

Original Research

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Hepatoprotective Effects of Vitamin E and L-Carnitine Against Linezolid-Induced Oxidative Liver Injury in Adult Rats

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ABSTRACT: Background: Linezolid (LZD) is a member of the oxazolidinone group of antibiotics which are used clinically in the treatment of resistant Gram-positive infections. Routinely, its toxicity to the liver has been reported to occur with long-term use, as well as toxicity to the skin by causing excessive oxidation.

Objective: To assess the protective effect of Vitamin E and L-Carnitine against the liver toxic effect of LZD in adult rats.

Methods: Adult Wistar rats were randomly divided into Control group, Linezolid group (600 mg/kg b.w) and Linezolid supplemented with Vitamin E group (400 IU/kg b.w), Linezolid with L-carnitine group (600 mg/kg b.w.) Oral linezolid 30-day therapy. Liver function tests (ALT, AST and ALP) were performed. Histopathological examination of liver sections was done to determine tissue damage by hematoxylin and eosin (H&E) staining.

Results: In the first group, severe pathological histological changes such as degeneration and congestion of liver cells appeared, resulting from the treatment of linezolid with a significant increase in liver enzymes (ALT, AST). These liver toxic changes were significantly alleviated by the simultaneous administration of L-Carnitine and Vitamin E with linezolid (G2, G3), and a significant decrease in altitudes (ALT, AST) was also seen with the combined treatment of L-Carnitine and Vitamin E. The results showed that the treated groups suffered less damage to liver cells than the linezolid group.

Conclusion: Vitamin E and L-carnitine had significant hepatoprotective activity against linezolid induced liver injury in rats as revealed from biochemical and histopathological parameters. All these findings show that these could serve as the adjuvants in the prevention of drug induced hepatotoxicity.

INTRODUCTION

Linezolid (LZD) is a synthetic oxazolidinone antibiotic that is more effective against Gram-positive bacteria by disrupting bacterial protein synthesis that is used extensively for the treatment of serious infections such as methicillin-resistant *Staphylococcus aureus* and multidrug-resistant tuberculosis. While in general it is an effective treatment, it has also been associated with damaging effects including lactic acidosis and liver injuries, some of which perhaps are due to liver mitochondrial toxicity and formation of oxidative stress [2].

Clinical trials have shown that hepatic impairment has been a potential adverse effect of linezolid treatment [3,4]. The liver damage caused by LZD was indicated by the release of transaminases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) along with serum bilirubin and lactate in the rats in the study [5].

It is thought that Hepatotoxicity is triggered by LZD's inhibition of mitochondrial protein synthesis and resulting inhibition of production of energy and generation of RO. The disparity between the production of ROS and endogenous antioxidant causes lipid peroxidation, disruption of membranes and hepatocellular injury, which is reflected by the increase in the serum level of liver enzymes such as ALT, AST, and ALP [6].

Vitamin E is an lipid soluble antioxidant which works as a scavenger of free radicals and disrupts lipid peroxidation in the membranes of cells. Some experimental model studies have reported that vitamin E supplementation can help to counteract hepatotoxic and nephrotoxic oxidative damage by increasing endogenous antioxidant status and decreasing the malondialdehyde (MDA) content, which is an indicator of lipid peroxidation. [7].

L-Carnitine is involved in β -oxidation and fatty acid transport into the mitochondria and thus has an influence on the energy metabolism of cells. It also displays antioxidant activity – decreases ROS production, increases the activities of SOD and CAT, and maintains the oxidative integrity of mitochondria in different models of oxidative damage.

L-threo-carnitine is chemically given as L-3-hydroxy-4-N,N,N-trimethylaminobutyrate and is an essential component of the body, which is used for the transport of fatty acids across the inner mitochondrial membrane for conversion to energy via β -oxidation. It also decreases the cell metabolic stress as has been reported to be effective Antioxidants against 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radicals, against superoxide anion radicals, against hydrogen peroxide, and on total reducing power (TRP) for L-carnitine.

Earlier, it has been found that long-term L-carnitine supplementation can also protect rats against hepatocarcinogenesis mechanism, possibly because of its ability to maintain mitochondrial functions [8] and can also prevent alcohol-induced liver damage in rats [9].

In people, early intravenous L-carnitine administration has been linked to a decrease in mortality based on its efficacy in treating severe hepatotoxicity resulting from taking an excessive amount of valproic acid [10], and the in vitro experiments demonstrate a reduction in the killing of cultured rat hepatocytes caused by MPTP poisoning [11].

Although individual role of vitamin E and L-carnitine against hepatotoxicity is known but limited studies have been conducted on their combined effect against hepatotoxicity induced by Linezolid. The aim of the present study, therefore, was to examine the protective effect of vitamin E and L-carnitine against linezolid induced liver oxidative damage both biochemically and histopathologically in adult rats.

MATERIALS AND METHODS:

Animals

In the present study, the number of adult male rats was 40. Ten rats in each group were randomly placed into four experimental groups. The mean body weight of the animals was ~250 g. Throughout the experimental period all rats received food and water, and were kept under standard laboratory conditions.

The rats were randomly divided into four experimental groups:

Control Group: given distilled water orally (by gavage) daily for 30 days.

Group 1: orally (gavage) administered linezolid 600 mg/kg b.w. daily for 30 days. Group 1: Linezolid given orally (gavage) 600mg/kg b.w. per 24 hrs., for 30 days each.

Group 2: received an oral gavage of linezolid and L-carnitine–600 mg/kg b.w. per day for 30 days.

Group 3, received linezolid (600 mg/kg b.w.) and vitamin E (400 IU/kg b.w) were given orally (by gavage) once daily for 30 days.

Statistical Analysis

Data are shown as the means $\pm$ standard error (SE). The data obtained were analysed statistically using the SPSS software (Version 28.0, IBM Corp., Armonk, NY, USA), which comprised an overall test of the group differences at the 1-way ANOVA level with F-test at the $p = 0.05$ level followed by Fisher's LSD test for multiple comparison at the same level, where differences $p \leq 0.05$ were considered significant.

Results

Biochemical Results (Liver Function Tests)

Linezolid administration (G1) caused significant ($p \leq 0.05$) elevations in serum total bilirubin (TSB) and the liver enzymes GOT (AST), GPT (ALT), and ALP compared with the control group, (Table 1).

Co-treatment with L-carnitine (G2) significantly ($p \leq 0.05$) reduced TSB, GOT, ALP, and GPT levels compared with the linezolid-treated group (G1) (Table 1), with values approaching those of the control group, indicating a protective effect against linezolid-induced hepatocellular injury.

The treatment with vitamin E (G3) induced a more significant ($p \leq 0.05$) reduction of TSB, GOT, ALP and GPT as compared to G1, with levels that approached those in the control group confirming the antioxidant and membrane stabilising effects of vitamin E in experimental models of liver injury.

Table 1. Effect of linezolid, L-carnitine, and vitamin E on serum liver function markers (mean $\pm$ SD, n = 10 per group). Means within a column bearing different superscript letters (a, b, c) differ significantly ($p \leq 0.05$); NS = not significant.

Group	TSB(mg\ dL)	GOT\AST(IU\L)	GPT\ALT(IU\L)	ALP(IU\L)
Control	0.060 $\pm$ 0.01 C	122.00 $\pm$ 11.20 C	34.5 $\pm$ 3.40 C	311.00 $\pm$ 9.80 C
G1	0.320 $\pm$ 0.07 A	335.00 $\pm$ 28.00 A	78.50 $\pm$ 7.90 A	402.00 $\pm$ 14.50 A
G2	0.125 $\pm$ 0.04 BC	185.00 $\pm$ 19.80 BC	50.20 $\pm$ 5.50 BC	292.00 $\pm$ 13.00 BC
G3	0.215 $\pm$ 0.06 B	252.00 $\pm$ 20.50 BC	62.30 $\pm$ 6.40 B	328.00 $\pm$ 17.20 B
L.S.D	0.2700 *	210.000 *	72.000 NS	185.000 NS
P-Value	0.0498	0.0476	0.4286	0.4818

The liver sections from the control group showed normal structure of the liver with typical cords of hepatocytes around the central vein and normal sinusoids. (Figure 1).

The liver sections obtained from the linezolid treated group (G1) exhibited significant histopathological changes such as hepatocellular degeneration, cytoplasmic vacuolization, necrosis, inflammatory cell infiltration and congestion of the central vein and sinusoids (Figure 2).

However, co-treatment with L-carnitine (G2) resulted in noticeable improvement in liver histology, as evidenced by reduced cellular degeneration and mild inflammatory infiltration, with partial restoration of normal hepatic architecture. (Figure 3).

Similarly, the vitamin E-treated group (G3) demonstrated a more pronounced protective effect, with liver sections showing nearly normal hepatocyte structure, minimal cellular damage, and slight congestion. (Figure 4).

Representative histological images are presented in (Figures 1)

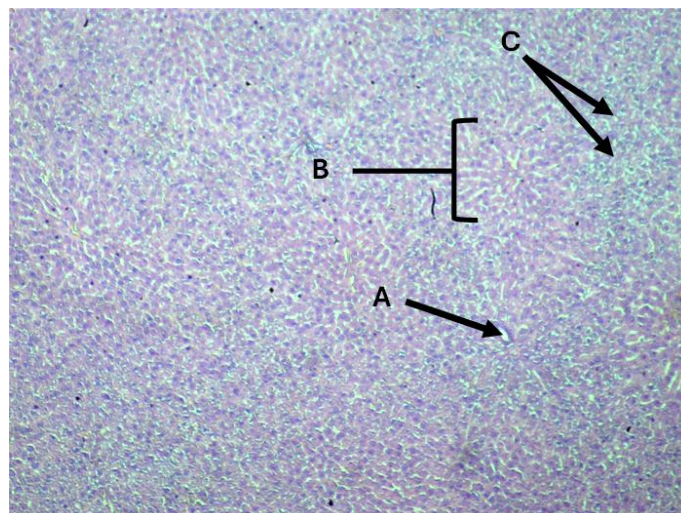


Figure 1: The liver of male rat of Control group represented central vein (A), liver cords (B) and hepatocytes (C) (H &E 40X).

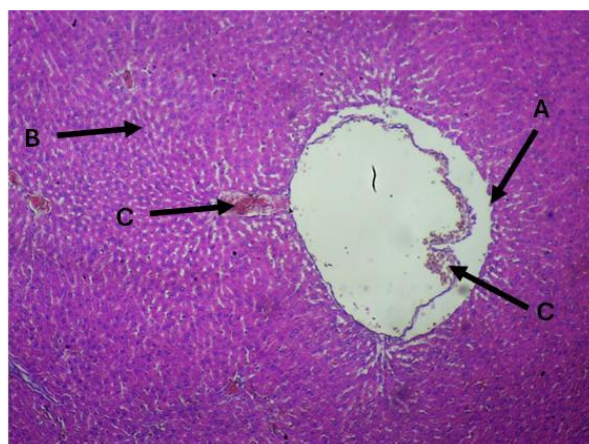


Figure 2: liver of male rats treated with linezolid 600 mg/kg b.w. showed high dilation of central-vein (A), hemorrhages in liver tissue (B), high congestion in the central vein (C) (H&E40X).

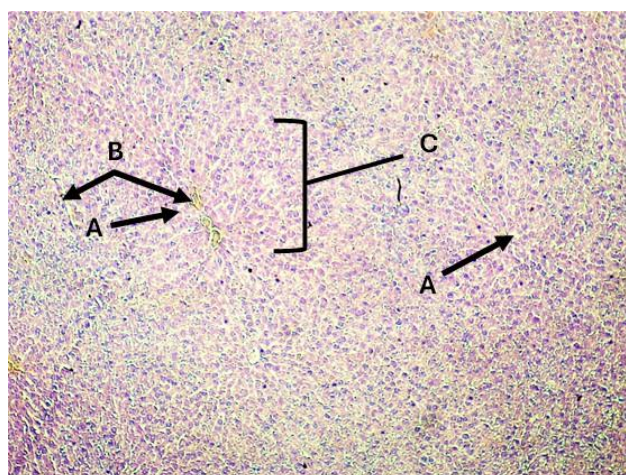


Figure 3: liver of rats with vitamin E 400 IU/kg b.w., showed less dilation of blood vessels (A), less congestion in the blood vessels (B), and less dilation of sinusoidal spaces (C) (H &E 100X).

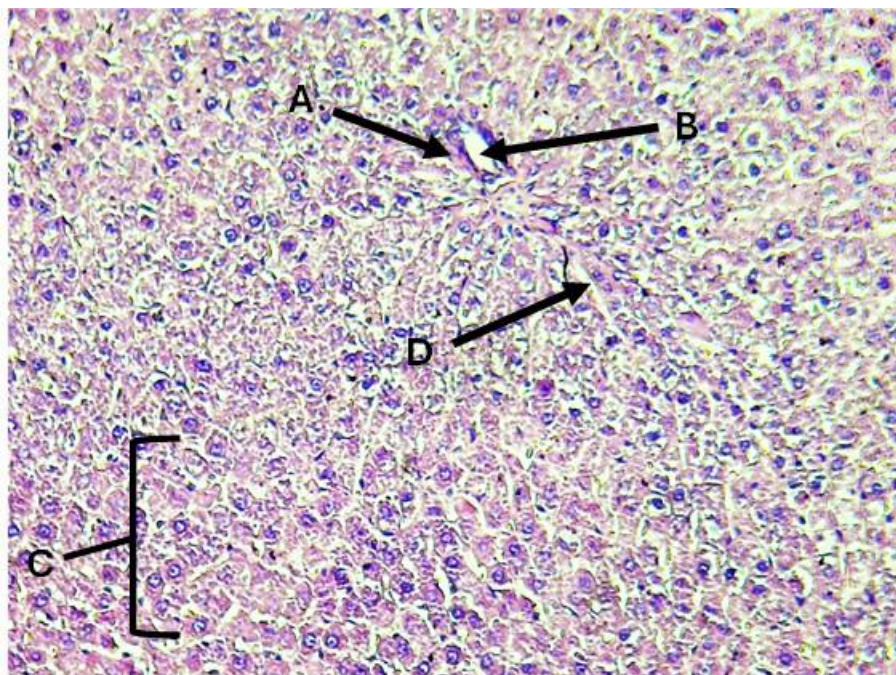


Figure 4: liver of rats with L-Carnitine 600 mg/kg b.w. and Linezolid showed less infiltration of lymphocytes less inflammatory cell infiltrations (A), less dilation of blood vessels (B), less dilation of sinusoidal spaces (C), and less congestion in the blood vessels (D) (H &E 100X).

DISCUSSION

Protection of liver against linezolid-induced liver injury was investigated in adult rats in the present study with respect to the role of vitamin E and L-carnitine (L-Ca). Bilirubin levels and levels of liver enzymes (ALT, AST and ALP) were significant, reflecting hepatocellular injury with Linezolid therapy. Also, the observed changes indicate differential protection resulting from antioxidants (V10) and/or mitochondrial supportive (L-carnitine) treatment to abate liver injury and restore biochemical homeostasis.

The linezolid-treated group had evidence of liver tissue damage upon histopathological assessment, in the shape of hepatocellular degeneration and congestion. The results of this experimental model corroborate the biochemical data, in that cellular injury and vascular congestion have been noted, which correspond with elevated liver enzyme levels and liver malfunctions. Liver damage reduction and maintenance of liver architecture as seen from the improvement in treated groups indicate protective action of vitamin E and L-carnitine on liver tissue by maintaining the cells from damage.

Linezolid is known to impair mitochondrial function, and to cause the overproduction of reactive oxygen species (ROS) in liver tissue [6]. It is consistent with Ibrahim et al., [27] who attributed antibiotic toxicity to liver changes, which impair lipid profiles, along with kidney/liver problems, oxidation properties and inflammation. These results are consistent with previous studies that showed linezolid-induced hepatotoxicity in experimental animal models [26,6].

Lipid soluble vitamin E, which can be used to scavenge free radicals and prevent lipid peroxidation in cell membranes, can prevent these kinds of damage from occurring. Vitamin E acts as a lipid-soluble antioxidant and is able to neutralise free radicals and prevent lipid peroxidation in cell membranes. There was less hepatocyte degeneration in the vitamin E group, suggesting its protective effect, per histopathology analysis. The findings are similar to previous studies of the antioxidant and hepatoprotective effects of Vitamin E against liver damage caused by drugs [26,25].

L-carnitine has a crucial role in the transfer of fatty acids to mitochondria and in β -oxidation processes, regulating energy homeostasis. It is also antioxidant which decreases the generate of ROS and stimulates the activity of antioxidant enzymes. This study indicates that the co-treatment of L-carnitine with linezolid has a beneficial effect on liver histological changes. Our

results confirm the previous reports showing the protective effect of L-carnitine against hepatotoxicity caused by different xenobiotics [28,17].

Dayanandan et al. [29] found similar effects on L-Carnitine that reduces lipid imbalance, protects from atherosclerosis and other associated issues.

This improvement is most likely attributed to antioxidant activity of L-Carnitine that contributes to maintaining the structure and function of mitochondria through modulating oxidative stress and the activation of survival pathways [30].

CONCLUSION:

Taken together, the results suggest that linezolid causes liver injury in the adult rat, with a significant increase in liver enzyme levels and histopathological changes. The hepatoprotective effect of vitamin E is noteworthy and is observed separately from that of L-carnitine. These findings highlight the potential of using antioxidant therapy to prevent linezolid-induced hepatotoxicity.

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