

Effect of Cefixime on the Liver of male Albino Rats

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Abstract

The present study was designed to evaluate the histopathological and biochemical responses of the liver in adult male Swiss albino rats following oral administration of cefixime (Suprax®), a third-generation oral cephalosporin antibiotic. The study included sixteen animals, aged four months, which were equally divided into two groups: a control group and a treatment group. The treatment group received a daily oral dose of cefixime equivalent to the approved therapeutic dose of 1.33 mg/kg body weight for thirty consecutive days. Liver tissue specimens were collected and processed for histopathological examination using routine hematoxylin and eosin (H&E) staining. Biochemical parameters were assessed by measuring serum liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), along with total bilirubin levels. Histopathological examination of hepatic tissues from the treatment group revealed statistically significant degenerative alterations, comprising focal hepatocellular ballooning degeneration (swollen hepatocytes), necrotic foci, marked karyopyknosis (nuclear condensation), dilation of hepatic sinusoids, and periportal lymphocytic infiltration. In contrast, liver sections from the control group retained their normal intact histological architecture. These morphological changes were associated with a marked elevation in serum levels of ALT, AST, ALP, total bilirubin, urea, and creatinine when compared to the control group values. These findings are in agreement with the well-established scientific literature that confirms the association of cephalosporin compounds with hepatotoxic syndromes, although the minor discrepancies observed in enzyme kinetics may reflect the temporal characteristics of the specific dose regimen employed in this study. The study concludes that continuous or cumulative therapeutic doses of cefixime possess the potential to induce dose-dependent hepatocellular injury, thereby necessitating meticulous and continuous monitoring of hepatic function during the clinical application of this antibiotic

Keywords: Cefixime; Liver; Hematoxylin; Hepatotoxicity; Albino Rats

الخلاصة :

هدفت هذه الدراسة إلى تقييم الاستجابات النسيجية المرضية والكيميائية الحيوية لكبد ذكور الجرذان البيضاء السويسرية البالغة إثر إعطاء عقار Cefixime (Suprax) وهو مضاد حيوي من جيل السيفالوسبورينات الثالث يُعطى عن طريق الفم. شملت الدراسة 16 حيوان بعمر أربعة أشهر، وُزعت بالتساوي بين مجموعتين: ضابطة وعلاجية، إذ تلقت المجموعة العلاجية جرعة يومية فموية من Cefixime تعادل الجرعة العلاجية المعتمدة البالغة 1.33 ملغم/كغم لمدة ثلاثين يوماً متتالياً. جُمعت عينات نسيج الكبد وغُولجت للفحص النسيجي باستخدام صبغة الهيماتوكسيلين والإيوزين (H&E) وفق الأسلوب الاعتيادي، فيما قُيِّمت المؤشرات الكيميائية الحيوية بقياس إنزيمات الكبد في المصل، شاملة ناقلات أمين الالانين (ALT)، وناقلات أمين الأسبارتات (AST)، والفسفاتاز القلوي (ALP)، إلى جانب البيليروبين الكلي. كشف الفحص النسيجي لأنسجة كبد المجموعة العلاجية عن تغييرات تنكسية ذات دلالة إحصائية، تضمنت: التورم الخلوي الكبدي البؤري (swollen hepatocytes Focal Hepatocellular)، وبؤر النخر (Necrotic Foci)، والتكثف النووي (Karyopyknosis)، واتساع الجيوب الدموية الكبدية، والتسرب اللفغوي المحيط بالقناة البابية؛ في حين احتفظت أكباد المجموعة الضابطة بالبنية النسيجية الطبيعية السليمة. ارتبطت هذه التغيرات المورفولوجية بارتفاع ملحوظ في مستويات ALT و AST و ALP والبيليروبين واليوريا والكرياتينين مقارنة بقيم المجموعة الضابطة. تتوافق هذه النتائج مع الأدبيات العلمية الراسخة التي تُثبت ارتباط مركبات السيفالوسبورين بمتلازمات سُمية الكبد، وإن كانت الفوارق الطفيفة المُلاحظة في حركية الإنزيمات قد تعكس الخصائص الزمنية للجرعة المُستخدمة في هذه الدراسة. وخلص البحث إلى أن الجرعات العلاجية المتمادية أو التراكمية من Cefixime تمتلك القدرة على إحداث إصابة كبدية تعتمد على الجرعة، مما يستوجب الرقابة الدقيقة والمستمرة على وظائف الكبد خلال التطبيق السريري لهذا المضاد الحيوي.

الكلمات المفتاحية: Cefixime؛ الكبد؛ الهيماتوكسيلين؛ سُمية الكبد؛ الجرذان البيضاء

1. Introduction

Background: The liver is the largest and most important solid organ in the body, located predominantly in the right upper quadrant of the abdominal cavity, beneath the diaphragm and protruding marginally toward the left upper quadrant [1], [2]. Size: In healthy adults, the liver mass usually ranges from 1.2 to 1.5 kilograms (kg) (2.6 to 3.3 pounds) and has a reddish-brown color and a spongy texture. The liver is divided into a larger right and smaller left morphological lobes,

and it is supplied by a unique dual blood supply, comprising the hepatic artery and the hepatic portal vein; the latter is enriched with nutrients from the gastrointestinal tract, and the former contains oxygen, allowing hepatocytes to have an ideal flow of both nutrients and oxygen [2].

Functionally, the liver is a hub of human metabolism, with ongoing regulation of serum glucose, lipids, and amino acids and secretion of bile salts that are involved in enteric emulsification and absorption of lipids [3]. It is also the major

organ of xenobiotic metabolism, inactivating and/or activating psychotropic, alcoholic, and toxic exogenous substances into water-soluble metabolites for excretion through urine or bile [4]. Furthermore, the liver produces important plasma proteins, such as albumin, which fulfills oncotic pressure, and all the factors of coagulation, which bear importance in hemostasis [5]. Impairment of hepatic function can result from multiple causes, including viral hepatotropic agents (hepatitis B and C in particular), chronic alcohol abuse, and exposure to environmental or industrial hepatotoxins, and lead to advancing hepatic fibrosis, cirrhosis, and, in late stages, multi-organ failure [6]. Histologically, the liver is composed of numerous classical hepatic lobules, each roughly hexagonal in shape and centered around a central vein. Hepatocytes, the principal functional cells of the liver, are polygonal cells with large round nuclei and are arranged in one-cell-thick plates or cords radiating from the central vein toward the periphery of the lobule. Between these hepatic cords lie the hepatic sinusoids, which are specialized capillary channels lined by fenestrated endothelial cells that facilitate the exchange of nutrients, metabolites, and plasma constituents between the blood and hepatocytes[6]. Resident hepatic macrophages, known as Kupffer cells, are located within the sinusoidal lumen and play a critical role in phagocytosis, immune surveillance, and the removal of pathogens and cellular debris. At the periphery of each hepatic lobule lies the portal triad, which consists of a branch of the portal vein, a branch of the hepatic artery, and an interlobular bile duct. The normal structural organization of these components is essential for maintaining hepatic function, whereas disruption of this architecture is a characteristic feature of drug-induced liver injury and other hepatic disorders[7]. The history of cephalosporins dates back to 1945, when a compound was isolated from a fungal culture later identified as Acremonium, previously known as Cephalosporium. Ten years later, English scientists

under Edward Abraham (1913-1999) determined the molecular structure of cephalosporin C, the major antibiotic metabolite of that strain, thus providing the basis for further drug design development [7]. Cefixime is a third-generation oral cephalosporin with broad-spectrum antibacterial activity; it is widely prescribed for respiratory tract infections, urinary tract infections, and gonorrhea [8], [9], [10]. Despite its clinical utility, the hepatotoxic potential of cephalosporin-class antibiotics, including cefixime, remains a subject of active investigation [11], [12], [13], [14], [15].

The present study was therefore undertaken to evaluate the histopathological effects of therapeutic-dose cefixime administration on hepatic tissue in adult male Swiss albino rats, and to correlate morphological findings with serum biochemical markers of liver injury.

2. Materials and Methods

2.1 Animal Experiment

The current study was performed during March–April 2026. The study used 16 healthy male Swiss albino rats (4 months old, 200 ± 25 g). In order to minimize variability in biochemical parameters and histopathology responses associated with estrous cycle (female) hormonal fluctuations, only male rats were chosen. Male rats were used in this study to exclude physiological fluctuations which might occur with the estrous cycle and hormonal cycles of females that may impact hepatic metabolism, biochemical parameters, or histopathological responses causing increased experimental variability. Before to the experiment, animals were clinically examined and none displayed signs of illness or cutaneous lesions. Animals were kept in aluminum cages (0.5× 0.5 m) with a wire-mesh floor at standard laboratory room temperature conditions and up to five rats per cage respectively. They had access to a standard pellet diet and water ad libitum. The cages were cleaned with Dettol antiseptic solution every two days and left in sunlight for around 2 h to reduce bacterial load. Two weeks before the experiment, all animals were

adapted to laboratory conditions for health status and acclimation purposes. The experiment was conducted between March and April 2026.

2.2 Drug and Preparation

A purified powder of cefixime (Suprax) a semi-synthetic third-generation cephalosporin antibiotic formulated for oral administration was used throughout the trial. The human therapeutic dose is 400 mg/day. The equivalent dose for male rats was calculated using the following body-weight allometric equation:

$$X1 \times Y2 = X2 \times Y1$$

Where X1 = body weight of an adult human (60,000 g), X2 = mean body weight of male rat (200 +/- 25 g), Y1 = human Suprax dose (400 mg), and Y2 = dose to be administered to rats. Substituting:

$$60,000 \text{ g} \times Y2 = 200 \text{ g} \times 400 \text{ mg} \Rightarrow Y2 = 1.33 \text{ mg}$$

The volume of solution to be administered was subsequently determined from:

$$V1C1 = V2C2 \Rightarrow 20 \text{ mL} \times 1.33 \text{ mg} = V2 \times 18 \text{ mg} \Rightarrow V2 = 1.48 \text{ mL}$$

Accordingly, 18 mg of pure cefixime powder was dissolved in 50 mL of distilled water to produce the stock solution, and 1.48 mL per dose was administered by oral gavage to achieve the therapeutic level of 1.33 mg/day per animal.

2.3 Animal Grouping

Animals were assigned to two groups (n = 8 per group) as follows:

Group A (Control). Rats received standard diet and water only throughout the 30-day study period.

Group B (Treatment). Rats received a daily oral dose of cefixime (Suprax) at 1.33 mg/day by oral gavage for 30 consecutive days (therapeutic dose).

2.4 Histological Preparation

At the conclusion of the experimental period, animals were Euthanized under chloroform anaesthesia. Organs were excised, weighed, and immediately fixed. Tissues were processed by following the routine Bancroft and Stevens histology protocol [16] and included the subsequent sequential steps:

1. Fixation: The tissues were fixed in 10% neutral buffered formalin for 22 hr.

2. Dehydration: The tissue was rinsed under tap water and dehydrated in alcohol baths of increasing concentrations.

3. Tissue was passed through xylene baths to clearing out any remaining alcohol.

4. Paraffin embedding: The cleared tissue was processed through paraffin infiltration and embedded in paraffin using stainless steel molds.

5. Preparation: Paraffin blocks were cut into 4-6 μm sections with a Minot-type rotary microtome.

6. Section adhesion: Sections were adhered to glass slides with Mayer's glycerol-albumin adhesive, and then covered with a coverslip.

7. Dewaxing and rehydrating: The sections were deparaffinized in xylene and rehydrated in a series of decreasing concentrations of alcohol.

8. Staining: H&E staining was done with Harris' hematoxylin (2.5 g hematoxylin in 25 mL absolute alcohol, mixed with 50 g potassium alum in 500 mL distilled water, buffered with 1.25 g mercuric oxide, and 20 mL glacial acetic acid) and counterstaining with eosin.

9. Mounting: Coverslips were mounted with DPX mountain.

The stained histological sections were examined under a light microscope (Olympus BX43, Olympus Corporation, Tokyo, Japan). Representative photomicrographs were captured using a digital microscope camera (Olympus DP27,

Olympus Corporation, Tokyo, Japan) at the appropriate magnifications for histopathological evaluation.

2.5 Statistical Analysis

Data were expressed as mean $\pm$ standard deviation (Mean $\pm$ SD). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 26.0 (IBM Corp., Armonk, NY, USA). Comparisons between the control and treated groups were carried out using

the independent samples t-test. Differences were considered statistically significant at $P < 0.05$.

3. Results

The liver sections of the control rats (Group A) showed normal histoarchitecture with normal appearance of hepatocytes and patent sinusoids, and none of the features of cellular degeneration or inflammatory infiltrate were observed, as shown in Figure A.

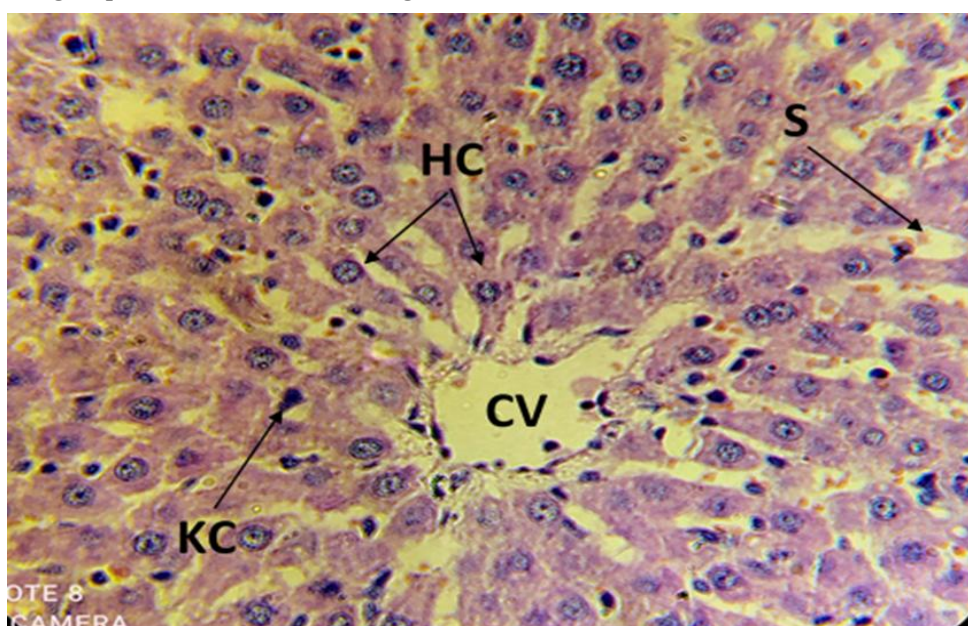


Figure (A): A photomicrograph of a control rat liver section showing normal central vein (CV), hepatocytes (HC), and sinusoids (S) with Kupffer cells (KC). (H&E stain, $\times 200$).

Liver tissue from the Group B animals (cefixime) also showed varying degrees of significant degenerative and inflammatory changes. In particular, treated livers showed focal hepatocellular ballooning degeneration, necrotic

foci, marked karyopyknosis (nuclear condensation), dilation of hepatic sinusoids, and periportal lymphocytic infiltration, as depicted in Figures B and C.

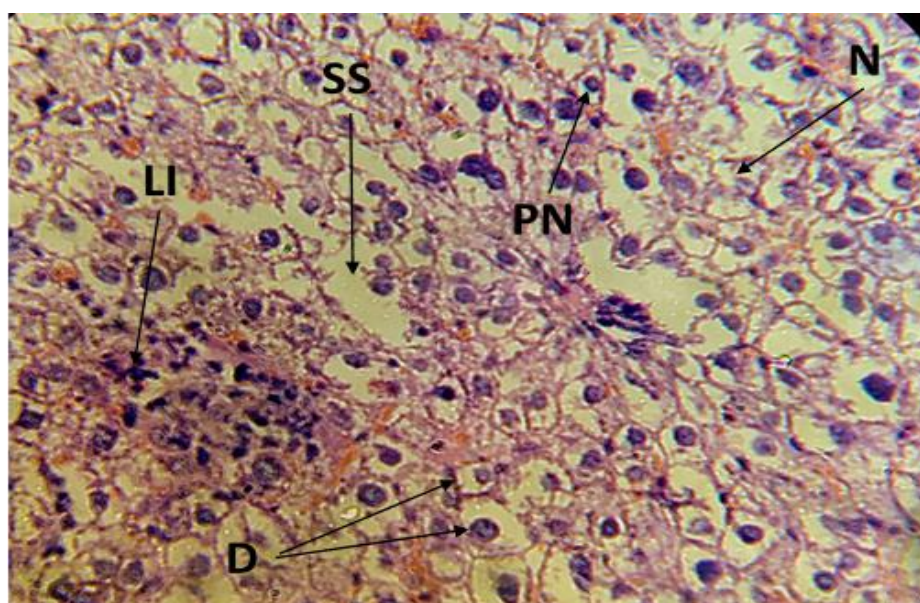


Figure (B): A photomicrograph of the cefixime-treated rat liver section showing hepatocellular degeneration (D), necrosis (N), nuclear condensation (PN), dilated sinusoids (SS), and lymphocyte infiltration (LI). (H&E stain, ×400).

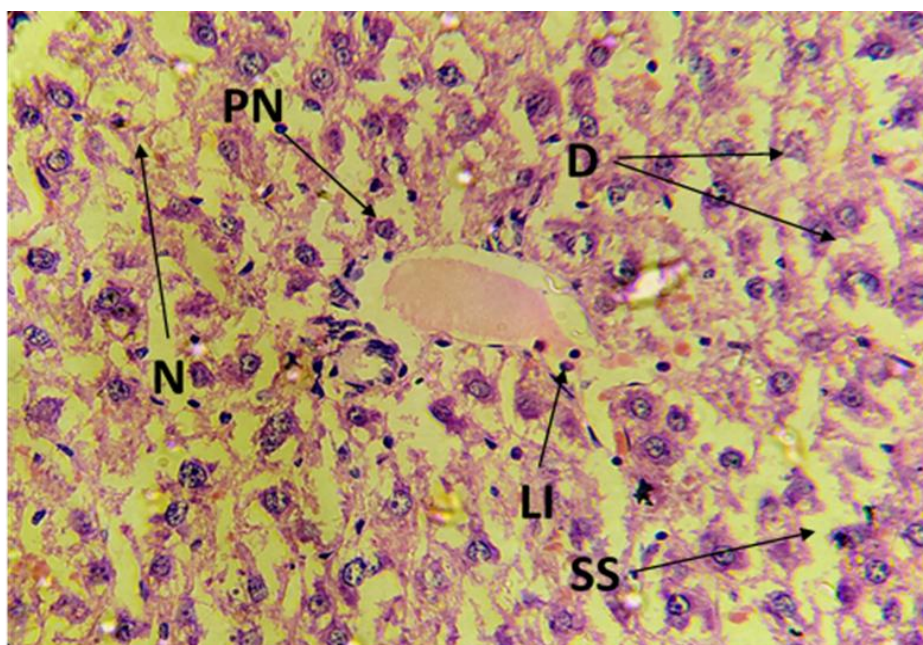


Figure (C): A photomicrograph of the cefixime-treated rat liver section exhibiting severe degeneration (D), necrosis (N), pyknotic nuclei (PN), congested sinusoids (SS), and periportal lymphocytic infiltration (LI). (H&E stain, ×400).

The results of biochemical profiles in Group B were consistent with hepatocellular injury and cholestatic perturbation, with significant increases in serum ALT, AST, ALP, and total bilirubin levels

compared to Group A controls. During the first 10 days of the treatment the serum urea and creatinine values showed no significant variation.

Table (1): Biochemical parameters of liver and kidney functions in control and cefixime-treated male albino rats (Mean $\pm$ SD)

Parameter	Control Group (n=8)	Cefixime-Treated Group (n=8)	P-value
ALT (U/L)	42.50 $\pm$ 3.80	118.70 $\pm$ 8.50	< 0.001
AST (U/L)	78.30 $\pm$ 5.90	192.40 $\pm$ 12.70	< 0.001
ALP (U/L)	135.60 $\pm$ 9.20	289.50 $\pm$ 18.60	< 0.001
Total Bilirubin (mg/dL)	0.42 $\pm$ 0.05	1.38 $\pm$ 0.15	< 0.001
Urea (mg/dL)	22.40 $\pm$ 2.80	26.10 $\pm$ 1.20	< 0.001
Creatinine (mg/dL)	0.51 $\pm$ 0.04	0.95 $\pm$ 0.03	< 0.001

4.

Discussion

The current study at the University of Kirkuk, College of Science, revealed that cefixime induced significant hepatotoxicity in adult male Swiss albino rats. The histopathologic changes such as hepatocyte degeneration, necrosis, nuclear condensation, sinusoidal dilation, and periportal lymphocytic infiltration correlate with drug-induced hepatocellular injury [17], [18].

These results are in accordance with previous reports of increased liver enzymes after therapy with cefixime and its potential to induce hepatitis and cholestatic jaundice [19], [20]. Moreover, the hepatotoxicity demonstrated in this study is consistent with that of Soliman [21], who had observed hepatorenal manifestations in albino rats with the related drug cefotaxime, as well as with that of the narrative literature review by Cano, Cifuentes, and Amariles [22], who listed hepatic toxicity related to a variety of drugs, including the cephalosporins.

The elevations of enzymes, including AST, ALT, and ALP, observed in our study are in line

with those reported previously for other structurally related cephalosporins. Chen et al. [23] described drug properties and host factors as predictors of drug-induced liver injury severity, and Peker, Cagan, and Dogan [24] reported on toxic hepatitis caused by ceftriaxone, validating the hepatotoxic potential of this class of antibiotics.

The magnitude of liver enzyme abnormalities in the current findings differed slightly from that in some earlier studies. Al Haboob [25] has described the hepatotoxicity of the third-generation cephalosporin, cefixime, with acute renal failure. Thangaraju et al. [26] similarly reported cephalosporin causing hepatic enzyme derangement. The slight discrepancy might be due to the relatively brief duration of the study, as noted by Owoade, Adetutu, and Olorunnisola [27] and Abdul, Rahim, and Saleh [28]. More recent clinical evidence confirms cephalosporin-induced hepatotoxicity: Yang et al. [29] presented a case of fulminant cholestatic drug-induced liver injury due to cephalosporin use (severely increased bilirubin and transaminases), since stopping drug therapy led

to complete recovery, whereas Sheth [30] confirmed that even fifth-generation cephalosporins may cause drug-induced liver injury, upholding the class-wide hepatotoxic potential risk. El-Sayed et al. Further insights into the mechanism of cephalosporin-induced hepatocellular injury at the cellular level were provided by [31], who reported that cefotaxime caused oxidative stress, activation of the NF- κ B pathway, and disruption of MAPK signaling in rat liver tissue—observations in agreement with the necrosis and inflammation detected by histopathology in the present study. In line with these observations, Hanafy and Zakaria [32] found that antibiotic treatment in rats led to remarkable biochemical and histopathological hepatic changes similar to those observed in this study, including hepatocyte vacuolation, lymphocytic infiltration, and elevated aminotransferases. At the population level, a comprehensive 2023 review by Ballotin et al. [33] reaffirmed evidence that antibiotics, particularly beta-lactams, are the drug class most commonly associated with DILI worldwide and that they account for the largest share of hepatotoxicity cases reported in prospective registries. Herein, a multicenter genomic and clinical study by the Drug-Induced Liver Injury Network [34] further defined cephalosporins as mainly cholestatic or mixed forms with immune features, serving as a conclusive platform on which the hepatic sequelae recapitulated by our novel experimental model may be understood.

The lack of marked alterations in serum urea and creatinine in the first 10 days indicates that renal function was not acutely compromised at this dose in the early stage of treatment.

5. Conclusion

The data presented in this article are consistent with the established literature on the association between cephalosporin-class antibiotics and hepatotoxicity. Prolonged or repeated treatment with cefixime can cause hepatocellular damage in a

dose-dependent manner, as indicated by histopathologic changes and serum biochemical abnormalities. These findings underscore the imperative of vigilant hepatic function surveillance during clinical applications of this antibiotic, particularly in patients receiving prolonged courses of treatment.

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