International Journal of Endorsing
HEALTH SCIENCE RESEARCH

IJEHSR

Original Article

Histomorphometric features of hepatic toxicity caused by carbamazepine and its amelioration with vitamin E.

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Doi: 10.29052/IJEHSR.v10.i1.2022.15-23
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Received 24/05/2021
Accepted 26/08/2021
First Published 20/12/2021

OPEN ACCESS

Abstract

Background: Carbamazepine, a commonly prescribed anti-epileptic drug, is potentially hepatotoxic. This laboratory-based experimental study was designed to observe the toxicity of Carbamazepine and the ameliorative effects of Vitamin E on liver tissue.

Methodology: A total of 54 rats were randomly divided into 3 groups. Group A was the control; group B was given oral Carbamazepine, and group C was given Carbamazepine with Vitamin E daily for 6 weeks. At the end of the study period, animals were sacrificed, their liver was preserved, and tissue was stained with Hematoxylin and Eosin.

Results: The mean final body weights of Carbamazepine treated group B (147.27 ± 13.72 gm) and Carbamazepine + Vitamin E protected group C (164.43 ± 10.73 gm) were decreased significantly in comparison to control A (194.03 ± 14.87 gm). Mean absolute and relative liver weights were increased significantly in groups B & C as compared to group A. Histological examination of liver in group B showed disturbed architecture of hepatic lobules including congested central vein, dilated sinusoids, pyknotic nuclei, steatosis, portal vein dilatation, hemorrhages, and mononuclear infiltration in the portal triad and around the central vein. These changes were reduced in group C. Micrometry confirmed the histological findings, with a significant decrease in mean hepatic cell count and mean hepatocyte nuclear diameter of group B as compared to control group A (6.00 ± 1.41 & 5.62 ± 0.69 µm respectively), and a significant increase in mean hepatocyte diameter of group B in comparison to group A (17.44 ± 1.29 µm).

Conclusion: This study showed that Carbamazepine caused hepatotoxicity while Vitamin E was helpful in its amelioration.

Keywords

Antioxidant, Carbamazepine, Liver, Toxicity, Vitamin E.

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Introduction

Liver, the largest organ and gland present in the abdominal cavity, is involved in more than 500 complex vital metabolic functions essential for the homeostasis of the human body[1]. It is a mixed gland, producing and secreting bile through bile ducts into the digestive system and important hormones needed for growth stimulation[1,2]. It has a dual blood supply[2]. It receives oxygen-rich blood for cellular respiration from hepatic arteries, branches of aorta, and receives nutrient-rich blood from the gastrointestinal tract through portal circulation for metabolism and storage. Thus, a bridge between the splanchnic and systemic circulations is established within the liver[1,2]. It is also the first recipient of the ingested drugs and xenobiotics, causing their detoxification and thus becoming the site for their first-pass metabolism, making it the major target organ for drug toxicity[2,3]. Over 1000 chemicals, drugs, and herbs have been documented to cause hepatotoxicity. Drug-induced toxicities cause around half of acute liver failures and 5 percent of hospital admissions. It is the commonest reason for removing FDA-approved drugs from the market[4].

Carbamazepine is an iminostilbene (Dibenzaozepine) derivative, introduced for trigeminal neuralgia pain treatment initially, but now is also used for partial and tonic-clonic seizures, neuropathic pain, and psychiatric disorders[5]. It acts by postsynaptic inhibition of action potential and presynaptic suppression of neurotransmitter release through inactivation of sodium channels[5]. This leads to synaptic transmission blockage needed for pain control and seizures[5]. Carbamazepine has a narrow therapeutic index affected by an individual's age, gender, genetics, absorption, and disease state, making its safe use difficult[5-7]. Its metabolism occurs in the liver through the cytochrome P-450 oxidase system. The end product is water-soluble and excreted by kidneys, but few byproducts are also formed, which cause toxicities in several organs[5]. In the liver, Carbamazepine can produce liver damage ranging from minor hepatocellular injuries leading to a transient increase in liver enzymes to severe cholestatic hepatitis and granuloma formation due to its oxidative stress caused by metabolites known as reactive oxygen species[5-7].

Various antioxidant agents have been used in studies for their role in hepatic injuries. Vitamin E is a commonly used natural antioxidant proven in the literature to reduce oxidatively stressed injuries, especially at cellular membrane level[8].

This study was planned to observe the hepatotoxic effects of Carbamazepine and to analyze its amelioration with Vitamin (Vit) E. Sprague Dawley rats were selected for this experimental study because their hepatic architecture resembles that of the human liver.

Methodology

This experimental study was conducted at the Anatomy Department of Baqai Medical University, Karachi, between December 2016 to January 2017. The study protocol was approved by the Institutional Ethics Committee (ERC Ref: BMU-EC/2016-03, dated 14th October 2016).

For this lab-based experimental study, 54 adult Albino Sprague Dawley rats were acquired from Aga Khan University. The animals were housed in Baqai University's Animal house. A controlled environment of 14/10 hours day/night cycle and 30°C temperature was maintained in the animal house. They were acclimatized for 10 days before the beginning of the study. They were provided with free water and a standard rat diet.

The inclusion criteria were healthy rats with weights ranging from 150 to 200 grams and 10 to 12 weeks (age range). The exclusion criteria were rats showing signs of sickness during the study. Animals were randomly divided into 3 groups (group A, B, and C) with 18 rats in each group. Group A was the control group that received no intervention. Group B received a single daily dose of Carbamazepine 50 mg/kg through gastric gavage for 6 weeks[9], after overnight fasting. Group C received a single daily dose of Carbamazepine 50 mg/kg through gastric gavage and Vit. E 200 mg/kg/day[10] after one hour of Carbamazepine for 6 weeks.

The animals were weighed at the beginning and 2 weeks intervals till the end of the study on an electronic weighing scale. At the end of the study, animals were weighed and dissected to harvest liver. Absolute liver weight was recorded, and relative weight or liver index was calculated with the help of the formula[11].

Relative liver weight = [Weight of the liver (gm)] / [Final body weight (gm)] × 100

The liver was fixed in 10% neutral formalin. It was processed, and paraffin blocks were made. Four to five micron thick sections were stained with H & E for the morphometric study of hepatic architecture under a light microscope.

The morphometric measurements were taken with the help of a micrometer scale. All data were analyzed using SPSS version 22.0. Student's t-test analyzed the difference in groups, and the significant difference between groups was accepted at p≤0.05.

Results

Over the six weeks of the study, Group A control rats had significantly increased (p=0.003) final body weights (Table 1) while Carbamazepine treated group B rats and Vit. E protected group C rats had significantly decreased final body weights (p=0.001) & (p=0.005) (Table 1). There was a significant decrease in the mean body weight of Carbamazepine treated group B and Vit. E protected group C rats (p<0.001) when compared to the mean final body weight of Group A rats. The final mean body weight of Vit. E protected group C rats, though decreased, were significantly increased (p=0.004) in comparison to Carbamazepine treated group B rats.

Table 1: Body weights of different groups (n=54).

Variable	Group A No Treatment	Group B CBZ	Group C CBZ + Vit. E
		Mean ± SD	
Initial body weight (gm)	175.73±10.79	177.65±14.65	175.48±15.34
Final body weight (gm)	194.03±14.87[a]	147.27±13.72[a,b]	164.43±10.73[a,b,c]

[a]Significantly different from mean initial body weight within-group (p≤0.05)
[b]Significantly different from the final mean body weight of control group A (p≤0.05)
[c]Significantly different from the final mean body weight of CBZ group B (p≤0.05)

The mean absolute weight of the liver was increased significantly in only Carbamazepine treated group B rats (p=0.048) while in Vit. E protected group C rats it increased less than in group B. Mean relative weight of the liver was increased significantly in both Carbamazepine treated group B (p=0.002) and Vit. E protected group C rats (p=0.016) as compared to control rats, but group C increased relative weight was not significant as group B rats (Table 2).

Table 2: Liver weights of different groups.

Variable	Group A No Treatment	Group B CBZ	Group C CBZ + Vit. E
		Mean ± SD	
Absolute Liver weight (gm)	7.02±0.74	9.03±1.65[a]	8.50±1.43
Relative Liver weight (gm)	3.64±0.49	6.2±1.3[b]	5.54±1.12[b]

[a]Significantly different from the mean absolute liver weight of the control group (p≤0.05)
[b]Significantly different from the mean relative liver weight of the control group (p≤0.05)

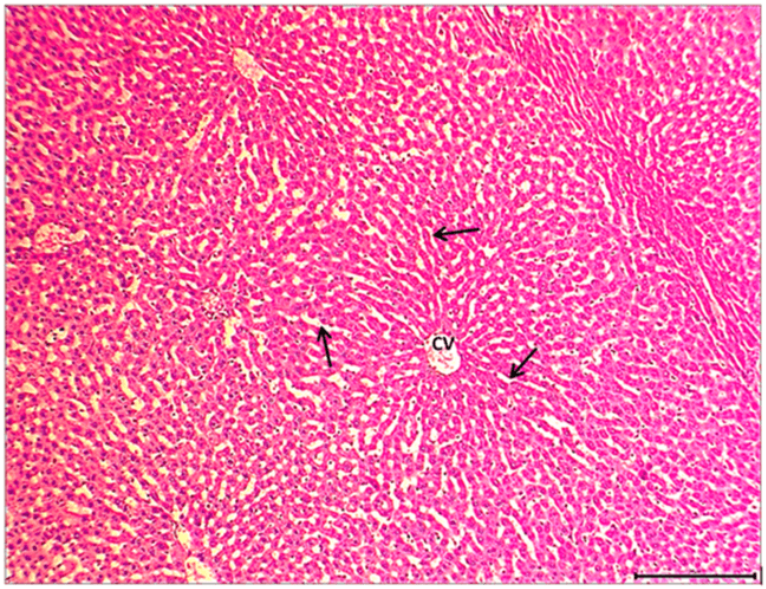

Figure 1: Photomicrograph of Group A rat liver section showing normal central vein (CV) with radiating cords of hepatocytes and intervening sinusoids (arrows). H & E x 100

Hematoxylin & Eosin dyed liver sections of Group A control showed a normal hexagonal architectural arrangement of hepatic lobules, characterized by a central vein with radiating, anastomosing cords of hepatocytes. The single-celled hepatocyte cords are separated by adjacent narrow blood-filled sinusoids (Figure 1).

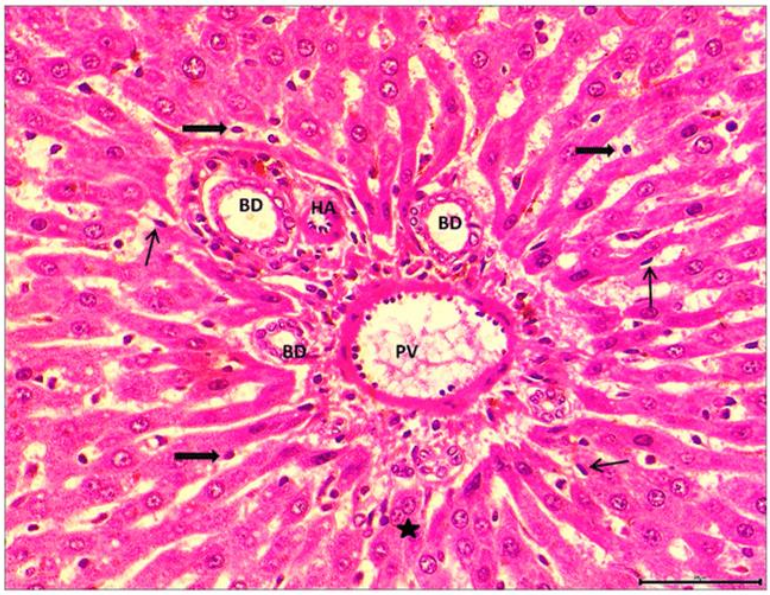

Figure-2: Photomicrograph of Group A control rat liver section showing portal triad, with branches of the hepatic artery (HA), portal vein (PV), and bile duct (BD). Endothelial cells (thin arrows) line the sinusoids with kupffer cells (thick arrows). Vesicular nuclei and acidophilic cytoplasm are seen within the hepatocytes. Binucleate hepatocytes (star) are also seen. H & E x 400

Higher magnification observations showed the sinusoids to be lined by flat endothelial cells and large phagocytic Kupffer cells. The hepatocytes are polyhedral in shape, with a darkly stained nucleus and an acidophilic cytoplasm. Bi-nucleated hepatocytes were also seen. The portal triads present at the periphery of the hepatic lobules containing a branch of hepatic artery and portal vein and 1 to 2 tributaries of bile duct were also seen (Figure 2).

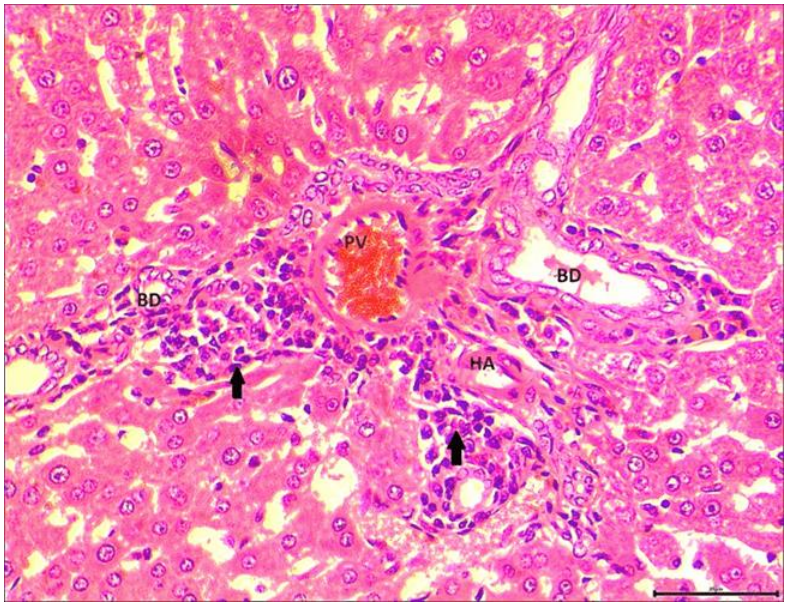

Figure 3: Photomicrograph of Group B CBZ-treated rat liver section showing portal triad, congested and dilated portal vein (PV), hepatic artery (HA), and bile duct (BD). There is marked lymphocytic infiltration (arrows). H & E x 400

In the Carbamazepine treated group, areas of hemorrhage, necrosis, and degeneration were seen in hepatic parenchyma. The radial architectural arrangement of hepatocytes in hepatic lobules was disturbed. The central vein was distorted, dilated, and congested with dense lymphocytic infiltration around it. Sinusoidal dilation was also observed. Hepatocytes showed advanced hydropic degenerative changes in their cytoplasm and pyknosis and fragmentation in their nuclei. Fatty degeneration in the parenchyma was present in the form of micro-vesicular and macro-vesicular steatosis. The portal vein showed congestion and dilatation. There was marked mononuclear cell infiltration present around and within the portal triad (Figure 3).

In protected Group C treated with Carbamazepine and Vit. E, the observed histological sections of the liver showed minimal distortion of the hepatic lobule architecture. The hepatocyte cords maintained the normal radiating pattern. Minimal dilatation was seen in the central and portal veins. The sinusoids appeared almost normal. The periportal area showed mild inflammatory cell infiltration (Figure 4). Hepatocytes showed minimal hydropic degeneration of cytoplasm and few fragmentations in nuclei, mostly surrounding the central vein.

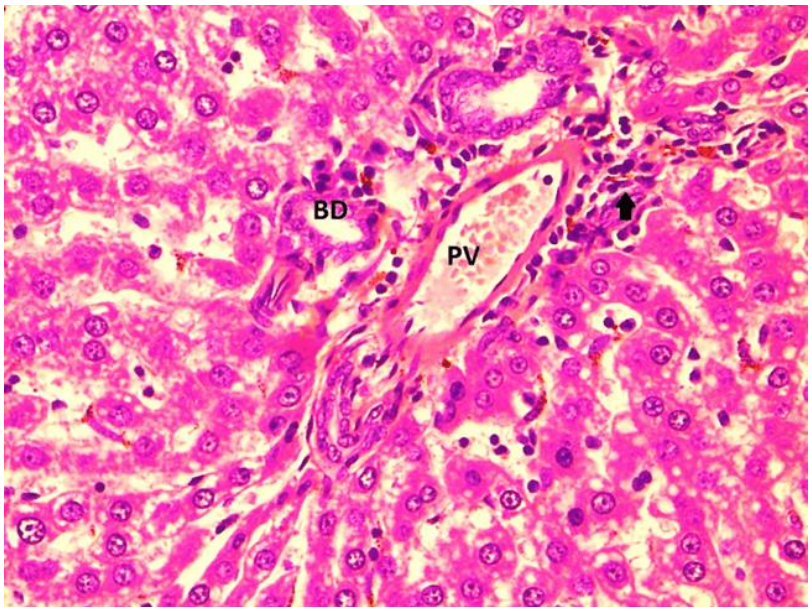

Figure 4: Photomicrograph of group C, CBZ, and Vit. E treated rat liver section showing near-normal portal triad. The portal vein (PV) appears mildly dilated, and the hepatic artery (HA) and bile duct (BD) appear normal. There is mild periportal lymphocytic infiltration (arrow). H & E x 400

Histopathological findings were also confirmed with micrometric measurements. The mean hepatic cell count of control was significantly decreased ($p<0.001$) in group B as compared to the control group A, while the mean hepatocyte cell count of group C increased significantly ($p=0.013$) in comparison to group B. The mean hepatocyte diameter of control group A was increased significantly ($p<0.001$) in group B, while the hepatocyte diameter of group C was decreased significantly ($p=0.002$) in comparison to group B. The mean nuclear diameter of control group A was also significantly decreased ($p<0.001$) in group B, and the nuclear diameter of group C was insignificantly increased compared to that of group B ($p=0.294$) (Table 3).

Table 3: Mean hepatic cell count per reticule, hepatocyte diameter, and nuclear diameter of rats in different groups.

Variable	Group A No Treatment	Group B CBZ	Group C CBZ + Vit. E
		Mean ± SD	
Hepatic Cell Count/reticule	15.40 ± 3.53	6.00 ± 1.41[a]	9.40 ± 1.96[b]
Mean Hepatocyte Diameter (µm)	13.31 ± 1.44	17.44 ± 1.29 [a]	15.20 ± 1.26 [b]
Mean nuclear diameter (µm)	7.22 ± 1.01	5.62 ± 0.69[a]	6.20 ± 0.8

[a] Significantly different from the control group ($p\leq0.05$)
[b] Significantly different from CBZ group ($p\leq0.05$)

Discussion

Drug-induced liver disease may be dose-dependent or idiosyncratic[12]. Carbamazepine is a drug known to cause idiosyncratic liver injury, as well as a subtle liver injury with long-term use[13]. The pathophysiology of Carbamazepine induced hepatic toxicity is due to its active metabolites, namely reactive oxygen species (ROS)[14]. This causes hepatitis that is the hepatic tissue inflammation and lymphocytic infiltration, leading to liver apoptosis and necrosis[15]. Various antioxidants have been shown to treat and prevent liver injuries. Vitamin E is a well-known antioxidant. Its protective action as a radical scavenger prevents the propagation of free radicals at the tissue level, reducing the oxidative stress in hepatic tissue[16]. In this study, Carbamazepine caused toxicity in liver tissue while Vit. E worked as an antioxidant and ameliorated the toxic effects.

The mean body weight of the animals of Carbamazepine treated group B was decreased in this study, as also seen by Osuntokun et al. and Santhrani et al.[17,18]. Studies have also reported weight gain and no change in weight with the use of Carbamazepine[19,20]. The reduction in body weight could be attributed to Carbamazepine-induced anorexia and disturbed hepatic metabolism. Improvement in mean body weight in Carbamazepine + Vit. E protected (group C) was also observed by Zubair et al.[21], which may be attributed to improved food intake due to Vit. E[22].

Absolute organ weight is considered to be a sensitive indicator of organ toxicity without morphological alterations[23], but it should be normalized with body weight to get relative organ weight, which then associates best with the toxicity[24]. Thus, the drug toxicity contributes to the increase in relative and absolute weights of the liver in Carbamazepine treated group B. Maronprot et al. and Santhrani et al. discussed that Carbamazepine as an inducer of CYP450 enzyme system, would increase the liver weight due to hepatocellular hyperplasia, hypertrophy, and dilatation of the central and portal vein and sinusoids[18,25]. Co-administration of Carbamazepine with Vit. E in group C caused a decrease in absolute and relative weights. This may be attributed to the decrease in inflammatory changes, secondary to Vit. E antioxidant action, as observed by Zhang et al.[26].

H & E dyed sections of the liver in Carbamazepine treated group B showing disruption of hepatic architecture, including marked necrosis in the pericentral area, correlated with studies of Sasaki et al[15]; hydropic degeneration in agreement with Almansour et al[27], the reason for this vacuolated swelling could be anoxia and disturbances in membrane functions causing a massive influx of water and sodium ions inside the hepatocyte, leading to leakage of lysosomal hydrolytic enzymes and ultimately degeneration of the hepatocytes[28]; dilated and congested central and portal vein due to an adaptive response to overcome hypoxia; pericentral and periportal mononuclear infiltration as also seen by Azhari et al[29]; micro-vesicular and macro-vesicular steatosis with the proposed mechanism of inhibition of mitochondrial β-oxidation[30]. These liver architectural insults were improved in Carbamazepine + Vit. E protected group C; this can be attributed to the antioxidant effects of Vit. E, especially as a cellular membrane protectant, in lieu with the studies of Ibrahim et al. and Cuce et al[31,32].

Micrometric findings in the Carbamazepine treated liver revealed decreased hepatic cell count per unit area, which may be due to hepatic cellular necrosis, as seen by Santhrani et al. and Eghbal et al.[18,33]; increase in hepatocyte diameter is attributed to cell enlargement secondary to ballooning degeneration with irregularly clumped cytoplasm and remaining large clear spaces, as observed by Mirani et al. and Habib-ur-Rehman et al[34,35]; and decrease in nuclear size due to decreased activity of the cell, as recorded by Bhadoria et al. and Omotoso et al[36,37]. Carbamazepine + Vit. E protected group C showed improvements in micrometric findings due to reactive oxygen species scavenging abilities of Vit. E[8].

The selection of the rat model was a strength of this research as its liver architecture is similar to that of humans, and the hepatotoxic effects of

Carbamazepine and hepatoprotective role of Vit E were well-elicited in the rat specimens. Being an animal study, the actual estimation of Carbamazepine toxicity in humans was a limitation of the research. Also, we were unable to determine confounding variables.

It is recommended that further studies should be carried out to validate the use of Vitamin E as a prophylactic agent and dietary supplement in humans against Carbamazepine-induced hepatotoxicity.

Conclusion

This histomorphometric experimental study established the potential hepatotoxic effect of Carbamazepine on rats. It was observed that Vit. E successfully improved these histopathological changes.

Conflicts of Interest

The authors have declared that no competing interests exist.

Acknowledgment

We wish to acknowledge our supervisor, Professor Dr. Kishwar Sultana, for her immense support.

Funding

The author(s) received no specific funding for this work.

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