RESEARCH ARTICLE

Study the Effect of Vitamins (C and E) on Oxidative Stress and Antioxidants Changes Induced by VCM in Male Rats

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ABSTRACT

The current study was designed to determine the antioxidant effects of vitamin C and vitamin E against oxidative stress induced by vancomycin in some antioxidants changes in the male rats. The study was conducted in the animal house of the Faculty of Science/University of Kufa for the period from April, 2018 to May, 2018 on 119 animals of male rats aged 2.5–3 months and the weight of 150-200 gm. Two experiments designed in this study addressed the first and two experiments to study the oxidative effect of vancomycin in addition to the protective effects of vitamin C and vitamin E to reduce these effects in the treatment of animals for one week and three weeks with vancomycin and vancomycin plus vitamins. The results indicated a significant increase ($p < 0.05$) in the MDA, CAT, and significant decrease ($p < 0.05$) in SOD, and GPX. In the animals treated with vancomycin 40,60 mg/kg only compared to the control group for the two periods of administration at the same time occur a significant decrease($p < 0.05$) in the MDA, CAT and a significant increase ($p < 0.05$) in the SOD and GPX after treated animals with vancomycin 40,60 mg/kg with vitamin C and vitamin E for a period of one and three weeks compared with vancomycin group.

Keywords: Vancomycin, Vitamin c, Vitamine, Antioxidant, Oxidative stress.

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INTRODUCTION

Oxidative stress represents a situation where there is an imbalance between the reactive oxygen species (ROS) and the availability and the activity of antioxidants. This balance is disturbed by the increased generation of free radicals or decreased antioxidant activity. It is very important to develop methods and find appropriate biomarkers that may be used to assess oxidative stress *in vivo*. It is significant because appropriate measurement of such stress is necessary in identifying its role in lifestyle-related diseases.[1] Oxidative stress from oxidative metabolism causes base damage, as well as strand breaks in DNA. Base damage is mostly indirect and caused by reactive oxygen species (ROS) generated, e.g., O^{2-} (superoxide radical), HO (hydroxyl radical) and H_2O_2 (hydrogen peroxide).[2] Thus, oxidative stress can cause disruptions in normal mechanisms of cellular signaling.[3] In humans, oxidative stress is thought to be involved in the development of Parkinson's disease,[4] alzheimer's disease[5;6] atherosclerosis,[7] sickle Cell Disease.[8]

Vancomycin is a glycopeptide antibiotic that remains the "gold standard" for treating methicillin-resistant Staphylococcus aureus (MRSA) infections, but the adverse side effects include nephrotoxicity and ototoxicity.[9:10] The occurrence rate of vancomycin-induced nephrotoxicity is approximately 10–40% in different populations.[11] Vancomycin is a key antibiotic in the management of severe Gram-positive infections. The recent emergence of methicillin-resistant staphylococcal strains with reduced susceptibility to vancomycin has prompted internists to administer high-dose treatment to achieve trough levels of 15 to 20 mg/L. Such high doses might be causative in nephrotoxicity.[12] Long-term parenteral nutrition (PN) can induce intestinal atrophy, leading to a loss of epithelial integrity in the small intestines. This change 31/52 may alter the intestinal permeability of vancomycin (VCM), a non-absorbable antibiotic.[13]

Vancomycin reducing the gram-positive bacteria in the gut without overtly modifying the Gram-negative microbes, in order to target one particular aspect of the microbial influence on host metabolism. Additionally, vancomycin is known to be poorly partitioned across the mammalian gastrointestinal mucosa, and since it does not have systemic absorption, it should not perturb host biochemistry directly.[14] Vancomycin is a cornerstone antibiotic for the management of severe Gram-positive infections. Introduced into clinical practice in 1956,

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it is a bactericidal glycopeptide with a molecular weight of 1446 Da.

An antioxidant is "any substance that delays, prevents or removes oxidative damage to a target molecule."[15] The recognition of vitamin c (ascorbic acid) is essential for the development and maintenance of connective tissue. It plays an important role in bone formation, wound healing gums. Vitamin C plays an important role in a number of metabolic functions, including the activation of vitamin B, folic acid, the conversion of cholesterol to bile acids, and the conversion of amino acids, tryptophan to the neurotransmitter serotonin.[16] Out of the three different antioxidant defense systems, vitamin C is classified as a chain-breaking antioxidant, specifically, an aqueous phase chain-breaking antioxidant.[17] Vitamin E is an essential fat-soluble micronutrient whose effects on human health can be attributed to both antioxidant and non-antioxidant properties.[18] Tocochromanols, a subset of isoprenoids better known as vitamin E, include four tocopherols and four tocotrienols. These lipophilic antioxidants are synthesized by plants and other photosynthetic organisms only.[19]

MATERIALS AND METHODS

The current study was designed to determine the antioxidant effects of vitamin C and vitamin E against oxidative stress induced by vancomycin in some antioxidants changes in the male rats. The study was conducted in the animal house of the Faculty of the Science/University of Kufa for the period from April/2018 to May/2018 on 119 animals of male rats aged 2.5–3 months and the weight of 150–200 gm.

Two experiments designed in this study, addressed the first and two experiment to study the oxidative effect of vancomycin in addition to the protective effects of vitamin C and vitamin E to reduce these effects in the treatment of animals for a periods of one weeks and three weeks, Used in these experiments 119 rats were animals of the male rats which were divided randomly into nine subgroups each subgroup contains seven animals, the first subgroup promised to negative control subgroup which were administrated normal saline only, the second subgroup administrated vancomycin at dose 40, 60 mg/kg of body weight per day and promised a positive control, the third subgroup administrated vancomycin dose of 40,60 mg/kg of body weight with vitamin C per day also promised a positive control, the forth subgroup administrated vancomycin at dose of 40,60 mg/kg of body weight with vitamin E per day and promised a positive control , the fifth subgroup administrated vancomycin at dose of 40,60 mg/kg of body weight with vitamin C and vitamin E per day and promised a positive control for a period of one and three weeks. After one and three weeks, all number of rats from each subgroup were sacrificed and blood collecting.

RESULTS

Results of statistical analysis for each of Catalase, Glutathione, Malondialdeyde, and Superoxide serum levels of control and treated groups for 1w(dose 40) in the table (1–1).

In this table, results exhibited a significant ($p < 0.05$) increased mean level of catalase was found in treated groups for 1w with van.40(0.140 ± 0.0025), as compared to the control group (0.046±0.0024). In addition, a significant

Table 1–3: Effect of Vit.c and Vit.e on Catalase, Glutathione peroxidase Malondialdehyde, and Superoxide Dismutase in male rats treated with vancomycin for one-weeks.

Parameters / *Dose (mg/kg)*	*Catalase (u/mg)*	*Glutathione Peroxidase (pg/mL)*	*Malondialdehyde (ng/mL)*	*Superoxide Dismutase (ng/mL)*
Control	0.046 ± 0.0024	99.6 ± 0.40	11.40 ± 0.187	1.14 ± 0.024
Van.40	0.140 ± 0.025	79.6 ± 1.63	20.86 ± 0.299	0.52 ± 0.037
Van.40 + vit.c	0.088 ± 0.0020	96.0 ± 0.55	10.34 ± 0.293	1.46 ± 0.024
Van.40 + vit.e	0.052 ± 0.0037	109.4 ± 4.61	15.10 ± 0.874	1.53 ± 0.116
Van.40+vit.c+vit.e	0.040 ± 0.0045	139.8 ± 4.33	7.06 ± 0.211	1.41 ± 0.040
LSD	0.033	8.66	1.33	0.175
Van.60	0.220 ± 0.058	79.0 ± 0.058	21.08 ± 0.271	0.58 ± 0.037
Van. 60+vit.c	0.116 ± 0.0211	95.2 ± 0.021	10.40 ± 0.077	1.59 ± 0.059
Van.60 + vit.e	0.084 ± 0.0040	150.8 ± 0.004	10.46 ± 0.093	1.16 ± 0.024
Van.60+vit.c+vit.e	0.082 ± 0.0037	94.0 ± 0.0037	19.74 ± 0.218	1.57 ± 0.058
LSD	0.082	10.18	0.54	0.13

Values are mean ±SE, LSD 0.05.
Number of animals = 5 for each group
Van: vancomycin, Vit.c: vitamin c, Vit.e, vitamin e

($p < 0.05$) decreased in van.40+c , van.40+e, and van.40+vit. c+e when compared with van.40 it was highest in van.40+vit. c+e, respectively. The mean value of Glutathione serum level indicate a significant ($p < 0.05$) decreased in treated groups for 1w with van.40 (79.6±1.63) as compared to the control group (99.6 ± 0.40). In addition, a significant ($p < 0.05$) increased in van.40+c, van.40+e and van.40+c+e when compared with van.40 it was highest in van.40+vit. c+e, respectively. The results revealed a significant ($p < 0.05$) increased in serum level Malondialdeyde in treated groups for 1w in van.40 (20.86 ± 0.299) , when compared to the control group(11.40±0.187). Also significant ($p < 0.05$) decreased in van.40+vit.c, van.40+vit.e and van.40+vit.c+vit.e when compared with van.40, respectively. Mean of Superoxide Dismutase was statistically significant ($p < 0.05$) increase noted in treated groups for 1w with van.40 (0.52 ± 0.037) as compared to the control group (1.14 ± 0.024) respectively. Also a significant ($p < 0.05$) in decreased in van.40+vit.c, van.40+vit.e and van.40+vit.c+vit.e when compared with van.40, respectively.

In same table 1w (dose 60)

These results exhibited a significant ($p < 0.05$) increased mean level of Catalase was found in treated groups for 1w with van.60 (0.220 ± 0.058) as compared to the control group (0.046 ± 0.0024). In addition, a significant ($p < 0.05$) decreased in van.60+c , van.60+e, and van.60+vit.c+e when compared with van.60, respectively. The mean value of Glutathione serum level indicate a significant ($p < 0.05$) decreased in treated groups for 1w with van.60(79.0±0.058) as compared to the control group(99.6 ± 0.40). Also significant ($p < 0.05$) increased in van.60+vit.c, vin.60+vit.e and van.60+vit.c+vit.e as compared with van.60, respectively. The mean value of the malondialdeyde serum level indicates of a significant ($p < 0.05$) increased in treated groups for 1w with van.60(21.08 ± 0.271) as compared to the control(11.40 ± 0.187). Also significant ($p < 0.05$) decreased van.60+vit.c, van.60+vit.e and increased in van.60 + vit.c+vit.e as compared with van.60 respectively. The mean value of the Malondialdeyde serum level indicates of a significant ($p < 0.05$) increased in treated groups for 1w with van.60(0.58 ± 0.037) as compared with control group (1.14 ± 0.024). Also significant ($p < 0.05$) decreased in van.60 + vit.e and van.60+vit.c and van.60 + vit.c+vit.e as compared with van.60 respectively.

DISCUSSION

Vancomycin induced oxidative stress was evident by decreased activity of antioxidant enzyme levels such as SOD, GPX and increased catalase, production of lipid peroxidation product MDA compared with a control group. The free radicals produced by vancomycin may inactivate SOD and catalase in the renal cortex in vancomycin treated rats, as it is well known that peroxynitrite radicals impair SOD activity and superoxide radicals inactivate catalase.[20] Impaired functioning of antioxidant enzymes by vancomycin would result in unopposed production of free radicals. This ROS causes destructive peroxidation of cell membrane lipids, leads to cell membrane damage, and yields a wide variety of lipid peroxidation end products, including MDA.[21,22]

This study explains the decreased SOD, GPX, and increased catalase, MDA, which is agreed with the study above. Several reports indicate that oxidative stress might be responsible for vancomycin mediated nephrotoxicity. Oxidative stress is an imbalance between free radical production and antioxidant activity. So the measurement of lipid peroxidation products e.g.: MDA and free radical scavenging antioxidant enzymes like

Table 4–10: Effect of Vit.c and Vit.e on Catalase, Glutathione peroxidase Malondialdehyde and Superoxide Dismutase in male rats treated with vancomycin for three-weeks.

Parameters / *Dose (mg/kg)*	*Catalase (u/mg)*	*Glutathione Peroxidase (pg/mL)*	*Malondialdehyde (ng/mL)*	*Superoxide Dismutase (ng/mL)*
Control	0.046 ± .0024	99.6 ± 0.40	11.40 ± 0.187	1.14 ± 0.024
Van.40	0.160 ± 0.0025	63.4 ± 0.81	28.64 ± 0.330	0.60 ± 0.066
Van.40+vit.c	0.096 ± 0.0023	121.6 ± 0.93	24.26 ± 1.135	0.84 ± 0.051
Van.40+vit.e	0.096 ± 0.0026	145.6 ± 1.69	20.50 ± 0.170	1.16 ± 0.040
Van.40+vit.c+vit.e	0.058 ± 0.0060	159.4 ± 3.70	19.66 ± 0.271	1.40 ± 0.032
LSD.	0.03	5.63	1.63	0.133
Van.60	0.164 ± 0.0026	94.6 ± 1.57	21.56 ± 0.499	0.72±0.073
Van. 60 +vit.c	0.094±0.0025	162.8±1.39	14.14±0.574	1.40±0.033
Van.60+vit.e	0.094±0.0023	170.6±1.21	15.14±0.117	0.90±0.032
Van.60+vit.c+vit.e	0.076±0.0051	177.6±2.50	19.90±0.118	1.04±0.025
LSD	0.009	4.623	1.058	0.122

Values are mean ±SE, LSD 0.05.
Number of animals = 5 for each group
Van: vancomycin, Vit.c: vitamin c, Vit.e: vitamin e

superoxide dismutase(SOD), catalase, and antioxidant protein glutathione(GSH) are good markers for studying the effect of oxidative stress. SOD catalyzes the conversion of superoxide radicals to hydrogen peroxide (H**2**O**2),** and GSH and Catalase remove H_2O_2 produced by SOD.[23;24]

In this study also record increased level of SOD, GPX and CAT after treated with vancomycin this result is disagreement with study present by[25] which explain decreased activities of antioxidant enzymes (SOD, GPX) and agreement with increased CAT were observed in the renal tissue, which indicates the failure of antioxidant defense system to overcome the influx of ROS on VAN exposure. Thus the inhibition of enzymes involved in free radical removal leads to the accumulation of H_2O_2, which promotes lipid peroxidation and modulation of DNA, altered gene expression and cell death Administration of GA increased the activities of SOD, CAT, GPx and GST in VAN-treated rats which might be due to the ability of GA in reducing the accumulation of free radical generation during VAN induced lipid peroxidation.[26]

Impaired functioning of antioxidant enzymes by vancomycin would result in unopposed production of free radicals, this ROS results in destructive peroxidation of cell membrane lipids, leads to cell membrane damage and yields a wide variety of lipid peroxidation end products, including MDA, which is accepted as an indicator of lipid peroxidation.[27]

In this study after used of vancomycin with vitamin result the significant reduced level of MDA, increased levels of SOD, GPX compared with vancomycin group this agreed to study present by[28] and increased catalase disagreement of this study which explain the used vitamin with vancomycin which lead to decreased of MDL level, increased of SOD, GPX, and Catalase. Treatment with vitamin has been proved to suppress lipid peroxidation pathway as effective as preventing the rise of MDA level.[29,30] suggested that treatment with vitamin averted oxidative damage, probably through its capacity to quickly and efficiently scavenge lipid peroxide radicals before they attack the membrane lipids. This ability might be related to the fact that lipid peroxyl radicals react more rapidly with vitamin than with membrane lipids.

In this study, the result of a significantly decreased level of SOD, GPX disagreement, and decreased CAT agreement after treated with drug and vitamin study present by[31] We noted a significant perturbation of oxidative stress markers in renal tissue of treated group equally. The MDA augmentation proves the implication of lipid peroxidation. Moreover, the SOD, CAT, and GPx activities are significantly declined. Hence, these observations reveal that oxidative stress may be the underlying mechanism of nephrotoxicity due to antibiotic. Oxidative stress has been reported to have a central role in tubular toxicity caused by many drugs, including gentamicin, amikacin, vancomycin, and cisplatin, reactive oxygen species (ROS) generated via mitochondria have been shown to initiate renal cell apoptosis, ultimately leading to renal dysfunction.

On the other hand, (32) found that co-treatment with vitamins E and C, alone or in combination, reinforces the resistance of renal tissue to drug aggression. The combination of vitamins E and C brought about better protection concerning their single dose. Thus, the results demonstrate that vitamins decrease the nephrotoxic effect of drugs and support the previous hypothesis.

In this study also record decreased level of SOD after treated with drugs and vitamin this result is disagreement with study present by[33] which explain used of vancomycin with vitamin c and E which suppress vancomycin –induced MDA, the result suggest that supplementation of vitamin C and E may be useful in reducing vancomycin –induced nephrotoxicity.

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