thyroid function abnormalities or other endocrinopathies were excluded. Patients receiving other medications, likely to interfere with the drug under study or serum lipid profile, three months prior to the trial and patients taking concomitant chemotherapy or estrogenic hormones or who had undergone hysterectomy or oophorectomy were also excluded. Patients were given tablet tamoxifen 20mg (Tamoxifen citrate–Dabur India Ltd.) per oral daily for 6 months.

Lipid profile was done in new patients of early stage breast cancer who were to be started on tamoxifen as an adjuvant therapy. A total of 55 patients of breast cancer participated in this study and finally 49 patients completed the study. Out of total 49 patients 14, were pre-menopausal and 35 were postmenopausal patients. Each patient was kept under treatment for six months and had to undergo three post registration visits at 0 day, 3 months and at 6 months. During first (0 day) visit, serum TC, LDL-c, TG, VLDL-c and HDL-c were recorded and were considered as pre-drug values. During follow up visit at 3 months and at 6 months, same parameters were reassessed. All adverse effects experienced during the trial were also recorded.

Estimation of plasma lipid: Subjects were asked to report after an overnight fasting. Three ml of venous blood was withdrawn and allowed to clot at room temperature. Plasma was obtained by centrifugation at 3000 revolutions per minute. Plasma lipids were estimated by standard enzymatic method in a semiautomatic analyzer (ERBA – CHEM PRO). Total cholesterol was estimated by cholesterol oxidase peroxidase method (CHOD/PAP method) using cholesterol reagent set provided by Ranbaxy Labs Ltd. Triglycerides were estimated by GPO – ESPAS method using Enozokit-triglycerides kit procured from Ranbaxy Labs. Ltd. Whereas, LDL-c kit from Diagnostic Systems International was used for the estimation of LDL-c by select F.S.(fluid stable) method and HDL-c kit from Dr. Reddy’s Lab was used for estimation of HDL-c by PEG precipitation and enzymatic method. VLDL was estimated using the Friedwald’s formula as: VLDL = TG/5.

**Statistical analysis**: The data was expressed in Mean ± SEM or percentage. The results obtained (Mean ± SEM) were analyzed by applying unpaired-t-test for evaluation of intergroup significance. The intragroup significance was assessed using paired-t-test. Chi-square test was used for the data expressed in percentage. Adverse effects were analyzed using chi-square test.

### Results

**Effect of tamoxifen on plasma lipids (Table 1). Pre-menopausal patients (mean age 37.92 ± 1.30 years)**

After drug administration there was decrease in total cholesterol by 6.57mg/dl at 3 months (P< .05) and by 9.93 mg/dl at 6 months (P < 0.01).Whereas, there was decrease in LDL Cholesterol by 7.14 mg/dl (P<0.05) at 3 months and by 8.93 mg/dl (P< 0.01) at 6 months, in comparison to pre drug treatment. The peak fall in total cholesterol and LDL-c was observed at 6 months. No significant change in triglyceride levels up to 6 months.
study period was observed, though there was trend towards increase in triglyceride levels by 1.35 mg/dl and 0.15 mg/dl after 3 and 6 months respectively. After drug administration the increase in VLDL-c was observed by 0.43 mg/dl at 3 months and by 0.03 mg/dl at 6 months. However, observed small increase in VLDL-c values were not statistically significant in comparison to base line. Similarly, no statistically significant change in the levels of HDL-c was observed after 3 and 6 months of therapy. Although a slight increase (0.07 mg/dl) at 3 months and a slight decrease (0.15 mg/dl) at 6 months were observed. These changes were statistically insignificant throughout the trial.

Postmenopausal Patients (mean age 54.31 ± 1.23 years)

In postmenopausal patients also, after tamoxifen therapy there was significant reduction in total cholesterol levels by 10.42 mg/dl at 3 months (P<0.001) and by 16.42 mg/dl (P<0.001) at 6 months. The peak reduction in the total cholesterol values occurred at 6 months. LDL-c also significantly decreased by 12.5 mg/dl at 3 months (P<0.001) and by 21.26 mg/dl at 6 months (P<0.001), with the peak decrease in the LDL-c at 6 months.

After therapy there was increase in triglycerides by 1.00 mg/dl at 3 months and by 2.6 mg/dl at 6 months but these values were statistically non significant in comparison to pre drug treatment. No significant change even in VLDL-c levels was observed during 6 months study period, though there was trend towards increase in VLDL-c levels (0.2 mg/dl, 1.1 mg/dl) after 3 and 6 months respectively. Similar increase in HDL-c levels from baseline value was observed (0.17 mg/dl, 0.65 mg/dl) after 3 and 6 months respectively, but it was statistically non significant.

Comparative effects of tamoxifen on plasma lipids in pre-menopausal and post-menopausal patients (Table 1)

Comparison of the effects of tamoxifen in premenopausal and postmenopausal patients on lipid profile revealed that in both groups of patients, tamoxifen caused significant fall in TC and LDL-c. However, fall was significantly higher in postmenopausal patients at both 3 and 6 months (P<0.01) in case of TC and with (P<0.001 and P<0.05) at 3 months and 6 months in case of LDL-C. Whereas, statistically non-significant difference was recorded in case of TG, VLDL-c and HDL-c at both 3 and 6 months of the therapy between the two groups.

Adverse effects profile of tamoxifen therapy in pre-menopausal and post menopausal breast cancer patients is shown in Table 2. When these adverse effects were compared among pre-menopausal and post menopausal breast cancer patients they did not differ in significant manner statistically.

| Table 2: Incidence of adverse effects with tamoxifen |
|-----------|----------------|----------------|
| S. No. | Parameter | Premenopausal (n = 14) | Postmenopausal (n = 35) |
| 1 | Hot flashes | 14.28% | 17.75% |
| 2 | Night sweating | 7.14% | 11.24% |
| 3 | Vaginal discharge | 7.14% | 7.10% |
| 4 | Pruritis vulvae | 14.28% | 5.91% |
| 5 | Endometrial Polyp | — | 3.55% |
| 6 | Simple cystic hyperplasia | — | 1.77% |

# Non significant using chi square test

**DISCUSSION**

In the present study, effects of tamoxifen were evaluated and compared on plasma lipid profile in premenopausal and postmenopausal patients of early stage breast cancer. Tamoxifen was found to cause significant reduction in TC and LDL-c in both pre-menopausal and postmenopausal patients. Similar observations have been made on premenopausal women and postmenopausal women in past also. The favorable effects on these parameters are compatible with estrogen agonistic effects of tamoxifen in both pre-menopausal and postmenopausal patients as estrogens lower LDL-c by up regulating apo B-100 receptors.

However, our findings on pre-menopausal women differ from Caleffi et al and Sharma et al who failed to show any change in these parameters. This disparity may be due to the fact that although tamoxifen increases estrogen levels in pre-menopausal patients but at the same time peripheral competition for estrogen receptors may lead to abrogation of the effect of increased estradiol on target tissues.

No change in TG was observed in pre-menopausal patients while numerical increase was observed in postmenopausal patients. Rise in TG is a pharmacological effect resulting from the hepatic first pass effect of estrogens. However, tamoxifen does not share this pharmacological effect resulting from the hepatic first pass effect of estrogens. However, tamoxifen does not share this estrogen agonist effect. Our findings on premenopausal and postmenopausal women are in conformity with the previous studies which failed to show any effect on TG. However, our findings on postmenopausal women are contrary to the findings of Sharma et al, Miyauuchi et al and Ataley et al who have reported that being estrogenic, tamoxifen increases the levels of triglycerides.

Levels of HDL-c at both 3 and 6 months did not show any change in both pre-menopausal and postmenopausal patients. Estrogens are known to increase HDL-c and particularly HDL2 sub-fraction, which is protective against the development of atherosclerosis by inhibiting hepatic lipase activity. This action of estrogens is not shared by tamoxifen. Similar findings have been reported by numerous
These findings are in agreement with the previous postmenopausal patients evaluated in the present study. A difference in number of pre-menopausal and significantly. This may probably be due to gross adverse effects were compared none of them differed

Comparison of the effects of tamoxifen in pre-menopausal and postmenopausal patients on lipid profile revealed that in both groups of patients, tamoxifen caused significant fall in TC and LDL-c levels. However, fall was significantly higher in postmenopausal patients. TC and LDL-c are modifiable risk factors for CAD. A 1% fall in total cholesterol is associated with 1.5% to 3% fall in subsequent rate of CAD. Reduction in LDL-c levels in women results in 46% lower risk of cardiovascular events. This implies that tamoxifen is beneficial in both pre-menopausal and postmenopausal patients in reducing the cardiovascular risk factors. Raised triglycerides and VLDL-c are other CAD risk factors. No change was observed in these parameters in both pre-menopausal and postmenopausal patients. Bruning, et al reported similar findings. Rise in HDL-c levels is protective against cardiovascular disease. For every 1mg/dl rise in HDL-c levels, the relative risk of CAD decreases by 2% - 3%. In the present study tamoxifen had no significant effect on HDL-c in both pre-menopausal and postmenopausal patients.

Besides these, other adverse effects were also observed during the study and they were - hot flashes in 14.28% and 17.75%, night sweating in 7.14% and 11.24%, vaginal discharge in 7.14% and 7.10%, puritis vulvae in 14.28% and 5.91% in pre-menopausal and postmenopausal patients respectively. When these adverse effects were compared none of them differed significantly. This may probably be due to gross difference in number of pre-menopausal and postmenopausal patients evaluated in the present study. These findings are in agreement with the previous findings.

Hence, the findings of present study suggest that tamoxifen favorably alters the surrogate end points of cardiovascular disease i.e. lipid profile and is well tolerated in both pre-menopausal and postmenopausal patients. ER/PR status was not done in our study because of non-availability of this facility in our institution. Furthermore, no CVS end-point was evaluated in our study, which remains the limitations of the present study.

REFERENCES


Announcement

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