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Evaluation of Ceftriaxone Nephrotoxicity in Albino Rats

M.G. Elsayed, A.A. Elkomy and M.H. Aboubakr*

Department of pharmacology, Faculty of Veterinary Medicine,
Benha University, Egypt.

Work Address: Department of Pharmacology, Faculty of Veterinary Medicine, Benha
University, 13736 Moshtohor, Toukh, Qalioubeya, Egypt.

Corresponding author* Mohamed Hafez Aboubakr, Fac. Vet. Med., Pharmacology Dept.,
Benha University, Egypt.

Po Pox: 13736, Fax: +20132460640,

Email address: mohamedhafez19@yahoo.com

Abstract

Nephrotoxic effect and biochemical alterations induced by ceftriaxone were investigated in rats following repeated intramuscular injections of 180 and 360 mg/kg b.wt. daily for five consecutive days. Ceftriaxone is a beta lactam third generation cephalosporin antibiotic of broad spectrum antibacterial activity, targeted for treatment of bacterial diseases. Some serum, urine biochemical parameters and histopathological changes of the kidney were performed during and after intramuscular injection of ceftriaxone in rats. Significant increase in the total amount of urine per day, urea and creatinine concentration in serum and urine and significant decrease in their clearance were recorded. Ceftriaxone caused also significant glucosuria and proteinuria and significant decrease in their serum concentrations. The effect of ceftriaxone on electrolytes were also determined. Ceftriaxone injection in the tested doses caused histopathological changes in kidney. The severity of these changes was dose dependant. In conclusion, the renal functions should be monitored and/or the dose should be adjusted during ceftriaxone therapy.

Key words: Ceftriaxone, Biochemical, Histopathology, Nephrotoxicity, Rats.

Introduction

Ceftriaxone is a broad spectrum cephalosporin resistant to various types of beta-lactamases, with potent activity against gram-positive and gram-negative bacteria ¹. The drug acts through inhibition of transpeptidase enzymes responsible for the final step in bacterial cell wall synthesis and has broad stability against beta-hydrolysis ². In human medicine, ceftriaxone is

**IJAVMS**

widely used, because of its prolonged terminal half-life (5.4– 8.2 h) that allows its prescription on a single administration per day basis ^{3,4}.

The regulation of the internal environment of the body cells is maintained mainly by the kidneys. The regulatory mechanism includes glomerular filtration, selective reabsorption and secretion by tubules of certain substances as well as exchange of hydrogen ions and reduction of ammonia for conservation of base. Threshold substances as urea, creatinine, protein, electrolytes and glucose are almost completely reabsorbed by the tubules when their concentrations in the plasma are within the normal level, but appear in the urine when their plasma level exceeds and/or due to defect in renal tubules as a result of nephrotoxicity. This fact is good predictive in correlation between their serum and urine levels as demonstrated in the present study.

Therefore, the purpose of this study was to investigate the biochemical changes in serum, urine and histopathological changes of the kidney during and after administration of ceftriaxone and these informations will be of benefits to physicians and their patients.

Materials and Methods**2.1. Materials****2.1.1. Ceftriaxone**

Ceftriaxone is a sterile, semisynthetic, broad-spectrum third generation cephalosporin antibiotic for intravenous or intramuscular administration. The chemical formula of ceftriaxone sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$. It has a calculated molecular weight of 661.59. Ceftriaxone is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. ceftriaxone is supplied for intramuscular or intravenous administration in strengths equivalent to 250 mg, 500 mg and 1 g of ceftriaxone sodium. It was produced by Smithkline Beecham for Novartis Pharma Company (Egypt) and has the commercial name Ceftriaxone[®].

2.1.2. Laboratory animal

Twenty seven adult male Wistar strain albino rats (150- 200 g) were obtained from the Animal House, Faculty of Veterinary Medicine, Benha University, Egypt. They were maintained on standard pellet diet and tap water ad libitum and each rat was kept in a single metabolic cages under a 12 hr light/dark cycle and room temperature 22-24°C. Rats were acclimatized to the environment for one week prior to experimental use. This investigation was approved by the Animal Research Ethics Committee, Benha University.

2.2. Methods**2.2.1. Biochemical effects of ceftriaxone in rats**

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Rats were divided in three groups, each of nine rats. First group were injected intramuscularly with saline for 5 days and considered as control group. Rats of the second and third groups were injected intramuscularly with ceftriaxone at dose 180 mg/kg. b.wt. as therapeutic dose (Group A) and 360 mg/kg. b.wt. as double therapeutic dose (Group B), once daily for 5 consecutive days. Blood and urine samples were collected during administration (at 1st, 3rd, 5th days) and after drug administration (at 7th, 9th, 11th and 13th days from the beginning of experiment). Blood samples were collected from the venous plexus at the medial canthus of the eye by mean of capillary tubes The collected blood samples was allowed to clot and serum samples was obtained by centrifugation at 3000 round per minute for 15 minutes and then obtained by self aspirating pipette. Blood samples were kept in deep freeze for quantitative determination of creatinine, urea, sodium, potassium, calcium, glucose and total protein. The urine samples voided during 24 hours were collected from each rat every other day in a clean, dry, sterile, labeled glass bottles. Small crystal of thymol was added to each bottle for urine preservation and all bottles were kept in deep freeze for quantitative determination as in serum samples. One day after the last administration, three rats from each group were scarified and two kidneys of each rat were taken, four days after the last administration another three rats from each group was scarified and the two kidneys of each rat were taken, eight days after the last administration, three rats were sacrificed and the two kidneys of each rat were taken. All kidneys were preserved in formalin solution for histopathological examination.

2.2.2. Assay kits

Creatinine, urea, glucose and total protein were determined in serum and urine using kits from Diamond Diagnostic Company, Egypt. While, sodium, potassium and calcium were determined in serum and urine using kits from Spinreact Company, Spain. All were measured by spectrophotometer.

2.2.3. Histopathological examination of kidney

The preparation of kidneys samples and procedures of staining were carried out according to ⁵.

2.2.4. Statistical analysis

Data were expressed as mean \pm S.E. and were statistically analyzed using Student t-test to express the differences between groups ⁶.

Results

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The present study was designed to evaluate the effect of ceftriaxone on the kidney and included:-

3.1. Effect of ceftriaxone on biochemical parameters in serum of treated rats:-

Intramuscular injection of ceftriaxone in therapeutic and double therapeutic doses caused significant increase in the total amount of urine per day. The effect of ceftriaxone on creatinine, urea, sodium, potassium, calcium, glucose and total protein in serum of treated rats was summarized in **table (1)** and showed that, significant increased in creatinine level from 3rd to 7th day in group(A) and from 1st to 11th day in group (B). Also, urea level increased significantly from 1st to 7th day in group (A) and from 1st to 9th day in group (B). Sodium level increased significantly from 3rd to 9th day in group (A) and from 3rd to 13th day in group (B), potassium level increased significantly from 3rd to 9th day in both treated groups and significant decrease in calcium level from 3rd to 13th day in both treated groups. Ceftriaxone significantly decreased the levels of glucose and proteins from 3rd to 11th day, and from 1st to 13th day in both treated groups respectively.

3.2. Effect of ceftriaxone on biochemical parameters in urine of treated rats:-

The effect of ceftriaxone on creatinine, urea, sodium, potassium, calcium, glucose and total protein in urine of treated rats was summarized in **table (2)** and showed that, significant decreased in creatinine level from 3rd to 9th day in group(A) and from 3rd to 5th day in group (B). Also, urea level decreased significantly from 3rd to 7th day in both treated groups. Sodium level increased significantly from 3rd to 9th day in group (A) and from 3rd to 5th day in group (B), potassium level increased significantly from 3rd to 13th day in group (A) and from 1st to 13th day in group (B), and significant increase in calcium level from 3rd to 13th day in group (A) and from 3rd to 9th day in group (B). Ceftriaxone caused highly significant glucosuria and proteinuria during all days of experiment in both treated groups.

Creatinine and urea clearances means the ability of the kidney to excrete certain amount of creatinine and urea in the urine in a given time. This gives a good indication about kidney function and glomerular filtration rate and in this study; creatinine and urea clearances were significantly decreased. This might be attributed to damage of renal tubules and decreased the glomerular filtration rate.

Histopathological effects of ceftriaxone on kidney were shown in **Figure (1)**.

Discussion

Ceftriaxone in doses of 180 and 360 mg/kg body weight caused significant increase in the total amount of urine per day. The diuretic effect of ceftriaxone might be explained on the basis of increased renal blood flow due to vasodilatation of the renal artery and failure of the

**IJAVMS**

tubular reabsorption of water due to renal tubular damage manifested histopathologically by degenerative changes in form of intertubular inflammatory cellular infiltration, edema, congestion and hemorrhage with necrotic cellular debris in lumen of some renal tubules. The obtained result was consistent with ^{7,8} who found that, an increase in the urine volume after administration of ceftizoxime and cefoperazone respectively in dogs. Cefamandole produced a slight increase in the amount of urine per day in rats ⁹. The obtained result was inconsistent with that reported by ¹⁰ who found that, cefprozil respectively decreased the urine volume in rats in dose-dependent manner. Also, decreased urine output after cefoperazone administration was reported by ¹¹.

The increase in serum creatinine after intramuscular injection of ceftriaxone and the decrease in urine creatinine were reported in the present study. This indicated that, ceftriaxone impaired the ability of the kidney to excrete creatinine in urine. This might be attributed to damage of renal tubules. This result was consistent with those reported by ¹² after the administration of ceftiofur sodium and cefazolin sodium in rabbits and ⁹ who stated that, the cefamandole induced a significant increase of creatinine in serum and a significant decrease of it in urine and also creatinine clearance was also decreased. Ceftriaxone had been associated with elevation of serum creatinine and interstitial nephritis ¹³. Treatment of male Sprague-Dawley rats with intravenous cephaloridine (1.2 g/kg) for 24 h markedly increased creatinine level and decreased creatinine clearance ¹⁴.

Urea is formed in the liver and represents the principle end product of protein catabolism. It is excreted almost entirely by the kidneys and about 25 to 40 % of the filtered urea is reabsorbed. Glomerular filtration rate is the main factor affecting the excretion of urea, when it increases, serum urea will decrease and vice versa. In the present study, intramuscular injection of ceftriaxone produced significant increase in urea concentration in serum and significant decrease in its concentration in urine. The urea clearance was significantly decreased and the degree of significance was dose dependant. This indicated that, ceftriaxone impaired the ability of the kidneys to excrete urea in urine. This might be attributed to damage of renal tubules. The obtained results were consistent with those obtained by ⁹ who stated that, the cefamandole induced a significant increase of urea in serum and a significant decrease in urine and also urea clearance was also decreased. Cefmetilone hydrochloride caused slight increase of urea nitrogen after oral dosing in rabbits ¹⁵. Treatment of male Sprague-Dawley rats with intravenous cephaloridine (1.2 g/kg) for 24 h markedly increased BUN level ¹⁴.

Sodium and potassium levels in serum and urine were significantly increased, this elevation might be attributed to the diuretic effect of ceftriaxone, decrease of the glomerular

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filtration and decrease of tubular reabsorption of sodium and potassium in the renal tubules. The obtained results were consistent with those obtained by ^{7,8,16} they found that, an increase in sodium and potassium excretion after administration of ceftizoxime sodium to female mongrel dogs, after administration of cefoperazone, and after intravenous administration of ceftoram pivoxil. Cefamandole increased the sodium and potassium concentration in serum and urine ⁹. The results were inconsistent with that reported by ¹⁰ who recorded that, cefprozil decreased urinary excretion of electrolytes in dose- dependent manners in rats.

Ceftriaxone significantly declined calcium concentrations in serum in both groups of treated animals which associated with elevation of calcium concentrations in urine .This might be attributed to renal lesions which lead to failure of kidneys in reabsorption of calcium and help in excretion of calcium. Also the decrease in serum calcium level might be attributed to hypoproteinemia, where serum calcium concentration is decreased with decrease level of protein in serum because of the reduced amount of protein – bound calcium , under these circumstances , the amount of ionized diffusible calcium will not usually be altered ¹⁷. The obtained data revealed that ceftriaxone in both doses induced hypoproteinemia and proteinuria as discusses before. The obtained results were dissimilar with that obtained by ¹⁰ who found that, cefprozil decreased urinary excretion of electrolytes in dose-dependent manners in rats. Cefamandole induced hypercalcemia and decrease in urinary calcium ⁹. Also, ceftoram pivoxil had no effects on electrolytes excretion at oral doses of 500-2,000 mg/kg b. wt. in rats ¹⁶.

Glucose is excreted in urine in minute undetectable amount which in turn reabsorbed by renal tubules. Glucose appears in urine when the blood glucose level exceeds the renal threshold and failure of glomerular filtration due to glomerular lesions. Ceftriaxone administration caused glucosuria and highly significant decrease in serum glucose, this result was similar with those reported by ¹⁸ who observed that, cefminox caused a slight decrease in serum glucose in male rats. Administration of cefpirome sulphate and cefazoline sodium in rabbits ¹² and after intramuscular injection of cefamandole in rats ⁹. Treatment of male Sprague-Dawley rats with intravenous cephaloridine led to increased urinary excretion of glucose ¹⁴.

Ceftriaxone caused proteinuria and decrease in serum proteins level. This was consistent with that recorded in rabbits following administration of both cefpirome sulphate and cefazoline sodium ¹² and after oral dosing of cefmtiline ¹⁵. Treatment of male Sprague-Dawley rats with intravenous cephaloridine led to increased urinary excretion of protein ¹⁴.

**IJAVMS**

These obtained biochemical changes might be attributed to damage of the kidney. The histopathological findings in kidneys of ceftriaxone treated rats obtained in this study were consistent with those obtained by ¹⁹ 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 ²⁰. Cefpirome sulfate produced necrosis and calcification in the proximal tubular epithelium of kidney after administration to Japanese white male rabbits ¹². Interstitial nephritis associated with cefepime and cefoperazone were reported by ^{13,11}. Treatment of male Sprague-Dawley rats with intravenous cephaloridine led to marked pathological changes in the proximal tubules ¹⁴. The mechanism of tubular and glomerular changes might be related to use of large dose of ceftriaxone which accumulated in the epithelial cells in concentrations sufficient to exert a direct cytotoxic effect ²¹.

From the present study, it could be concluded that, ceftriaxone produced significant increase in creatinine, urea, sodium, potassium and calcium concentrations in serum and decreased serum concentrations of both glucose and total protein. Ceftriaxone produced significant decrease in both creatinine and urea concentrations in urine and increased concentrations of sodium, potassium and calcium in urine of treated rats. Glucosuria and proteinuria appeared after ceftriaxone therapy.

ceftriaxone was not preferable in patient suffered from renal disorders, so must be monitoring the patient which suffering from renal affections.

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**IJAVMS**

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IJAVMS

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Table (1): Effect of ceftriaxone on biochemical parameters in serum of rats.

Table (2): Effect of ceftriaxone on biochemical parameters in urine of rats.

* → Represent the significance in comparison with data of the control group.

* P < 0.05

** P < 0.01

*** P < 0.001

(A) → Rats treated with 180 mg of ceftriaxone/ kg.b.wt. (Therapeutic dose).

(B) → Rats treated with 360 mg of ceftriaxone/ kg.b.wt. (Double therapeutic dose).

Parameters		Groups		Days				
		1 st day	3 rd day	5 th day	7 th day	9 th day	11 th day	13 th day
Creatinin (mg/dl)	Control	42.22±1.63	43.17±1.81	44.13±1.44	45.24±1.72	46.19±1.36	44.76±0.95	41.91±0.95
	(A)	41.27±1.59	36.78±1.56**	37.78±1.56**	38.57±1.22*	40.95±1.41*	41.91±0.95	39.05±1.91
	(B)	44.44±1.08	36.51±1.33**	32.38±0.95***	35.24±1.41	37.15±1.48	43.81±1.90	40.95±0.95
Urea (mg/dl)	Control	114.09±5.82	121.53±6.56	121.53±7.54	133.93±8.15	130.21±6.86	156.25±12.86	126.49±7.44
	(A)	121.53±6.56	91.77±5.82**	99.21±6.56*	100.45±9.56*	115.33±6.86	148.81±7.44	133.93±12.89
	(B)	119.05±7.44	76.88±6.56***	79.37±6.56***	93.01±6.86**	115.33±8.96	141.37±14.88	133.93±12.89
Sodium (mmol/l)	Control	56.95±2.89	55.34±1.70	60.95±2.74	60.29±2.27	61.28±2.82	63.09±3.52	66.74±3.36
	(A)	56.38±1.84	62.79±2.18*	71.38±2.86*	67.10±2.02*	74.58±2.29**	63.83±1.08	65.90±2.44
	(B)	57.69±1.97	69.85±3.29**	68.80±2.37*	66.74±2.73	67.78±1.88	66.73±3.16	69.44±1.67
Potassium (mmol/l)	Control	21.58±0.17	21.40±0.19	20.87±0.30	20.68±0.29	20.66±0.17	20.85±0.09	20.57±0.10
	(A)	21.93±0.18	29.81±0.54***	29.35±0.74***	25.97±0.50***	23.97±0.25***	22.02±0.12**	21.81±0.39*
	(B)	22.80±0.28*	27.99±0.66***	26.47±0.33***	25.97±0.48***	24.88±0.24***	24.83±0.42**	25.52±0.33**
Calcium (mg/dl)	Control	6.46±0.74	6.03±0.43	7.14±0.34	6.40±0.58	6.35±0.53	7.68±1.44	8.19±0.55
	(A)	7.31±0.47	12.09±0.47***	11.26±0.50***	10.58±0.71**	11.07±1.12**	13.73±0.62*	10.88±0.60*
	(B)	11.08±0.51	13.05±0.69***	11.48±0.95***	11.20±1.00**	10.15±0.56***	11.18±1.41	10.79±1.93
Glucose (mg/dl)	Control	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
	(A)	131.38±2.06*	138.53±2.54***	154.19±1.92***	110.11±3.00***	91.40±1.83***	98.94±3.02**	74.47±1.71***
	(B)	130.26±2.23*	121.39±1.87***	141.55±2.16***	150.97±2.50***	105.14±1.90**	86.70±2.32**	71.10±3.89***
T. protein (g/dl)	Control	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
	(A)	0.50±0.02**	0.49±0.03***	0.79±0.03***	0.43±0.03***	0.14±0.01***	0.05±0.01**	0.03±0.003***
	(B)	0.60±0.03**	0.64±0.04***	0.86±0.02***	0.30±0.02***	0.09±0.01***	0.06±0.01**	0.01±0.003*



Parameters		Groups			Days			
		1 st day	3 rd day	5 th day	7 th day	9 th day	11 th day	13 th day
Creatinine (mg/dl)	Control	1.43±0.08	1.39±0.05	1.45±0.04	1.27±0.03	1.37±0.05	1.53±0.04	1.28±0.02
	(A)	1.35±0.07	1.87±0.04***	1.75±0.04***	1.54±0.04***	1.73±0.06	1.28±0.10	1.29±0.19
	(B)	1.81±0.04***	1.99±0.03***	1.97±0.04***	2.06±0.03***	1.83±0.07***	1.33±0.05*	1.35±0.02
Urea (mg/dl)	Control	20.83±0.82	21.90±0.81	22.37±0.64	23.74±0.86	22.96±1.20	19.57±0.76	22.47±0.61
	(A)	24.33±1.05*	31.92±0.67***	39.46±0.60***	31.77±0.77***	26.56±1.44	21.80±0.97	20.83±0.52
	(B)	28.95±0.77***	33.46±0.77***	35.02±1.01***	31.51±0.55***	27.53±0.76**	21.28±1.09	21.50±0.71
Sodium (mmol/l)	Control	150.41±1.50	147.47±1.95	141.57±1.60	146.57±2.23	142.52±2.20	144.18±4.97	149.79±3.02
	(A)	145.53±1.80	160.22±1.18***	161.82±1.33***	174.58±2.46***	173.23±2.11***	159.36±2.44	150.31±2.90
	(B)	148.30±1.30	181.28±2.45***	182.74±1.76***	176.71±2.10***	175.94±2.30***	175.57±1.95**	161.33±0.99*
Potassium (mmol/l)	Control	4.84±0.07	4.82±0.05	5.08±0.07	4.85±0.09	4.87±0.08	5.03±0.13	5.16±0.08
	(A)	4.89±0.05	5.61±0.08***	5.49±0.08**	5.18±0.04**	5.14±0.06*	4.88±0.07	4.97±0.08
	(B)	5.03±0.07	5.63±0.09***	5.13±0.03	5.41±0.06***	5.37±0.09**	5.05±0.08	5.02±0.04
Calcium (mg/dl)	Control	13.43±0.24	14.09±0.20	13.50±0.24	14.15±0.19	14.28±0.25	14.34±0.45	14.52±0.46
	(A)	13.76±0.24	12.50±0.19***	11.97±0.19***	12.02±0.18***	12.31±0.20***	11.67±0.21**	12.06±0.12**
	(B)	13.46±0.25	11.69±0.22***	11.88±0.19***	11.77±0.22***	11.58±0.21***	11.30±0.28**	12.42±0.18*
Glucose (mg/dl)	Control	271.04±13.90	298.23±10.79	291.79±6.88	314.5±3.05	319.15±3.98	304.52±2.92	315.07±4.00
	(A)	299.77±6.58	251.46±5.56**	219.74±2.85***	245.92±8.94***	248.49±9.00***	98.94±3.02***	313.65±5.71
	(B)	296.39±8.03	231.38±9.23***	212.50±9.81***	189.81±7.66***	197.96±10.74***	289.54±1.88*	291.67±13.54
T. protein (g/dl)	Control	5.92±0.09	7.18±0.14	6.40±0.10	4.47±0.10	7.44±0.10	6.92±0.04	7.23±0.05
	(A)	5.44±0.05***	5.54±0.08***	5.41±0.09***	3.99±0.20***	5.72±0.11***	6.72±0.03*	7.02±0.05*
	(B)	5.20±0.06***	5.57±0.07***	5.06±0.12***	3.78±0.22**	7.22±0.10	6.91±0.09	6.83±0.03**

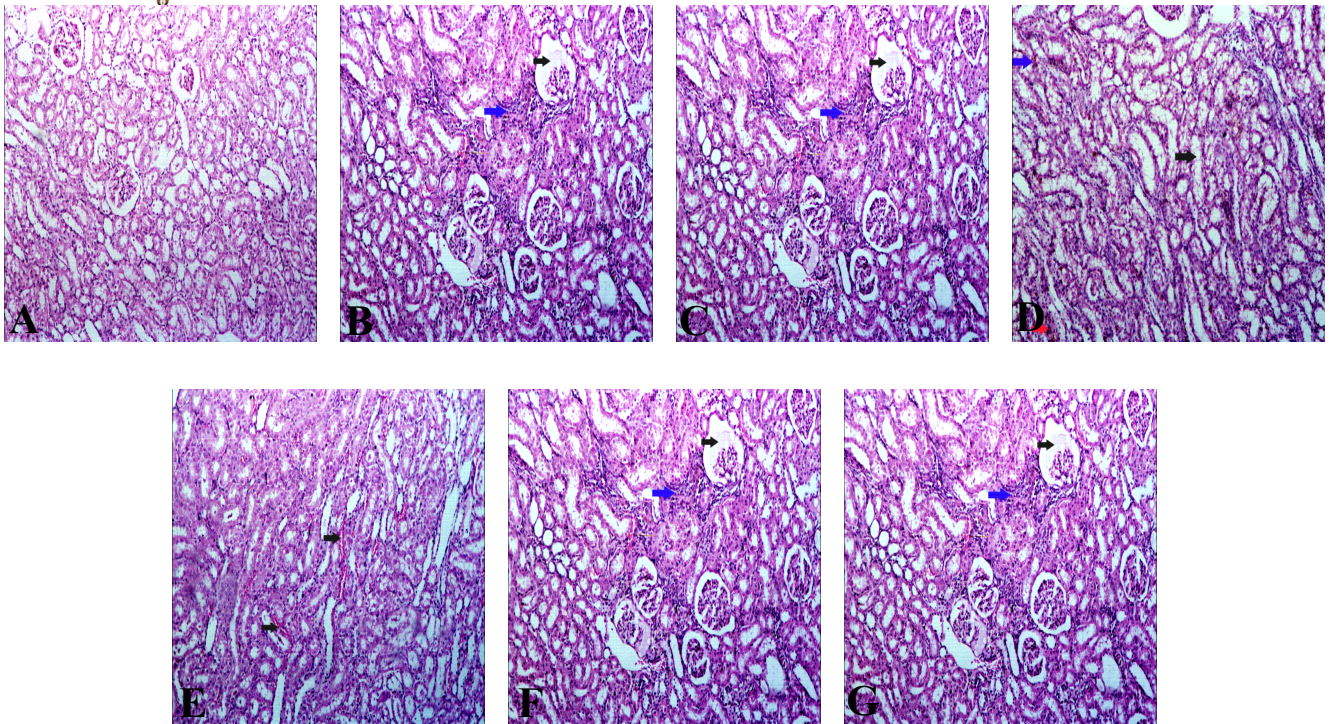


Fig (1):- Kidneys of rat administered normal saline, therapeutic (180 mg of ceftriaxone/ kg.b.wt.) and double therapeutic doses (360 mg of ceftriaxone/ kg.b.wt.). The stain was (H & E × 200).

- A)** Kidney of rat administered normal saline showing normal renal structure.
- B)** Kidney of rat injected with 180 mg of ceftriaxone/ kg.b.wt at 1st day post the last injection showing fatty changes in renal tubular epithelium especially proximal convoluted tubules.
- C)** Kidney of rat injected with 180 mg of ceftriaxone/ kg.b.wt at 4th day post the last injection showing proteinaceous materials in glomeruli and intertubular inflammatory cellular infiltration.
- D)** Kidney of rat injected with 180 mg of ceftriaxone/ kg.b.wt at 8th day post the last injection showing fatty changes in renal tubular epithelium with intertubular heamorrhage and heamosiderosis.
- E)** Kidney of rat injected with 360 mg of ceftriaxone/ kg.b.wt at 1st day post the last injection showing intertubular heamorrhage.
- F)** Kidney of rat injected with 360 mg of ceftriaxone/ kg.b.wt at 4th day post the last injection showing some renal tubules filled with hyaline cast and congestion of intertubular blood vessels
- G)** Kidney of rat injected with 360 mg of ceftriaxone/ kg.b.wt at 8th day post the last injection showing intertubular inflammatory cells, intertubular congestion and heamorrhage.