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Research Article

Protective effects of dehydroepiandrosterone (DHEA) against Carbimazol-induced toxicity in male mice

Wafaa Kadhim Jasim

Department of Veterinary, Physiology and Pharmacology, University of Kerbala- College of Veterinary Medicine, Karbala-Iraq

ABSTRACT

The present study conducted to evaluate the protective role of DHEA against the some side effects caused by carbimazole in male mice. Eighteen male mice were divided into three groups, the first group drenched distillated water as control, while second group gavaged with carbimazole and third group gavaged with carbimazole in combination with DHEA, all treatments were extended for thirty days. The results revealed that the mice treated with carbimazole caused significant decrease in serum T4 and T3 concentration, but TSH was significantly increased. An increase in serum values of AST, ALT, TG, TC, VLDL, LDL cholesterol, creatinin and Urea were also recorded. Combined DHEA with carbimazole significantly return these biochemical criteria to their values in control group. In spite of non-ameliorative effect of DHEA on thyroid hormones, the results refer to that DHEA ameliorates the lipid profile, hepatotoxicity and renal toxicity induced by Carbimazole in male mice.

Keywords: Carbimazole; DHEA; Hypothyroidism; lipid profile; mice.

INTRODUCTION

One of the antithyroid drugs that generally used to patient with hyperthyroidisim is Carbimazole (Kota et al., 2013). Carbimazole has an active metabolite called methimazole which prevent the peroxidase enzyme in thyroid from coupling and tyrosine iodination, leading to decrease the production of T3 and T4 (Robson, 1985). Administration of carbimazole as treatment usually lasted for one to one and a half year then a trial withdrawal will be follow (Vlase and Lungu, 1991). Numerous symptoms were observed with carbimazole treatment such as urticarial, rash, pruritus, fever, hepatotoxicity and jaundice (Vilchez et al., 2006). Carbimazole also caused an antiproliferative (Elias et al., 2004) and cytogenetic (Sutiakova et al., 1997) effect. the hepatocellular dysfunction resulting from methimazole as compared to Propylthiouracil is usually cholestatic.

Patients on antithyroid drug and their liver function tests deteriorate are typically advised to stop further use of these treatments, although there are shortage in data on the actual risk of rechallenge in this situation (Woeber, 2002). Heidari et al., 2012 reported that the two most significant adverse effects associated with administration of methimazole were agranulocytosis and hepatotoxicity.

In addition, carbimazole may elevate levels of lipid peroxides in serum and from thyroid gland (Joanta et al., 2005). Thyroid hormone deficiency caused by carbimazole represents a well-known cause of hypercholesterolemia (Chandurkar et al., 2008).

On the other hand, speculated role of dehydroepiandrosterone (DHEA) in protection decrease when years of age increase, in particular, sulfated derivative of DHEA, is present in high level in circulating blood. DHEA has been reported to different protective effects against cancer (Rao et al., 1992), atherosclerosis (Nafziger et al., 1991), obesity (Nestler et al., 1988), autoimmune diseases (Van Vollehoven et al., 1994), infections (Loria et al., 1988), diabetes (Buffington et al., 1991) and aging (Morales et al., 1994). These wide spectrum effects difficult to be explained in perfect manner by effects of the receptors of estrogen and / or androgen. Previous studies support the speculation of action of DHEA depend primarily on decreasing lipid peroxidation, *in vitro and in vivo* (Aragno et al., 1997). The beneficial effect of DHEA on many of the diseases have been related to its ability to repeat oxidative insult (Yu, 1996).

Interestingly, the injury of kidney that cause by ischemia-reperfusion was reduced by DHEA administration (Aksoy et al., 2004). From above mentioned finding, the anti-oxidative stress is an important role related to ability of DHEA in enhancing health status in many diseases.

* Corresponding Author
Email: wafaakadhim81@yahoo.com
Contact: +964781144180
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In the current study, we impose that DHEA treatment (as therapeutic dose) may has role in prevent or decrease the severity of harm effects caused directly by carbimazole or indirectly by hypothyroidism that induced by carbimazole in mice. This hypothesis was done by evaluate some of lipid profile, kidney and liver function markers

MATERIALS and METHODES

Experimental Design

Eighteen male mice were introduced in this study, their weight (40-50 gm), and their age ranged (70 -84) Days. Animals were introduced to the house of animal College of Veterinary Medicine, University of Kerbala. The mice reared in metal cages. The standard pellet were used to feeding mice and given with water *ad libitunm*. standard condition of temperature and light were provided to animals.

Eighteen male mice were distributed equally and randomly in to three groups as bellow:

Group (1): Treated orally with0.1 ml of normal saline for 30 days which used as control.

Group (2): Induced hypothyroidism group receiving (1.35 mg/Kg b.w) of carbimazole (Sakr et al., 2012), dissolved in normal saline daily for 30 days.

Group (3): Combination group male mice of this group were orally drenched carbimazole (1.35mg per Kg of body weight) and DHEA (2mg per kg of body weight) suspended in normal slain for 30 days.

Blood samples were collected via heart puncture and thyroid hormones and TSH were done by using ELISA technique and for this ELISA kits were purchased from Monobind Inc. company USA, and, all biochemical parameters were performed through spectrophotometric analysis by using kits of SPECTRUM- Company, Egypt. Serum LDL- and VLDL Concentration were calculated by following formulas

LDL-C = TC – HDL-C – TAG/5 and VLDL = TAG / 5 consequently (Friedewald et al., 1972).

The obtained data were expressed as mean plus minus standard error. The statistical analysis was performed by using the ready computerized program called (Statistical Program for Social Sciences). Analysis of variance was choose to done the comparisons between group and $P<0.05$ was the level of probability to determine the significance. Difference between groups was determined according to calculated least significant different test (LSD) (SPSS, 2001).

RESULTS and DISCUSSION

In the present study, the results revealed significant decline in the concentrations of T4 and T3 while TSH was increased significantly in induced hypothyroidism group in compare with control group (Table 1). Carbimazole was used to induce hypothyroidism in mice. carbimazole converted to the methimazole (its active form) which in turn lets the thyroid peroxidase enzyme unable to couple with residues of tyrosine and prevent iodination process on thyroglobulin, therefore, the production of hormones T3 and T4 will reduced consequently. (Nayakbindu and Burman, 2006**),** leading to elevate level of TSH which in turn causing hyperplasia and hypertrophy of thyrocyte (nodular type of goiter), by excreting their effect on thyroid gland (Stelios et al., 2007 and Zbucki et al., 2007).Our results agreed with that obtained by Haiying *et al.*, who found that hypothyroid with subnormal ranges of T4 and T4 levels, but TSH was exceed the normal rang. Several authors considered carbimazole as a good indicator of antithyroid drugs (Haschek and Rousseaux, 1991 and Serakides et al., 1999).

The results also revealed that the combination of carbimazole with DHEA exhibits no significant change with group of carbimazole alone in levels of T3 and T4 but TSH was near to value of control group (Table 1). There is an development in information about understanding the roles of DHEA and its sulfated form in different diseases within physiological aspect. However, there is little interest to its role in patients with thyroid disease. Lower DHEA-S concentrations was reported in patients with hypothyroidism but the relationship between DHEA-S and total T4 was not proved (Bassi et al., 1980). Another study recorded a decrease in levels of DHEA and DHEA-S in serums of hypothyroid patients as well as an elevation DHEA-S, while DHEA was unchanged, in patients with Graves' disease suggesting that serum concentration of DHEA and DHEA-S regulated by thyroid hormone but DHEA had no effect on the level of thyroid hormones in hypothyroidism (Foldes et al., 1983).

In the present study, the results revealed that the levels of Urea and Creatnine, ALT and AST were increased significantly in carbimazole group in compare with other treated and control group (Table 2). However, serum urea and creatinine concentrations represent the important indices of nephrotoxicity (Khorsandi and Orazizadeh, 2008**).** In this study, the data revealed that the oral drenched of carbimazole (1.35mg/Kg B.W/Day) for 30 consecutive days caused harm effects in kidney and liver of mice, as explained by the significantly elevation in serum levels of urea and creatinine as well as ALT and AST. The kidneys are play major role in the excretion of different types of xenobiotics, toxic chemicals and pollutants, therefore, high production of free radicals by kidneys result in increased the oxidative stress. Oxidative stress involved play in the pathogenesis of kidney damage (Ghosh et al., 2010). According to the results of the current study, DHEA when given with carbimazole ameliorated the harm effects of carbimazole in kidneys and liver of male mice according to the normal levels of urea, creatinine, AST and ALT that obviously noticed in the serum of these mice. The improvements in the indices of kidneys and liver

Table1 : The Effect of Carbimazol Alone and in Combination with DHEA on Thyroid Function Hormones Concentration in Serum of Male Mice (Means ± Standard error)

Parameters / Groups	T3 (ng /ml)	T4 (µg/dl)	TSH (µlU/ml)
Group 1 (Control)	A 1.37±0.02	A 5.53±0.28	A 0.45±0.01
Group 2 (Carbimazole)	B 0.49±0.03	B 2.87±0.18	B 0.69±0.01
Group3 (Carbimazole + DHEA)	B 0.56±0.04	B 3.02±0.04	AB 0. 57±0.07

Different Capital letters refer to presence significant difference at (p≤0.05) between groups

Table2 : The Effect of Carbimazol Alone and in Combination with DHEA on some biochemical Levels in Male Mice (Means ± Standard Error)

Parameters / Groups	Urea (mg/dl)	Serum Creatinine (mg/dl)	AST Units/ml	ALT Units/ml
Group 1 Control	A 34.22±3.22	A 0.391±0.032	A 121.13±21.41	A 42.68±1.89
Group 2 (Carbimazole)	B 67.36±5.93	B 0.98±0.016	B 288.33±45.12	B 64.15±4.29
Group 3 (Carbimazole +DHEA)	A 38.63±3.12	A 0.403±0.011	A 149.26±37.25	A 48.31±1.26

Different Capital letters refer to presence significant difference at (p≤0.05) between groups.

Table 3: The Effect of Carbimazol Alone and in combination with DHEA on lipid profile of Male Mice (Means ± Standard Error)

Parameters / Groups	TC. mg/dl.	HDL.mg/dl.	TG.mg/dl.	LDL.mg/dl.	VLDLmg/dl.
Group 1 (Control)	87.76±2.49 A	41.28± 2.53 B	71.01± 2.68 A	32.38± 3.02 A	14.09± 0.88 A
Group 2 (Carbimazole)	134.37±3.86 B	26.66± 3.67 A	95.96± 3.00 B	89.54± 3.62 B	19.24± 1.16 B
Group3 (Carbimazole + DHEA)	89.12±6.40 A	40.25± 1.65 B	70.05± 3.29 A	36.05± 6.16 A	13.90± 0.65 A

Different Capital letters refer to presence significant difference at (p≤0.05) between groups

functions may be resulted from the repair of glomerulus. The protective effect of DHEA recorded in the present experiment was in match with some studies that suggested the DHEA able to protect nephrons in various diseases (Richards et al., 2001). Based on the findings of current study, the ameliorative effect of DHEA in liver and kidney is primarily come from its antioxidant activity.

Concerning lipid profile, the analysis of variance of the present study appeared significant increase in Triglyceride (TG) total cholesterol (TC), VLDL and LDL cholesterol and decrease in HDL cholesterol in mice treated with carbimazole in compare with other groups (Table 3).

Thyroid hormone plays an important role in the regulation of lipid metabolism. Thyroid hormone deficiency represents a well-known cause of hypercholesterolemia in hypothyroid patients **(**Chandurkar et al., 2008). Therefore, carbimazole (as anti-thyroid used in the present study) was cause a thyroid hormone deficiency as shown in table 1 which in turn develops hypercholesterolemia in the male mice. In hypothyroidism, thyroid hormone had an effect on receptor expression of LDL and absorption of cholesterol exceed the effects of decreased synthesis of cholesterol in the liver, leading to elevation serum levels of LDL, and total cholesterol levels (Galman et al., 2008).

On the other hand, combination of DHEA with carbimazole in the present study lead to return the values of total cholesterol (TC), LDL cholesterol and HDL cholesterol close to that of control group (Table 3).

DHEA caused reduction in intake of fat as well as decreasing the body weight in rats (Richards et al., 2000). In another study, DHEA was able to decline of serum triglyceride levels in hyperlipidemic rats (Han et al., 1998). Peroxisomal β-oxidation the pathway was directly affected by DHEA in hepatocytes of mouse (Waxman**,** 1996). DHEA act to reduced expression of fatty acid synthesis via activation receptor α (PPARα), the later, in turn, support the transcriptional up-regulation of fatty acids transporting proteins which leading to more fatty acid entrance to the cells. PPARα

also induces the enzymes contributed in the β-oxidation pathway of fatty acids (Poynter and Daynes, 1998, Schoonjans et al., 1996 and Tang et al., 2007).

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