ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Effect of CYP2D6 on premenopausal breast cancer during use tamoxifen and anti-depressant drug

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ABSTRACT

Breast cancer starts when cells in the breast begin to grow out of control. Tamoxifen is bio transformed to the potent anti-estrogen, endoxifen, by the cytochrome P450 (CYP) 2D6 enzyme . Cytochrome P450 2D6 (CYP2D6) is an important drug metabolizing enzyme that is involved in the metabolism of 20-25% of commonly prescribed drugs . Present study was planned to determine the effect of tamoxifen on cytochrome P450 2d6 mechanism According to CYP2D6 enzyme activity and the SSRI fluoxetine an inhibitor of CYP2D6. tamoxifen is potent increasing the CYP2D6 enzyme activity which appears clearly in group (P1) when compared with control group while group (P2) show significantly decreased the CYP2D6 enzyme activity when compared with group (P1). CYP2D6 is an autonomous predictor of breast cancer result in pre-menopausal women receiving tamoxifen for early breast cancer.

Keywords: Breast cancer, tamoxifen, CYP2D6, Statistical analysis

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ISSN: 0975-8585

INTRODUCTION

Breast cancer is one of the most frequent malignant neoplasms occurring in women in developed countries, and metastasis is the main cause of cancer-related death in these patients [1] .Despite recent major advances in the understanding of the mechanisms of breast cancer progression and in the development of novel therapeutic modalities, breast cancer remains the second leading cause of mortality among women. Mortality is almost invariably due to metastasis. For example, between 25% and 50% of patients diagnosed with breast cancer will eventually develop deadly metastases, often decades after the time of diagnosis and removal of the primary tumor [2]. Early detection of cancer is a desirable goal as it often allows treatment with lower toxicity and predicts longer survival. In many cancers, however, the limited capabilities of existing diagnostic methods may contribute to high cancer mortality [3] . Hormone therapy, also called endocrine therapy, adds, blocks, or removes those chemicals to treat the breast cancer such tamoxifen [4]. tamoxifen has been widely used in the endocrine treatment of metastatic breast cancer as adjuvant therapy preoperative treatment, ductal carcinoma in situ and chemoprevention [5] . tamoxifen is transformed predominantly by the drug- metabolizing enzymes CYP3a4 and CYP2D6 into the therapeutically more efficient drug metabolites 4-hydroxy tamoxifen (4-OH-tamoxifen) and endoxifen [6] . By binding to the er α (erα) tamoxifen and its metabolites modulate, the estrogen-induced transcription of erα target genes. the metabolites 4-OH-tamoxifen and endoxifen show up to 100 times higher affinity to the erα than the parental compound . as a result, the efficacy of tamoxifen strongly depends on its appropriate bio activation by cytochrome P450 enzymes [7]. CYP2D6 is highly polymorphic and shows a high interindividual variability in its activity . Other enzymes involved in tamoxifen metabolism comprise CYP2C9, CYP2C19 and CYP2B6 . these three enzymes are also involved in the formation of 4-OH-tamoxifen and endoxifen, but their contribution may depend on actual tamoxifen concentrations and on CYP2D6 activity [8].

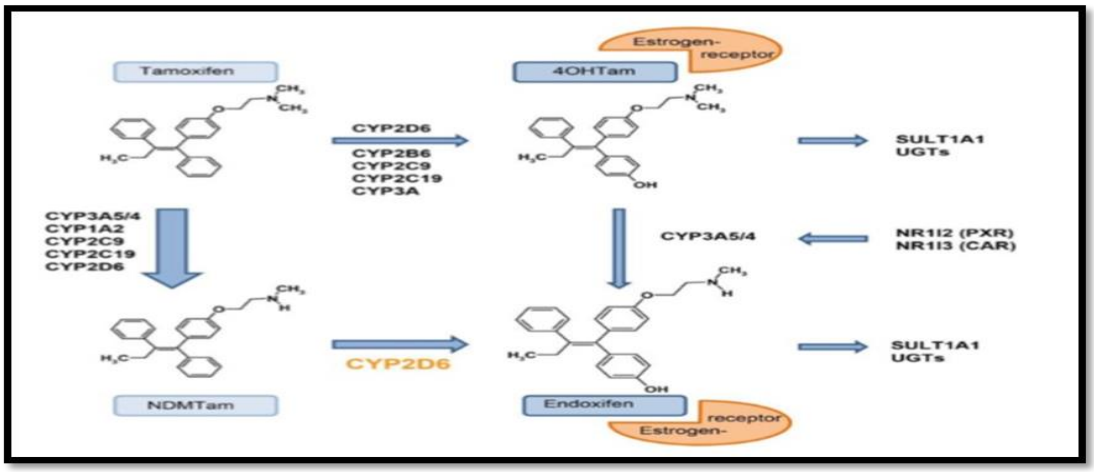

Figure (1): Tamoxifen metabolism [9]

MATERIALS AND METHODS

Study population

This study was performed on 60 women with breast cancer approved by pathological examinations and 30 control . The clinical data of the patients, including age, weight, height, waiste, hip, body mass index (BMI) , waiste to hip ratio (WHR) and Cytochrome p_{450}2d6 enzyme (CYP2D6) . 35 patients with Tamoxifen drug and 25 patients with tamoxifen and antidepresent drug were participated in this study. The blood samples were obtained from all patients 1-5 years after the end of chemotherapy treatment. The samples were centrifuged and the resulted serums were stored at −20 ◦C until the final analysis.

Assay of CYP2D6 enzymes

The levels of Cytochrome P_{450} 2d6 (CYP2D6) enzyme activity were measured by ELISA kit on an Micro ELISA system(washer and reader) (Thermo, Germany). All enzymes were analyzed by Human Cytochrome P450

ISSN: 0975-8585

2D6 (CYP2D6) ELISA kit, China (catalogue numbers:YHB0935Hu) All analyses were performed according to the manufacturer's instruction. The CYP2D6 enzyme levels were expressed in (U/L).

Statistical analysis

Statistical analyses were performed using the Graphpad prism version 16 . Clinical data were expressed as mean ± SD. One- way ANOVA was used for comparing control and group1 and group2 , data and statistical significance was considered as $p< 0.05$.

RESULTS AND DISCUSSION

Patient's clinical data has been summarized in Table1. Fig.1 shows serum levels of the cytochrome P_{450} 2d6 enzyme . The result of mean age (37.74 and 42.48 vs. 31.07), weight (80.66 and 82.88 vs. 67.80), height (163.2 and 160.5 vs. 164.3) and BMI (30.98 and 32.56 vs. 25.44), BMI showed a significant difference when compared each group with control ($P<0.0001$).

Table (1): mean (±SD) level of Age, BMI, WHR , in group (C), group (P1) and group (P2).

Parameters	Control (n=30)	Group (P1) (n=35)	Group (P2) (n=25)	P- value
Age (year)	31.07 ±8.077	37.74 ±6.099 a**	42.48 ±3.501 b*** c*	<0.0001
Weight (Kg)	67.80 ± 9.338	80.66 ±10.41 a**	82.88 ±15.57 b**	<0.0001
Height (cm)	164.3 ± 6.358	163.2 ±5.778	160.5 ±6.881	NS
BMI (kg/m²)	25.18 ±3.703	30.3 ±3.581 a****	32.1 ±5.383 b****	<0.0001
Waist (cm)	77.93 ± 9.563	78.40 ±12.79	80.08 ± 12.69	NS
Hip (cm)	103.4 ±8.811	104.3 ±12.97	105.7 ± 11.51	NS
WHR	0.7529 ±0.06157	0.7489 ±0.03959	0.7553 ± 0.06005	NS

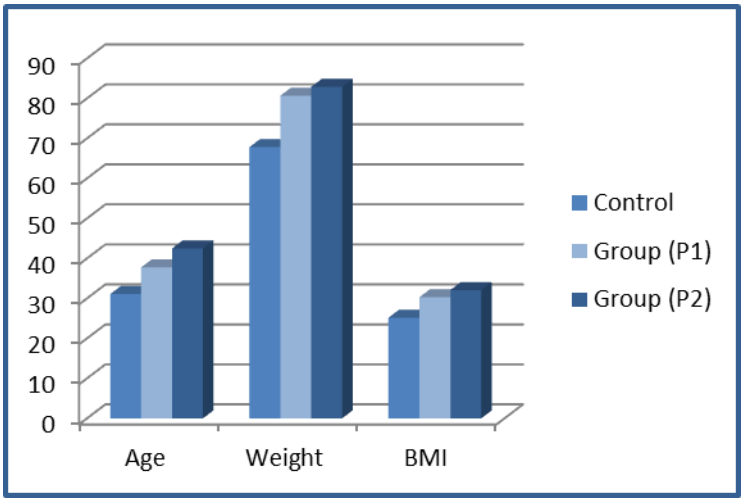

Figure (2): Mean distribution of Age, weight and BMI in studied groups (P1),(P2) and control

The result of cytochrome p450 2d6 enzyme level in serum samples for two different breast cancer groups and control group as shown in the table (2) and figure (2), showed significant differences between

groups (Control), (P1) and (P2) (P=<0.0001). A significant increase in the mean of cytochrome p450 2d6 was observed in the group (P1) in comparison with that of the control group (32.2 vs. 13.87) (P<0.0001). A significant increase in the mean of Cytochrome p450 2d6 was also observed in the group (P1) comparison with a group (P2) (32.2 vs. 19.43) (P< 0.0221).

Tamoxifen, a selective estrogen receptor modulator (SERM) [10]. Cytochrome P450 2d6 is responsible for the metabolic activation of tamoxifen to endoxifen [11]. In breast cells, tamoxifen acts as an antagonist and competes with estradiol to bind to the estrogen receptors (ER) and blocks the reproduction [12]. Selective serotonin reuptake inhibitors (SSRIs) have the capacity to decrease the efficacy of tamoxifen treatment, can inhibit CYPs [13]. The results of these study show that tamoxifen is potent increasing the CYP2D6 enzyme activity which appears clearly in group (P1) when compared with control group , which is consistent with Zeruesenay Desta [14] . while group (P2) show significantly decreased the CYP2D6 enzyme activity when compared with group (P1) , which is consistent with Matthew P. Goetz [15].

Table (2): Mean (±SD) level of serum CYP2D6 of Control, group (P1) and group (P2).

Parameter	Control (n=30)	Group (P1) (n=35)	Group (P2) (n=25)	P- value
CYP2D6 (U/L)	13.87 ±2.479	32.2 ±11.49 a****	19.43 ±2.962 b* c****	<0.0001

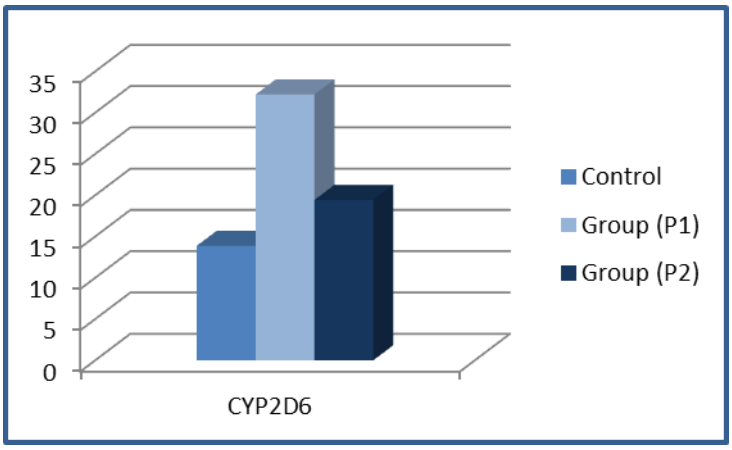

Figure (3): comparison of the mean CYP2D6 between the three groups Control, (P1) and (P2).

CONCLUSION

In tamoxifen treated patients , measured CYP2D6 enzyme activity. CYP2D6 is an autonomous predictor of breast cancer result in pre-menopausal women receiving tamoxifen for early breast cancer and it appears CYP2D6 inhibitors should be avoided in tamoxifen-treated women.

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ISSN: 0975-8585

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