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Physiological Studies on the Effect of Cefepime on the Some Blood Components of Rabbits

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ABSTRACT

Objective: The objective of the present study is to get information about the physiological effect of Cefepime on some blood contents: Hemoglobin, Packed cell volume, White blood cells count, Red blood cells count and the differential white blood cells count in rabbits. Methodology: The present study was carried out in the farm of poultry and laboratories belonging to the Department of Animal Production, Faculty of Agriculture and Veterinary Medicine – Ibb University for a period of 7 days using 15 rabbits (weight about 1kg) were divided randomly into 3 groups each, and in each group there were 5 animals**.** The group I served as control and received normal saline (0.9% NaCl). The other 2 groups received different concentration of cefepime 50, 100mg/kg day, respectively to each rabbit into the muscle to study the effects of cefepime on some blood contents of rabbits such as, hemoglobin, packed cell volume, red blood cells, white blood cells count and the differential count of white blood cells. Results: After two hours of treatment by cefepime (in both doses) the treatment rabbits with cefepime showed significant increase of neutrophil percentage ($P<0.0002$), white blood cells count and monocyte percentage. However, lymphocyte percentage and eosinophils percentage showed significant decrease ($P<0.001$) and ($P<0.0001$), respectively. Also, in case of hemoglobin level, packed cell volume and red blood cell count it was found insignificant decrease. After seven days of treatment by cefepime, the treated rabbits with cefepime showed significant increase of neutrophils percentage ($P<0.0003$) and monocyte percentage ($P<0.01$). However, lymphocyte percentage showed significant decrease ($P<0.0001$) in treated rabbits by cefepime compared to non-treated group. Conclusion: This study concludes that, clinical hematological and chemistry data can be useful aids for hematological constituents reflect the physiological responsiveness of the animals to its internal and external environment which include feed and feeding. Therefore it worth's to understanding how the treatment by Cefepime change the blood and biochemical function of the bodies.

INTRODUCTION

The cephalosporin's are currently among the most widely prescribed class of antibiotics in hospitals[1]. The broad spectrum of activity both against Gram-positive and Gram negative and a low toxicity profile continue to their widespread use[2].

Cephalosporins have a β-lactam ring structure that interferes with synthesis of the bacterial cell wall which means that they kill bacteria by disrupt the synthesis of the peptidoglycan layer of bacterial cell wall, which causes the wall to break down[3].

Cefepime (a molecular formula of $C_{19}H_{25}ClN_6O_5S_2HClH_2O$) and a molecular weight of (571.5) is a parenteral fourth generation cephalosporin antibiotic with a wide spectrum of antimicrobial activity[4]. It is active against many Gram-positive and Gram-negative bacteria, such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Pseudomonas aeruginosa*[5], with less susceptibility to extended-spectrum-lactamases [6]. The chemical structure of cefepime allows it to bind to the penicillin-binding proteins and penetrate the outer membrane of gram-negative bacteria more rapidly than most cephalosporins.

In humans, cefepime has been approved for the treatment of lower respiratory tract, intra-abdominal, complicated and uncomplicated urinary tract infections as well as uncomplicated skin and skin structure infections[4] .Fever, which may be associated with many bacterial and viral diseases, changes various physiological parameters such as the heart rate, renal blood flow, hepatic and total splanchnic blood flow, diuresis, and enzyme activities[7], which can alter the pharmacokinetics of certain drugs. For example, an increased volume of distribution for penicillin-G has been reported in rabbits, pigs and dogs during endotoxin-induced fever. However, pigs, dogs and rabbits showed higher blood concentrations of sulphathiazole, sulphadimidine and gentamicin during endotoxin-induced fever[8] .

In rabbits, the level of cefepime in cerebral spinal fluid (CSF) was approximately 20% that in serum[9]. However, the bactericidal activity of cefepime against *S. pneumonia* in the CSF of infected rabbits was comparable to that of cefotaxime, which penetrates the CSF of rabbits with meningitis only moderately (3.5%)[10].

The overall effectiveness' of therapy with cephalosporins is largely influenced by the aggregate time, though not necessarily continuous during which effective plasma concentrations are maintained. The class of chemical example cephalosporin's can differ

widely in disease conditions like hepatic cirrhosis, liver abscess, acute pancreatitis, gastrointestinal disease, nephritic syndrome and chronic renal failure[11].

Values of key pharmacokinetic parameters after the administration of single and repeated intravenous and intramuscular doses to normal volunteers indicate that cefepime is safe and well-tolerated and exhibits linear pharmacokinetics within the 62.5 to 2000mg dose range.

In normal subjects, cefepime is cleared primarily by urinary excretion in the unchanged form. Previous clinical studies with other cephalosporins indicate that the elimination half-life is prolonged in elderly patients. Both male and female patients of different age groups are potential recipients of cefepime therapy[12].

Cefepime is a wide spectrum of antimicrobial activity, the objective of the present study is to get information about the physiological effect of cefepime on some blood contents: Hemoglobin, Packed cell volume, White blood cells count, Red blood cells count and the differential white blood cells count.

MATERIAL AND METHODS

The present study was carried out in the farm of poultry and laboratories belonging to the department of animal production, Faculty of Agriculture and Veterinary Medicine – Ibb University for a period of 7 days for the purpose of studding the effect of cefepime on some blood components of rabbits.

Experimental Animals

The experiment was conducted on 15 adult rabbits (weight about 1kg) kept for 1 week on a commercial diet in environmentally controlled conditions (25 ± 5 C0, 55 ± 5% humidity and 12h. light-dark cycle) with free access to diet and water *ad libitum*.

Experimental Design

The fifteen rabbits were divided randomly into 3 groups each, and in each group there were 5 animals. The group I served as control and received normal saline (0.9% Nacl). The other 2 groups received different concentration of cefepime 50, 100 mg/kg/day, respectively.

Drug Administration and Sample Collection:

Antibiotic: SM-1652 was synthesized in the laboratories of Cipla.

- SM-1652 dissolved in sterile physiological saline just before use. Cefepime was administered daily into the muscle of the 10 rabbits at the dose rate of 50mg/kg and 100 mg /kg for a period of 7 days.

- Blood samples were collected from Marginal ear vein with the help of insulin syringe into test tubes containing ethylene diamine tetraacetate (E.D.T.A) as anticoagulant before administration and at 2 hours and 7 days after administration for determination of hematological parameters. The animals were observed for any side effects during the study after administration of the drug.

Hematological Parameters:

Hemoglobin concentration was determined by the cyanmethemoglobin methods according to (Bernard *et al.,* 2000) [13]. The packed cell volume (PCV) was determined by microhematocrite capillary tubes filled with blood and centrifuged at 3000 rpm for 5 minutes (Bernard *et al.,* 2000)[13]. Red blood cells (RBC) and white blood cells (WBC) count were determined by a manual method using improved Neubaure's hemocytometer (Brar *et al.,* 2002)[14]. The differential WBC counts were made on blood films stained with Giemsa stain, using an average of 100 cells .

Statistical Analyses

Statistical analysis of data obtained was carried out by applying the computer program SAS, (1955). Duncan's test, (1955) [15] was applied between means to test the significance between them. The following statistical model was used for analysis the data obtained for hematological parameters:

$$Xijk=\mu+\alpha i+Rj+(\alpha R)ij+eijk$$

Where:

Xijk = The observation of the ith treatment and jth replicate.

μ = The overall mean.

αi = The effect of ith treatment.

Rj = The effect of jth replicate.

αRij = The interaction between ith treatment and jth replicate.

eijk= Experimental error.

RESULTS AND DISCUSSION

Effect of cefepime on some blood contents of rabbits at different periods:-

Hemoglobin (g/dl):-

After two hours of treatment with cefepime, it was found insignificant decrease of hemoglobin concentration in normal dose and overdose group which were (9.60 g/dl) (10.20 g/dl), respectively as compared with control group (10.60 g/dl). After seven days of treatment with cefepime, it was found not affected in hemoglobin concentration in normal dose and overdose group which were (10.20 g/dl) (10.20 g/dl), respectively as compared to control group (10.40 g/dl) as presented in Fig. (1).

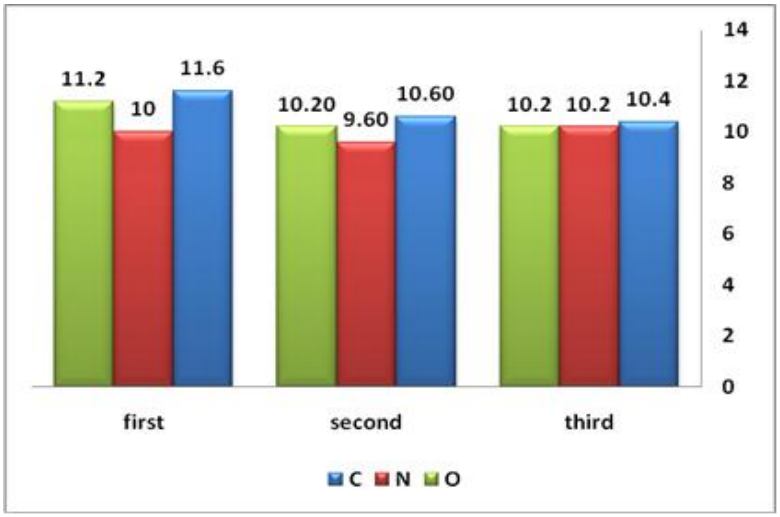

Figure No. 1: Means value of the effect of Cefepime on Hemoglobin on rabbits at different periods

First: Pre-administration, Second: After two hours of treatment, Third: After seven days of treatment, C = Control, N = Normal dose, O = Overdose.

Packed Cell Volume (Hematocrit) %: -

After two hours of treatment with cefepime, it was found insignificant decrease of packed cell volume concentration in normal dose group which was (34.40%) while it was found to be not affected in overdose group which was (36.20%) as compared with control group (36.20%). After seven days of treatment with cefepime, it was found insignificant decrease of

packed cell volume concentration in normal dose and overdose groups which were (33.80%) (34.00%), respectively as compared to control group (34.20%) as presented in Fig. (2).

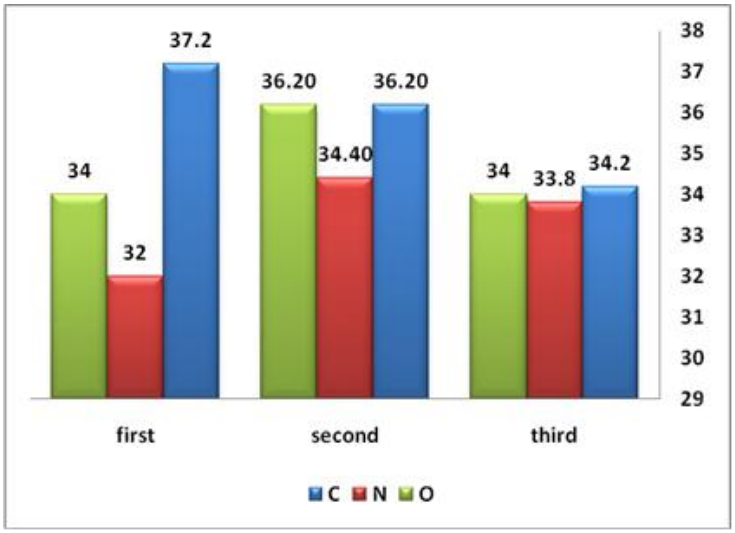

Figure No. 2: Means value of the effect of Cefepime on Packed Cell Volume (hematocrit) on rabbits at different periods

First: Pre-administration, Second: After two hours of treatment, Third: After seven days of treatment, C = Control, N = Normal dose, O = Overdose.

Red blood cells count ($\times 10^6$ mm^3):-

After two hours of treatment with cefepime it was found slightly decrease of red blood cells count in normal dose and overdose groups which were (5.28 $\times 10^6$ mm^3) (5.01$\times 10^6 mm^3$), respectively as compared to control group (5.45 $\times 10^6$ mm^3) as presented in Fig. (3). After seven days of treatment with cefepime, it was found that there were no statistical differences between red blood cells count in the two treated groups which were (5.23$\times 10^6$ mm^3) (5.11$\times 10^6$ mm^3), respectively as compared to control group (5.16$\times 10^6$ mm^3).

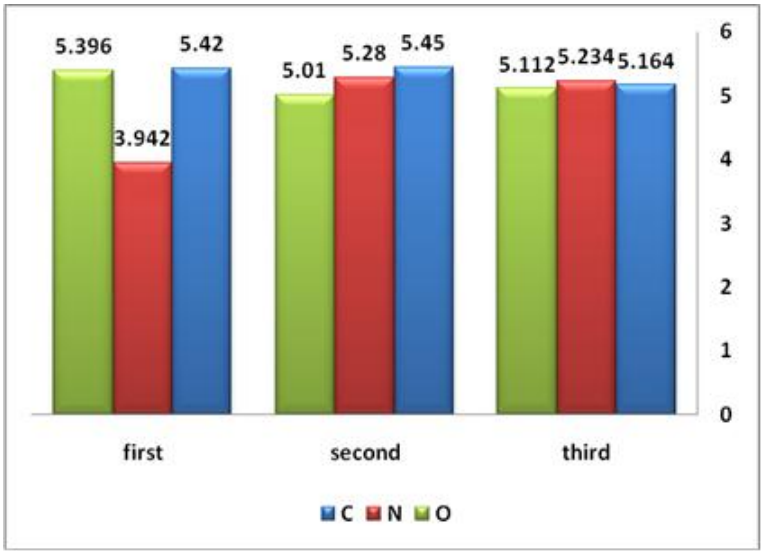

Figure No. 3: Means value of the effect of Cefepime on Red Blood Cell on rabbits at different periods

First: Pre-administration, Second: After two hours of treatment, Third: After seven days of treatment, C = Control, N = Normal dose, O = Overdose.

White blood cells count (×10^3 mm^3):-

After two hours of treatment with cefepime it was found slightly increase of white blood cells count in normal dose group which was (5.86 ×10^3 mm^3). However, it was found non-significant decrease in overdose group which was (4.48 ×10^3 mm^3) as compared to control group (5.28×$10^3$$mm^3$). After seven days of treatment with cefepime it was found non-significant increase of white blood cells count in normal dose and overdose groups which were (5.70×$10^3$$mm^3$) (6.18×$10^3$ mm^3), respectively as compared to control group (5.60×10^3 mm^3) as presented in Fig. (4).

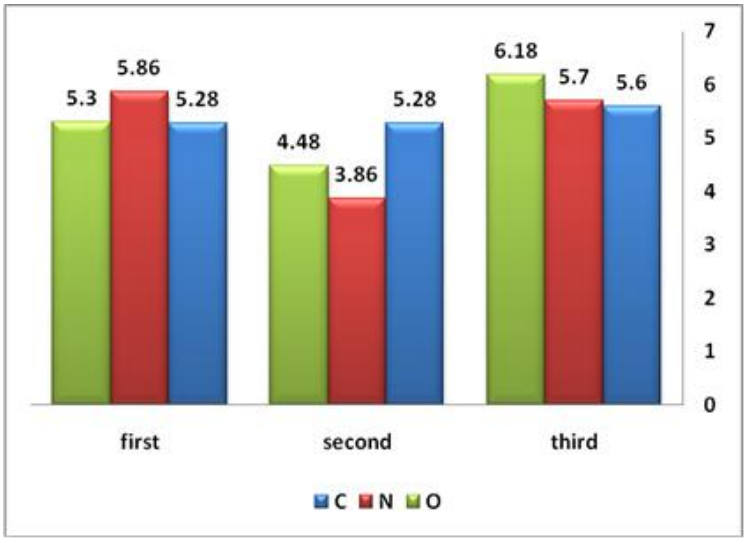

Figure No. 4: Means value of the effect of Cefepime on White Blood Cell on rabbits at different periods

First: Pre-administration, Second: After two hours of treatment, Third: After seven days of treatment, C = Control, N = Normal dose, O = Overdose.

The differential count of white blood cells:-

Neutrophils %:

After two hours of treatment with cefepime, it was found increased significantly ($P < 0.0002$) of neutrophils percentage in normal dose and overdose groups which were (24.40%) and (32.60%), respectively as compared to control group (17.00%) as presented in Fig (5). Also after seven days of treatment with cefepime, it was found increased significantly ($P < 0.0003$) of neutrophils percentage in normal dose and overdose groups which were (29.20% and 42.20%), respectively as compared to control group (20.20%).

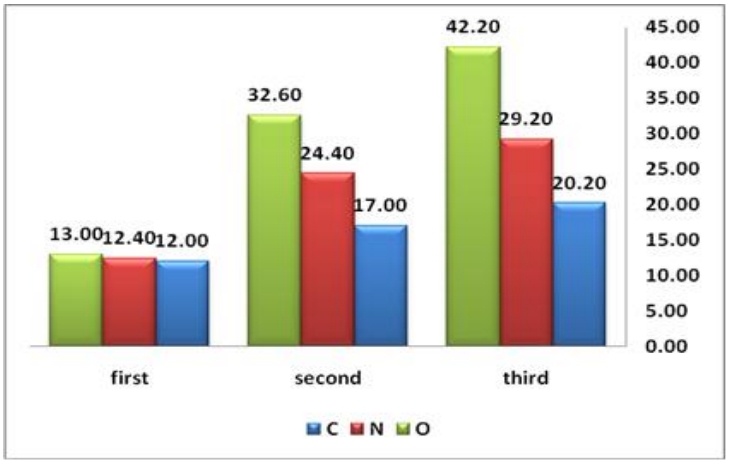

Figure No. 5: Means value of the effect of Cefepime on Neutrophils on rabbits at different periods

First: Pre-administration, Second: After two hours of treatment, Third: After seven days of treatment, C = Control, N = Normal dose, O = Overdose.

Eosinophil's %:

After two hours of treatment with cefepime, it was found significant decreased ($P < 0.0001$) of eosinophil's percentage in normal dose and overdose groups which were (7.80 % and 4.20%), respectively as compared to control group (11.00%) as presented in Fig. (6). After seven days of treatment with cefepime, it was found insignificant increase of eosinophil's percentage which was (3.0%) while in overdose group it was found slightly decrease of eosinophil's percentage which was (0.80%) as compared to control group (1.40%).

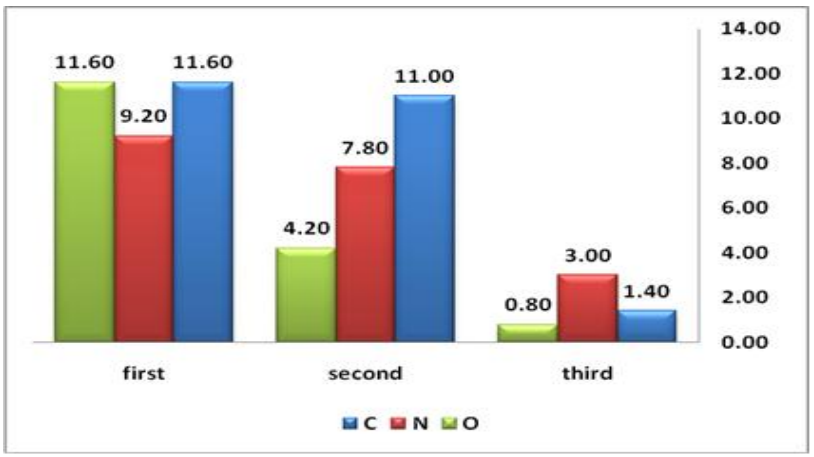

Figure No. 6: Means value of the effect of Cefepime Eosinophil's on rabbits at different periods

Basophils%:

After two hours and seven days of treatment with cefepime, it was found to be not affected in basophils percentage in normal dose and overdose groups which was (0.00%) as presented in Fig. (7).

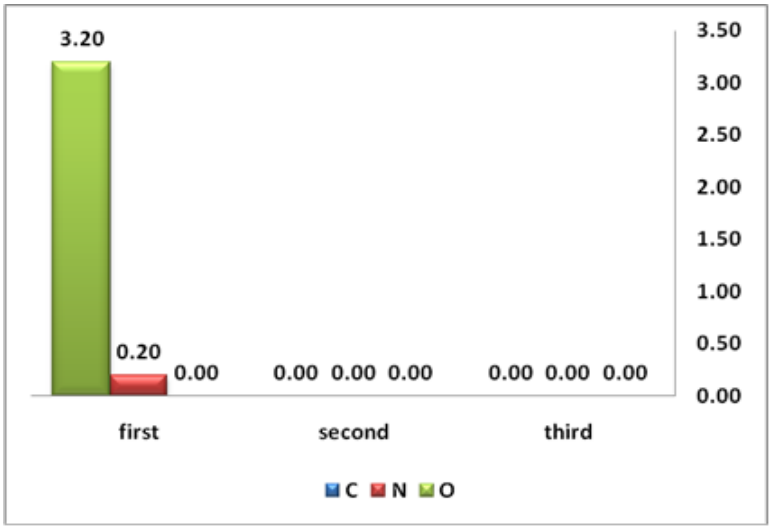

Figure No. 7: Means value of the effect of Cefepime on Basophils on rabbits at different periods

First: Pre-administration, Second: After two hours of treatment, Third: After seven days of treatment, C = Control, N = Normal dose, O = Overdose.

Lymphocyte %:

After two hours of treatment with cefepime, it was found decreased significantly ($P < 0.001$) of lymphocyte percentage in normal dose group and overdose group which were (67.40%) and (57.40%), respectively as compared to control group (71.80%) as presented in Fig. (8). Also after seven days of treatment with cefepime, it was found decrease significantly ($P < 0.0001$) of lymphocyte percentage in normal dose group and overdose groups which were (63.40% and 54.40%) as compared to control group (78.40%). This returned to the presence of a large number of lymphocytes in the area of inflammation for defense mechanisms.

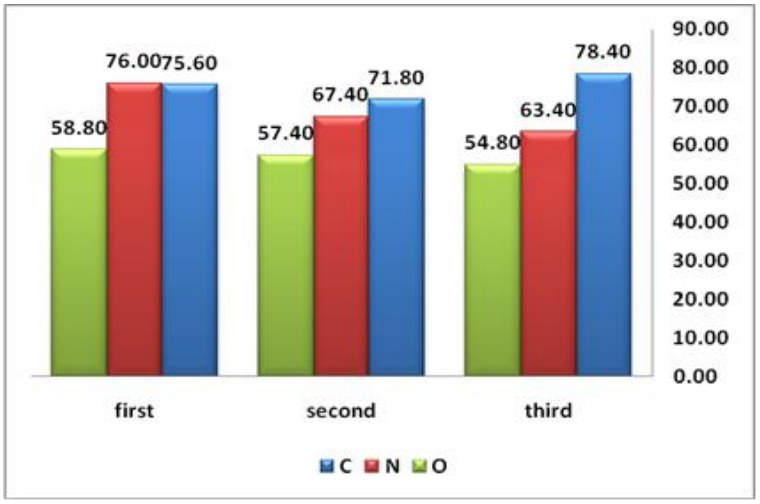

Figure No. 8: Means value of the effect of Cefepime on Lymphocyte on rabbits at different periods

First: Pre-administration, Second: After two hours of treatment, Third: After seven days of treatment, C = Control, N = Normal dose, O = Overdose.

Monocyte %:

After two hours of treatment with cefepime, it was found insignificant increase of monocyte percentage in normal dose group which was (0.40%). It was found increased significantly (P< 0.002) of monocyte percentage in overdose group which was (5.80 %) as compared to control group (0.20%) as presented in Fig. (9). After seven days of treatment with cefepime, it was found increase significantly (P < 0.01) of monocyte percentage in normal dose group and overdose groups which were (4.40 % and 2.20 %), respectively as compared to control group (0.001%).

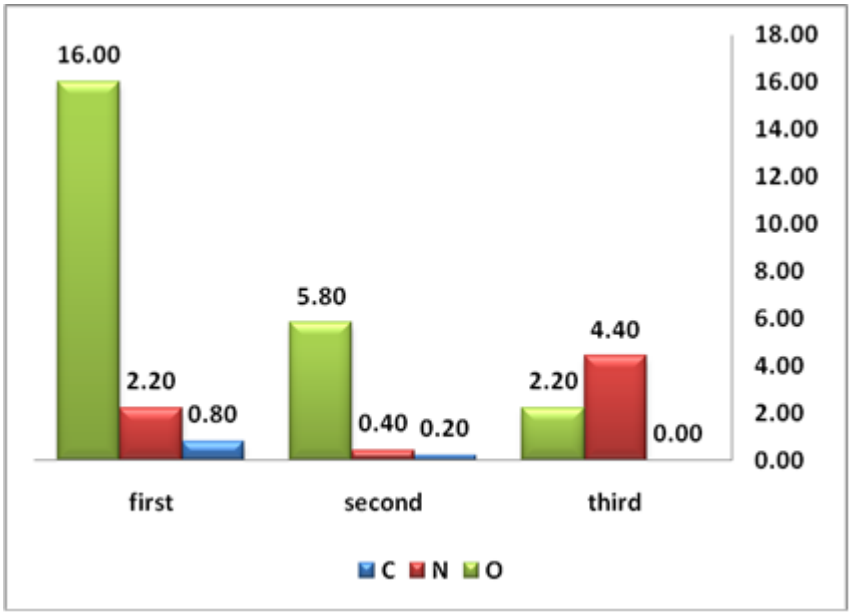

Figure No. 9: Means value of the effect of Cefepime on Monocyte on rabbits at different periods

First: Pre-administration, Second: After two hours of treatment, Third: After seven days of treatment, C = Control, N = Normal dose, O = Overdose.

CONCLUSION

The cephalosporin's are currently among the most widely prescribed class of antibiotic in hospitals. The broad spectrum of activity both against Gram-positive and Gram-negative and a low toxicity profile continue to their widespread use[2]. It should be mentioned that, clinical hematological and chemistry data can be useful aids for hematological constituents reflect the physiological responsiveness of the animals to its internal and external environment which include feed and feeding. Therefore it worth's to understanding how the treatment by cefepime change the blood and biochemical function of the bodies.

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