



Evaluation Effects of Cefepime and Ceftriaxone on Renal Function Tests in Albino Male Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The most commonly used antibiotics frequently mentioned in clinical reports of drug-induced nephrotoxicity. The study is designed to investigate the in vivo effect of cefepime and ceftriaxone on functions of kidney in wistar albino rats.

Materials and Methods: In this study, 18 male adult Wister albino rats were used. The animals were separated into three groups of six rats each. The rats in the first group were only given normal saline and served as the normal control group. While the rats in the other two groups were given cefepime at a dose of 90 mg/kg/day I.M. and ceftriaxone at a dose of 90 mg/kg/day I.M., respectively, and were treated as follows (for 10 days).

Results: By the end of the treatment period, urine was collected by metabolic cage for total protein, pH, and specific gravity measurements. Renal function parameters were measured using blood

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samples. Both kidneys were removed for histopathological examination after the animals were sacrificed. The data showed no significant differences in (creatinine, BUN, uric acid, and total protein levels) between the normal, cefepime, and ceftriaxone groups, nor in urine analysis data. Histopathological images revealed an important feature of injurious lesions that are more prominent with cefepime, as well as mild inflammation to acute interstitial nephritis in ceftriaxone specimens.

Conclusions: It can be concluded that cefepime has a more negative effect on renal function than ceftriaxone and that it should be used in critically ill patients.

Keywords: Cefepime; ceftriaxone; rats; renal function; creatinine; total protein levels.

1. INTRODUCTION

Kidneys are matched retroperitoneal structures that are typically located between the transverse and transverse peritoneum. T12-L3 vertebral procedures, The left kidney is slightly superior to the right. The upper poles are typically oriented more medially and posteriorly than lower poles. Because the liver is located above the kidney on the right side, and the left kidney is slightly higher than the right one [1]. The kidneys are the most vigilant organs of the urinary system. The kidneys regulate blood properties while also excreting wastes and foreign substances in urine such as Ionic composition is controlled by varying the concentrations of several ions, including sodium (Na⁺), potassium (K⁺), calcium (Ca²⁺), chloride (Cl⁻), and phosphate (HPO₄²⁻). Excreting hydrogen ions (H⁺) and maintaining bicarbonate ions (HCO₃⁻) regulates PH. In addition to controlling Osmolarity, it also controls the loss of water and solutes in the urine [2]. A failure of The kidneys remove metabolic waste from the blood, regulate fluid levels and electrolytes, and keep extracellular fluid pH balanced. Kidney failure is classified as an acute or chronic condition [3].

Cefepime is a semi-synthetic, broad-spectrum, fourth-generation cephalosporin antibiotic for parenteral use that has proven effective in the treatment of severe and multi-drug resistant infections. It is effective against staphylococcal and pseudo-monase infections and has excellent gram-positive and gram-negative coverage. It also inhibits the production of -lactamase by organisms.

A large dose of cefepime can be used to identify the mechanism of kidney tubular and glomerular changes, which aggregated in concentrations sufficient to have a direct cytotoxic effect on epithelial cells [4]. Ceftriaxone is an anion that binds at high blood concentrations, calcium ions combine To produce insoluble complexes that

precipitate in the bile system. This side effect, also known as biliary pseudolithiasis or reversible cholelithiasis, affects 25-45% of ceftriaxone patients [5]. Ceftriaxone-In ceftriaxone-treated patients, Calcium precipitates in the urinary tract have been observed, which can be identified as sonographic abnormalities [6-8]. Asymptomatic patients may develop urolithiasis or ureteral obstruction, as well as post-renal acute renal failure symptoms. It appears to be reversible if therapy is discontinued and appropriate management is implemented; maintain adequate hydration. Patients with urolithiasis, oliguria, or renal failure, along with sonographic findings, should be evaluated, and therapy should be discontinued [9].

Ceftriaxone has been linked to biliary pseudolithiasis [10] and nephrolithiasis in several studies [11].

However, ceftriaxone-associated PARF 46 has been reported infrequently. The kidneys eliminate around 33-67% of this agent, with the remainder being eliminated through the biliary system. During ceftriaxone treatment, urine crystals that adhere to renal tubular cells have been observed, with the potential to cause acute renal failure; however, only a few studies have reported this condition [12]. Stone formation in the renal collecting system is thought to follow the same mechanism, An urinary tract infection and obstruction, a positive family history, Ceftriaxone at high doses (over 2g/day), rapid administration of the drug, dehydration in conjunction with nephrotoxic drug administration, and metabolic disorders such as hypercalciuria are all risk factors for ceftriaxone-induced nephrolithiasis [13] The study aims to investigate the in vivo effect of cefepime and Ceftriaxone on function of kidney in albino rats.

2. METHODOLOGY

Eighteen apparently healthy albino rats weighed (150-310 gm.). That were kept in standard

temperature conditions (22 ± 3 °C), relative humidity ($55 \pm 5\%$), and light (12h light –dark cycle) before and during the study where included in the experiment. They were fed with standard pellet diet (purchased from local market in Karbala city) and unlimited access to water. All experimental animals were obtained from animal house, College of pharmacy / Karbala University. The animals were separated into three groups with six animals for each one as the following:

Group 1: control group; Rats were fed and watered on a regular schedule. *ad libitum* for 10 consecutive days.

Group 2: Cefepime group; injected with (90 mg/kg/day) I.M. for 10 consecutive days.

Group 3: Ceftriaxone group; injected with (90 mg/kg/day) I.M. for 10 consecutive days.

2.1 Collection and Analysis of Urine

After 24 hours, all rats were placed in Individual metabolic cages were used to collect urine samples the 10th day of administration for each group. Urine volume was determined. The diagnostic kit estimated various urine parameters such as glucose, protein, bilirubin, PH, specific gravity, Urobilinogen ketone, nitrite, and leukocyte.

2.2 Blood Collection and Serum Analysis

At the end of the experiment, all groups were subjected to blood collection under ketamine and xylazine hydrochloride anesthesia. The blood was obtained through a heart puncture. Blood samples were collected in dry test tubes and left to coagulate. for 30 minutes at room temperature. The serum from blood samples was separated and analyzed by centrifugation at 5000 RPM for 5 minutes for creatinine, total protein, blood urea nitrogen, and uric acid. The rats were slaughtered, and kidney sections were prepared for histological examination.

2.3 Histopathology of Rats Kidney

Each To remove both kidneys, the animal's abdomen was cut open. Extraneous tissue was removed from isolated kidneys, which were then rinsed in tap water, and histopathology was performed. Isolated left kidneys were fixed in series grades of ethyl alcohol (50-100%)

embedded in paraffin blocks and stained with hematoxylin and eosin (H&E stain). A light microscope was used to examine the sections.

2.4 Statistical Analysis

The statistical analysis was performed using statistical package for social sciences SPSS, version 19). Least significant difference – LSD test (ANOVA analysis) was used to compare between means of groups in this study, data were expressed as mean \pm SEM, P value ($P \leq 0.05$) was considered to be significant. one –way analysis of variance (ANOVA) was used to compare between study groups. Chi square is used to analyze the C-reactive protein values [14].

3. RESULTS

3.1 Blood Analysis

According to blood analysis, Table 1 displays the mean values \pm standard errors of all of parameters. Cefepime and ceftriaxone creatinine values are (0.35 ± 0.050 mg / dL) and (0.3 ± 0.031 mg / dL) respectively, both values are higher than control group (0.24 ± 0.024 mg / dL) although there is no statistical difference between them. The results revealed that ceftriaxone caused an increased serum uric acid level with value of (1.24 ± 0.196 mg / dL) as compared with control group (1.08 ± 0.096 mg / dL). The results also revealed that Cefepime caused an increased serum uric acid level with value of 1.56 ± 0.147 mg / dL as compared with control group. The results demonstrated that the increase in serum uric acid level caused by Cefepime with value of 1.56 ± 0.147 mg / dL is relatively higher as compared with that of Ceftriaxone 1.24 ± 0.196 mg / dL. Blood urea nitrogen value of cefepime (35.4 ± 4.366 mg / dL) and ceftriaxone (31 ± 3.628 mg / dL) groups have higher values comparing with control group (24 ± 2.702 mg / dL). However, the blood urea nitrogen value of cefepime is higher than ceftriaxone. The results revealed that ceftriaxone caused a decreased serum total protein level with value of 5.58 ± 0.625 mg / dL as compared with control group (6.70 ± 0.230 mg / dL). The results also revealed that Cefepime caused a decreased serum total protein level with value of 6.16 ± 0.483 mg / dL as compared with control group. The results demonstrated that the decrease in serum total protein level caused by Ceftriaxone with value of (5.58 ± 0.625 mg / dL) is relatively higher as compared with that of Cefepime (6.16 ± 0.483 mg / dL). The data

presented in Table 1 and in Figs. 1,2,3 and 4 indicated no significant differences in (creatinine, BUN, uric acid and total protein levels) between normal, cefepime and ceftriaxone. The data

presented in Table 2 and in Figs. 5,6 and 7 indicated no significant differences in (protein, PH and Specific gravity levels) between normal, cefepime and ceftriaxone.

Table 1. Effects of multiple treatments on blood parameters in experimentally-induced nephrotoxicity

Groups / Parameters	G1 Control	G2 cefepime	G3 Ceftriaxone
Creatinine (mg / dL)	0.24 ± 0.024	0.35 ± 0.050	0.3 ± 0.031
Uric acid (mg / dL)	1.08 ± 0.096	1.56 ± 0.147	1.24 ± 0.196
BUN (mg / dL)	24 ± 2.702	35.4 ± 4.366	31.4 ± 3.628
T.P (mg / dL)	6.7 ± 0.230	6.16 ± 0.483	5.58 ± 0.625

Values are expressed as mean ± SEM. Results between the study groups were considered non-significantly different

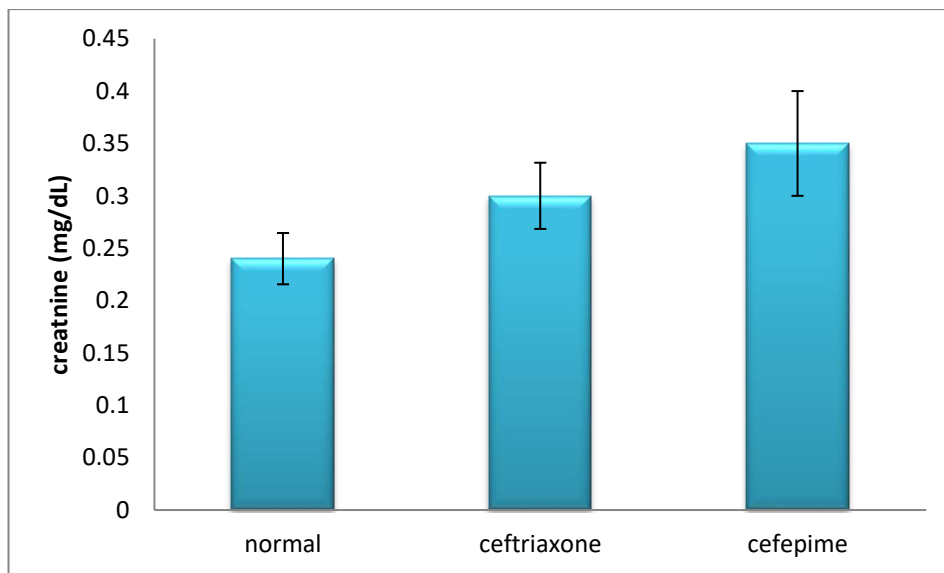


Fig. 1. Effects of different drug on serum creatinine measured in unit (mg /dL)

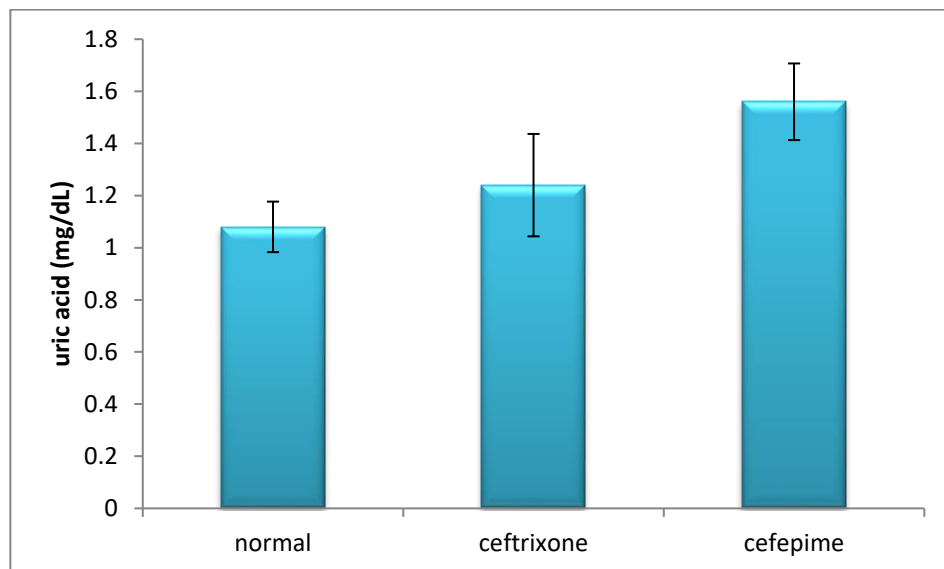


Fig. 2. Effects of different drug on serum uric acid measured in unit (mg /dL)

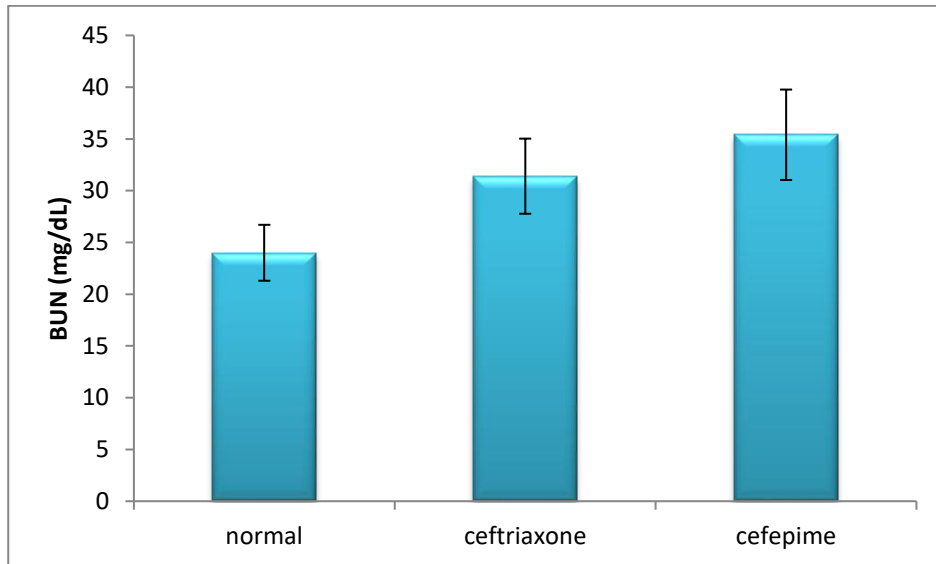


Fig. 3. Effects of different drug on blood urea nitrogen measured in unit (mg /dL)

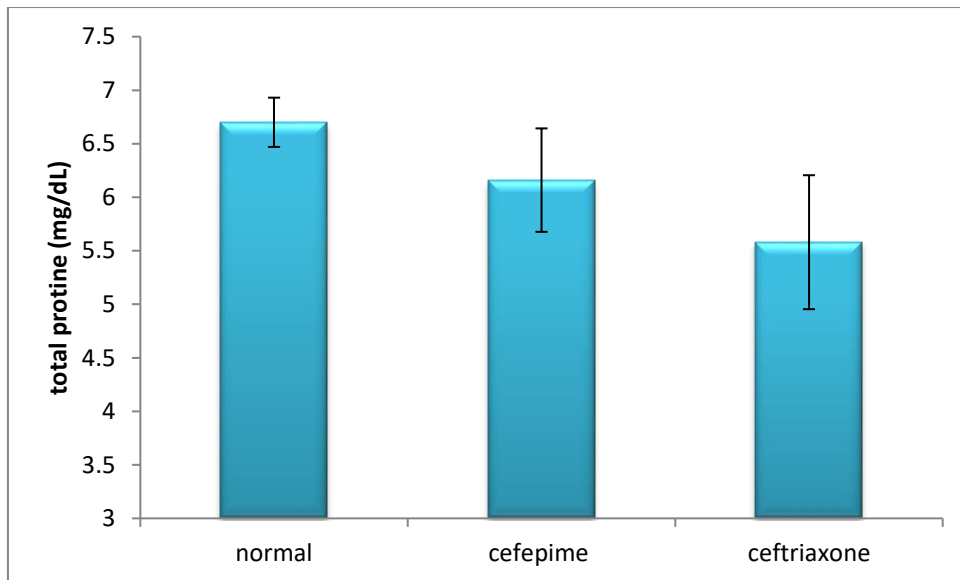


Fig. 4. Effects of different drug on serum total protein measured in unit (mg /dL)

The data presented in Table 2 and in Figs. 5,6,7 and 8 indicated no significant differences in (protein, PH and Specific gravity levels) between normal, cefepime and ceftriaxone.

Table 2. Effects of multiple treatments on urine parameters in experimentally-induced nephrotoxicity

Groups / parameters	G1 control	G2 cefepime	G3 Ceftriaxone
protein	0.84 ± 0.54	1.66 ± 0.56	2.1 ± 0.90
PH	8 ± 0.31	8.8 ± 0.20	9 ± 0.0
S.G	1.001 ± 0.0010	1.002 ± 0.0012	1.003 ± 0.0033

Values are expressed as mean ± SEM. Results between the study groups were considered non-significantly different

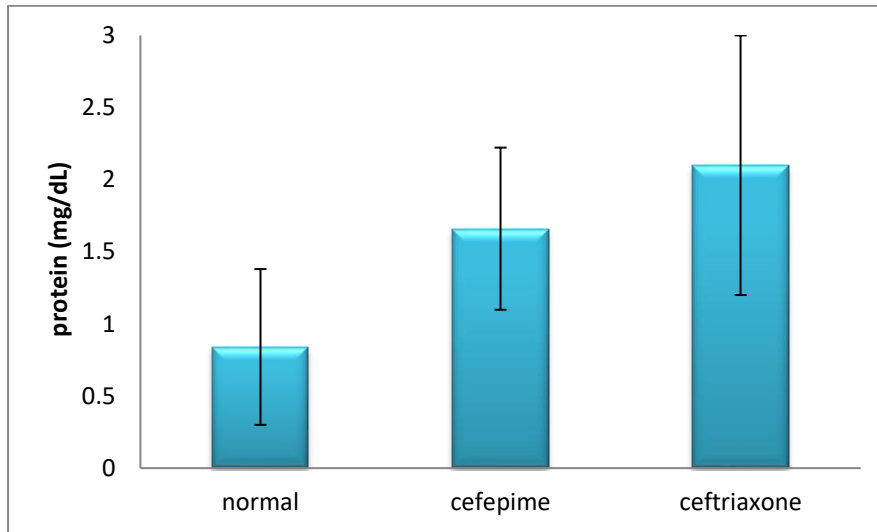


Fig. 5. Effects of different drug on urine protein measured in unit (mg /dL)

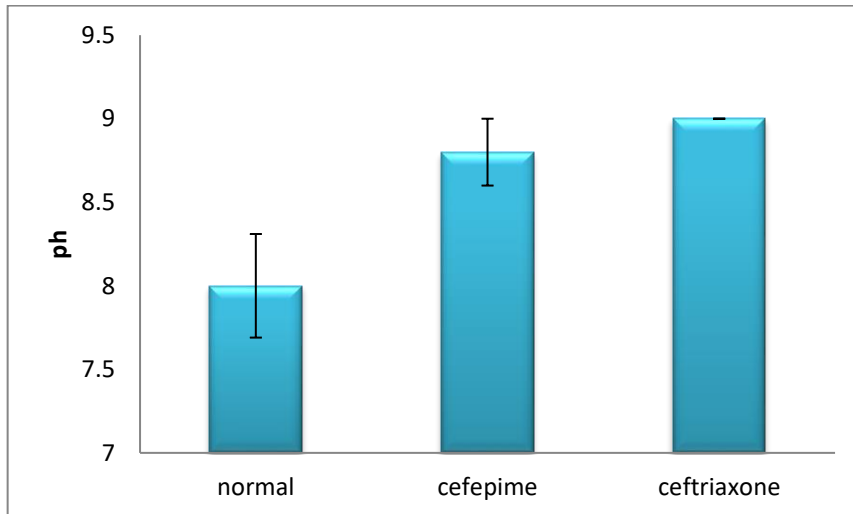


Fig. 6. effects of different drug on urine PH

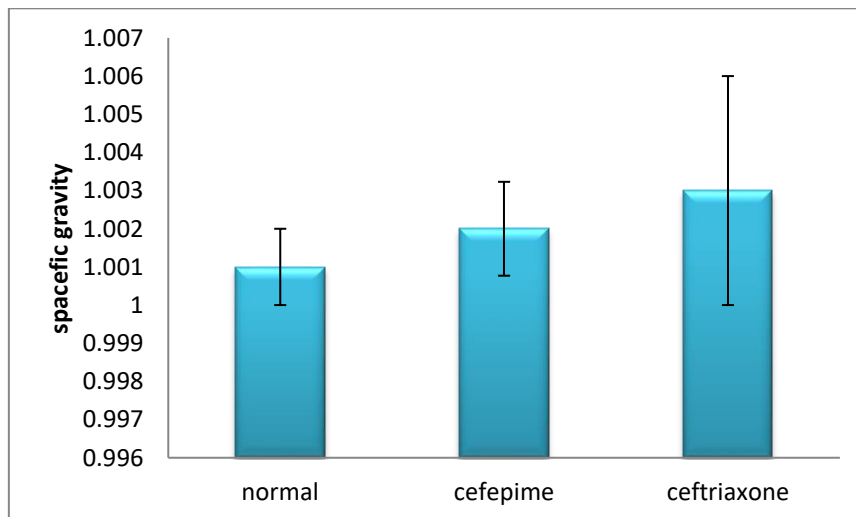


Fig. 7. Effects of different drug on urine specific gravity

3.2 Histopathological Studies

The renal glomeruli have normal structure, with the proximal lining being Typical thick cubic epithelium and distal lining being relatively low simple cubic epithelium. The glomeruli are organized, and there is a flat The epithelium lining the glomerular capsule has a distinct capsular space.as in Fig. 8. According to the histopathology of cefepime at 90mg/kg for 10 days, we discovered that important features such as injurious features are more prominent. There is no inflammation. Ballooning is an activity

Cytoplasmic vacuolation and focal tubular necrosis (especially in the periphery), as in Fig. 9. While, Ceftriaxone at a dose of 90 mg/kg for ten days, according to histopathology. The specimen revealed significant features such as mild inflammation and acute interstitial nephritis. Peripheral tubular necrosis with focal tubular necrosis. Before necrosis, there are ballooning degenerative changes. on the outskirts With prominent degenerative changes, there is subcapsular focal necrosis tubular, as in Fig. 10.

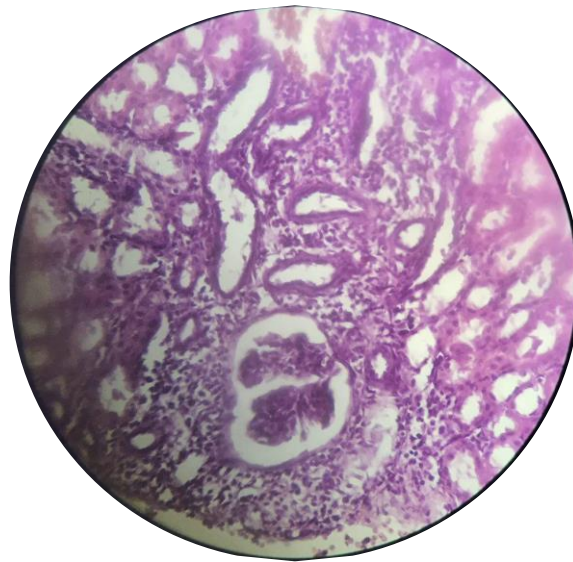


Fig. 8. Transverse section in kidney region of Control group 40X

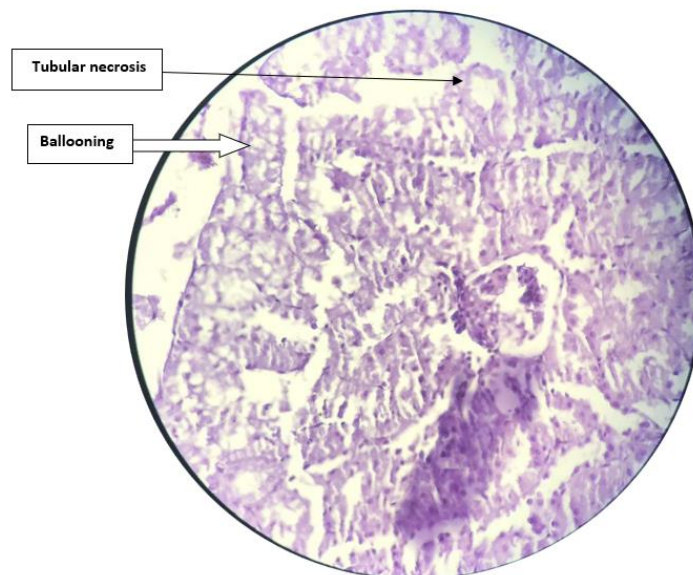


Fig. 9. Transverse section in kidney region of Cefepime group 40x

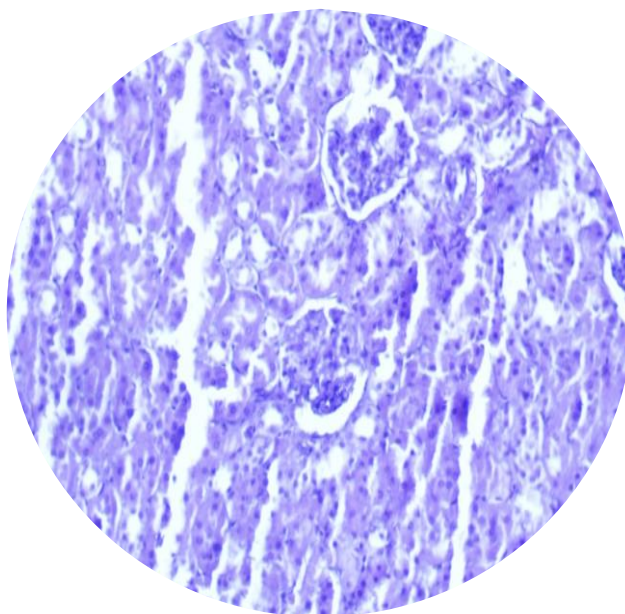


Fig. 10. Transverse section in kidney region of Ceftriaxone group 40x

4. DISCUSSION

The kidney maintains the inner condition of body cells primarily glomerular filtration and selective reabsorption, and tubular secretion, as well as hydrogen ion exchange and ammonia reduction for base conservation. When plasma concentrations The tubules almost completely reabsorbed Urine, creatinine, protein, electrolytes, and glucose are examples of threshold substances, However, they appear in the urine when their plasma concentration exceeds a certain threshold and/or a defect in the renal tubules as a result of nephrotoxicity. As demonstrated in the current study, this factor is a good predictor of the relationship between their serum and urine concentrations. Despite their broad spectrum and curative efficacy against drug-resistant pathogens, as well as their lack of nephrotoxicity, impairments in renal function were observed during clinical treatment with the two most commonly used 3rd and 4th generation cephalosporins, ceftriaxone and cefepime, respectively. The current study sought to elucidate the precise effects of these factors on renal structure and function. Ceftriaxone and cefepime caused significant damage to renal structures in the current study, and cefepime with tubular damage may be more renal cytotoxic than is excreted unchanged in the urine while 11-65% is excreted unchanged in the bile [15]. Using a high dose of cefepime may be linked to the mechanism of glomerular and tubular changes in the kidney. which accumulated in

epithelial cells in sufficient amounts to cause direct cytotoxicity [16].

Thus, acute I.M. doses of cefepime 90mg/kg cause dose-related proximal tubular necrosis, affecting the S2 segment of the tubule only, as revealed by histopathological analysis, Cefepime is an organic anion with a cationic (N-methylpyrrolidin) group. Cefepime is actively transported from the blood into proximal tubular cells by organic anion transporters (OATs), with the majority of cephalosporins transporting by OAT1 and OAT-3. This requires both a hydrophobic and an anionic group, is expressed specifically in the kidney, and exports -ketoglutarate in the opposite direction. In contrast, the anionic transport system for uptake into the tubular cell is more active, resulting in active accumulation [17].

Because cefepime is a zwitterion, the movement of cefepime out of the tubular cell into the lumen appears to be limited, and thus the intracellular concentration remains high. This accumulation of cefepime is due to the cationic group reducing efflux via OATs. However, nephrotoxicity is more than just this accumulation; the toxicity mechanism is not fully understood, but a number of hypotheses have been propose [18].

To begin, the hypothesis discusses Metabolic activation to reactive metabolites via cytochromes P-450. As some inhibitors of cytochromes P-450 reduce toxicity and some

inducers of monooxygenases increase toxicity, a reactive intermediate has been proposed. Other inducers and inhibitors, on the other hand, have no effect on toxicity, and these treatments have an effect on the renal concentration of cephaloridine in a way that corresponds to the effect on toxicity. Due to the instability of the β -lactam ring, a chemical rearrangement to produce a reactive intermediate is also possible. Second, the hypothesis discusses lipid peroxidation/oxidative stress. Lipid peroxides cause toxicity via two distinct mechanisms. Because Lipids are responsible for cellular membrane integrity and extensive peroxidation Lipids affect the assembly, composition, structure, and dynamics of lipid membranes. Lipid peroxides, as highly reactive compounds, can generate more ROS or degrade into reactive compounds that can crosslink DNA and proteins. Glutathione (GSH), which is responsible for peroxide elimination, appears to be depleted by oxidation rather than conjugation, and prior GSH depletion increases toxicity. Because NADPH is depleted, Glutathione disulfide (GSSG) cannot be reduced back to GSH. Alternatively, they can degrade into reactive compounds capable of crosslinking DNA and proteins. Glutathione (GSH), which is in charge of peroxide elimination, It appears to be depleted through oxidation rather than conjugation, and prior GSH depletion increases toxicity. Because NADPH is depleted, Glutathione disulfide (GSSG) cannot be reduced back to GSH.

Third, the hypothesis discusses mitochondrial damage and intracellular respiratory processes. The other mechanism is acylation of target proteins, which causes respiratory arrest in cells by deactivating mitochondrial anionic substrate carriers.

On the third day of cefepime administration, The total amount of urine produced daily increased significantly. This diuretic-like effect could be attributed to increased renal blood flow as a result of vasodilation of the renal arteries and histopathologically demonstrated failure of tubular resorption of water as a result of Renal tubular damage caused by degenerative changes in the form of cloudy swelling [19].

The majority of the observed renal damage occurred by 90mg/kg ceftriaxone administered I.M. was mild interstitial nephritis caused by hypersensitivity, with the related mechanism being by causing inflammatory changes in the interstitium. ceftriaxone is thought to bind to

kidney antigens or act as antigens that are then deposited in the interstitium, inducing an immune response [20].

When activated by antigens or damage signals, normally quiescent DCs endocytose, The incriminated antigenic components are processed and expressed as Peptides on the surface MHC-II molecules. Following activation, and express the antigenic components involved as peptides on their MHC II surface molecules. After activation, which are then activated and move to The antigenic source or the site of injury emits a danger signal [21]. Furthermore, The renal interstitium contains dormant macrophages and fibroblasts, which, when activated, play an important role in the initial inflammatory response, which is augmented by specific neutrophils, including eosinophils. This initial phase of antigen presentation T cell activation is followed by a period of immune response integration [22], The effector phase that follows is Humoral factors released by infiltrating and residual renal cells act as mediators. Bidirectional communication between enlisted invading inflammatory cells and renal parenchyma, either via direct contact or via local soluble cytokines, eventually regulates The progression and severity of renal contribution [23].

The growing evidence that toxic and Postischemic kidney disease are largely driven by the associated inflammatory response prompted the question of whether inflammation was also the driving factor in crystal-induced kidney disease [24].

CaOx crystals have recently been shown to activate the NLRP3 inflammasome, which leads to progressive renal failure [25] Other studies found that cystine crystals, like CaOx, are endogenous inflammasome-activating stimuli [26] These findings on the molecular mechanisms of crystal-induced inflammation support a new perspective on crystal-related kidney injury. The nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3) is the most extensively studied [27], NLRP3 activates caspase-1 and pro inflammatory cytokines like IL-1 β and IL-18 by assembling a multiprotein complex called the inflammasome, which includes a caspase recruitment domain (Asc). The NLRP3 inflammasome is the most extensively studied of all inflammasomes [28] Numerous studies have found that oxidative stress can play an important role in the formation

of kidney stones [29] urolithiasis, acute kidney injury was linked to ROS production and reduced antioxidant activity [30].

Aside from the possibility of Mesenchymal transition, activation of tubular epithelial cells and vascular endothelial cells regulates Their expression of various cytokines that prolong macrophage and fibroblast function [31] As a result, macrophages secrete collagenases, elastases, and reactive oxygen species exacerbates the damage initiated by lymphocytes. The activation of invading cells and their collaborations with renal parenchymal cells either suppresses or intensifies the effector phase, as in mild types of AIN. The results contradicted those reported by those who recorded that, Cefitofur treated rodents; the microscopical examination of the parenchymatous organs of ceftiofur sodium treated rodents revealed no histopathological changes in the kidneys, which were normal like the control group [32].

In present study show kidney profile functions such as serum creatinine, uric acid, BUN, total protein, the results revealed that the effect of cefepime on these parameters was relatively higher than that of ceftriaxone .as mention in Table 1. Recent studies proposed that few transporters, for example, OCT2, OCT3, OAT2, MATE1, and M ATE2-K, are likely associated with the development of creatinine from the blood into the kidney proximal tubular cells and then into the urine. In this way, there are numerous purposes of connection that can result in variations in serum creatinine [33].

Organic anion transporter in the kidney. Male mice exhibited higher levels of 1 mRNA expression than female mice, indicating a gender difference in creatinine secretion. As a result of the organic anion transport system, creatinine excretion is significantly influenced by secretory mechanisms. Despite the fact that this characteristic complicates estimating endogenous creatinine filtration in mice [34.]

Because A decrease in renal secretion and clearance may increase systemic drug exposure and cause clinically significant changes the drugs' overall pharmacokinetics, The most common type of renal DDI is competitive inhibition of proximal tubular secretion. The basolateral membrane of proximal tubular cells, OAT1 and OAT3 are expressed, putting them in the path of drug-related nephrotoxicity [35] these

result was consistent with Cefotaxime Creatinine concentrations increased significantly at doses of 90 and 180 mg/kg b. wt twice daily for 7 days in treated rats' serum [36] Regarding serum uric acid parameter, OAT1 and OAT3 are dicarboxylate-anion exchangers located on the basolateral membrane of the proximal tubule that transport urate in vitro , Individual excision in mice results in reduced urate excretion [37]

This result was consistent with the fact that Cefmetaline caused a significant increase in serum urea while decreasing urine, as well as a reduction in urea clearance. In rabbits, Following oral administration, Cefmetaline hydrochloride caused a slight increase in urea nitrogen [38] Protein uria and a decrease in serum protein levels were caused by cefepime and ceftriaxone. This could be attributed to the current study's histopathological evidence of progressive cellular and tubular dysfunction. Urinary protein was detected, which was consistent with the intravenous dose of Cefepime [18,39-41].

5. CONCLUSION

Cefepime has a more negative effect on renal function than ceftriaxone, so Cefpirome should be used with caution in clinical settings. The data showed no significant differences in (creatinine, BUN, uric acid, and total protein levels) between the normal, cefepime, and ceftriaxone groups, nor in urine analysis data. Histopathological images revealed an important feature of injurious lesions that are more prominent with cefepime, as well as mild inflammation to acute interstitial nephritis in ceftriaxone specimens.

6. RECOMMENDATIONS

Administration of cefepime is preferred on ceftriaxone according to nephrolithiasis. Further studies are recommended on biliary system. Transporter system is an important point in pharmacogenicity regarding to variation in renal organic anion transporter mRNA expression between male and female. ADR profile should be studied to reduced the risk of these antibiotics. Future exvivo studies to determine the specific renal organic anion transporter associated with effects of cefepime and ceftriaxone that show on kidney profile . Other parameters can be tesred like glucose mcalcium ,coagulation profile . As these antibiotics are B lactum group other ADRS should also be looked for ,like rashes , itching , allergic reaction , Blood pressure ,Respiratory rate . anaphylactic reaction

ETHICAL APPROVAL

The study's methodology was authorized by the Scientific and Ethical Committee of the College of Pharmacy, University of Kerbala, and the approval reference number for this research is 2023An.15 on March 2023.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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