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Study theeffect ofTamoxifenon Lipid profilein Male Albino Rats

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Abstract

Tamoxifen(TAM) is an effective anticancer drug. This study was conducted to evaluate the side effects of Tamoxifenon the lipid profile. 40 rats divided into 4 equal groups,3 groups were given different doses (30, 40, 50)mg/kg body weight of TAM three times a week for 8 weeks as well as control group that was given with physiological solution.At the end ofexperiment, The results showed significant differences in the treated groups were the results showed a significant degrees ($p<0.05$) in the HDL level in the treatment group (50mg/kg) while the three groups showed a significant increase in the levels of (Ch, TG, LDL, VLDL). The results of the study showed that Tamoxifen caused an accumulation in fats.

Keywords: Tamoxifen, Albino rats, lipid profile.

دراسة تأثير عقار التاموكسيفين على صورة الدهون في ذكور الجرذان البيض

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الخلاصة

تاموكسيفين هو دواء فعال مضاد للسرطان. أجريت هذه الدراسة لتقييم الآثار الجانبية للتاموكسيفين على صورةالدهون.استخدم لهذا الغرض أربعونجرذ بيضوقسمت إلى 4 مجموعات متساوية .أعطيت 3مجموعات جرعات مختلفة (30, 40, 50)ملغم/كغم من وزن الجسم من عقار التاموكسيفين ثلاث مرات في الأسبوع و لمدة ثمانية أسابيع . فضلا عن مجموعة السيطرة التي تم تجريعها بالمحلول الفسيولوجي.في نهاية التجربة أظهرت نتائج الاختبارات البايوكيميائية وجود فروق معنوية في مجموعة المعاملة حيث أظهرت النتائج وجود انخفاض معنوي ($P<0.05$)في مستوى HDL في مجموعة المعالجة (50) ملغم/كغم بينما أظهرت المجموعات الثلاث زيادة معنوية في مستويات(Ch, TG, LDL, VLDL) مقارنة مع مجموعة السيطرة .وأظهرت نتائج الدراسة أن التاموكسيفين يسبب تراكم في الدهون.

Introduction

Tamoxifen (Nolvadex-D) induce fatty liver [1, 2]. Tamoxifenis a synthetic non-steroidal medication that is widely used for treatment of patients with estrogen receptor-positive breast cancer [3].Non-alcoholic fatty liver disease (NAFLD) is the results of accumulation of lipids, especially triglycerides in the liver cells in patients without a history of alcohol abuse. Several factors are causing NAFLD, including fatness, metabolic syndrome, and consumption of some drugs [4].Tamoxifenis one of the drugs eligible of inducing macrovascular,steatosis and steatohepatitis. This may be refer to the drug ability to impair mitochondrial respiratory chain thus causing not only fatty acid oxidation impairment and steatosis but also enhanced reactive oxygen species (ROS) production [5]. Nonalcoholic steatohepatitis (NASH) is a common merit of the metabolic syndrome and toxic

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reactions to pharmacological drugs. Tamoxifena widely used anti-breast cancer.Tamoxifen-treated livers have increased satiate fatty acid content despite changes in gene expression [6].

The aim of studyis to estimate lipid profile(Ch, TG, VLDL, HDL, IDL and LDL) in blood serum.

Materials and Methods

Preparation of TAM Drug

Tamoxifen citrate (Nolvadex-D) produced by AstraZeneca Oak Limited. In this study, animals were administration orally by a feeding tube 6 cm^2 after grinding discs with a clean mortar. Add 2 ml of regular salt water and mix very well to form a suspension solution[7].

Tamoxifen tablets are weighed after grinding in a sensitive balance to obtain the three doses to study their effect, which is: (30 mg, 40 mg and 50 mg). And according to the weight of the rat and its metabolism compared to the weight of the human.

Experimental Animal

The experimental animals used in this study were male albino ratsweigh (225 – 250 g). Rats were maintained in standard laboratory conditions with a 12 h/12 h light-dark cycle at room temperature (22 °C – 25 °C) [8].

Experimental Design:

A total 32 of male rats were divided at random into 4 groups of 8 animals each group and treated as following:

- **Group 1 (control):**Animals were received orally with normal saline (0.9 %) 4 times/week for 8 weeks.
- **Group 2 (treated):**Animals were received orally with TAM (30mg/kg) 4 times/week for 8 weeks.
- **Group 3 (treated):**Animals were received orally with TAM (40mg/kg) 4 times/week for 8 weeks.
- **Group 4 (treated):**Animals were injected orally with TAM (50mg/kg) 4 times/week for 8 weeks.

Statistical Analysis

In order to comparison between parameters in each (Lipid profile),Using analysis of variance, F-test, t-test, in complete randomized design. Different between means have analyzed by least significant differences (LSD) at ($p<0.05$) and expressed as (Mean ± SEM) [9].

Results

Lipid Profile

Total Cholesterol (TC)

In the Table-1 it showed that there was a significant increase ($P<0.05$) in the level of cholesterol in blood in all groups treated with TAM (30, 40, 50) mg/kg respectively (218.750±1.048, 227.250±1.962, 234.5000±1.000) compared with control group (187.000±2.507).

Table 1-Lipid profile in rats treated with TAM.

Parameters / groups	HDL	VLDL	LDL	Cholestrol	Triglyceride
G 1	41.750 a ± 0.940	26.300 d ± 0.530	118.950 c ± 3.221	187.000 d ± 2.507	131.500 d ± 2.652
G 2	40.000 a ± 1.134	27.825 c ± 0.110	150.925 b ± 1.533	218.750 c ± 1.048	139.000 c ± 0.655
G 3	33.375 b ± 1.017	42.650 b ± 0.445	151.225 ab ± 2.218	227.250 b ± 1.962	213.250 b ± 2.226
G 4	31.000 b ± 0.866	46.150 a ± 0.195	157.350 a ± 0.892	234.500 a ± 1.000	230.750 a ± 0.977
LSD P ≤ 0.05	**2.880**	**1.054**	**6.220**	**5.066**	**5.297**

Similar letters are non-significantly differences between means at ($p\leq 0.05$) while different etters are significant differences between means at ($p\leq 0.05$)

Triglyceride (TG)

The result of the current study in Table-1 showed significant differences (P<0.05) in all TAM doses (30, 40, 50)mg/kg respectively (139.000±0.655, 213.250±2.226, 230.750±0.977) compared with control group (131.500±2.652).

High Density Lipoprotein Cholesterol (HDL-C)

The Table-1 shows a significant increase (P<0.05) in control group of (41.750±0.940) compared with treatment groups with TAM (40, 50)mg/kg which are (33.375±1.017, 31.000±0.866) while it was observed that there is decrease but no significant in treatment group with TAM (30)mg/kg which is (40.000±1.139).

Low Density Lipoprotein Cholesterol (LDL –C)

The Table- 1 shows the results of the current study that there is a significant increase (P<0.05) in all treatments (30, 40, 50)mg/kg with TAM respectively are (150.925±1.533, 151.225±2.218, 175.350±0.892) when it is compared with control group which is of (118.950±3.221).

Very Low Density Lipoprotein Cholesterol (VLDL- C)

The results of the current study in Table-1 showed a significant increase (P<0.05) in the level of VLDL in all treatments (30, 40, 50)mg/kg respectively (27.825±0.110, 42.650±0.445, 46.150±0.195) compared with control group which was (26.300±0.530).

Discussion

In view of the results of the current study there is a significant increase in the level of serum Lipids when treated with TAM and elevation increased as the dose multiplied increased by the level of (30, 40, 50)mg/kg compared to the control group and this is consistent with [10-13].

As for the HDL level, there was a significant decrease in the given dose of TAM and this reduction increased with increasing of dose compared with control group which has a significant increase in blood serum and this corresponds to the results [14, 6, 11].

Abdul-Barry and Al-Naama [15] mentioned that significant increases in TC level might be attributed to the high exposure of free radicals which might be stimulated the rate limiting enzyme hydroxyl-methyl glutaryl CoA SH reductase (HMG CoASHreductase) which is responsible for liver cholesterol synthesis.

Nonalcoholic steatohepatitis (NASH) is a common feature of the metabolic syndrome and toxic reactions to pharmacological drugs.

Tamoxifen in high dose is a known liver carcinogen in rats, which are due to oxygen radical overproduction, which occurs during TAM metabolism. Lipid peroxidation (LPX) via subtraction of hydrogen from unsaturated fatty acids forms carbon-cantered lipid radicals [12].

Lipid peroxidation is an autocatalytic process, which results in cell death because of continuous generation of free radical. Polyunsaturated fatty acids (PUFAs) are plentiful in cellular membranes. PUFAs allow for fluidity of cellular membranes [16].

Evidence from several independent research groups supports TAM induced impairment of mitochondrial fatty acid oxidation (FAO) as a primary cause of lipid accumulation in the liver[17]. Co-administration of tetradecylthioacetic acid, which improves mitochondrial and peroxisomal FAO, prevents TAM-induced fatty liver. Tamoxifen also inhibits hepatic triacylglyceride secretion leading to liver lipid accumulation. Therapeutic intervention to prevent TAM-induced fatty liver condition has the potential to improve the safety of long-term TAM usage for breast cancer treatment [18].

The impairment of mitochondrial electron transport chainactivity is also associated with enhanced reactive oxygen species(ROS) production and increased lipid peroxidation that is favoredby lipid accumulation and the release of aldehydic derivatives thatpromote deleterious effects on hepatocytes and other hepatic cells [19, 20].

Lipid peroxidation is a well-established mechanism of cellular injury, and it is used as an indicator of oxidative stress in cell and tissues. Increased levels of lipid peroxidation products have been associated with a variety of chronic diseases in both human and animals [21, 22].

Lipid peroxidation is composed of three major steps; initiation, propagation and termination. The initiation step is the process of producing lipid radicals by ROS. In the propagation step the lipid radical from the initiation step attacks other unsaturated fatty acid molecules on the cell membrane or steals the electron from O_2 to form lipids [23,24]. In the termination step, which is the end stage of the lipid peroxidation reaction, free radicals combine to form paired stable electrons, this step can be stopped earlier by antioxidants that can trap free radicals [25].

Conclusion

In this study, it was observed that the drug TAM caused the accumulation of fats in the liver because of the process of oxidation of fats and thus increase the cirrhosis of the liver where the higher the dose increased the process of oxidation and accumulation of fat and increase in serum level.

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