Biochemical Effect Of L-Carnitine Against Doxorubicin And Vancomycin Induced Lipid Disorders In Rats

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ABSTRACT

The ameliorative effect of L-carnitine on the lipid, liver and kidneys disorders induced by doxorubicin and vancomycin was examined. Ninety male albino rats were randomly divided into six groups (15) each; control, L-carnitine treated, Doxorubicin treated, vancomycin treated, doxorubicin + L-carnitine, Vancomycin + L-carnitine. Animals were sacrificed after 3, 10, 15 days. Blood and tissue samples were collected. Leptin, insulin, MDA, HDL, TC, TP and albumin levels, LDH and GGT activities were determined. mRNA expression levels of leptin, leptin receptors and GAPDH genes were determined in adipose tissues. There was a significant increase of serum insulin, leptin, MDA, HDL, TC levels, GGT and LDH activities and significant decrease of Albumin, TP levels in the groups treated with doxorubicin and Vancomycin. In conclusion; DOX and VAN had a bad effect on the lipid profile as they induced obesity, also; they increase liver enzymes and heart markers and increase the oxidative stress in the body tissues due their ability to increase the level of MDA. L-carnitine administration ameliorated the hazards effect of DOX and VAN on the lipid sate in the body.

INTRODUCTION

Leptin, a product of ob gene, is a hormone secreted mainly by adipocytes; it acts mainly as the most important regulator of energy balance *(1)*. It has a role in regulating food intake and energy balance, affects thyroid and growth hormones, as well as hematopoiesis, bone formation and immune system *(2)*. Leptin deficiency is characterized by hyperlipidemia, excessive storage of lipid in tissues such as liver and skeletal muscle, and insulin resistance. These defects are markedly improved by the administration of leptin in humans and rodents *(3)*. Leptin receptors are found in many areas of the brain, including the hypothalamus, cerebellum, cortex, hippocampus, thalamus and choroid plexus *(4)*; it is also expressed in peripheral tissues, like lungs, kidneys, liver, pancreas, adrenals, ovaries, hematopoietic stem cells, and skeletal muscle *(5)*, This wide expression may imply the great role of leptin *(6)*.

Doxorubicin (DOX) the anthracycline antibiotic obtained from *Streptomyces peucetius* has been used against breast and esophageal carcinomas, osteosarcoma, Kaposi's sarcoma, soft tissue sarcomas *(7)*. The DOX-induced hyperlipidemia resulted from reduced lipid storage and utilization and reduction of mitochondrial oxidation of long chain fatty acids in kidney and heart *(8)*.

Vancomycin is a glycopeptides antibiotic that has been used clinically for nearly 50 years as a penicillin alternative to treat methicillin resistant *S. aureus* (MRSA) infections. One of the major adverse effects of vancomycin is nephrotoxicity which has limited its administration. Vancomycin mono therapy may cause nephrotoxicity at an incidence of 5 to 10%; while in combination with aminoglycosides has increased the incidence of nephrotoxicity to 14 and as high as 35% *(9)*. Records demonstrated a significant reduction in

serum leptin level in albino rats received vancomycin *(10,11)*.

L-Carnitine is biosynthesized primarily in the liver and kidneys from the amino acids lysine (via trimethyl lysine) or methionine *(12)*. The requirement of L-carnitine might exceed its natural production in certain circumstances like growth and pregnancy *(13)*. There are many studies that reported the protective effect of L-carnitine against doxorubicin *(14,15)*. Doxorubicin (DOX) may cause adenosine 5'-triphosphate (ATP) depletion by inhibition of carnitine palmitoyl transferase at both mitochondrial outer and inner membrane *(16)*. Administering L-carnitine can facilitate the transport of long chain fatty acids into the mitochondria and promotes fatty acid oxidation *(17)*. In rats, administration of L-carnitine prevented DOX-induced histological and metabolic damage *(18)*.

This study was designed to investigate the protective effect of L-carnitine against DOX and vancomycine induced adverse effects on lipid metabolism.

MATERIALS AND METHODS

Drugs

Adricin (Doxorubicin HCl) from EIMC United pharmaceuticals, Badr city-Cairo-A.R.E. Each vial (5ml) contains Doxorubicin HCl 10 mg.

Rat were injected intraperitoneal (I/P) dose with adriamycin, 2.5 mg/kg B.wt. once/week for 4 successive weeks *(19)* and examined 3, 10 and 15 days post administration.

Vancomix from Sigmatec pharmaceutical industries, Egypt. One gm Vial contains Vancomycin HCL chromatographically purified equivalent to 1 gm vancomycin activity). Rat were injected I/P daily with vancomycin (1 gm/kg B.wt/every 12 hr for 7-10 successive days. The dose per rat was calculated according to the surface area *(20)*.

L-Carnitine from MEPACO Medifood Co. Enshas- Sharkeya. Egypt. Each 5 ml ampoule contains 1 gm L-Carnitine. Molecular Rat were injected I/P daily with L-carnitin (200 mg/kg B.wt) daily for 2 successive weeks *(21)*.

Experimental animals: Ninety mature male albino rats (weight mg 120 ± 20 gm, 6 month old) were used. They were obtained from the Laboratory Animal unit, Faculty of Veterinary Medicine, Zagazig University. The animals were clinically healthy, kept under hygienic conditions, housed in metal cages with hard wood shavings as bedding. They were maintained on balanced ration composed of barley, milk, green fodder and water *ad-libitum*. The animals were accommodated at the laboratory condition for two weeks before being experimented.

Experimental design: The rats were acclimatized for 2 weeks and randomly divided into six groups of 15 rats at each. First group served as control and didn't receive any treatment, Group II treated with L-carnitine, Group III treated with Doxorubicin, Group IV treated with Vancomix. Group V treated DOX and L-carnitine. Group VI treated with Vancomix and L-carnitine. The rats were kept for 3, 10 and 15 days after last treatments of each group then were sacrificed and samples were collected.

Sampling: Blood samples were collected into two clean, dry, sterile, and labeled centrifuge tubes, the first tube contained sodium fluoride for determination of blood glucose whereas, the second tube contained no anticoagulants where blood used for separation of serum for determination of total proteins, albumin, total cholesterol, HDLc, GGT, MDA, LDH and leptin.

Tissue sampling: Adipose tissue was immediately removed from each animal after sacrificing and they are washed out from contaminated blood with normal saline weighted and immediately kept in liquid nitrogen until be used for determination of gene expression of *Ob* gene.

Statistical analysis: The obtained data were analyzed and graphically represented using the statistical package for social science (SPSS, 18.0 software, 2011) for obtaining means and standard error. Duncan's test was used for making a multiple comparisons among the groups for testing the inter-grouping homogeneity *(22)*.

RESULTS

Effect of different treatments on body gain

Body weight was significantly increased in the Vancomycin and doxorubicin treated groups while there was none significant changed in L-carnitine treated groups compared with the control.

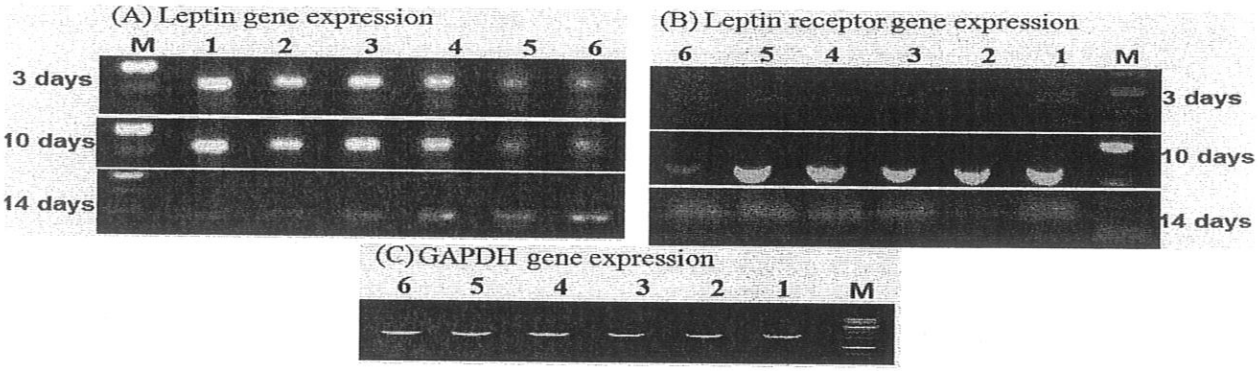
Table 1. Weight gain in albino rats after 3, 10 and 15 day post treatment

Group	Weight gain (grams)		
	3 day	10 day	15 day
Control	128.00 ± 3.14^{D}	128.00 ± 3.14 ^{D}	128.00± 3.14 ^{D}
L- Carnitine	126.75± 5.15^{D}	125.75± 5.16 ^{D}	125.15± 5.13 ^{D}
DOX	172.50 ± 4.78 ^{B}	199.25± 11.37 ^{B}	197.50± 15.92 ^{B}
Vancomix	206.25± 9.87 ^{A}	215.00± 8.42 ^{A}	217.50± 9.24 ^{A}
DOX + L	149.75b± 11.52 ^{C}	154.00± 11.19 ^{C}	155.00± 11.75 ^{C}
Vancomix + L	167.50± 8.54 ^{B}	203.50± 10.44 ^{B}	204.75± 10.37 ^{B}

Means in the same raw that carry different subscripts are significant at P<0.05

Molecular Biological determinations

Figure (1): The electophorteic photograph of mRNA expression levels in A; leptin B; leptin receptors and C; GAPDH genes in the adipose tissues of rats; the product sizes are 195, 171, 455 bps respectively.



N.B M; 100bp-1000bp DNA-ladder, **1;** Male rats (control)**2;** Male rats treated with L-carnitine, **3;** Male rats treated with doxorubicin, **4;** Male rats treated with Vancomycin, **5;** Male rats treated with doxorubicin and L-carnitine and **6;** Male rats treated with Vancomycin and L-carnitine.

Figure 1 represents a decrease in the level of gene expression of leptin and leptin receptors in the groups treated with DOX and Vancomycin and this decrease was ameliorated by supplementation with L-carnitine. GAPDH control gene show almost stable pattern in all groups.

Biochemical findings

Our results represents that there were a significant decrease in the level of serum leptin, insulin, total protein and albumin in the groups treated with DOX and vancomycin, this decrease was improved by treatment with L-carnitine that can ameliorates their effect. Whereas the levels of MDA, LDH, TC, HDL-c and GGT were significantly increased due to DOX and Vancomycin treatment and L-carnitine succeeded to restore this increase.

Table 2. Biochemical determinations in albino rats treated with Doxorubicin and Vancomycin after 3, 10, 15 days respectively

Group	Time (Day)	Leptin (ng/ml)	Insulin (ng/ml)	MDA (nmol/ml)	LDH (U/l)	HDL (mg/dl)	Cholesterol (mg/dl)	T. protein (g/dl)	Albumin (U/l)	GGT (U/l)
Control	3	6.5 ±0.25^{a}	99.6± 3.8^{a}	8.1± 1.45a	869.2± 25^{c}	49.2± 0.4^{c}	121.2± 0.3^{c}	5.4± 0.18^{a}	5.29 ± 0.12^{a}	1± 0.14^{b}
	10	6.5 ± 0.2^{a}	97.9± 3.7^{a}	8.1 ± 1.4^{c}	869.2± 25.0^{ab}	49.2± 0.4^{e}	121.2± 0.3^{d}	5.4± 0.18^{d}	5.29± 0.12a	1± 0.14^{b}
	15	6.5 ± 0.2^{a}	98.5 ± 3.6^{a}	8.1± 1.4^{c}	869.2± 25^{cd}	49.2± 0.4^{c}	121.2± 0.3^{d}	5.4± 0.18^{a}	5.29± 0.12^{a}	1± 0.14^{bc}
L- Carnitine	3	6.4± 0.3^{a}	99.0±7.2^{a}	1.6± 0.9^{b}	407± 77^{d}	43.5± 0.6^{d}	90.9± 4^{e}	5.3± 0.14^{a}	4.5± 0.25^{b}	0.7± 0.2^{b}
	10	6.3± 0.2^{a}	97.1±6.4^{a}	1.6± 0.9^{d}	407± 77.7 c	43.5± 0.6^{f}	90.9± 4^{e}	5.3± 0.14^{a}	4.5± 0.25^{b}	0.7± 0.20^{b}
	15	6.35± 0.2^{a}	99.0±6.5^{a}	1.6± 0.9^{d}	407± 77.7^{e}	43.5± 0.6^{d}	90.9± 4e	5.3± 0.14^{a}	4.5± 0.25^{b}	0.7± 0.20^{c}
DOX	3	8.2± 0.14^{b}	101.7 ±8^{c}	10.8± 1.1^{a}	1485.5± 64^{a}	64.2± 0.38^{a}	166.4± 0.6^{a}	4.2± 0.14^{c}	2.3± 0.01^{d}	4.4± 2.2^{ab}
	10	8.1± 0.12^{b}	107.3 ±8^{c}	29.8± 0.8^{a}	1057± 32.7^{ab}	70.2± 0.3^{b}	176.7± 0.8^{a}	4.1± 0.26^{b}	2± 0.00^{e}	8± 2.48^{a}
	15	8.01± 0.2^{b}	101 ± 8^{c}	13.9± 2.3^{b}	1451.5±135.1^{a}	65.8± 0.7^{a}	168.8± 1^{a}	4.2± 0.16^{c}	3.48± 0.16^{c}	3.2± 0.58^{a}
Vancomix	3	5.98± 0.33^{b}	79.7± 4.2^{d}	9.3± 1.3^{a}	1345.5± 83^{a}	61.9± 0.39^{a}	130.3± 3.4^{b}	4.7± 0.23^{b}	2.7± 0.25^{d}	5.7± 2.2^{a}
	10	5.9± 0.3^{b}	80.1± 4.8^{d}	16.0± 0.8^{b}	1111.7± 50.7^{a}	67.7± 0.7^{b}	143.9± 1.8^{b}	4.8± 0.27^{ab}	2.7± 0.19^{d}	7.5± 1.93^{a}
	15	5.9± 0.2^{b}	77.7± 4.9^{d}	19.7± 0.7^{d}	1020± 40^{bc}	63.6± 0.3a	138.5± 0.6^{c}	4.4± 0.07^{bc}	2.8± 0.10^{d}	2.1± 0.45^{ab}
DOX + L	3	6.31± 0.3a^{b}	99.4±3.9^{c}	3.2± 0.9^{b}	1226.5± 76^{ab}	50.8± 0.27^{c}	127.9± 0.9^{bc}	4.9± 0.17^{ab}	4.0± 0^{c}	1.5± 0.2^{b}
	10	6.3± 0.23a^{b}	97.1±4.8^{c}	6.7± 0.2^{c}	886± 133.57^{ab}	59.6± 0.5^{c}	134.5± 1.6^{c}	4.8± 0.23^{ab}	3.5± 0.08^{c}	2.5± 0.78^{b}
	15	6.2± 0.13a^{b}	98.5±4.6^{c}	5.4± 0.4^{cd}	1197.7±35.7^{ab}	52.8± 1.6^{b}	125± 1.3^{b}	4.8± 0.20^{b}	4.1± 0.01^{b}	1.4± 0.67^{bc}
Vancomix + L	3	6.18±0.27^{ab}	96.3± 2.6^{b}	2.1± 0.6^{b}	952± 49^{bc}	53.8± 1.6^{b}	101.5± 2.4^{d}	4.1± 0.11^{c}	3.8± 0.22^{c}	1.13± 0.4^{b}
	10	6.12± 0.2ab	96.8± 2.8^{b}	6.5± 0.63^{c}	868.75± 89.4^{b}	53.837±0.7^{d}	133.10± 1.9^{c}	4.64± 0.21^{b}	3.25± 0.25^{c}	3.4± 0.82^{b}
	15	6.27±0.25ab	96.4± 2.5^{b}	7.9± 2.7^{c}	898±151.37^{de}	52.1± 1.13^{b}	126.15± 2^{d}	4.73± 0.12^{bc}	3.24± 0.12^{cd}	0.6± 0.22^{c}

Means in the same raw that carry different subscripts are significant at P<0.05.

DISCUSSION

In the present study we tended to evaluate the effect of doxorubicin and Vancomycin on the lipid state. Our results showed an increase in body weight in case of treatment with doxorubicin that may be due to leptin resistance which is related to the development of insulin resistance *(23)*. Hyperinsulinemia and insulin resistance has been demonstrated and obesity is associated with a marked increase in circulating leptin concentration *(24)*. The increase in the body weight till reaches obesity in case of treatment with vancomycin was in agreement with *(25)* who reported that Vancomycin caused reducing of leptin in circulation. In the same line the genetic defect of leptin has the ability to induce severe obese phenotypic traits *(26)*.

Leptin is a main hormone that conveys signal containing information of energy storage in the body and it functions to suppress energy intake as a response of adequate energy requirement *(27)*. In our study we relived the effect of some antibiotics as doxorubicin and vancomycin on leptin level with antioxidant as L-carnitine on the leptin level and their effect on body weight and the occurrence of obesity which happened after treatment of the infection as in case of treatment with vancomycin after operation which named intensive care obesity and also obesity which happened after treatment of cancer when the treatment with doxorubicin.

Our results showed that, there is an increase in leptin level after treatment with doxorubicin, which agrees with *(28)*, and this may be due to increase synthesis of leptin mRNA and serum leptin level in obese individuals as detected in table 2 and figure1 when compared to non-obese individuals which brings into hypothesis of leptin resistance *(29)*.

Leptin resistance is related to the development of insulin resistance in individuals with type II diabetes *(24)*. Our results showed an increase in insulin level in groups treated with doxorubicin. This results agreed with *(30)* who mentioned that insulin resistance syndrome, have been linked to an increased risk of developing cancer.

Oxidative stress leads to tissue damage and has been linked to impairment of insulin action and β-cell function with the resultant development of type II diabetes *(31 ,32)*.

Our result presented that, there were an increase level of LDH as also reported by *(33,34)*, they attributed that to the inflammatory cells forming granulomatous lesions and periportal fibrosis were detected after doxorubicin administration which has been shown to induce accumulation of inflammatory cells, associated with increased activity of LDH, indicating hepatic damage. These results also was in agreement with *(35)* who mentioned that heart tissue injury induced by doxorubicin in rats was indicated by elevated level of the marker enzymes such as serum LDH and CPK. The increase of LDH level in serum and extracellular fluid suggests an increase leakage of this enzyme from mitochondria as a result of toxicity induced by treatment with doxorubicin.

Our result also revealed an increase in the activities of gamma glutamyl transferase (GGT) in groups treated with doxorubicin and this in agreement with *(36)* that doxorubicin induce liver disorders manifested by an increase liver enzymes (GGT) *(37)*.

Serum albumin is the most important member of export proteins. Export proteins are synthesized on polyribosomes bound to the rough endoplasmic reticulum of the hepatocyte. In contrast, proteins destined for intracellular use are synthesized on free rather than polyribosomes *(38)*. In the relation to the effect of doxorubicin and Vancomycin on plasma proteins and albumin. Our results showed that doxorubicin afforded a significant decrease in serum total proteins four weeks post treatment which is represented by a significant decrease in serum albumin. L-carnitine and its combination with doxorubicin elicited a significant increase in serum total proteins when compared with the groups given doxorubicin alone and normal control group respectively. Other investigation by *(39)* showed that rats that received doxorubicin had

low plasma albumin by losing protein in urine consistent with hyaline droplets presented in capsular space and tubular lumen. The mechanism may associate with alteration of glomerular capillary permeability due to sieving defect.

Malondialdehyde is a metabolite derived from lipid peroxidation which has been widely used as an indicator of oxidative stress *(40)*. The measurement of this MDA provides a convenient index of lipid peroxidation *(41)*. The body develops several endogenous antioxidant systems to deal with the production of reactive oxygen species. Antioxidants act as radical scavengers, inhibit lipid peroxidation and other free radical mediated processes, and there by protect human body from several diseases attributed to the reactions of radicals *(42,43)*. The present study demonstrated that treatment with DOX increased MDA (an index of lipid peroxidation). These results correlate well with previous studies. DOX treatment was shown to induce peroxidative alterations in various tissues which were evident by significant elevation in MDA production in the rat's heart, kidneys and liver tissues *(44,45)*. Doxorubicin either given alone or in combination with L-carnitine enhanced lipid peroxidation measured as malondialdehyde (MDA) along the course of the experiment when compared with normal control group. Doxorubicin induced marked biochemical alterations characteristic of cardiac toxicity including enhanced lipid peroxidation as measured by malondialdehyde (MDA). Furthermore, it has been demonstrated that 20 mg/kg single dose of DOX resulted in renal lipid peroxidation and protein oxidation at 10^{th} day of DOX injection in rats *(46,47)*.

Vancomycin carries the potential to exacerbrate metabolic disorders by increasing adiposity and body mass index when it used to treatment the gut microbial or as probiotic *(48, 49)*.

Several investigators have suggested that oxygen free radicals are considered to be important mediators of gentamicin-induced nephrotoxicity *(50)*. The genetic defect of leptin-deficient ob/ob mice, which causes a severe obese phenotype, is associated with increased sensitivity to roinflammatory monocyte/macrophage-activating stimuli and impairment of phagocytic functions, as well as reduced T-cell function *(26)*.

Our results showed decrease in leptin level in rats treated with VAN and this in agreement with *(10)* who reported that that one week of VAN treatment led to a significant reduction in serum leptin levels. Despite a 41% reduction in serum leptin levels by VAN. Also, *(25)* mentioned that VAN may be able to affect a biphasic protection of the myocardium by reducing the level of leptin in the circulation. As demonstrated in the current study, decreased leptin levels in the circulation decreases the myocardium's susceptibility to acute injury from ischemia/reperfusion while other studies have showed that reduced leptin signaling through blockade of the leptin receptor results in decreased chronic cardiac hypertrophy. Administration of VAN in treatment of a case respiratory failure resulted in decreasing the frequency of in blood glucose measurement and improve glycemic status *(51)*.

Our result showed an increase level of LDH and this agrees with *(52)*. In cased of anosocomial infection I/V VAN 1000 mg every 12 hours. The increase in LDH level may be due to patient has hematologic abnormalities and developed leukocytosis, eosinophilia, normocytic anemia; schistocytes present on a peripheral blood sear *(53)*.

Gamma-glutamyl transferase (GGT) is shown to be an independent risk factor for the mortality and morbidity of cardiovascular diseases in recent epidemiological and clinical studies. In addition, several prospective studies reported that baseline serum GGT concentration was an independent risk factor for the development of coronary artery disease (CAD), diabetes mellitus, stroke and hypertension. GGT plays an important role in antioxidant defense systems. Elevated GGT levels could be a marker of oxidative stress and sub clinical inflammation *(54, 55)*. Some epidemiological studies also suggest that higher

serum GGT levels is associated with development of CVD risk factors, including diabetes, hypertension, and the metabolic syndrome. GGT may play a role in early diagnosis of metabolic syndrome with a high predictive value for both metabolic syndrome and cardiovascular disease presence *(56)*. But VAN administration in combination with L carnitine resulted in decrease in GGT level. This result agrees with *(35)* who used VAN in combination with L carnitine as a chemotherapy for acute lymphoblastic leukemia.

Our results showed reduction in albumin level and this agreed with *(57)* who said that serum albumin concentration was significantly lowered in burns patients when treated with VAN.

VAN could enhance cellular ATP concentrations and stimulate oxygen consumption, supporting the role of VAN as a stimulant of oxidative phosphorylation and the free radical production. Vancomycin induced free radical injury may be generated directly or indirectly *(58)*. This destructive lipid peroxidation leads to breakdown of membrane structure and function. Further decomposition of per oxidized lipids yields a wide variety of end products, including MDA. There was a significant increase of MDA concentration in renal tissue of rats treated with vancomycin; suggesting the involvement of oxidative stress-induced nephrotoxicity. This result was agreed with reports by *(59,60)*.

Our results showed increase level of cholesterol in case of VAN treatment and this agrees with *(61)* who used vancomycin in treatment of cytotoxicity of human glial cell. But in case of vancomycin and L-carnitine showed decrease cholesterol level. Also there were an increase in HDL plasma and this agrees with *(62)* in treatment of gut microbial. But L-carnitine when given in combination with vancomycin makes improve HDL level but still more than normal.

Conclusion

Both doxorubicin and vancomycin have a bad effect on the lipid sate as they increase leptin and insulin receptors inducing obesity in experimental animals, also; they increase liver enzymes and heart markers as well as increase the oxidative stress in the body tissues due their ability to increase the level of MDA in the serum of the experimental animals. L-carnitine administration ameliorates the hazards effect of DOX and VAN on the lipid sate in the body.

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الملخص العربى

التأثير الكيميائى للكرياتينين ضد التأثير الضار لكل من الدوكسيروبسين والفانكومايسين فى الفئران

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أجريت هذه الدراسة على الفئران لدراسة التأثير المضاد لمادة الكارنيتين على الاضرار النتاجة عن إستخدام كل من الدوكسيروبسين والفانكومايسين على الكبد ومستوى الدهون والكلية.

استخدم فى هذه الدراسة عدد ٩٠ فأر قسموا لست مجموعات متساوية (١٥ فأر لكل مجموعة) وبعد المعاملات تم ذبح الفئران بعد ٣ ، ٥ ، ١٥ يوم من إنتهاء المعاملات.

اسفرت النتائج عن نقص فى مسبة هرمون الليبتن والأنسولين فى الدم وكذلك نقص مستوى البروتينات الكلية والألبيومين مع زيادة فى مسبة الممالونالديهايد واللاكتيك ديهيروجينيز والجاما جلوتاميل ترانسفيريز والكلوستيرول الكلى والعالى الكثافة ولكن استخدام الكارنيتين كان له من الاثر من تعديل فى المستويات المضطربة وعودتها للنسب الطبيعية مما يدل على فوائد الكارنيتين فى مجابهة التأثير الضار لكل من الدوكسيروبسين والفانكومايسين.