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Physiological Changes of Some Biochemical Parameters in Blood, Liver and Kidney Result by used Antibiotic Cefixime

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Abstract:
In the present, using of antibiotics frequently in the treatment of many acute and chronic diseases common to be wide especially in the Middle East. Most of these diseases are frequent and require treatment daily for long and frequent periods. Cefixime, one the antibiotic medicine, it belong to the third-generation of cephalosporin family-like ceftriaxone and cefotaxime. Cefixime is highly stable in the presence of beta-lactamase enzymes and is widely used to treat cold or against influenza virus. The results of this study were shown that the treatment of male of rats with Cefixime in the usual, double and excessive therapeutic dose led to no significant differences ($P \leq 0.05$) in the level of RBCs and Hb when compared with the control group. There is a simple significant increase in the level of WBCs in male of rats treated with Cefixime in the usual, double, and excessive therapeutic doses compared with the control group. About liver function parameters,the result showed a group of significant differences ($p \leq 0.05$) in the liver enzymes (ALT, ALP, and AST) which present in a significant increase in the level of ALT, ALP, and AST in the group of double and excessive doses, while it was no significant difference in the level of ALT and AST in the group of usual or normal dose when compared with the control group. As for the kidney factors Creatinine, Urea, Sodium, and Potassium the result shown no significant differences($p \leq 0.05$) in levels of Creatinine and Urea in groups (normal), double, and excessive doses when compared with the control group. The current study found that a short course of Cefixime therapeutic treatment normal, double, and excessive doses had no effects on blood, liver, and kidney studying parameters.
Keywords: AST, ALT, Cefixime Urea, ALP, Sodium, Potassium, WBCs.

1.Introduction

The Cefixime, one the antibiotic medicine, belong to the third-generation of cephalosporin family-like ceftriaxone and cefotaxime. Cefixime is a white to light yellow powder. Slightly soluble in water, soluble in methanol, sparingly soluble in ethanol, practically insoluble in ethyl acetate [1]. The antibacterial activity of cefixime return to the ability of inhibition mucopeptide synthesis in the bacterial cell wall.. (Cefixime trihydrate) is an oral antibiotic, a broad spectrum bacterial killer, semi-synthesized third-generation cephalosporins, with high stability to beta-lactamase; therefore, there are many types of bacteria have resistant to penicillins and some cephalosporins, as a result of the presence are directly sensitive to cefixime. By inhibiting the cell wall construction of the following group of Gram-positive microorganisms: Streptococciumonia, Streptococciobugens and Streptococcal Agalactia, Gram-negative: *Hemophilus influenza*, *Paraphrenia hemophilus*, *Moraxylacatis*, *Escherichia coli*, *Proteomic rebels*, *Protisflgaris*, *Nissirigonuria*, *Klebsilanonia*, *Klebsiella oxytocin*, *Pasturelamaltucida*, *Providencia* species, *Salmonella* species, *Shigella* species, *Citrobacter diver susyarAshymar schiness* [2]. Approximately 40-50% of the given Cefixime doses are absorbed, the absorption process is not significantly affected by the presence of food. Cefixime can be metabolized and separate in many parts of body tissues and body fluids, including albumen fluid, cardiac membrane, lung membrane, peritoneum, bile, sputum, urine, bone, heart muscle, skin, and soft tissues. Cefixime is excreted by urine and bile, 50% of

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Cefixime dose is effectively excreted by glomerular filtration in the urine[3,4]. Body ability to remove the drug or metabolism product depends on the amount of blood flow, the part of drug unbound in blood, and the ability of the organ to remove the drug. Environmental and genetic are controlled by most of these factors [5,6]. The liver plays an important role in the metabolism process of the drug, protein synthesis, and in maintaining the biologic equilibrium, of organisms. Due to these important roles, liver enzymes are used as markers in the assessment of drug safety or toxicity [7].It was necessary to identify the side effects of these antibiotics drugs. hence the proposal of this research project to study the effects of these drugs on the physiological Parameters of the liver and kidney vital functions and the extent to which the level of enzymes in the blood; hematology testes of (RBCs, WBCs, and Hb),Study the effect of cefixime on liver function(AST, ALT, ALP) and Kidney function (Urea, Creatinine, sodium, and Potassium).

2.Materials and Methods

2.1.Animals which are used in this study

Albino rats (males) (*Rattus Norvegicus*) aged one-year-old with weights of (165-225 g) were obtained from University of Baghdad - College of Veterinary Medicine, the animals were placed in cages covered with metal covers made for this purpose. Dimensions of the cages were 30 x 25 x 15cm. The cages were cleaned and disinfected with the sawdust switched every single day. The animals underwent appropriate experimental conditions of light time13 hours and darkness for 11 hours. The temperature was set at (25 ± 1 °C). Animal's diet consisting of 35% wheat, 34% maize, 20% soybeans, 10% protein, and 1% powdered milk plus 50 g / 100 kg antifungal agents [8]. Water and food were given free and in sufficient quantities throughout the project period from May to July 2020.

2.2.Experimental Design

The animals were randomly distributed into four groups (5 animals for each group). After the end of the preparatory period(2 weeks), the treatment of rats began daily for 10 days. Dosage was twice daily done by using tubular feeding according to a study of [9]. As the following:
-The first group (control group) was administered with distilled water (1 ml) for (10) days.
-Group 2 (normal dose) this group was administered cefixime at a dose of 4 mg / kg twice for 10 days.
-Group III (double dose) this group was administered cefixime at a dose of 8 mg/kg twice for 10 days.
-Group IV (overdose) this group was treated with cefixime at a dose of 16 mg/kg twice for 10 days.

2.3.Collection of samples

2.3.1.Blood samples and tests

After the last day of the experiment, all the animals were starved for 12 hours, after that blood samples were withdrawn by the Tail vein for preparation for biochemical tests. Then blood samples were left at room temperature for (20) minutes until the blood clotted and then centrifuged quickly (3000) RPM for (15) minutes to obtaining blood serum and the blood serum were kept at a temperature degree (- 20) ° C until the procedure Pending biochemical, hormonal and enzymatic tests. Blood tests include RBCs, WBCs, and Hb were measured and compared with the control group.Methodology: The methods used to derive CBC parameters are based on the Coulter® method of counting and sizing, in combination with an automatic diluting and mixing device for sample processing, and a single beam photometer for hemoglobinopathy. The differential of WBC was carried out by using of VCS technology.

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Analysis and classification of WBCs was undergone by using of three simultaneous measurements of individual cell volume (V), high-frequency conductivity (C), and laser light scatter (S). The scatter gram plots the cells based upon the measurements of these three parameters according to the Laboratory Procedure Manual [10].

2.4.Biochemical tests

2.4.1.Blood test

Blood test includes RBCs, WBCs, and Hb count as laboratory procedure.

2.4.2.Determination of liver enzymes (AST, ALP, and ALT) activity

The activity of AST, ALP, and ALT was estimated using the German-based Reflotron measuring tapes based on the enzymatic method. After 32 microliters of serum were placed on the test strip, the serum flowed into the reaction zone and in the case of the presence of the enzymes is converted to produce pyruvate. The second step of the reaction is stimulated by the Pyruvate oxidase (Pyo) enzyme. The resulting pyruvate wasspliced into acetyl phosphate, CO2, and H2O2. In the case of the enzyme Peroxidase, the H2O2 was converted the reagent into a blue oxidized according to the following formula:

α-Ketoglutarate + L-Alanine, AST, Glutamate + Pyruvate + SO_3^{-2}

Pyruvate + SO_3^{-2} +O_2 + H_2O Pyo Acetyl phosphate + H_2O2 + CO_2

H_2O_2 + Indicator (red) Peroxidase Indicator (ox) + H_2O

The reactions were performed at 37 °C and the colour intensity of the dye formed was measured at 567 nm as enzyme activity. The enzyme activity value was shown on the device screen after 142 seconds in a unit of U/L.

2.5.Renal function tests

2.5.1. Urea determination of blood serum

The amount of urea in the blood serum was estimated using a ready-made analysis kit from the French company Biolabo SA. Urease enzymes act to hydrolysed urea to ammonia, which gives coloured compounds with chloride (Chloride) and Salicylate, and the greater the concentration of urea in serum, the more intense colour intensity. As in the following equation:

Urea + H_2O ¾urease¾¾¾® 2NH3 + CO_2

2,2- Dicarboxyindophenol 2NH3 + Salicylate + Hypochlorite.

Forcalculation;the concentration of urea in blood serum was calculated according to the following law:

(A) Sample

Urea Conc. (mg/dl) = × Standard Conc.

(A)Standard

(A) = Absorbance

Standard

Conc = 50 mg / dl

2.5.2.Determination of Blood Serum Creatinine Level

Serum levels of creatinine were measured by using kit supplied from Biolabo SA, company France.For basic principle; Reddish yellow salt is formed as a result of the reaction of creatinine with Picric acid in an alkaline medium. The rate of colour formation is directly proportional to the serum creatinine concentration.

For calculation

(A2-A1) Sample

Creatinine Conc. (m g/dl) = × Standard Conc.

(A2-A1)Standard

2.5.3.Serum sodium and potassium

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Level of sodium and potassium in serum were determined by following the flame photometric method [11]. Urea level of serum was a determination based on the method of [12]. Creatinine level in serum was determined according to Rehberry Method.

2.6.Statistical analysis

Results were statistically analysed by analysis of variance (ANOVA) and the significant differences were determined according to Duncan's Multiple Ranges and at a significant level ($P \leq 0.05$).

3. Results and Discussion

3.1. Blood values

Results were showed that the treatment of male of rats with Cefixime in the usual, double and excessive therapeutic dose led to no significant differences ($P \leq 0.05$) in the level of RBCs and Hb when compared with the control group. There is a simple significant increase in the level of WBCs in male rats treated with Cefixime in the usual, double, and excessive therapeutic doses in compared with the control group.

Table 1. values of hematology RBCs, WBCs, and Hb.

Parameters / Groups	RBCs ($X10^{12}$/l)	WBCs ($X10^{6}$/l)	Hb (mg/100ml)
Control	112.43 ± 3.13 a	8590.5± 564.25 b	13.5 ± 0.7 a
Usual dose	113.56 ± 2.9 a	8870.11± 1123.2 a	13.3±0.3 a
Double dose	114.41± 4.2 a	8900.07± 552.1 a	13.4±0.9 a
Excessive dose	114.9±2.2 a	8870.90±654.6 a	13.6± 1.4 a

Mean, ± standard error, n=5, $P \leq 0.05$, and - Small letters mean significant difference.

3.2. Biochemical testes of ALT, ALP, and AST.

Results in table 5-2 show a group of significant differences ($p \leq 0.05$) in the liver enzymes (ALT, ALP, and AST) which present in a significant increase in the level of ALT, ALP, and AST in the group of double and excessive doses, while there is no significant difference in the level of ALT and AST in the group of usual or normal dose when compared with the control group.

Table 2. Biochemical values of AST, ALT.

Parameters / Groups	ALT (U/l)	ALP (U/l)	AST (U/l)
Control	35± 0.3 c	132± 1.3 c	152± 1.2 b
Usual dose	41±1 c	1391±1.2 c	178±1.2 b
Double dose	65± 0.2 b	155± 0.2 b	227±2.1 a
Excessive dose	84±0.2 a	174±0.2 a	236± 0.8 a

Mean, ± standard error, n=5, $P \leq 0.05$ and - Small letters mean significant difference.

3.3. Result of renal parameters Urea, Creatinine, Sodium and Potassium.

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For kidney factors include Creatinine, Urea, Sodium, and Potassium, the results showed no significant differences($p \leq 0.05$) in the level of Creatinine and Urea in groups of usual(normal), double, and excessive doses when compared with the control group.

Table 3. Kidney parameters Creatinine, Urea, Magnesium, and Potassium.

Parameters / Groups	Creatinine (mg/dl)	Urea (mg/dl)	Sodium (mmoles/L)	Potassium (mmoles/L)
Control	0.78±0.3 a	51± 2 a	133.5±4.249 a	4.98 ±.6.87 a
Usual dose	0.71±0.2 a	45±1.3 a	130.3±5.12 a	4.96 ± 0.98 a
Double dose	0.70±0.3 a	43±0.9 a	129.4± 2.23 a	4.87± 1.20 a
Excessive dose	0.54±0.2 a	45± 1.4 a	126.8± 0.97 a	4.79 ±1.15 a

Mean, ± standard error, n=5, $P \leq 0.05$ and - Small letters mean significant difference.

4. Discussion

Cefixime is a broad antibiotic which considered as an effective bactericidal activity against many types of bacteria (gram negative and positive). In our study we measured the RBCs, WBCs, and hemoglobin levels in these groups of the treatment with the different doses of Cefixime (normal, double, and excessive) the result we show no significant change in the parameter values and cefixime treatment didn't have affect,due to the limit time for an antibiotic used. We explain our finding with no hematology parameters changes because we used the antibiotic without any infection or disease[9]. Our result agreement with [9, 13]. ALT, AST level, and ALP are showing significantly increasing in study results which are referred to clinically significant, it is unknown how cefixime induces such this increase in hepatic enzymes level. On the Other hand that might have other reasons that caused this reaction include sepsis, and jaundice [10, 11]. Results of the present study showing agreement with [13].There are several cases of hepatotoxicity caused by antibiotic administration such as cephalosporins or others[1, 7]. A third-generation of cefixime, cefproxil, hasthe same pharmacokinetics, and adverse effect has been associated with hepatitis [3,8]. Cefixime-induced AST, ALT, and alkaline phosphate elevations were reported respectively [9, 14]. Our result agreed with [15,16] of treatment with Cefixime induce of hepatic damage lead to abnormal AST and ALT levels in the animal in this experiment. Many previous studies and case reports were described the role of cefixime and the development of liver enzymes [17, 18, 19]. Cefixime not known to be caused hepatotoxic;, .Our results disagreed with [1]in the parameters of liver function ALT, AST, and ALP, this might bedue to time was limit of our study[20]. Our resultswere agreed with the finding of [21,22,23], and disagreed with other studies[1,2, 11,24]. Results observed that Cefixime administration did not alter urea and creatinine levels in rats for the period of administration 10 days. In our study, Cefixime does not show any severe side effects or adverse effects in the majority of tested samples[12, 25,26,27].

5. Conclusion

The current study found that there is a short course of Cefixime treatment of normal, double, and excessive doses had no effects on blood, liver, and kidney studying parameters.

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