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Original Article

HEPATO-RENAL EFFECTS OF CEFOTAXIME IN ALBINO RATS

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ABSTRACT

Objective: The present study was carried out to evaluate the adverse effects of cefotaxime at two different doses on some biochemical parameters in albino rats. Histopathological changes in liver and kidney induced by cefotaxime were also investigated.

Methods: Thirty rats were randomly divided into 3 equal groups; the first group was received distilled water and kept as a control. The second group was received cefotaxime (90 mg/kg b. wt), while the third group was received cefotaxime (180 mg/kg b. wt). Cefotaxime at different doses were injected intramuscularly (IM) twice daily at 12 h intervals for 7 consecutive days.

Results: The obtained results showed that, cefotaxime produced significant elevation in creatinine, urea, sodium, potassium, calcium concentrations and decrease concentrations of both glucose and total protein in the serum of treated rats. Also, cefotaxime caused an elevation in some biochemical parameters as (Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), total bilirubin, Cholesterol, Triglycerides and Low density lipoprotein-cholesterol (LDL-chol) and decrease in albumin, High density lipoprotein-cholesterol (HDL-chol) concentrations in serum of treated rats. Histopathological alterations were observed in liver and kidney.

Conclusions: It could be concluded that administration of cefotaxime induced some adverse effects on biochemical parameters as well as histopathological changes in liver and kidney.

Keywords: Cefotaxime, Biochemical, Hepatotoxicity, Nephrotoxicity, Rats.

INTRODUCTION

Cefotaxime is a third-generation cephalosporin antibacterial drug commonly used to treat upper respiratory tract infections and bacterial meningitis. Approximately 40%-60% of cefotaxime is excreted unchanged in the urine [1, 2]. Cefotaxime has an excellent bactericidal activity against a wide variety of Gram-negative and most of the Gram-positive micro-organisms, particularly β-lactamase producing strains [3].

It has a very important place in antimicrobial therapy because of its relatively expanded spectrum of antimicrobial activity, greater resistance to β-lactamase [4]. Cefotaxime belongs to class 3 of the Biopharmaceutics Drug Disposition Classification System (BDDCS), which are characterized by high water solubility, poor passive permeability, and poor metabolism [5].

Liver plays a central role in metabolism of drug and xenobiotics, protein synthesis and in maintaining biologic equilibrium, of organisms. Due to these important roles, liver enzymes are used as markers in the assessment of drug safety or toxicity [6]. The transaminases are involved in intermediary metabolism and are thus present in high concentration in the liver; they are rapidly released into the serum in cases of acute destruction of tissues as in myocardial infarction or hepatocellular necrosis [7].

Kidney is an important organ having not only excretory function but also other functions such as production of the substances that activates a living body, enzymatic reaction, immunization. The kidney is often involved in the development, maintenance and counter regulation of complex electrolyte disturbances [8].

Since antibiotics are used for treatment of infections that may cause changes in some biochemical parameters, the physician or veterinarian must take in consideration the changes caused by these drugs to avoid incorrect diagnosis. I hypothesized that chronic administration of cefotaxime in high doses may severely damage the liver and kidneys with significant alterations in the parameters. The main purpose of this study is to investigate and provide an overview of the biochemical changes in serum of treated rats and histopathological changes of the liver and kidney following intramuscular administration of cefotaxime as its misuse or over dosage administration may cause a lot of adverse effects in human and veterinary medicine.

MATERIALS AND METHODS

Drug

Cefotaxime is used for IM or IV injection in strengths equivalent to 250 mg, 500 mg and 1gof cefotaxime sodium. It is produced by Egyptian International Pharmaceutical Industry Company (EIPICO) with a commercial name Cefotax®.

Animals

Thirty adult male waster albino rats (150-180 g body weight) were obtained from the Animal House, Faculty of Veterinary Medicine, Cairo University, Egypt. They were maintained on the standard pellet diet and tap water ad libitum and were kept in plastic cages under a 12 hr light/dark cycle and room temperature 22-24 °C. Rats were acclimatized to the environment for two weeks prior to experimental use. The protocol for the albino rat study was approved by the Institutional Animal Care and Use Committee (IACUC) of Cairo University (108-2015).

Experimental design

Rats were randomly divided into three groups. Group 1: injected with 1 ml of distilled water and served as control; Group 2: IM injected with cefotaxime (90 mg/kg b. wt.) and Group 3: IM injected with cefotaxime (180 mg/kg b. wt.). Cefotaxime was injected by IM route twice daily at 12 h intervals for 7 consecutive days. Blood collection was performed 24 h after the end of the7th d by retro-orbital sinus puncture from each anesthetized rats with ether. The collected blood samples were allowed to clot and serum samples were obtained by centrifugation at 3000 rpm for 10 min, the serum was separated immediately and stored at-20 °C until determination of biochemical parameters.

Biochemical analysis

Creatinine[9], urea[10], glucose, total protein[11], AST, ALT [12], albumin[9], total bilirubin [13]were determined in serum using kits from Diamond Diagnostic Company, Egypt. Sodium, potassium [14]

and calcium [15] were determined using kits from Spin react Company, Spain. Cholesterol [16], Triglycerides [17], HDL-cholesterol and LDL-cholesterol [18] were determined using kits from Vitro Scient Company, Egypt. All biochemical analysis was measured by using spectrophotometer.

Histopathological studies

Following complete necropsy of the experimental male rats, small fresh specimens from liver and kidney were collected and rapidlyfixedin 10 % formalin solution for at least 24 h. The specimens were processed through the conventional paraffin embedding technique (dehydration in ascending grades of ethylalcohol, clearing in different changes of xylene and embedding in different changes of melted paraffin wax at 60 °C). Paraffin blocks were cut by microtome into 5 microns. Thick sections which were stained with Haematoxylin and Eosin (H. E.) according to the method described in [19].

Statistical analysis

The data were expressed as (mean±SE) and analyzed using SPSS (16) Software (SPSS Inc., Chicago, USA) and differences between the averages were examined by Duncan's multiple range test. Mean values within a row with different superscript letters is significantly different ($P \leq 0.05$).

RESULTS

Serum biochemical parameters

The present study was designed to evaluate the effect of cefotaxime on the liver and kidney functions. Cefotaxime administration at two doses (90 and 180 mg/kg b. wt.) led to significant ₽0.05 increase in serum liver function marker enzymes (AST and ALT), total cholesterol, total bilirubin, triglyceride as compared with the control group. Renal products (urea and creatinine), sodium, potassium, calcium ions was significantly increased and the total serum protein showed a significant decrease as compared with the control group with the marked decrease of serum glucose level (table 1 and 2).

Histopathological study

Histopathological effects of cefotaxime on liver and kidneys were shown in fig. 1. The liver of the tested groups showed disturbed architecture with vacuolar degeneration of the hepatocytes. Main inflammatory cells were lymphocyte and plasma cells with expanded portal area and peri-vascular heamorrhages. The kidney of the tested groups showed inter-tubular hemorrhage with necrotic cellular debris in lumen of some renal tubules and intracellular inflammatory cellular infiltration, mainly mononuclear cells.

Table 1: Serum AST, ALT, bilirubin, albumin, cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol levels in rats 7 d after treatment with cefotaxime (90 and180 mg/kg b. wt. Twice daily) as compared to control group

Parameters	Control	Group 1 Cefotaxime (90 mg/kg b. wt. twice daily)	Group 2 Cefotaxime (180 mg/kg b. wt. twice daily)
AST (U/l)	49.27±1.92^{c}	68.07±2.01^{b}	77.97±1.87^{a}
ALT (U/l)	35.46±1.75^{c}	46.71±1.97^{ab}	47.05±3.09^{ab}
T. bilirubin (mg/dl)	0.56±0.04^{c}	0.74±0.05^{b}	0.86±0.07^{a}
Albumin (g/dl)	4.19±0.18^{a}	3.06±0.12^{bc}	2.99±0.11^{bc}
Cholesterol (mg/dl)	96.31±2.13^{c}	129.16±2.15^{b}	142.71±3.01^{a}
Triglycerides (mg/dl)	68.32±2.68^{c}	77.36±2.13^{b}	81.96±3.17^{a}
HDL-Cholesterol (mg/dl)	54.61±2.08^{a}	41.56±1.89^{bc}	42.97±1.91^{bc}
LDL-Cholesterol (mg/dl)	33.15±2.39^{c}	51.96±2.51^{b}	54.02±2.97^{a}

Note: Data are expressed as mean±SE, Values with different letters in the same row are significantly different at ₽0.05 (ANOVA with Duncan's multiple range test).

Table 2: Serum creatinine, urea, sodium, potassium, calcium, glucose and total protein levels in rats 7 d after treatment with cefotaxime (90 and 180 mg/kg b. wt. Twice daily) as compared to control group

Parameters	Control	Group 1 Cefotaxime (90 mg/kg b. wt. twice daily)	Group 2 Cefotaxime (180 mg/kg b. wt. twice daily)
Creatinine (mg/dl)	1.08±0.03^{bc}	1.12±0.03^{bc}	1.39±0.04^{a}
Urea (mg/dl)	15.09±0.78^{c}	18.36±0.82^{b}	23.13±0.97^{a}
Sodium (mmol/l)	138.31±2.97^{c}	156.96±3.11^{ab}	162.02±3.24^{ab}
Potassium (mmol/l)	4.87±0.09^{c}	5.59±0.08^{ab}	5.63±0.07^{ab}
Calcium (mg/dl)	12.91±0.39^{c}	15.07±0.40^{b}	17.36±0.38^{a}
Glucose (mg/dl)	286.05±8.13^{a}	253.19±7.31^{b}	133.72±7.05^{c}
T. protein (g/dl)	6.05±0.23^{a}	5.13±0.21^{bc}	5.09±0.25^{bc}

Note: Data are expressed as mean±SE, Values with different letters in the same row are significantly different at ₽0.05 (ANOVA with Duncan's multiple range test).

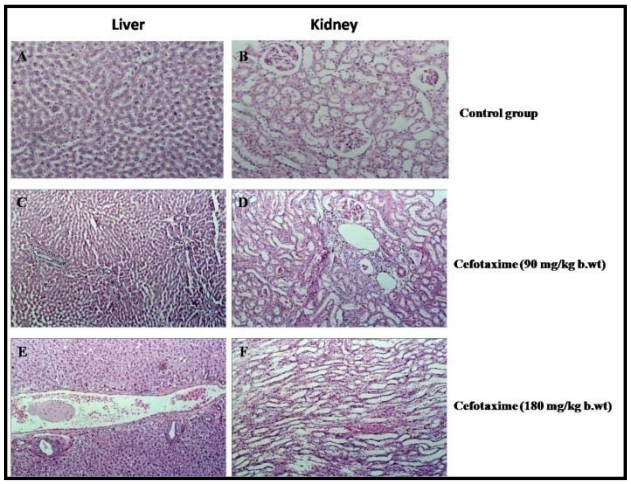

Fig. 1: Photomicrographs of Hematoxylin–Eosin staining of hepatic and renal sections of control and experimental rats. Hepatic and renal tissue sections were showen at 200× magnification

A) Liver of rat injected with distilled water showing normal hepatic structure.

B) Kidney of rat injected with distilled water showing normal renal structure.

C) Liver of rat injected with cefotaxime (90 mg/kg b. wt. Twice daily for 7 d) showing peri-vascular hemorrhage and peri-ductal inflammatory cells.

D) Kidney of rat injected with cefotaxime (90 mg/kg b. wt. Twice daily for 7 d) showing intracellular inflammatory cellular infiltration, mainly mononuclear cells.

E) Liver of rat injected with cefotaxime (180 mg/kg b. wt. twice daily for 7 d) showing congestion of portal blood vessels with fibrin emboli.

F) Kidney of rat injected with cefotaxime (180 mg/kg b. wt. twice daily for 7 d) showing inter-tubular hemorrhage with necrotic cellular debris in lumen of some renal tubules.

DISCUSSION

The biochemical indices evaluated in this study are useful parameters to indicate impairment in functional capacities of the organs. Cefotaxime produced significant increase in both liver enzymes (AST and ALT) concentrations in the serum of treated groups than those recorded in the control group. Similar results were observed by [20] who found that, ceftriaxone therapy associated with elevated liver enzymes in rats. On the other hand, these results were inconsistent with those obtained after SC injection of cefazolin to male rats, which lead to significantly decreased alanine aminotransferase and aspartate aminotransferase activities in the serum of treated rats [21]. Cefotaxime produced asignificant increase in total bilirubin and asignificant decrease in albumin concentrations in the serum of treated groups. The obtained results were similar to those obtained by [22] who suggested that ceftriaxone which displaced bilirubin from albumin and increased erythrocyte-bound bilirubin and unbound bilirubin should be used with caution in high-risk jaundiced newborns. Cefotaxime produced significant elevation in total cholesterol, triglycerides, low density lipoprotein-cholesterol and significant decrease in high density lipoprotein-cholesterol concentrations in serum of treated groups than recorded in the control group. Similar results were obtained by [20] after IM injection of ceftriaxone to rats. These obtained biochemical changes might be attributed to damage to hepatocytes. The histopathological finding in the liver of cefotaxime treated rats obtained in this study was consistent with those recorded following cefdinir administration which produces a mixed inflammatory infiltrate in the portal area with neutrophils, plasma cells, lymphocytes and occasional eosinophils. Moreover, liver biopsy demonstrated mixed inflammatory infiltrate in the lobule with mild central venulitis and moderate hepatocellular and canalicularcholestasis [23]. Toxic hepatitis associated with ceftriaxone had been also recorded [24].

The functional capacity of the kidney can be measured by blood concentrations of excretory and electrolyte constituents. Furthermore, renal function tests are required either to demonstrate the presence or absence of an active lesion in the kidney or to assess the normal functioning capacity of different parts of the functioning unit, nephron [25]. Cefotaxime in doses of 90 and 180 mg/kg b. wt. twice daily for 7 d caused asignificant increase in creatinine and urea concentrations in the serum of treated rats. This result was consistent with those reported by [26] who found that treatment of male Sprague-Dawley rats with intravenous cephaloridine (1.2 g/kg) for 24 h markedly increased plasma creatinine and blood urea nitrogen levels. Moreover, ceftriaxone produced an increase in serum creatinine and urea levels of treated rats [27]. This result was inconsistent with those reported after the administration of cefpiromesulphate and cefazoline sodium in rabbits [28]. Sodium, potassium and calcium levels in serum were significantly increased; this elevation might be attributed to the diuretic effect of cefotaxime, decrease of the glomerular filtration and decrease of tubular reabsorption of these electrolytes in the renal tubules. Hypernatremia could in a way serve as an indicator of liver disease [29]. Hyperkalemia is a more dangerous condition because of its effect on the heart, but it rarely occurs unless renal function is depressed. The significant increase in serum Ca^{2+}may be due to cell membrane damage as a result of exposure to drugs or inhibition of uptake by cells and tissues [30].

The obtained results were consistent with those obtained after administration of cefoperazone to rats [31]. Moreover, cefamandole induced hypercalcemia in rats [32]. Cefotaxime administration caused highly significant decrease in serum glucose, this result was similar with those reported by [33] who observed that, cefminox caused a slight decrease in serum glucose in male rats, administration of cefpiromesulphate and cefazoline sodium in rabbits [28] and after IM injection of cefamandole in rats [32]. Cefotaxime caused adecrease in serum protein level; this was consistent with that recorded in rabbits following administration of both cefpiromesulphate and cefazoline sodium [28] and after oral dosing of cefmtaline [34]. These obtained biochemical changes might be attributed to damage of the renal tubules cells. The histopathological findings in kidneys of cefotaxime treated rats obtained in this study were consistent with those obtained by [35] who observed that, cephaloridine administration to rats produced degeneration and/or necrosis of the renal proximal tubular epithelia. Cefodizime caused renal proximal tubular changes such as necrosis, hyaline cast and calcification, suggesting renal disorders [36].

CONCLUSION

It could be concluded that IM administration of cefotaxime caused a significant alterations in some biochemical parameters as serum (AST, ALT, total bilirubin, Cholesterol, Triglycerides, LDL-cholesterol, albumin and HDL-cholesterol concentrations). Cefotaxime caused hepatic and renal histopathological alterations. Cefotaxime is not a drug of choice and not preferable to animals or patients that suffering from hepatic and renal disorders.

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CONFLICTOF INTERESTS

There is no conflict of interests regarding the publication of this paper.

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