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The effects of Clindamycin on serum oxidative stress and liver histopathology

Efectos de la clindamicina sobre el estrés oxidativo sérico y la histopatología hepática

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ABSTRACT

Clindamycin is used to treat upper respiratory tract, dental, skin, and anaerobic infections. Long-term, high-dose clindamycin may also be used in conditions such as bone infections. However, there is limited information regarding the safety of long-term, high-dose clindamycin use. The study aims to clarify the effects of long-term clindamycin treatment at various doses on serum oxidative stress values and liver histopathology. The study included 40 female Wistar albino rats, divided equally into four groups. While no treatment was administered to the first group (Control group), the other three groups were administered. Clindamycin orally at doses of 150, 300, and 600 mg/kg/day, respectively (treatment 5 days/week, resting 2 days/week) for 4 weeks. At the end of the study, blood and liver tissue samples were taken from the rats for analysis. Serum superoxide dismutase, glutathione peroxidase, and catalase levels were measured using an enzyme-linked immunosorbent assay reader. The liver tissue was examined histopathologically. At a dose of 600 mg/kg, catalase levels were found lower compared to the Control group ($P < 0.05$). In liver histopathology, interface necrosis, confluent necrosis, hydropic degeneration, portal inflammation, and steatosis scores were higher in the 300 and 600 mg/kg groups compared to the Control group ($P < 0.05$). Additionally, only the 600 mg/kg dose group had a higher bile duct proliferation score compared to the Control group ($P < 0.05$). In conclusion, since clindamycin was observed to affect oxidative stress parameters and cause hepatotoxicity at high doses, it can be suggested that clindamycin may be safe for the liver at recommended therapeutic doses and duration.

Key words: Clindamycin; oxidative stress; hepatotoxicity; rats.

RESUMEN

La clindamicina es un antibiótico que se utiliza para tratar infecciones de las vías respiratorias superiores, dentales, cutáneas y anaeróbicas. La clindamicina a largo plazo y en dosis altas también puede utilizarse en afecciones como infecciones óseas. Sin embargo, existe información limitada sobre la seguridad del uso prolongado de clindamicina en dosis altas. El estudio tiene como objetivo determinar los efectos de la administración prolongada de clindamicina en diferentes dosis sobre los parámetros de estrés oxidativo sérico y la histopatología hepática. El estudio incluyó 40 ratas Wistar albinas ratas, divididas equitativamente en cuatro grupos. Mientras que al primer grupo (grupo control) no se le administró ningún tratamiento, a los otros tres grupos se les administró clindamicina por vía oral en dosis de 150, 300 y 600 mg/kg/día, respectivamente (tratamiento 5 días/semana, descanso 2 días/semana) durante 4 semanas. Al final del estudio, se tomaron muestras de sangre y tejido hepático de las ratas para su análisis. Los niveles séricos de superóxido dismutasa, glutatión peroxidasa y catalasa se midieron utilizando un lector ensayo por inmunoabsorción ligado a enzimas. El tejido hepático fue examinado histopatológicamente. A una dosis de 600 mg/kg, los niveles de catalasa fueron menores en comparación con el grupo control ($P < 0.05$). En la histopatología hepática, la necrosis de interfase, la necrosis confluente, la degeneración hidrópica, la inflamación portal y las puntuaciones de esteatosis fueron mayores en los grupos de 300 y 600 mg/kg en comparación con el grupo control ($P < 0.05$). Además, solo el grupo de dosis de 600 mg/kg tuvo una puntuación de proliferación de conductos biliares mayor en comparación con el grupo control ($P < 0.05$). En conclusión, dado que se observó que la clindamicina afecta los parámetros de estrés oxidativo y causa hepatotoxicidad a dosis altas, se puede sugerir que la clindamicina puede ser segura para el hígado en las dosis y duración terapéuticas recomendadas.

Palabras clave: Clindamicina; estrés oxidativo; hepatotoxicidad; ratas.

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INTRODUCTION

Clindamycin, lincomycin, and pirlimycin are antibiotics belonging to the lincosamide group [1]. Clindamycin (7-chloro-lincomycin), semisynthetic derivative of lincomycin, was first used as an antibiotic in the 1960s. The drug is available in preparations for oral and parenteral (intramuscular, intravenous) administration. When clindamycin is taken orally, the drug is absorbed from gastrointestinal system and reached peak blood levels after around 45 minutes (min). It is metabolized into three main biologically active metabolites. The drug is mainly excreted via bile, with approximately 20 % excreted through the kidneys. The elimination half-life of drug is approximately 2 to 4 hours (h), which remains unchanged in patients with severe renal disease, but impaired hepatic function leads to extended elimination [2].

Clindamycin shows its bacteriostatic effect by binding to the 50S subunit ribonucleic acid (RNA) of the bacterial ribosome, thereby inhibiting the synthesis of microbial proteins. Clindamycin possesses many exceptional pharmacological properties that improve its effectiveness, as well. It decreases bacterial adhesion to epithelial cells, inhibits bacterial enzymes, proteins, toxins, and cytokines produced some pathogens [3].

While the drug is administered at doses of 5.5 mg/kg (oral, twice a day(d)) or 11 mg/kg (oral, intramuscular, intravenous, once a d) for 7–10 d in the treatment of routine bacterial infections in cats and dogs, it is used for 6 weeks for the treatment of osteomyelitis. In the treatment of toxoplasmosis, it is administered at doses of 10–50 mg/kg (oral, intramuscular, twice a d) for 2–3 weeks [1, 4].

Clindamycin is much more effective than lincomycin against *Staphylococcus* spp. and *Streptococcus* spp. infections. It is especially preferred in the therapy of anaerobic infections, lower respiratory tract infections, pyoderma, abscesses, dental infections, bone infections, bite wounds, toxoplasmosis, and babesiosis. Its use in cats and dogs is approved in Veterinary Medicine [1].

Its efficacy against pathogens in fish [5] and dogs [6] has also been studied. Long-term antibiotic use is required for the treatment of bone and joint infections [7]. The potential side effects of high-dose and long-term antibiotic use have been investigated [8].

Main side effects of clindamycin include diarrhea, nausea, loss of appetite, and. abdominal discomfort [3]. Clindamycin may cause transient adverse effects such as diarrhea and pseudomembranous colitis related to *Clostridioides difficile*. In addition to these, skin rash, esophagitis, Stevens-Johnson syndrome, hypotension, rarely rheumatoid arthritis, augmented serum transaminases, neutropenia, eosinophilia, leukopenia, agranulocytosis, thrombocytopenic purpura may occur. In extraordinary cases, kidney-related side effects such as proteinuria or azotemia may be observed [3, 9].

On the other hand, it has been reported that hepatotoxicity may also appear infrequently [10, 11]. In a case report, clindamycin caused chronic liver cell disease, jaundice, increased serum total bilirubin and transaminases have been reported. The patient reported that clindamycin treatment was discontinued, and the enzymes returned to normal levels in the following weeks [10].

In a review, it has been stated that clindamycin treatment may induce transient enhancements in serum transaminases, which typically resolve spontaneously after the discontinuation of the treatment. If these enhancements are determined to be due to clindamycin, withdrawal of the clindamycin may decrease the increase in transaminase enzymes [11].

Clindamycin decreases pro-inflammatory cytokines and interferon. By decreasing reactive oxygen species, clindamycin edges oxidative stress and damage. Furthermore, it affords another mechanism for reducing oxidative damage by inhibiting nitric oxide synthase [11].

In a study was reported that clindamycin administration can prevent the oxidative stress caused by chemotherapeutic agent (doxorubicin) in the kidneys. In cases of doxorubicin-induced significant renal damage, characterized by inflammatory cell infiltration, congestion, and edema, along with elevated serum creatinine and urea levels, prior administration of clindamycin has been reported to alleviate the symptoms. Furthermore, it has been reported that glutathione depletion and decreased catalase levels caused by doxorubicin are significantly prevented by prior clindamycin administration, thus preventing doxorubicin-induced oxidative damage in renal tissue. The study concludes that clindamycin has a potential protective effect against doxorubicin-induced acute nephrotoxicity by inhibiting oxidative stress, inflammatory cascades, and apoptotic tissue damage [12].

During the energy production in living cells, oxygen-derived reactive oxygen radicals (singlet oxygen, superoxide radical, hydroxyl radical, hydrogen peroxide) are continuously produced. Reactive oxygen species that cannot be neutralized damage surrounding structures [lipids, proteins, carbohydrates, deoxyribonucleic acid (DNA)]. These radicals are neutralized in living organisms by non-enzymatic or enzymatic substances (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), etc. However, when excessive reactive oxygen species are generated in living organisms or when antioxidant capacity is inadequate to neutralize these substances, oxidative stress develops [13, 14].

Considering that long-term clindamycin treatment is required for the treatment of special infections [7], clindamycin may reduce free oxygen radicals [11], and it causes an increase in liver enzymes [10, 15], it has been hypothesized in this study that long-term and high-dose clindamycin administration could affect serum oxidative stress parameters and liver histopathology.

The aim of the study is to determine the effect of long-term clindamycin treatment on various doses on serum oxidative stress values (SOD, CAT, GPX) and liver histopathology.

MATERIALS AND METHODS

Animals and experimental design

In the present study, 40 female Wistar Albino rats (Rattus norvegicus) of 8–12 weeks old, 174–210 g body weigth (SF-400D scale Gromy Industry, Zhejiang, China) gained from the Experimental Medicine, Application, and Research Center of Selcuk University (SUDAM) were used. The rats were kept in

polycarbonate cages at room temperature (22 ± 2 °C) and 55 ± 5 % humidity under a 12/12-h light/dark cycle. They were fed food and water *ad libitum*.

The 40 female rats were equally divided into 4 groups (n: 10). While no treatment was administered to the first group (Control group), the other 3 groups (experimental groups) were orally administered doses of 150, 300, and 600 mg/kg/d (Klindan 600 mg ampule, Bilim Ilac, Istanbul, Türkiye), respectively, for 4 weeks (treatments - Monday, Tuesday, Wednesday, Thursday and Friday, 5 d/week, resting Saturday and Sunday, 2 d/week).

At the end of the experiment, the rats were anesthetized with a combination of Xylazine (8 mg/kg, intraperitoneal, Xylazine Bio 2 % injection, Bioveta, Ankara, Türkiye) and Ketamine (75 mg/kg, intraperitoneal, Ketasol® 10 % injection, Interhas, Ankara, Türkiye), blood samples were collected from their hearts. The animals were euthanized by cervical dislocation. Liver samples were immediately collected from the euthanized animals for histopathological examination.

Oxidative stress parameters

The collected blood samples were centrifuged (Sigma 3K-18, Osterode am Harz, Germany) at 3000 g for 10 min for serum extraction. In the current study, rat-specific Enzyme-Linked Immunosorbent Assay (ELISA) kits obtained from a marketable company (BT-Lab Bioassay Technology Laboratory, Shanghai, China) were used to measure serum oxidative stress values SOD (Cat. No: E0168Ra), CAT (Cat. No: E0869Ra) and GPX (Cat. No: E1242Ra) using an ELISA reader (MWGtLambda Scan 200, Bio–Tec Instruments, Winooski, VT, USA)

Histopathological evaluation

Liver samples fixed in formaldehyde for 24 h were trimmed and placed in tissue tracking cassettes and the formaldehyde solution was replaced to ensure a second fixation for 24 h. The tissue samples fixed were removed from the formaldehyde solution and washed for 24 h in running tap water. The tissues washed were placed in an automatic tissue tracking device (Leica TP 1020, Germany) and processed through graded alcohols (70, 80, 90, 96, and 100 % absolute alcohol), xylene, xylene-paraffin, and paraffin series.

Finally, the tissue samples were embedded in paraffin blocks to prepare them for microtome sectioning. Sections with a thickness of 4–5 µm were cut from the frozen paraffin blocks using a microtome device (Leica RM-2125 RT, Germany), placed on slides and stained with Hematoxylin-Eosin (HE) staining [16]. Following the staining process, the preparations covered with lamella were examined under a binocular light microscope (Olympus, BX51, Japan) and photographed using a camera (Olympus, EP50, Japan) with different objectives. Based on Modified Ishak Scoring System, histopathological changes in the liver were evaluated through a comprehensive semi-quantitative grading system by adding hydropic degeneration, steatosis, cholestasis and bile duct proliferation parameters that are specific to drug-induced liver injury (DILI) [17, 18, 19]. TABLE I shows criteria used for scoring.

TABLE I
Scoring protocol used to assess clindamycin-induced liver damage

Modified Liver Damage Scoring Chart		
Interface necrosis	0	None
	1	Mild (focal)
	2	Mild to moderate, involving most portal tracts
	3	Moderate to marked, widespread
	4	Severe, widespread
Confluent necrosis	0	None
	1	Focal confluent necrosis
	2	Zone 3 necrosis in a few areas
	3	Zone 3 necrosis in multiple areas
	4	Bridging necrosis
	5	Multilobular necrosis
	6	Panacinar / Massive necrosis
Hydropic degeneration	0	Normal histopathological appearance; no degeneration
	1	Mild cytoplasmic swelling and vacuolization in < 25 % of hepatocytes (usually centrilobular)
	2	Distinct swelling in 25-50 % of hepatocytes; clear cell borders and cytoplasmic pallor
	3	Widespread hydropic changes in 50-75 % of hepatocytes
	4	Severe swelling and ballooning in > 75 % of hepatocytes
Lobular inflammation	0	None
	1	Mild
	2	Moderate
	3	Marked
	4	Severe
Portal inflammation	0	None
	1	Mild
	2	Moderate
	3	Marked
	4	Severe
Fibrosis	0	None
	1	Focal portal fibrosis
	2	Fibrosis in multiple portal areas
	3	Portal fibrosis with focal parenchymal fibrosis
	4	Portal fibrosis with prominent parenchymal fibrosis
	5	Bridging fibrosis
	6	Cirrhosis
Steatosis	0	None or Minimal (< 5 % of hepatocytes involved)
	1	Mild (5 % - 33 % of hepatocytes involved)
	2	Moderate (34 % - 66 % of hepatocytes involved)
	3	Severe (> 66 % of hepatocytes involved)
Cholestatic patterns	0	None
	1	Minimal to focal
	2	Moderate to multifocal
	3	Marked, widespread bile plugs
Bile duct proliferation	0	None
	1	Mild
	2	Moderate
	3	Marked

Statistical analysis

The data were presented as mean ± standard deviation (SD). Oxidative stress parameters were measured in randomly selected seven samples from each group and values were evaluated using ANOVA and Tukey's test as a post-hoc test. All animals were assessed for liver histopathology. Non-parametric liver histopathology scores were evaluated using Kruskal-Wallis and Dunn's multiple comparison test as a post-hoc test (SPSS 29.0). The value of $P < 0.05$ was accepted as the statistical significance level.

RESULTS AND DISCUSSION

Clindamycin is a lincosamide-group antibiotic that shows a bacteriostatic effect by inhibiting bacterial protein synthesis. As it is primarily used to treat infections caused by Gram-positive bacteria, it is also highly effective against anaerobic and bone infections [1]. In the treatment of bone infections, long-term antibiotic therapy may be used [7].

TABLE II shows the effect of clindamycin on serum oxidative stress values. While the highest dose group (600 mg/kg) had lower CAT levels than the Control group ($P < 0.05$), no statistically significant differences were observed in SOD and GPX levels ($P > 0.05$).

TABLE II

Effect of different doses of clindamycin (150, 300 and 600 mg.kg^{-1}, peroral, once a day, 5 days treatment, 2 days of resting, 4 weeks) on serum oxidative stress parameters (mean ± standard deviation)

Parameters	Control	150 mg.kg^{-1}	300 mg.kg^{-1}	600 mg.kg^{-1}
SOD ng-mL^{-1}	3.32 ± 0.31	3.29 ± 0.48	3.18 ± 0.30	3.16 ± 0.21
CAT ng-mL^{-1}	51.90 ± 6.96^{a}	41.42 ± 7.57^{ab}	41.63 ± 7.55^{ab}	40.55 ± 8.41^{b}
GPX nU-mL^{-1}	841.01 ± 324.17	1052.70 ± 165.77	1013.69 ± 91.14	1144.64 ± 235.16

SOD; superoxide dismutase, CAT; catalase, GPX; glutathione peroxidase.
^{a}, ^{b}: Different letters in the same line show statistically significant ($P < 0.05$).

In this study, it was observed that the highest dose of clindamycin (600 mg/kg) lowered levels of CAT enzyme ($P < 0.05$), which detoxify hydrogen peroxide (TABLE II). When the effect of clindamycin on oxidative stress parameters has been examined, similar results were not observed. It has been reported that the administration of clindamycin (30 mg/kg) to hamsters lowered GPX levels [20], had no effect on lipid peroxidase levels [21] and elevated CAT levels in brain tissue [22].

Additionally, it has been reported that the administration of 300 mg/kg clindamycin (intraperitoneal, once daily, for 5 d) to rats did not affect CAT and glutathione levels in kidney tissue [12]. Differences between studies may stem from variations in the administered dose, duration, animal species, and the tissue examined. In this study, the decrease in CAT levels can be explained by the fact that clindamycin inhibits CAT synthesis or the enzyme is consumed by causing production of hydrogen peroxide.

TABLE III

Effect of different doses of clindamycin (150, 300 and 600 mg.kg^{-1}, once a day, 5 days treatment, 2 days of resting, 4 weeks) on liver histopathological scores (mean ± standard deviation)

Parameters	Control	150 mg.kg^{-1}	300 mg.kg^{-1}	600 mg.kg^{-1}
Interface necrosis	0.60 ± 0.52^{c}	1.60 ± 0.52^{bc}	2.80 ± 0.63^{ab}	3.00 ± 0.47^{a}
Confluent necrosis	0.00 ± 0.00^{b}	0.30 ± 0.48^{b}	1.60 ± 1.26^{a}	2.00 ± 0.82^{a}
Hydropic degeneration	0.90 ± 0.32^{b}	2.20 ± 0.92^{a}	2.90 ± 0.32^{a}	3.00 ± 0.00^{a}
Lobular inflammation	0.20 ± 0.42	0.40 ± 0.70	0.50 ± 0.71	0.90 ± 0.74
Portal inflammation	0.40 ± 0.52^{b}	1.20 ± 0.63^{ab}	1.40 ± 0.52^{a}	1.60 ± 0.52^{a}
Steatosis	0.10 ± 0.32^{b}	0.60 ± 0.52^{ab}	1.50 ± 0.53^{a}	1.80 ± 1.32^{a}
Bile duct proliferation	0.30 ± 0.48^{b}	0.80 ± 0.63^{ab}	0.90 ± 0.32^{ab}	1.60 ± 0.52^{a}

^{a}, ^{b}, ^{c}: Different letters in the same line show statistically significant ($P < 0.05$).

FIGURE 1 shows the effects of different doses of clindamycin (150, 300 and 600 mg/kg, peroral, once a d, 5 d treatment, 2 d of resting, 4 weeks) on liver histopathology, and TABLE III shows liver scores. The 300 and 600 mg/kg groups had higher interface necrosis scores than the Control group ($P < 0.05$), while interface necrosis score of the 150 mg/kg group was lower than the 600 mg/kg group ($P < 0.05$).

The confluent necrosis scores in the 300 mg/kg and 600 mg/kg groups were higher than the Control and 150 mg/kg groups ($P < 0.05$), while the hydropic degeneration score in the Control group was lower than the 150 mg/kg, 300 mg/kg, and 600 mg/kg groups ($P < 0.05$).

The portal inflammation and steatosis scores in the 300 mg/kg and 600 mg/kg groups were higher ($P < 0.05$) than the Control group, while the bile duct proliferation score in the Control group was lower ($P < 0.05$) than the 600 mg/kg group.

No statistically significant change was observed in the groups in terms of lobular inflammation scores ($P > 0.05$). Due to the lack of information regarding clindamycin-induced liver damage, it has been reported that a reliable conclusion could not be reached to confirm or refuse whether clindamycin is the causative agent in the developing hepatotoxicity [23]. However, elevated liver enzymes have been reported in patients using clindamycin [10, 15, 24].

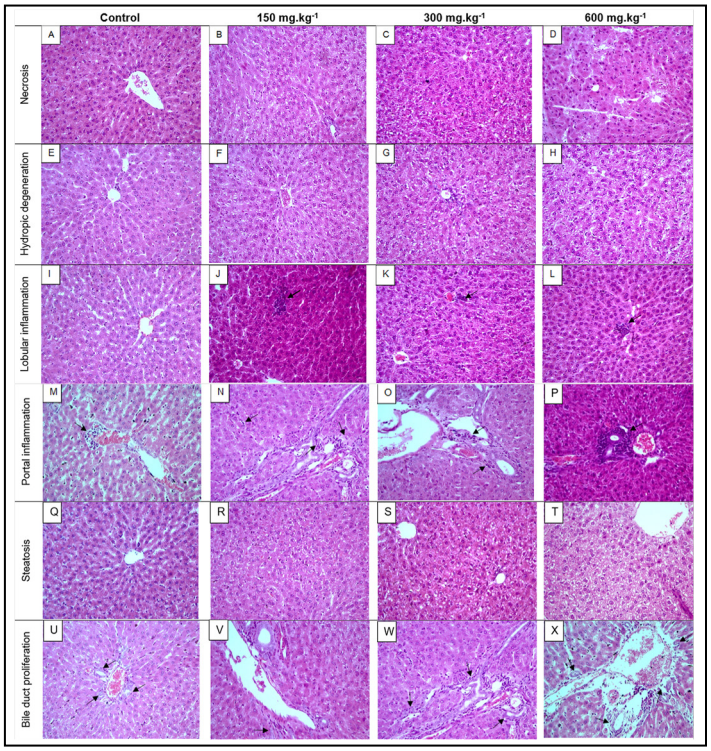

FIGURE 1. Representative histopathological microphotographs of liver tissues from control and clindamycin-treated groups. (A) Control group, HE, 40X: Normal histological architecture of the liver parenchyma. (B) 150 mg/kg clindamycin group, HE, 40X: Mild hydropic degeneration and focal necrotic areas. (C) 300 mg/kg clindamycin group, HE, 40X: Moderate hydropic changes, necrotic areas and loss of sinusoidal structure (D) 600 mg/kg clindamycin group, HE, 40X: Severe widespread necrosis, significant hydropic degeneration, and loss of sinusoidal structure. (E) Control group, HE, 40X: Normal histological appearance of hepatocytes with well-preserved cytoplasmic structure. (F) 150 mg/kg clindamycin group, HE, 40X: Mild cytoplasmic swelling and early vacuolization in hepatocytes. (G) 300 mg/kg clindamycin group, HE, 40X: Distinct hydropic changes characterized by cytoplasmic pallor and cellular enlargement. (H) 600 mg/kg clindamycin group, HE, 40X: Widespread hydropic degeneration with ballooning of hepatocytes. (I) Control group, HE, 40X: Normal liver histology. (J) 150 mg/kg clindamycin group, HE, 40X: Presence of focal inflammatory cell clusters (arrows) within the hepatic lobules. (K) 300 mg/kg clindamycin group, HE, 40X: Lobular inflammation characterized by multiple scattered inflammatory foci (arrows). (L) 600 mg/kg clindamycin group, HE, 40X: Inflammatory cell infiltration (arrow). (M) Control group, HE, 40X: Normal portal tract architecture with mild inflammatory infiltration. (N) 150 mg/kg

clindamycin group, HE, 40X: Moderate inflammatory cell infiltration in portal area and periportal parenchyma (arrows). (O) 300 mg/kg clindamycin group, HE, 40X: Moderate portal inflammation characterized by a denser accumulation of inflammatory cells around the portal triad (arrows). (P) 600 mg/kg clindamycin group, HE, 40X: Severe and prominent portal inflammation with extensive inflammatory cell clusters (arrow) expanding into the periportal parenchyma. (Q) Control group, HE, 40X: Normal liver histology with no visible lipid accumulation in hepatocytes. (R) 150 mg/kg clindamycin group, HE, 40X: Mild steatosis characterized by small, scattered lipid droplets within the cytoplasm. (S) 300 mg/kg clindamycin group, HE, 40X: Moderate steatosis showing a higher frequency of lipid vacuoles across the parenchyma. (T) 600 mg/kg clindamycin group, HE, 40X: Severe and widespread steatosis with prominent micro- and macrovesicular fat droplets, indicating significant metabolic disruption. (U) Control group, HE, 40X: Normal portal area with a mild bile duct structure. (V) 150 mg/kg clindamycin group, HE, 40X: Mild proliferation of small bile ducts (arrows) within the portal triad. (W) 300 mg/kg clindamycin group, HE, 40X: Prominent and extensive bile duct proliferation (arrows) accompanied by mild inflammatory cell infiltration. (X) 600 mg/kg clindamycin group, HE, 40X: Prominent and extensive bile duct proliferation (arrows) in the periportal areas accompanied by mild inflammatory cell infiltration.

Studies on liver histopathology are generally in the form of case reports. The case reports have reported that hepatocyte swelling and necrosis, lobular disruption, numerous pseudogranulomas, eosinophilic bodies, mononuclear cell infiltration [24], centrilobular and portal cholestatic hepatitis [25] or moderate cholestasis, mild sinusoidal mononuclear infiltrate and focal mild-to-moderate periportal chronic inflammation were observed in liver histopathology of patients treated with clindamycin [26]. In this study, considering that adverse findings in liver histopathology were observed only at the highest doses despite the high-dose and long-term use of clindamycin, it can be asserted that clindamycin may not cause significant histopathological changes in the liver when used at recommended therapeutic doses and duration.

CONCLUSIONS AND IMPLICATIONS

In this study, clindamycin was administered at high doses over a longer period to determine its controversial effects on oxidative status (SOD, CAT, GPX) and liver histopathology. Based on the results of this study, considering that the highest dose reduced CAT levels and caused changes in liver histopathology, it can be stated that at routine therapeutic doses, clindamycin may not affect the oxidative status and may not cause histopathological changes in the liver. However, it should be noted that routine liver function tests must also be evaluated to determine whether clindamycin is safe for the liver when used for long periods and at high doses. When long-term, high-dose treatment with clindamycin is preferred, liver function tests should be monitored. Furthermore, given that clindamycin hepatotoxicity is generally determined through case reports, more studies at the biochemical and molecular level in the target animal species are needed to determine dose-dependent toxicity.

Ethical approval

Ethical clearance for this study was granted by SUDAM under approval number 2026/37.

Conflict of interest

The authors state no conflicts of interest.

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