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Protective Effects of Octreotide on Acetaminophen-Induced Liver Damage in Rats: Biochemical and Histopathological Evaluation*

Abstract

This study aimed to evaluate the potential protective effects of octreotide, a somatostatin analogue, against acute liver injury induced by acetaminophen in rats. 28 male *Wistar albino* rats, aged 8–10 weeks, were randomly assigned into four experimental groups. Group 1 served as the control, and Group 2 received 1 g/kg of acetaminophen orally, Group 3 was administered 300 µg/kg of octreotide intraperitoneally, Group 4 was treated with both agents, where octreotide was given 30 minutes after acetaminophen administration. The experiment was terminated by taking liver tissue and blood samples under general anesthesia 24 hours after drug administration. Hematoxylin and Eosin staining was performed on the liver sections, and serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase activities, as well as total antioxidant capacity, total oxidant capacity and malondialdehyde levelswere analyzed. Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase activities, and total oxidant capacity were significantly higher in acetaminophen-treated rats compared to the other groups. Similarly, malondialdehyde levels were also higher, but these values were not statistically significant. Total antioxidant capacity were lower in the acetaminophen group compared to the other groups. In contrast, the treatment group showed a significant reduction in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase activities and total oxidant capacitycompared to the acetaminophen group. Histological analysis revealed severe hepatic damage in the acetaminophen group, while less tissue damage was noted in the treatment group. Although malondialdehyde was lower in the treatment group on average, the difference was not statistically significant. These findings suggest that octreotide may offer partial protection against acetaminophen-induced liver injury. However, further investigation is required to elucidate its precise mechanism of action.

Keywords: Acetaminophen, liver injury, octreotide, oxidative stress.

Sıçanlarda Asetaminofen Kaynaklı Karaciğer Hasarına Oktreotidin Koruyucu Etkileri: Biyokimyasal ve Histopatolojik Değerlendirme

Öz

Bu araştırmanın amacı, somatostatin analoğu olan oktreotidin sıçanlarda asetaminofenle oluşturulan akut karaciğer hasarına karşı olası koruyucu etkilerini değerlendirmektir. Çalışmada, 8–10 haftalık toplam 28 yetişkin erkek *Wistar albino* sıçan rastgele dört gruba ayrıldı. Grup 1 kontrol olarak kullanıldı, Grup 2'ye 1 g/kg oral asetaminofen verildi, Grup 3'e 300 µg/kg intraperitoneal oktreotid uygulandı, Grup 4 her iki ajanla tedavi edildi, oktreotid asetaminofen uygulamasından 30 dakika sonra verildi. İlaç uygulamasından 24 saat sonra genel anestezi altında kan ve karaciğer dokusu örnekleri alındı. Karaciğer dokuları

Hematoksilen-Eozin ile boyandı; serum örneklerinden aspartat aminotransferaz, alanin aminotransferaz, alkalin fosfataz, total antioksidan kapasite, total oksidan kapasitesi ve malondialdehid düzeyleri ölçüldü. Asetaminofen uygulanan sıçanlarda aspartat aminotransferaz, alanin aminotransferaz, alkalen fosfataz aktiviteleri ve toplam oksidan kapasitesi diğer gruplara göre anlamlı derecede yüksekti. Benzer şekilde, malondialdehit seviyeleri de daha yüksekti, ancak bu değerler istatistiksel olarak anlamlı değildi. Toplam antioksidan kapasite değerleri ise diğer guplara göre asetaminofen grubunda düşüktü. Tedavi grubunda ise aspartat aminotransferaz, alanin aminotransferaz, alkalin fosfataz ve total oksidan kapasitesi, yalnızca asetaminofen verilen gruba kıyasla anlamlı şekilde düşüktü. Histopatolojik değerlendirmede asetaminofen grubunda ciddi doku hasarı gözlenirken, tedavi grubunda daha az hasar tespit edildi. Malondialdehid düzeyleri tedavi grubunda daha düşük seyretse de bu fark istatistiksel olarak anlam kazanmadı. Elde edilen bulgular, oktreotidin asetaminofen kaynaklı karaciğer hasarını kısmen hafifletebileceğini göstermektedir. Ancak bu etkinin mekanizmasının daha iyi anlaşılabilmesi için ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Asetaminofen, karaciğer hasarı, oktreotid, oksidatif stres.

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Introduction

Liver failure is broadly classified into two categories: acute and chronic, both of which are associated with high mortality rates.[1] Among the primary causes of acute liver failure is drug-induced hepatotoxicity, with acetaminophen (APAP; N-acetyl-p-aminophenol, also known as paracetamol) being a major contributor.[2]

APAP is a nonsteroidal anti-inflammatory drug (NSAID) commonly used for its antipyretic and analgesic properties.[3-6] Although generally safe at therapeutic doses, excessive intake can result in serious liver and kidney toxicity, potentially leading to life-threatening outcomes.[3,5,7,8] In the United States, APAP toxicity is a leading cause of acute liver failure and ranks as the second most frequent reason for liver transplantation.[3] In Turkey, drug poisonings constitute 59.6% of emergency department visits, with analgesics accounting for approximately 43% of those cases.[9]

Under physiological conditions, APAP metabolism produces free radicals, which are normally neutralized by endogenous antioxidant mechanisms.[10] However, when APAP is consumed in excessive amounts, this balance is disrupted, leading to elevated oxidative stress and hepatocyte damage. The liver metabolizes APAP primarily via the cytochrome P450 (CYP) enzyme system.[11] During this process, APAP is either converted into inactive sulfate and glucuronide conjugates or metabolized into N-acetyl-p-benzoquinone imine (NAPQI), a highly reactive and toxic intermediate. Normally, glutathione (GSH) binds to NAPQI, allowing for its detoxification and renal excretion. However, in overdose conditions, GSH reserves are depleted, resulting in the accumulation of NAPQI, which binds to hepatic proteins and mitochondria, increasing oxidative stress and triggering hepatocellular injury.[8,10,11] N-acetylcysteine is currently the only U.S. Food and Drug Administration (FDA)approved antidote for APAP poisoning. It acts as a potent antioxidant by replenishing GSH levels and enhancing the detoxification of NAPQI.[11-14] N-acetylcysteine also improves peripheral tissue oxygenation by increasing nitric oxide (NO) levels through vasodilation. Nevertheless, its use is often limited due to adverse effects such as nausea, bloating, vomiting, diarrhea, gastroesophageal reflux, and even anaphylactic reactions.[12,15] As a result, alternative compounds with hepatoprotective potential are being actively investigated.[12,16,17]

Recent studies have examined the hepatoprotective roles of somatostatin and its synthetic analogs through various biological pathways. Somatostatin is a 14-amino acid peptide secreted by pancreatic D cells, the hypothalamus, and immune and inflammatory cells.[18,19] It inhibits both endocrine and exocrine gastrointestinal secretions, reduces the transport of glucose, lipids, and amino acids, suppresses intestinal and gallbladder motility, and decreases splanchnic blood flow, thereby affecting hepatic circulation.[19]

Octreotide, a synthetic analog of somatostatin, possesses a longer half-life and greater potency than its endogenous counterpart.[20] Experimental models have shown that octreotide confers protection in conditions such as immobilization stress,[21] ischemia-reperfusion injury,[20,22,23] bile duct ligation-induced cirrhosis,[24] carbon tetrachloride (CCl_4)-induced hepatic fibrosis,[25] and post-hepatectomy liver injury.[26] However, there remains a paucity of data on its efficacy in APAP-induced acute liver injury.

Based on this context, the present study aims to evaluate whether octreotide demonstrates hepatoprotective activity against APAP-induced acute liver toxicity. To this end, we employed a rat model of APAP-induced liver injury to assess the potential protective effects of octreotide.

Materials and Methods

Experimental Animals

This study employed 28 male *Wistar albino* rats, aged 8 to 10 weeks and weighing between 250–300 g. The effect size obtained in the reference study[27] was found to be strong (F=0.799). Assuming that an effect size of this magnitude could be obtained, a power analysis for 4 groups showed that a power of 90% at a 95% confidence level could be achieved with a minimum of 28 rats (at least 7 rats per group) in the study. The animals were supplied by the Experimental Animal Center of Pamukkale University. All experimental animals were kept in plastic cages in rooms located in the same centre, where lighting (12 hours light/dark cycle), humidity (60-70%) and temperature (21±3 °C) were controlled, for one week to allow them to acclimatise. During the experiment, all animals were fed ad libitum with pellet feed containing 21% protein and tap water.

Drugs and Dosage Regimen

Acetaminophen (Parol, 500 mg/tablet, oral formulation) was obtained from Atabay Pharmaceutical Industry and Trade Inc. (Türkiye), while octreotide (Sandostatin, 0.1 mg/mL ampoule) was purchased from Novartis, Türkiye. Acetaminophen was prepared in distilled water and administered via oral gavage at a single dose of 1000 mg/kg (1 mL per rat) according to previous studies.[5,25,26] Octreotide was administered subcutaneously at a single dose of 300 µg/kg dissolved in physiological saline.[25,27] APAP was freshly diluted in 1 mL of distilled water per rat, while the octreotide dose was prepared in 3 mL of physiological saline.

Experimental Protocol

The 28 rats were randomly assigned to four experimental groups, with seven animals per group. The groups, drug dosages and administration routes are summarized in Table 1. G1, the healthy control group, received a single intraperitoneal injection of 0.9% saline; G2, the APAP group, received a single dose of 1000 mg/kg acetaminophen via oral gavage; G3, the Oct group, received a single dose of 300 µg/kg subcutaneous octreotide, and G4, the APAP+Oct group, received a single 300 µg/kg s.c. injection of octreotide one hour after acetaminophen (a single dose of 1000 mg/kg via oral gavage).

Table 1. Experimental Study Design

Group	Treatment	dosage
G1	Control	Normal saline 2 ml/kg i.p.
G2	APAP	1000 mg/kg oral gavage, a single dose
G3	Oct	300 µg/kg s.c. a single dose
G4	APAP + Oct	APAP (1000 mg/kg oral gavage) + Oct (300 µg/kg s.c.)*

* In the combination group (G4), octreotide was administered 30 minutes following APAP administration.

After octreotide injection in APAP+Oct group, rats in all groups were allowed to feed normally and then fasted overnight. Twenty-four hours after octreotide administration, all rats were anesthetized using intraperitoneal injections of xylazine hydrochloride (10 mg/kg) and ketamine hydrochloride (90 mg/kg). Blood was collected via cardiac puncture and liver tissues were collected for further analysis. The rats were then euthanized and the experiment terminated.

Biochemical Analyses

Blood samples were centrifuged (Hettich Rotofix 32, Germany) at 3000 rpm for 10 minutes at +4°C to obtain serum, which was then stored at −80°C until tested. The serum samples were analyzed for levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) activities, as well as total antioxidant capacity (TAC), total oxidant capacity (TOC) and malondialdehyde (MDA) levels.

Measurement of Liver Enzyme Activities

Liver enzyme activity (AST, ALT, and ALP) was quantified spectrophotometrically using a Mindray BS300 autoanalyzer and commercial assay kits (MyBiosource Inc. San Diego, USA, Cat No: MBS7253853, MBS264333, MBS2023690 respectively) in accordance with the manufacturer's instructions.

Assessment of Malondialdehyde (MDA) Levels

Malondialdehydelevels was measured via commercially available enzyme-linked immunosorbent assay (ELISA) kits using a YLBiont double-antibody sandwich kit (YL Biotech Co., Ltd, Shanghai, China; No: YLA0029RA). Samples and standards were added to antibody-coated wells, followed by secondary antibodies and streptavidin-HRP. After incubation, unbound material was washed away. Chromogenic substrates A and B were added, and the plate was incubated at 37°C for 10 minutes. The reaction was stopped, and the color intensity was measured at 450 nm using a microplate reader.

Determination of Total Antioxidant Capacity (TAC) and Total Oxidant Capacity (TOC)

Total antioxidant and oxidant capacitieswere assessed using commercial kits (Rel Assay Diagnostics, Gaziantep, Türkiye, lot no: DR16069A and lot no: DR160800). Total oxidant capacity (TOC) was quantified based on lipid peroxide reactions with peroxidase, whereas TAC was measured via the interaction between antioxidants in the sample and exogenous hydrogen peroxide (H_2O_2). Absorbance was read at 530 nm using an ELISA microplate reader (μQuant, BioTek®, Winooski, Vermont, USA). Calibration was performed against standard curves, and results were expressed in μmol/L. All measurements were performed in duplicate.

Histopathological Evaluation

Liver tissues were fixed in 10% buffered formalin for 24 hours. After dehydration in ascending alcohol concentrations and clearing with xylene, samples were embedded in paraffin blocks. Sections were sliced at 5 μm thickness using a microtome and stained with hematoxylin and eosin (H&E). Microscopic evaluation was conducted using a light microscope (Olympus BX-145, Japan).

Histological damage was graded semi-quantitatively based on the following scoring system (3):

0: Normal architecture or minimal change

1: Mild damage (e.g., cytoplasmic vacuolization, nuclear pyknosis)

2: Moderate injury (e.g., pronounced nuclear pyknosis, cytoplasmic hypereosinophilia, and loss of cell borders)

3: Severe damage (e.g., hepatic cord disintegration, hemorrhage, extensive necrosis with neutrophil infiltration)

All histopathological evaluations were conducted in a blinded manner.

Statistical Analysis

Data were presented as mean ± standard error (SE). Statistical analyses were conducted using SPSS 22 (IBM SPSS Statistics 22, Armonk, NY, USA). Group differences were evaluated using one-way ANOVA, followed by Tukey post hoc testing to determine pairwise significance. A p-value < 0.05 was regarded as statistically significant.

Results

Liver Enzyme Activity

Table 2 presents the serum levels of liver enzymes (AST, ALT, and ALP). The acetaminophen (APAP) group (Group 2) showed a significant elevation in all three enzyme levels compared to the other groups (In Group 3 (Oct), enzyme levels were slightly higher than in the control group but did not reach statistical significance. Notably, co-administration of octreotide in Group 4 resulted in a reduction of AST, ALT, and ALP values to levels comparable with the control and Oct-only groups, indicating a hepatoprotective effect. No significant differences were observed between groups control (group 1), octreotide (group 3), and acetominophen + octreotide (group 4).

Malondialdehyde (MDA) Levels

The APAP group exhibited higher serum MDA levels relative to the other groups, reflecting enhanced lipid peroxidation. However, this increase reached statistical significance only when compared to the Oct group. Malondialdehyde levels in the control, Oct, and APAP + Oct groups remained statistically similar (Table 2).

Total Antioxidant Capacity (TAC)

Among the groups, the APAP group demonstrated the lowest mean TAC values. Despite this reduction, the differences among groups were not statistically significant. The control and Oct groups exhibited the highest TAC values, but these increases were also not significant (Table 2).

Total Oxidant Capacity (TOC)

Total oxidant capacity was markedly elevated in the APAP group, with values significantly higher than those of the other groups, mirroring the pattern observed in liver enzymes. Although Group 4 showed a slight elevation compared to the control and Oct groups, this difference did not reach statistical significance. The lowest and most similar TOC were recorded in the control and Oct groups (Table 2).

Table 2. Effect of octreotide on acetaminophen on liver function of rats

Group parameters	Control (G1) (*n*=7)	Acetaminophen (G2) (*n*=7)	Octreotide (G3) (*n*=7)	Acetaminophen+ Octreotide (G4) (*n*=7)	*p*
AST (IU/L) Mean ± SE	78.5±6.89$^{\alpha}$	124.43±20.2*	85.5±10.34$^{\alpha}$	98.57±18.46$^{\alpha}$	0.001
ALT (IU/L)	48.83±9.90$^{\alpha}$	187.14±48.41*	54.4±8.69$^{\alpha}$	59.14±11.99$^{\alpha}$	0.001

Mean ± SE					
ALP (IU/L) Mean ± SE	231.66±26.29α	350.6±45.57*	269.28±19.51α	265.57±33.78α	0.000
MDA (µmol/ml) Mean ± SE	0.47±0.035	0.51±0.034	0.44±0.033α	0.46±0.032	0.013
TAC(µmol/ml) Mean ± SE	1.85±0.39	1.51±0.33	1.86±0.53	1.55±0.44	0.283
TOC (µmol/ml) Mean ± SE	6.38±1.93 α	34.32±20.74*	7.83±1.73α	11.45±8.54 α	0.001

* Statistical significance indicating a higher value compared to the control group (*p* **<0.05).**
α Statistical significance indicating a lower value compared to the acetaminophen group (*p* **<0.05)**.
SE: Standard Error.

Histopathological Observations

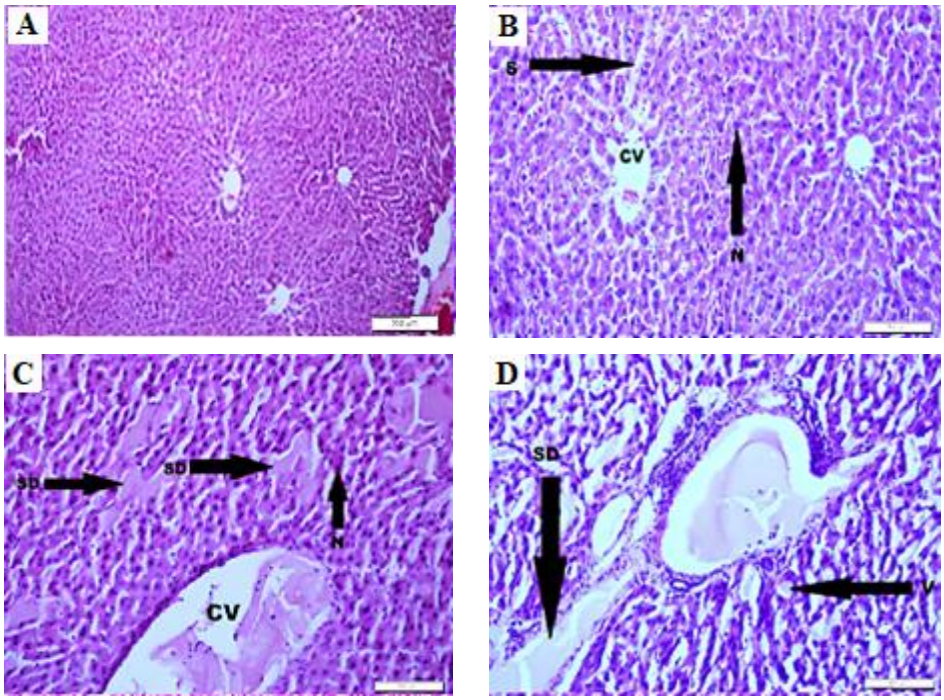
Histological examination of liver tissues stained with H&E revealed distinct morphological differences among the experimental groups (Figure 1, Table 3):

Control Group (G1): Liver architecture appeared normal, with well-organized hepatic cords radiating from the central vein. Hepatocytes exhibited polygonal shapes with centrally located nuclei containing loose chromatin and prominent nucleoli. No pathological alterations were observed in the portal or sinusoidal regions (Figure 1A, 1B).

APAP Group (G2): Severe hepatocellular damage was observed. Five of seven animals showed fragmentation, infiltration, and severe necrosis of the liver cords, and two exhibited intense nuclear pyknosis and loss of intercellular boundaries. Sinusoidal dilatation was consistent in all subjects. Additional findings included hepatic cord rupture, tissue loss, and focal hemorrhagic areas (Figures 1C, 1D, Table 3).

Oct Group (G3): Liver tissue largely resembled that of the control group. Only mild sinusoidal dilation was noted. No vacuolization or inflammatory cell infiltration was present. Hepatocytes maintained clear cellular boundaries with centrally located nuclei. Only one animal exhibited mild pyknosis (Figure 1E, 1F).

APAP + Oct Group (G4): Histopathological findings were significantly reduced in the Acetaminophen + Octreotide group compared to the acetaminophen group (p=0.037), but a significant increase (p=0.035) was observed compared to the control group. Mild sinusoidal dilation was observed in the livers of this group, and structural changes were limited to a small number of hepatocytes near the central vein. Vacuolization was absent, and nuclear pyknosis was seen in only a few cells. Inflammatory cell infiltration occurred in only one rat (Figure 1G, 1H). Overall, concomitant treatment attenuated APAP-induced liver injury.



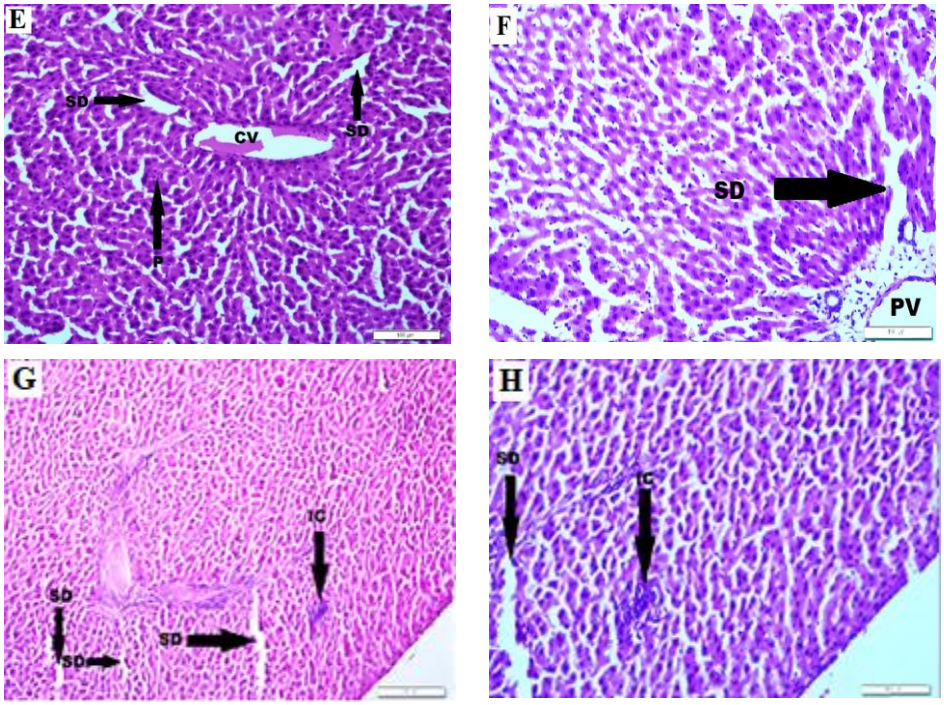


Figure 1. Effects of octreotide on acetaminophen (APAP)-induced hepatic histopathology. **A**: Liver tissue from the control group, general view (H&E, scale bar = 200 µm). **B**: Liver tissue from the control group. Sinusoids (S) with mononuclear hepatocytes extending radially towards the central vein (CV), polyhedral hepatocytes with centrally located nuclei (N) (H&E, scale bar = 200 µm). **C**: Liver tissue from the acetaminophen group. Notable sinusoidal dilatation (SD) adjacent to the central vein (CV). The nuclei (N) of hepatocytes show darkening (H&E, scale bar = 100 µm). **D**: Liver tissue from the acetaminophen group. The portal area and surrounding regions exhibit severe sinusoidal dilatation (SD) and vacuolated (V) spaces with disrupted cellular structures. Additionally, hepatocyte nuclei show a loss of roundness (H&E, scale bar = 100 µm). **E**: Liver tissue from the octreotide group. Very mild sinusoidal dilatation (SD) is observed, with centrally located, slightly pyknotic nuclei (P) in areas adjacent to the central vein (CV) (H&E, scale bar = 100 µm). **F**: Liver tissue from the octreotide group showing very mild sinusoidal dilatation (SD). **G**: Liver tissue from the treatment group. In this image, areas of infiltration (IC) and sinusoidal dilatation (SD) are visible (H&E, scale bar = 200 µm). **H**: Liver tissue from the treatment group. Infiltration areas (IC) and sinusoidal dilatation (SD) are observed in this image (H&E, scale bar = 100 µm).

Table 3. Number of rats with histopathological findings according to groups

Findings/Groups	Control (*n=7*)	Acetaminophen (*n=7*)	Octreotide (*n=7*)	Acetaminophen+ Octreotide (*n=7*)
No or minimal damage	6	0	6	0
Cytoplasmic vacuolization, nuclear pyknosis	1	0	1	5
Intense nuclear pyknosis, disappearance of intercellular boundaries	0	2	0	1
Fragmentation of hepatic cords, infiltration, severe necrosis	0	5	0	1

Discussion

Acetaminophen (APAP) is a commonly used analgesic and antipyretic medication. When administered at recommended doses, it is typically considered safe, with a short plasma half-life. Furthermore, its bioavailability reaches up to 75% at therapeutic doses, suggesting efficient distribution throughout the body.[28] However, overdose can result in hepatotoxicity, leading to severe clinical consequences and even death. In experimental animal models, APAP is often administered through intraperitoneal injection or gastric gavage at doses ranging from 300 mg/kg to 5 g/kg to induce hepatotoxicity.[29] In our study, a dose of 1000 mg/kg of APAP was administered orally via gastric gavage to induce liver toxicity.

Emergency treatment options for APAP overdose are limited. Compounds with strong antioxidant properties have emerged as a promising therapeutic approach to mitigate APAP-induced liver damage.[2]

Among these, N-acetylcysteine (NAC) is the most widely used and clinically proven potent antioxidant.[29] NAC is effective within the first 24 hours following an APAP overdose, but long-term use is thought to potentially be harmful.[30] Therefore, alternative treatment strategies for APAP toxicity should be explored. In this experimental study, we aimed to examine the hepatoprotective effects of octreotide (Oct), a somatostatin analog known for its antioxidant and anti-inflammatory properties, against APAP-induced liver toxicity. Oct is a synthetic cyclic octapeptide that suppresses the levels and activities of hormones such as growth hormone, insulin, gastrin, secretin, glucagon, and active neuropeptides like serotonin and vasoactive intestinal polypeptide. Compared to somatostatin, Oct has a longer half-life (1 to 2 hours) and effectively inhibits hormone production when administered three times daily. Oct has a broad therapeutic range and is used in various clinical settings, including reducing portal pressure in cirrhotic patients, minimizing complications following pancreatic surgery, and treating gastrointestinal tumors.[31,32] In our study, Oct was administered at a dose of 300 µg/kg intraperitoneally, 30 minutes after APAP administration. This timing was chosen to simulate acute clinical interventions and limit the hepatic transfer of toxic metabolites.

Liver enzymes are widely recognized as biomarkers for assessing drug-induced liver damage.[33] During liver injury, cellular transaminases such as AST and ALT, along with ALP, are released into the bloodstream. Elevated levels of these enzymes indicate liver damage.[34-37] Studies by Chen et al. and Bhadauria have shown that serum AST, ALT, and ALP levels are significantly higher in APAP-treated groups compared to controls.[34,38] Similarly, multiple studies have reported elevated enzyme levels following APAP administration.[39,40] In our study, significantly increased serum AST, ALT, and ALP levels in the APAP group, measured 24 hours post-administration, confirmed the development of hepatotoxicity. These findings are consistent with previous research reporting elevated liver enzyme levels following APAP administration.[25] In addition, studies have demonstrated that both APAP[2,3,41] and carbon tetrachloride (CCl_4)[25] cause liver damage and increase these enzyme levels. However, the administration of caffeic acid phenyl ester,[41] adenosine triphosphate,[3,] and ghrelin[2] has been shown to reduce enzyme activity. Furthermore, a study on CCl_4-induced liver toxicity reported that octreotide treatment restored enzyme levels to normal.[25] Likewise, our study demonstrated that octreotide significantly reduced APAP-induced liver enzyme elevations, supporting its hepatoprotective effect.

Numerous studies have emphasized the role of oxidative stress in APAP toxicity, which contributes to the development of APAP-induced hepatotoxicity by causing cellular damage. The primary mechanisms behind APAP-induced liver injury include an increase in reactive oxygen species (ROS) and a decrease in antioxidant enzyme activity.[42] Glutathione (GSH) plays a critical role in the detoxification of NAPQI and the clearance of peroxynitrite in APAP-induced hepatotoxicity. Excessive NAPQI formation leads to GSH depletion, covalent binding to protein cysteine residues, and subsequent lipid peroxidation. MDA, a byproduct of lipid peroxidation, is widely recognized as a biomarker of oxidative damage resulting from NAPQI accumulation.[43,44] In our study, serum MDA levels in the APAP group were higher than those in the other groups; however, this difference was not statistically significant. This may be due to the relatively short duration of our study (24 hours) and the absence of tissue analysis. Previous experimental studies have reported increased MDA levels in the APAP group compared to controls. While plasma MDA levels were elevated in the APAP group, hepatic MDA levels showed a more pronounced increase.[41] In our study, serum MDA levels in the APAP+Oct group were similar to those in the control group. This result suggests that Oct has a regulatory effect on lipid peroxidation.

In this study, a statistically insignificant decrease was observed in TAC in the APAP group compared to the other groups. Total oxidant capacity showed a significant increase in the APAP group compared to the others. The high TAC level and the decrease in TOC in the Oct group suggest that Oct has an effect on oxidative stress parameters. In other long-term studies, antioxidant levels were found to be statistically significant.[11] The fact that our experimental design focused on the acute phase intervention (24 hours) may explain the differences in findings compared to other studies.

In our study, inflammatory cell infiltration was observed in 70% of the rats in the APAP group, while sinusoidal dilation was present in all samples. Additionally, hepatic cord fragmentation, tissue loss, and hemorrhage were detected in some cases. Masson's trichrome (MT) staining was performed; however, due to the short duration of the study (24 hours), no increase in fibrous tissue was observed in the liver sections. Therefore, MT-stained sections were not included in the analysis. These findings are consistent with previous studies reporting significant hepatocellular damage following high-dose APAP administration.[45] An earlier study investigating rats subjected to prolonged hepatectomy found acute liver failure characterized by significant parenchymal necrosis. In that study, Oct administration was found to inhibit early liver regeneration while significantly improving liver histology, function, and survival in 90%

of the hepatectomized rats.[34] The Oct treatment group in our study exhibited better preservation of hepatic architecture, with minimal sinusoidal dilation and limited inflammatory cell infiltration. These histological improvements were accompanied by reduced liver enzyme levels, highlighting the hepatoprotective effects of Oct. Additionally, no significant pathological findings were observed in the Oct group, confirming the safety of the administered dose.

Conclusion

In conclusion, high-dose APAP administration led to elevated AST, ALT, ALP, MDA, and TOC levels while reducing TAC levels. Our histopathological and biochemical findings confirmed the hepatotoxic effects of high-dose APAP, consistent with previous studies. The somatostatin analog octreotide alleviated liver damage caused by experimentally induced acetaminophen toxicity. However, the effectiveness of any drug depends on its appropriate dosage, timing, and method of administration. While our study demonstrated the protective effects of octreotide against acetaminophen toxicity, further research is required to evaluate its therapeutic potential and clinical applicability.

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