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Effect of cytochrome p 450 3A4 (CYP3A4) on premenopausal breast cancer during use tamoxifen and anti-diabetic drug

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Abstract

Tamoxifen is one of the most hormonal therapy that using in breast cancer treatment, its pro-drug that is metabolized to its active metabolites by the cytochrome P450 (CYP) enzymes including CYP3A4.this enzyme is responsible for the conversion of tamoxifen to the therapeutically more efficient drug metabolites 4- hydroxy tamoxifen (4-OH-tamoxifen) and endoxifen. Cytochrome P450 3A4 (CYP3A4) is an important drug metabolizing enzyme that is involved in the metabolism about 50% of commonly marketed drugs. Present study was aimed to determine the effect of tamoxifen on cytochrome P450 3A4 mechanism According to CYP3A4 enzyme activity and the glyburide an inhibitor of CYP3A4. Tamoxifen is potent increasing the CYP3A4 enzyme activity which appears clearly in group (P1) when compared with control group while group (P2) show significantly decreased the CYP3A4 enzyme activity when compared with group (P1).

Keywords: Breast cancer, tamoxifen, CYP3A4, Statistical analysis

1. Introduction

Breast cancer is the most common type of cancer in women, with an estimated about 1·7 million cases in 2012 [1]. Endocrine therapy, also called Hormone therapy, adds, blocks, or removes those chemicals to treat the breast cancer such as tamoxifen [2]. It is an important anticancer drug also known as a selective estrogen receptor (ER) modulator. Its estrogen antagonist activity has been widely used to treatment ER-positive breast cancer [3]. Tamoxifen is converted generally by the drug- metabolizing enzymes CYP3A4 and CYP2D6 into the more efficient drug metabolites 4- hydroxy tamoxifen (4-OH-tamoxifen) and endoxifen [4]. Both of them show higher affinity to the estrogen Receptor (ER) than the tamoxifen [5]. As a result, the efficacy of tamoxifen strongly depends on its appropriate bio activation by cytochrome P450 enzymes [6] Cytochrome P450 3A4 (CYP3A4) is the most abundant form in most adult humans. It metabolizes about 50% of all marketed drugs [7]. The involvement of P450 3A4 in the metabolism of a wide range of drugs, hormones, chemicals and xenobiotics is well established and largely documented [8]. The effect of cytochrome P450 3A4 metabolism can involve pro-drug activation.CYP3A4 enzyme is extensively metabolizedtamoxifen by converting it to *N*-desmethyl tamoxifen4-hydroxytamoxife [9, 10]

2. Materials and Methods

2.1 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, body mass index (BMI) and Cytochrome p4503A4 enzyme (CYP3A4). 30 patients with Tamoxifen drug (group p1) and 30 patients with tamoxifen and anti-diabetic drug (group p2) were examined 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 serums were stored at −20 ◦C until the assay day.

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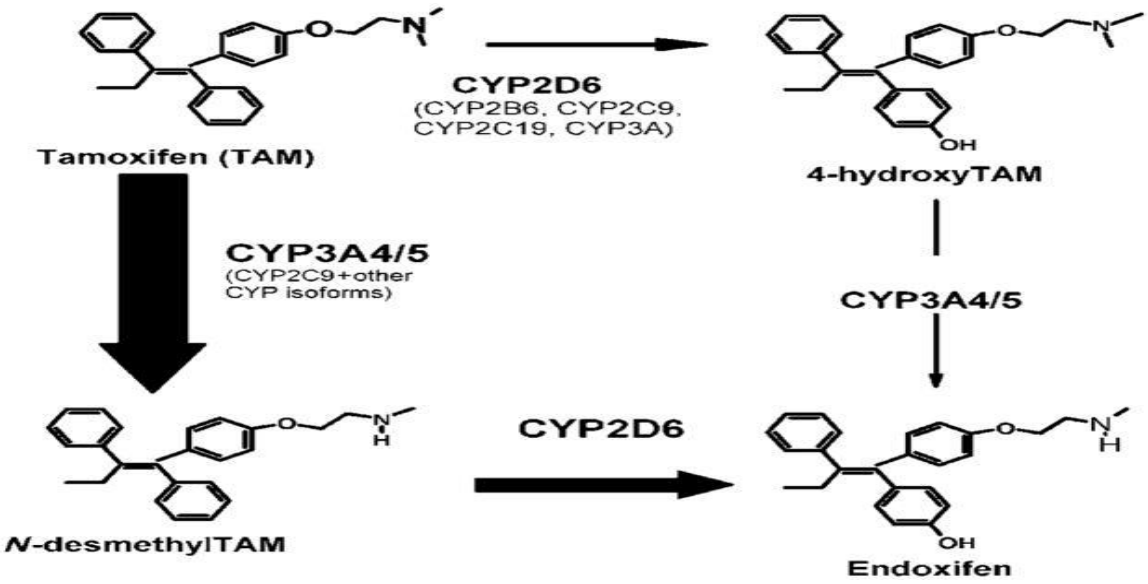

Figure 1: Tamoxifen metabolism by human cytochrome P450 [11]

2.2 Assay of CYP3A4 enzymes

The levels of Cytochrome P450 3A4 (CYP3A4) enzyme activity were measured by ELISA kit on a Micro ELISA system (washer and reader) (Thermo, Germany). All enzymes were analyzed by Human Cytochrome P450 3A4 (CYP3A4) ELISA kit, China (catalogue numbers: YHB0937Hu) All analyses were performed according to the manufacturer's instruction. The CYP3A4 enzyme levels were expressed in U/L).

2.3 Statistical analysis

Statistical analyses were performed using the Graphpad prism version 7. Clinical data were expressed as mean ± SD. One-way ANOVA was used for comparing control and group (P1) and group (P2), data and statistical significance was considered as $p< 0.01$.

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

Parameter	Group (c) (n = 30)	Group (p1) (n = 30)	Group (p2) (n = 30)	P – value
Age (Year)	37.53 ±2.713	40 ±4.556 a*	40.83 ±3.524 b**	0.0023
Weight (Kg)	69.03 ±6.739	80.87 ±12.79 a*	84.4 ±9.954 b****	0.0001
Height (cm)	163.8 ±6.288	161.8 ±6.185	162 ±6.759	N.S
BMI (kg/m2)	25.77 ±2.539	30.97 ±5.082 a****	32.28 ±4.247 b****	0.0001
P***<0.001 a) Indicate significant difference between groups (C) and (P1) b) Indicate significant difference between groups (C) and (P2) c) Indicate significant difference between groups (P1) and (P2)				

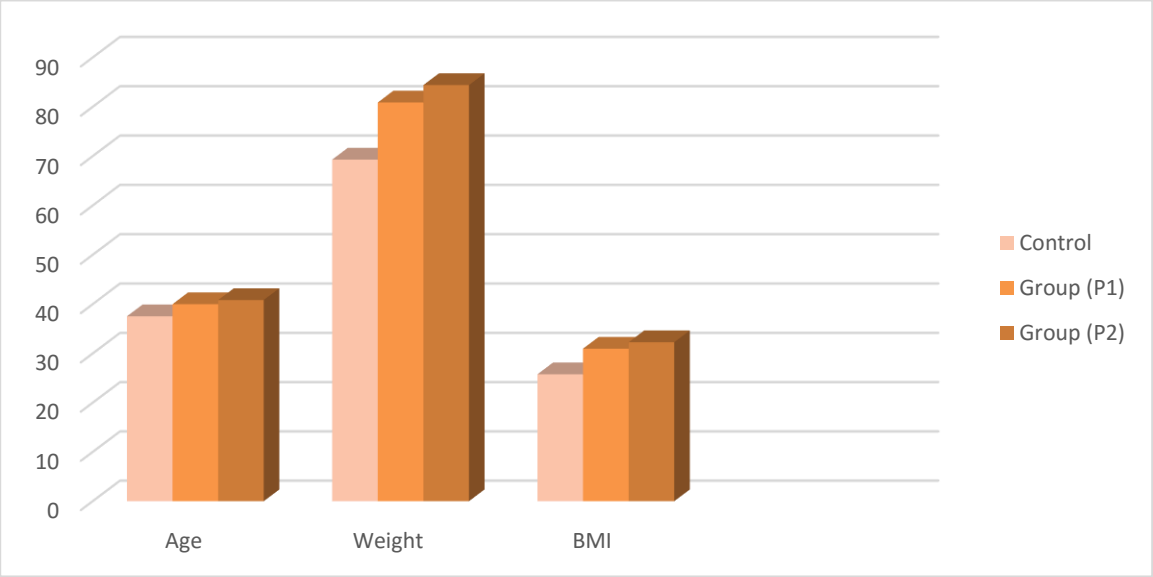

Figure 2: Mean distribution of age, weight and BMI in studied groups (P1), (P2) and control

The result of CYP3A4 enzyme level in serum samples of two different breast cancer groups and control group are shown in the table (2) and figure (3), showed Significant differences between groups (C), (P1) and (P2) (P=<0.0001) were found. A significant increment in the mean level of CYP3A4 was observed in the group (P1) in compared to the control group (32.41vs.12.47U/L) (P<0.0001). A significant increase in the mean level of CYP3A4 was also observed in the group (P1) in comparison with a group (P2) (32.41vs. 18.53 U/L) (P< 0.002). Tamoxifen, a selective estrogen receptor modulator (SERM) [12]. Cytochrome P450 3A4 enzyme is extensively metabolized tamoxifen by converting it to N-desmethyl tamoxifen and 4-hydroxytamoxifen [10]. Many of treatments can effected on CYP3A4 activity. For example some of anti-diabetic drugs Such as glyburide (glibenclamide) can reduced CYP3A4 level in group (P2), glyburide showed weak inhibition on CYP3A4 [13]. Enzyme inhibition occurs when 2 drugs sharing metabolism via the same isozyme compete for the same enzyme receptor site. The more potent inhibitor will predominate, resulting in decreased metabolism of the competing drug. The CYP3A4 enzyme contributes 92% of tamoxifen metabolism and also it's a major CYP enzyme involved in the metabolism of glyburide] 13]. The results of these study show that tamoxifen is potent increasing the CYP3A4 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 CYP3A4 enzyme activity when compared with group (P1), which is consistent with Kyoung-Ah Kim [15].

Table 2: Mean (±SD) level of serum CYP3A4 of (C), (P1) and (P2) groups

Parameter	Group (C) (n=30)	Group (P1) (n=30)	Group (P2) (n=30)	P- value
CYP3A4 (U / L)	12.47 ±4.104	32.41 ±8.246 a****	18.53 ±5.198 b** c****	<0.0001
P***<0.001 (a) Indicate significant difference between groups (C) and (P1) (b) Indicate significant difference between groups (C) and (P2) (c) Indicate significant difference between groups (P1) and (P2)				

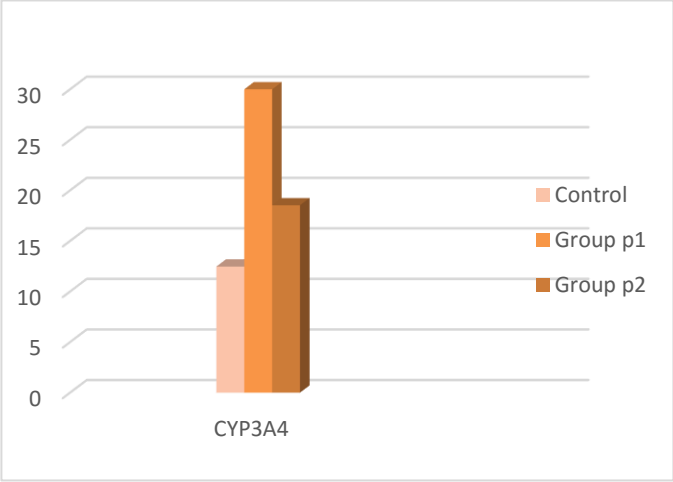

Figure 3: Comparison of the mean level of CYP3A4 between the three groups (C), (P1) and (P2).

3. Conclusion

Measured CYP3A4 enzyme activity is an autonomous predictor of breast cancer result in pre-menopausal women receiving tamoxifen for early breast cancer and it appears CYP3A4 activity reduced by drug shearing the same enzyme in our metabolism, So must avoided drugs that reduced the activity of this enzymes that responsible for tamoxifen metabolism.

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