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THE EFFECTS OF THIOSEMICARBAZONE DERIVATIVE SCHIFF BASE 1-(1-PHENIL-1-METHYLCYCLOBUTANE-3-YL)-2-SUKSINIMIDO ETANON THIOSEMICARBAZONE ON ANTIOXIDAN VITAMINS IN LIVER, KIDNEY AND SERUM OF RABBITS

ABSTRACT

Thiosemicarbazones (TSC) are a class of compounds very promising in the treatment of many diseases, cancer in particular, and its development is still in progress. The purpose of the present study was to evaluate the effect of 1-(1-phenil-1-methylcyclobutane-3-yl)-2-suksinimido etanonthiosemicarbazone (FSTSC) on antioxidan vitamins (A, E, C) in liver, kidney and serum of rabbits. Twenty male rabbits were randomly divided into two groups. The first group was used as a control which injected subcutaneously of 250µl, 10% dimethylsulphoxide was given to the control group every otherday. FSTSC compound (25mgkg^{-1}, dissolved in 250µl, 10% dimethylsulphoxide) was administered to the other group of rabbits.This administration was done for a period of 32days.The vitamin levels (A, E and C) were determined by high performance liquid chromatography (HPLC). The liver tissue and serum vitamin C levels were significantly decreased compared to control group ($P<0.05$). Levels of vitamins A in kidney was significantly decreased compared to control group ($P<0.05$). In addition to many pharmacological properties of the TSC derivatives examined, it will contribute to the knowledge of the literature.

Keywords: Thiosemicarbazone, Antioxidants, Liver, Kidney, Serum, Rabbit, HPLC

1. INTRODUCTION

Thiosemicarbazone (TSC) derivatives exhibit diverse biological activities possibly due to the presence of –NH–NH–CS–NH2 moiety. Thiosemicarbazone derivaties exhibit diverse biological activities such as cancer, antineoplastic, antiviral, antifungal, antitumour, antivirus and antioxidant [1, 2, 3, 4, 5 and 6]. Shih and Ke showed that some thiosemicarbazone compounds antioxidant properties. The antioxidant system is divided into two groups as enzymatic and nonenzymatic [7 and 8]. Nonenzymatic system constitutes antioxidant vitamins such as vitamin A, E, C and MDA have been shown to react with organic free radicals and to protect biomembranes from damage induced by these free radicals [9 and 10].

2. RESEARCH SIGNIFICANCE

We synthesised 1-(1-phenil-1-methylcyclobutane-3-yl)-2-suksinimido etanonthiosemicarbazone (FSTSC). It can be suggested that FSTSC produces more free radicals and in turn this decreases the level of antioxidant vitamins in the liver, kidney and serum of rabbits.

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3. MATERIALS AND METHODS

3.1. Experimental Animals

A total of 20 male YeniZellanda White rabbits (2 months old, 450±600g) were used in this study. Upon arrival, the animals were allowed to acclimatize for two weeks. The rabbits were housed in a temperature controlled room (22–25°C) with a 12:12 light-dark cycle; water and food were given ad libitum. All animals were on a normal diet throughout the experimental period. Animals were divided into two groups; one control group (n=10) and an experimental group (n=10). The experimental group was administered the 1-(1-phenil-1-methylcyclobutane-3-yl)-2-suksinimido etanonthiosemicarbazone (FSTSC). While only an injection of 250µl, 10% dimethylsulphoxide (DMSO) in corn oil was given to the control group, (FSTSC) (25mgkg^{-1}, dissolved in 250µl of 10% DMSO) was injected to the other group of rabbits, the every other day. Injections continued for 32 days. Samples were kept at –20°C until analyzed. In this study, a new compound was used. FSTSC was synthesized by Cukurovali et al. [11]. The chemical structure is shown below (Figure 1).

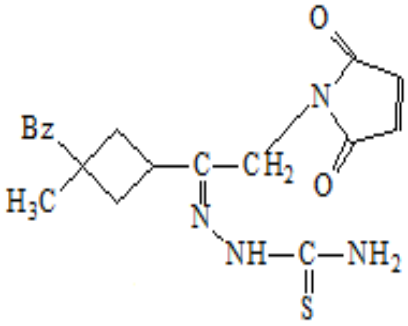

Figure 1. 1-(1-phenil-1-methylcyclobutane-3-yl)-2-suksinimido etanon thiosemicarbazone (FSTSC)

3.2. Determination of Vitamin A and E Levels in Tissues

Tissue samples were centrifuged at 4000 rpm for 3 min at 4°C and separated. In this tissue, antioxidant vitamins (A, E) levels were determined by using HPLC. Determination of the amounts of vitamin A and E was performed according to cited reference [12]. Separations were carried out at room temperature with the Cecil liquid chromatography system (Series 1100) consisting a sample injection valve (Cotati 7125) with a 20µl sample loop, an ultraviolet (UV) spectrophotometric detector (Cecil 68174), 326 and 296 nm for vitamin A and E, respectively. Integrator (HP 3395) and a Techsphere ODS-2 packed (5µm particle and 80°Ä pore size) column (25.0×4.6 ID) with a methanol/acet-onitrile/ chloroform (47:42:11, v/v) as a mobile phase at 1.0ml min –1 flow rate.

3.3. Determination of Vitamin C in Tissues

Vitamin C was extracted [13], the supernatant was filtered and then the vitamin C level was determined according to cited reference [14]. The Supelcosil LC-18-DB HPLC reversed-phase column (3µm particle size and 25.0x3.9 ID) was utilized for the detection of vitamin C levels. While mobile phase (3.7mM phosphate buffer, pH 4.0) used 1.0 ml min –1 flow rate to vitamin C level.

3.4. Determination of Vitamin A, E and C Levels in the Serum

Blood samples were centrifuged at 3500 rpm for 5 minutes at 4°C and the serum was separated. Antioxidant vitamins (A, E, C) levels

were determined in serum samples.The quantifications were performed according to Miller et al. [12].

3.5. Chemistry

All chemicals and reagents used were of analytical grade and were purchased from Merck Chemical Co. (Darmstadt, Germany). Bidistilled water was used to in the all studies.

3.6. Statistical Analysis

The SPSS software (SPSS, Chicago, IL, USA) was used for statistical analyses. Results for the groups are expressed as mean ± S.D. Differences between the groups were analyzed for significance using the student's t-test. Statistical significance was defined as $p<0.05$.

4. RESULTS

Parameters to the results of experimental studies with control groups in each of the groups throughout the application was given in the tables show.

Table 1. Levels of antioxidant vitamins (A, E and C) in liver (FSTSC) and control groups in rabbits. Results given are mean ± S.D

	Control(n:10)	FSTSC(n:10)
VitaminA ($mgmL^{1}$)	0.43±0.08	0.42±0.06
VitaminE ($mgmL^{1}$)	3.08±0.67	2.64±0.04
VitaminC ($mgmL^{1}$)	51.72±0.82	26.46±1.41[b]

a: p<0.05, b:p<0.001

Table 2. Levels of antioxidant vitamins (A, E and C) in kidney (FSTSC) and control groups in rabbits. Results given are mean ± S.D

	Control(n: 10)	FSTSC(n:10)
VitaminA ($mgmL^{1}$)	0.35±0.02	0.13±0.01[b]
Vitamin E ($mgmL^{1}$)	1.92±0.26	1.73±0.11
VitaminC ($mgmL^{1}$)	8.77±0.09	8.78±1.08

a: p<0.05, b:p<0.001

Table 3. Levels of antioxidant vitamins (A, E and C) in serum (FSTSC) and control groups in rabbits. Results given are mean ± S.D

	Control(n: 10)	FSTSC(n: 10)
VitaminA ($mgmL^{1}$)	0.16±0.03	0.11±0.01
Vitamin E ($mgmL^{1}$)	0.66±0.02	0.61±0.02
VitaminC (mgm^{L1})	32.02±2.00	20.86 ±0.61[b]

a:p<0.05, b:p<0.001

FSTSC has been decreased in vitamin C levels in liver and serum ($p<0.01$) when compared to the control group.No statistically significant difference was observed in Vitamin E levels among FSTSC and control groups ($p>0.05$). Also, FSTSC has been decreased in vitamin A levels in kidney ($p<0.01$) when compared to the control group.

5. DISCUSSION

Free radicals and other reactive oxygen species (ROS) are generated by all aerobic cells and are known to participate in a wide variety of deleterious reactions [15]. In normal conditions aerobic organisms are protected against oxidative damage by a variety of

antioxidant systems. The antioxidant system is divided into two groups as enzymatic and non-enzymatic. Non-enzymatic antioxidant system, which consists of vitamin A, E, C, has been shown to react with organic free radicals and protect biomembranes [10]. In Table 1, it was observed that the rabbits subcutaneously injected 1-(1-phenil-1-methylcyclobutane-3-yl)-2-suksinimido etanonthiosemicarbazone (FSTSC) had the low levels of antioxidant vitamins (E, C) in liver when compared with the control group. Findings, and in the control group, injected under the skin of rabbits Thiosemicarbazone-derived Schiff basescontaining the kidney tissue vitamin A levels decreased, depending on the duration of injection was observed ($p<0.05$).

Reductions in the level of vitamin A can be explained by antioxidant properties of this vitamin. α-Tocopherol stops lipid peroxidation by trapping the free radicals. In this process α-tocopherol is converted to α-tocopheroxyl radical. Vitamin C regenerates α-tocopherol from α-tocopheroxyl radical [16 and 17]. Moreover, an important antioxidant—vitamin E—is transported by seleno-proteins as a free radical scavenger; ascorbate works lipid rich areas of the cell, interacting with vitamin E in the later medium. The same property of vitamin C prevents the formation of nitrosamines from nitrites and nitrates [18]. Vitamin C inhibits division and growth of cell through the production of hydrogen peroxide, which damages the cells probably through an unidentified free radical(s) generation/mechanism [19]. In this study, it was found that the levels of antioxidant vitamins A, E, C decreased in 1-(1-phenil-1-methylcyclobutane-3-yl)-2-suksinimido etanonthiosemicarbazone (FSTSC)-injected rabbits in comparison to control group ($p<0.05$). Antioxidant vitamins A, C and E are some of the major non-enzymatic antioxidants in the body [10]. There was no statistically significant differences kidney level of vitamin C (Table 2).

Water-based antioxidant capacity in environments with large vitaminC and lipid media is a powerful antioxidant vitaminE's antioxidant effect of taking on a role reminiscent of the primary antioxidant defense performs blood andother body fluids [20]. The environmental chemicals and some drugs can reduce the antioxidant levels of the organism and could thus lead to cancer and various diseases [21]. It can be suggested that FSTSC produces more free radicals and in turn this decreases the level of antioxidant vitamins in the liver, kidney and serum of rabbits. From these results, we could suggest that, antioxidant vitamins such as vitamin A, E, and C should be taken along with the medicine containing 1-(1-phenil-1-methylcyclobutane-3-yl)-2-suksinimido etanonthiosemicarbazone(FSTSC) groups to compensate the potential vitamin deficiency caused by these drugs. In addition to many pharmacological properties of the TSC derivatives examined, it will contribute to the knowledge of the literature.

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