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EFFECTS OF CEFEPIME ON SERUM LIVER AND KIDNEY FUNCTIONS IN RABBITS

Mai H. Helal^{1*}, Ahmed A. Said¹, G.El-Din Shams¹ and M.F. Abu El-Ftouh²

1. Pharmacol. Dept., Fac. Vet. Med., Zagazig Univ., Egypt

2. Forensic and Toxicol. Med. Dept., Fac. Vet. Med., Zagazig Univ., Egypt

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ABSTRACT: This study aimed to determine the effect of cefepime on different liver and kidney functions of healthy rabbits (35days/1kg) were injected with singular intramuscular dose once daily for 5 successive days with 75 mg/kg body weight. Twenty-four healthy rabbits of the same sex were divided into two groups (n=12). First group was injected with distilled water (control) and second group was injected with 75 mg/kg once daily for 5 successive days. Blood samples were taken at (1st, 3rd, 7th and 14th day) without anticoagulant, centrifuged and frozen. Samples were analyzed and the results indicated that there was non-significant effect on liver functions as there was no change in each of the serum AST, ALT, ALP, total protein, and total albumin. The results indicated also that there was insignificant effect of cefepime on kidney functions, in terms of insignificant difference of serum urea and concentration and creatinine levels, meaning the safety of the drug on public health.

Key words: Cefepime, serum, liver, kidney, rabbits.

INTRODUCTION

Antibiotics and chemotherapeutics in animals feedstuffs or diets must be present in lower concentration than a toxicologically accepted level. To check the recognized limits, laboratories depend on reliable methods. Estimation of antimicrobial residues can be done by immunological, biological and chemical methods. Means of detection can be categorized according to the degree of quantitative, semi-quantitative and qualitative methods.

Cefepime is a new fourth generation parenteral cephalosporin which holds promise for management of these severe infections (Gutierrez, 2004). It has been shown to be useful in critical pneumonias, soft and bone tissue infections, urinary tract infections and febrile neutropenia (Tsuji *et al.*, 1985). It eradicates organisms which have shown resistance to other β -lactam antibiotics. It is

stable to hydrolysis by the common plasmid and chromosomally mediated β -lactamases (Hardin and Jennings, 1994). The twice daily dosing and improved efficacy even at low dosage makes it a suitable alternative to ceftazidime and carbapenems. It is well tolerated by all age groups and is safe even for newborns (Capparelli *et al.*, 2005). Cefepime monotherapy gives both a good clinical response and an excellent microbiological clearance. In order to preserve its anti-bacterial potency, prudent use of cefepime is warranted. Research into its efficacy and safety with other β -lactamase inhibitors is ongoing and will benefit mankind (Shahid, 2010). In many poultry and rabbit forms, there is a hazard in using antibiotics for treatments. This certainly has unfavorable effects on people health due to consuming meats of animals. This work was planned to study the safety of cefepime drug on treated animals and in turn public health.

Corresponding author: Tel. : +201002970870

E-mail address: Memahamdy90@gmail.com

MATERIALS AND METHODS

Drug (Cefepime Description)

Cefepime hydrochloride is small powder. It was purchased from Sigma (3050 spruce street, Saint louis, Mo 63103, USA). The recommended intramuscular (I/M) dose in rabbit is 75 mg/kg BW once daily for 5 consecutive days (El-Dars, 2019).

Chemical Formula and Structure

$C_{19}H_{24}N_6O_5S_2$ is the formula of the drug. Its structure is shown in Fig. 1.

Experimental Animals and Diets

Twenty-four growing New Zealand rabbits, weaned at 35 days old (1 kg) were used (the Faculty of Veterinary Medicine, Zagazig University). The rabbits were distributed into galvanized wire cages batteries according to their experimental feeding treatment. They were fed on balanced commercial diet free from any medication for 2 weeks to ensure complete excretion of any drugs from their bodies. Water was provided *ad-libitum*. They were kept under restricted hygienic condition during investigational period.

Experimental Design

The experimental was conducted on growing New Zealand rabbits, which were randomly allocated into two equal groups; group 1 (negative control, n=12) was administered sterile normal saline and group 2 (n=12) was injected I/M with a single daily dose of 75 mg/kg BW cefepime hydrochloride for 5 successive days (El-Dars, 2019).

Determination of some Biochemical Parameters (Blood Sampling)

Alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) are liver specific enzymes and were estimated within a shorter time, according to the method of Reitman and Frankel (1957).

Total protein and albumin determination

Total protein and albumin were determined colorimetrically (Buzanovskii, 2017).

Creatinine and uric acid determination

Serum creatinine and uric acid were determined colorimetrically (Henry, 1974).

Statistical Analysis

Data was analyzed by using computerized SPSS (Statistical Package for Social Sciences) program version 25 (IBM Corp., Armonk, NY). Statistical evaluations of the results were done by using methods as mixed model analysis of variance (ANOVA) followed by Tukey test. Significant difference (Tukey's HSD) test as post hoc test was used. The level of significance was taken at $P < 0.01$. Data of serum biochemical parameters were analyzed by one-way ANOVA.

RESULTS AND DISCUSSION

The results of one-way ANOVA revealed that there was insignificant difference in values of some biochemical parameters among control and different days of experiment P value for each parameter was larger than 0.05.

Liver Function Test

Effect on serum AST

It was clearly shown from Table 1 that post I/M injection of cefepime in the therapeutic dose for 5 successive days to rabbits resulted in non-significant alternation of serum AST values at 1st day 3rd, 7th, and 14th day (10.45, 10.47, 10.88, and 11.08 U/L, respectively) when compared with control group (10.55 U/L).

Effect on serum ALT

There was insignificant change in the serum ALT concentration at 1st day 3rd, 7th, and 14th day (35.67, 28.50, 37.63, and 35.90 U/L, respectively) after I/M injection of cefepime in the therapeutic dose for 5 successive days to rabbits when compared with control group (30.18 U/L) as shown in Table 1.

Effect on serum ALP

Table 1, displays the post I/M injection of cefepime in the therapeutic dose for 5 successive days to rabbits that resulting in non-significant difference of serum ALP level at 1st day 3rd, 7th, and 14th day (81, 67.33, 74.67, and 90 U/L, respectively) when compared with control group (119 U/L).

Effect on serum total protein

There was insignificant change among 1st day 3rd, 7th, and 14th day (5.59, 6.14, 6.07, and 6.32 g/dl, respectively) after I/M injection of cefepime when compared with control group (6.19 g/dl) as shown in Table 1.

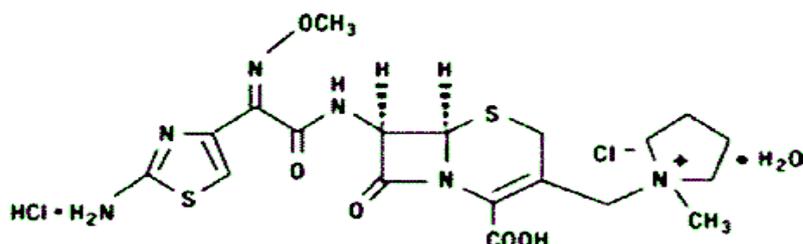


Fig. 1. Structure formula of cefepime

Table 1. Effect of Cefepime on serum liver function test in rabbits at 1st, 3rd, 7th and 14th day post treatment

Parameter	Control	Days of treatment			
		1 st day	3 rd day	7 th day	14 th day
Serum AST (U/L)	10.55	10.45	10.47	10.88	11.08
	± 0.48	± 0.30	± 0.56	± 0.24	± 0.23
Serum ALT (U/L)	30.18	35.67	28.50	37.63	35.90
	± 6.82	± 1.68	± 3.89	± 2.83	± 4.69
ALP (U/L)	119.00	81.00	67.33	74.67	90.00
	± 3.79	± 6.51	± 6.74	± 17.37	± 20.74
Serum total protein (g/dl)	6.19	5.59	6.14	6.07	6.32
	± 0.56	± 0.10	± 0.46	± 0.28	± 0.59
Serum albumin (g/dl)	3.14	3.09	3.21	3.20	3.13
	± 0.09	± 0.07	± 0.12	± 0.05	± 0.2

Effect on serum Albumin

Table 1, displays the post I/M injection of cefepime that results insignificant alternation of serum albumin level at 1st day 3rd, 7th, and 14th day (3.09, 3.21, 3.20, and 3.13 g/dl, respectively) when compared with control group (3.14 g/dl).

Results showed non-marked ($P < 0.05$) change for serum biochemical levels within days between treated and control groups. Our results revealed that treated group with cefepime had insignificant effect on liver function tests within days post administration. Other findings, showed that cefepime at low level (45 mg /kg b.wt. for 5 days) did not change liver function tests but, at high level (90 and 180 mg /kg b.wt. for 5 days) increased liver function tests in rats

(El-Sayed *et al.*, 2014). Also, cefepime caused decreased serum proteins level. This might be attributed to the progressive cellular and tubular dysfunction manifested histopathologically (El-Sayed *et al.*, 2014). This was consistent with that recorded in rabbits following administration of both cefpirome (Deki *et al.*, 1990) and after oral dosing of cefmtaline, urinary protein was detected (Kato *et al.*, 2001).

Kidney Function Test

Effect on serum urea

Results in Table 2 shows the effect of I/M injection of cefepime in the therapeutic dose for 5 successive days to rabbits that resulting insignificant difference of serum urea level at

Table 2. Effect of cefepime on serum kidney function test in rabbits at 1st, 3rd, 7th, and 14th day post treatment

Parameters	Control	Days of treatment			
		1 st day	3 rd day	7 th day	14 th day
Serum urea (mg/dl)	38.58	38.10	37.50	37.50	29.60
	± 5.59	± 5.84	± 7.3	± 1.42	± 2.19
Serum creatinine (mg/dl)	1.55	1.71	1.33	1.53	1.29
	± 0.20	± 0.18	± 0.31	± 0.32	± 0.22

1st, 3rd, 7th, and 14th day (38.10, 37.50, 37.50 and 29.60 mg/dl, respectively) when compared with control group (38.58 mg/dl).

Effect on serum creatinine

Results showed that there was insignificant change of serum creatinine level at 1st day 3rd, 7th, and 14th day post I/M injection of cefepime when compared with control group (Table 2).

Other findings, discovered that cefepime at low level (45 mg /kg b.wt. for 5 days) did not change serum concentration of urea but at high level (180 mg/kg b.wt. for 5 days) was significantly increased on the 5th day of administration in rats (**El-Sayed *et al.*, 2014**). Cefmetaline slightly increased urea nitrogen after oral dosing of 500 mg/kg b.wt. in rabbits (**Kato *et al.*, 2001**). The increase in serum urea and incidence of renal failure had been reported in some patients treated with cefepime during the post marketing experience (**Princeton, 2003**).

Under the conditions of this work, the results are clearly suggesting that cefepime administration at recommended therapeutic dose (75 mg/kg BW) is extremely safe

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تأثير السيفيبيم على وظائف الكبد والكلية في الأرانب

مي حمدي هلال¹ – أحمد عبده سعيد¹ – جمال الدين شمس¹ – مجدي فكري أبو الفتوح²

1- قسم الفارماكولوجي – كلية الطب البيطري – جامعة الزقازيق – مصر

2- قسم الطب الشرعي والسموم – كلية الطب البيطري – جامعة الزقازيق – مصر

تستهدف الدراسة معرفة تأثير دواء السيفيبيم على وظائف الكبد والكلية في الأرانب، أجريت هذه الدراسة على عدد 24 أرانب نيوزيلاندي عند عمر الفطام 35 يوماً، تم توزيعها عشوائياً على مجموعتين متساويتين، المجموعة الأولى (الضابطة، عدد = 12 أرنب) كانت تحقن بالمحلول الملحي المعقم والمجموعة الثانية (عدد = 12 أرنب) كانت تحقن عضلياً في الفخذ 75 ملجم/كجم من وزن الجسم سيفيبيم يومياً لمدة 5 أيام متتالية. ثم تم تجميع عينات الدم في (اليوم الأول، الثالث، السابع، الرابع عشر) بعد 24 ساعة من آخر جرعة من الدواء. تم تجميع العينات بدون مضاد تجلط ثم وضعها في جهاز الطرد المركزي ثم تفريزها، وبعد تحليل العينات نتج الآتي: تأثير دواء السيفيبيم غير مهم على وظائف الكبد لأن لم ينتج تغيير في انزيمات وظائف الكبد مثل (ALT,ALP,AST) والبروتين الكلي والاليومين وتأثير دواء السيفيبيم غير مهم على وظائف الكلى لأن لم ينتج تغيير في تركيز اليوريا في الدم وتركيز الكيراتينين في الدم، ولهذا فإن استخدام السيفيبيم آمن وصحى على صحة الانسان.

المحكمون:

1- أ.د. محمد حسن خيرى

2- أ.د. أحمد حسن دعادر

أستاذ الفارماكولوجي – كلية الطب البيطري – جامعة الزقازيق.
أستاذ الإنتاج الحيواني المتفرغ – كلية الزراعة – جامعة الزقازيق.

