رقم البحث (49)

RESIDUES OF CIPROFLOXACIN AND CEFOTAXIME SODIUM IN TISSUES OF TREATED RABBITS

BY

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ABSTRACT

The current study was carried out on 82 Newzealand white rabbits (2-2.5kg) to evaluate ciprofloxacin(20mg/kgb.wt) and cefotaxime sodium(50mg/kgb.wt) residues in their tissues (kidney, liver ,muscle) using microbial inhibition assay by plates seeded with bacillus subtilis. Moreover, the effect of heat treatment on the presence of these residues was also estimated . It was found that the highest residues of both drugs were recorded in kidney followed by the liver while traces were present in the muscles .Ciprofloxacin residues disappeared from kidney, liver and muscles after 6,6 and 4 days respectively ,from last administration, while cefotaxime sodium couldn't be detected in kidney, liver , muscle after 7, 4, 4 days respectively post treatment. It was observed that thermal treatment significantly decreased residues of both drugs in tissues of treated rabbits.

INTRODUCTION

Rabbits have an economic importance as a source of a high meat protein which is nutritious ,easily digestible and poor in fat. Moreover, they contribute to fur production**(Abd-El-Motelib et al.,1990)**. So it is very important to protect rabbit industry from many diseases threatening it , this can be achieved by using antibiotics for prophylaxsis and treatment as well as for growth promotion.

The use of antimicrobial drugs in food-producing animals including rabbits may leave residues in food stuffs of animal origin ,so administration of these drugs to food producing animals require not only consideration of effects on the animal but also the effects on human who ingest food from these animals**.** Concern has been expressed about possible harmful

effects on human through the use of drugs in food-producing animals, as follows: increased microbial drug resistance ,allergic reactions, teratogenesis and mutagenesis **(Alhendi et al.,2000**).

Studying the elimination and withdrawal time of these antibiotics from serum and tissues of animal is very important to ensure protection of public health against possible harmful effects of veterinary drug residues**(McEwen and Fedroka-Cray,2002)**. Among the well developed antibacterials that widely used in veterinary medicine are ciprofloxacin and cefotaxime.

Ciprofloxacin is a broad spectrum antimicrobial active against both Gram-positive, Gram-negative bacteria as well as Mycoplasma **(Drlica and Zhao,1997).** Ciprofloxacin is used to treat a number of infections including: infection of bones and joints, endocarditis, gastroenteritis, malignant otitis externa, respiratory tract infections, cellulitis, urinary tract infections, prostatitis, anthrax and others**(Young,2003, Schaeffer,2004 and Vardakas et al.,2008).**

Cefotaxime sodium is a semi-synthetic 3rd generation cephalosporins antibiotic. It is active against gram-negative and gram-positive bacteria with a highly expanded activity against gram-negative bacteria. It is highly stable to hydrolysis by most beta-lactamases and has greater activity than first-or second-generation cephalosporins against gram negative bacteria. It is rapidly absorbed after intramuscular administration**(Tippa and Singh,2010)**

The present work was performed to evaluate ciprofloxacin and cefotaxime sodium residues in tissues(liver, muscle, kidney) of treated rabbit. In addition to throw light on the effect of heat treatment on the levels of these residues.

MATERIALS AND METHODS

Drugs:

1. Ciprofloxacin (Ciproxin10%) (solution) (Alexandria Co for pharmaceuticals, Alexandria, Egypt.
2. Claforan® injection available as glass vials containing 1.048 gm cefotaxime sodium powder equivalent to 1 gm cefotaxime. Claforan® is produced by Sanofi-aventis Egypt s.a.e under license of laboratories Aventis/ France

RABBITS

A total of eighty two(82) Newzealand white rabbits weighing about 2-2.5 kg purchased from a private rabbitary were used in this experiment. They were housed in a disinfected metal cages in a well ventilated , well lightened and disinfected room. They received commercial non medicated pellet ration and clean water ad-libitum .

After one weak period of acclimatization in cages condition, rabbits were divided into 3 groups as follows:

1st group: (10 rabbits) negative control(non-medicated).

2nd group: (36 rabbits) were administered ciprofloxacin orally (20mg/kg b.wt.) for 5 successive days **(Hanan et al.,2000).**.

3rd group: (36 rabbits) were intramuscularly injected with cefotaxime sodium (50mg/kg b.wt.) for 3 successive days**(Gerding et al.,1982).**

Sampling:

Tissue Samples:

Tissue samples(liver, kidney and muscles) were obtained from six rabbits of each group on the 1st,2nd,3rd,4th,7th,14th days post administration of drugs. Each sample was divided into 2 parts; the 1st part was left as raw part, while the 2nd part was cooked by boiling.

Extraction of drug from samples :

One ml of phosphate buffer (ph 7.2) was added to 1 gm of each sample. Tissue samples were homogenized thoroughly using sterile morter with pistol then centrifuged at 3000 rpm for 10 minutes, then the supernatant was assayed microbiologically.

Antimicrobial assay:

The collected samples(serum and tissue) were assayed for determination of ciprofloxacin and cefotaxime sodium concentration by the microbiological assay method according to **Bennett et al., (1966)** and **Arret et al.(1971)** using Bacillus subtilis (ATCC 6633) as a test organism.

Statistical analysis:

Data obtained in this study were organized , summarized and statistically analyzed using statistical software program (SPSS for windows, version 20, USA). Independent t-test was used to test variance between cooked and raw samples **Selvian,(1996)**.

RESULTS

A-Standard curve of ciprofloxacin :

Standard curves of ciprofloxacin in antibacterial free rabbit's muscle, liver and kidney tissues using **Bacillus subtilis (ATCC6633)** as a test organism were recorded in Table (1) and Fig.(1-3).

A-1:Ciprofloxacin residues in tissues:

The obtained results showed that ciprofloxacin showed a highest concentration level (12.88±0.48µg/gm) in raw kidney on the 1st day post last dose .While ciprofloxacin concentration was declined gradually till reached 1.28±0.087µg/gm on the 4th day post dosing . Moreover, ciprofloxacin residues couldn't be detected in raw kidney on the 6th day after last dose.(Table 2).

Regarding the effect of cooking on the concentration of ciprofloxacin (µg/gm) in kidney tissues after daily oral administration of 20mg/kg b.wt. for 5 successive days. The data displayed a significant decrease in ciprofloxacin concentrations($P<0.05$) in kidney tissues(10.02±1.09, 3.25±0.25 and 0.8±0.01) on the 1st day, 2nd day and 4th day post dosing, respectively, compared to the concentrations obtained in raw tissues.

The obtained data showed also that, the concentrations of ciprofloxacin in raw liver tissues of treated rabbits were11.41±0.39, 2.89±0.24 and 0.6±0.05µg/gm on the 1st, 2nd and 4th day post treatment, respectively(Table 3). Moreover, cooking of liver tissues revealed a significant decrease($P<0.05$) in ciprofloxacin concentrations (5.4±0.19 and 1.17±0.17µg/gm) on the first and second day post dosing , respectively, compared to that recorded in raw tissues. The concentration of ciprofloxacin was not detected on 6th day post treatment in raw tissues ,while it is not detected in cooked tissues on 4th day post treatment .

The present study showed that ciprofloxacin concentrations in raw muscle were 5.75±0.24 and 1.41±0.13µg/gm on the 1st and 2nd day post treatment, respectively (Table 4). The cooking of muscle tissues samples reflected a significant decrease ($p> 0.05$) in ciprofloxacin concentrations to 2.6±0.25 and 0.38±0.015 µg/gm on 1st and 2nd day post dosing, respectively. Ciprofloxacin residues in raw and cooked muscle tissues were not detected on 4th day post treatment.

B-Standard curve of cefotaxime sodium:

Standard curves of cefotaxime sodium in antibacterial free rabbit serum, muscle, liver and kidney tissues using **bacillus subtilis** (ATCC6633) as a test organism were recorded in Table (5) and Fig.(4-6).

B-1:Cefotaxime sodium residues in tissues:

The recorded results showed that, cefotaxime sodium evoked a highest concentration level(25.41±0.41µg/gm) in raw kidney at the 1st day post dosing. The cefotaxime sodium concentrations were declined gradually till reached 1.016±0.065µg/gm at the 6th day after treatment (Table 6) .The cooking of kidney tissues reflected a significant decrease ($P<0.05$) in cefotaxime sodium concentration in tissues of treated rabbits compared to the concentrations recorded in raw tissues. Our data revealed that the cefotaxime concentrations in cooked kidney tissues were 19.3±1.02, 5.5±0.57, 2.36±0.22 and 0.75±0.08µg/gm at the 1st , 2nd , 4th and 6th days post treatment. No detected cefotaxime sodium levels in both raw and cooked kidney tissues at the 7th day after treatment were recrded.

The recorded data showed that, the concentrations of cefotaxime sodium in raw liver tissues of treated rabbits were 3.13±0.21& 0.9± 0.01µg/gm at the 1st and 2nd day post treatment, respectively(Table 7). Cooking of liver tissues revealed a significant decrease ($P<0.05$) in cefotaxime concentration (2.02±0.21µg/gm) at 1st day post treatment compared to that recorded in raw tissues. While the residues were not detected in cooked liver tissues at the second day after treatment.

The present data mirrored that the ,concentrations of cefotaxime sodium in raw muscle tissues of treated rabbits were 1.1±0.13 and 0.16±0.01 at the 1st and 2nd day post dosing respectively, Meanwhile no detected cefotaxime sodium residues in raw muscle tissues at the 4th day post treatment(Table 8) . Cooking of muscle tissues of treated rabbits induced a significant decrease ($P<0.05$) in cefotaxime in cooked tissues. Cefotaxime residue(0.66±0.05) was only recorded at 1st day post treatmernt .

DISCUSSION

The present work was carried out to estimate ciprofloxacin and cefotaxime sodium residues in tissues of treated rabbits after their administration in therapeutic doses (20mg/kg orallyb.wt.&50mg/kg b.wt. intramuscularly, respectively). Moreover, an investigation was undertaken to explain if cooking could destroy or decrease the level of biologically active ciprofloxacin and cefotaxime sodium in tissues and organs of treated rabbits.

A: Ciprofloxacin residues in tissues:

The recorded results showed that following oral administration of ciprofloxacin at a dose of 20mg/kg once daily for5 successive days in rabbits, it is widely distributed in all tested tissues . Kidney, liver, muscle contained the highest drug concentration (12.88±0.48,11.41 ±0.39,5.75±0.248 µg/gm, respectively) at 24h following the last dose. These results were in agreement with that of **Bergan,(1981)** who reported that the tissue penetration of ciprofloxacin is excellent and certainly represent a unique feature of fluoroquinolone compared to other antibiotics.

The obtained data showed that ciprofloxacin was highly concentrated in the kidney followed by the liver while traces were present in the muscle. It couldn't be detected in raw kidney , and liver on the 6^{th} day post last dose while it disappeared from muscle tissue on the 4^{th} day post last dose This findings agreed with that recorded by **Abou El-Nil,(2008)** who observed that following intramuscular injection of pefloxacin (10mg/kg)in rabbits for 5 successive days**,** pefloxacin highest concentration level was detected in kidney at 12 hr from last dose (28.32±2.261µg/gm) and then not detected on the 6^{th} day post treatment followed by the liver(26.32±2.31µg/gm) then shoulder muscle (18.21±1.011µg/gm)and its level showed significant decrease 72 hr. Also, **Abd El-Aziz et al., (1997)** mentioned that the tissue concentrations of fluoroquinolones were higher in kidney and liver following oral treatment of infected chicken. On the same ground **Shams et al.,(2002)** reported that after oral administration of pefloxacin at a dose of 10 mg/kg once daily for 5 successive days in chickens, Kidney, lung and liver contained the highest concentration of the drug at 24 hours following the last dose,

Ciprofloxacin residues were highest in kidney tissues and were lowest in muscle of rabbits. The observed high concentration of the drug in kidney could be attributed to renal route of ciprofloxacin excretion **(Edlund et al.,1988)**.

Concerning the effect of cooking on the residues of ciprofloxacin in rabbit tissues(kidney ,liver, muscle), it was found that ciprofloxacin concentrations were significantly decreased up to 10.016±1.09&5.4±0.19 and2.6±0.246µg/gm in cooked kidney, liver and muscle ,respectively ,on the 1st day post last dose. These results were nearly similar to that obtained by **Javadi et al.,(2011)** who recorded a significant decrease of enrofloxacin residues and its metabolite ciprofloxacin from edible tissues of broiler chicken after different cooking method. **Abou El-Nil,(2008)** mentioned also that boiling of kidney samples obtained from rabbits treated with pefloxacin (10mg/kg) for 5 successive days revealed a significant decrease in pefloxacin concentration from 28.32±2.261 to 16.516±0.421µg/g).

B: Cefotaxime sodium residues in tissues:

Following intramuscular injection of cefotaxime sodium at a dose of 50mg/kg once daily for 3 successive days in rabbits, cefotaxime was highly concentrated in kidney followed by the liver while traces were recorded in muscle tissue. It couldn't be detected in kidney on the 7th day post treatment. Cefotaxime sodium residues were completely disappeared from liver and muscle after 4 days from last administration. Thses results were in agreement with that of **Abd EL-Aty et al.,(2001)** who mentioned that after repeated intramuscular injection of caftazidim at a dose of 50 mg/kg b.wt. twice daily for 5 successive days in a rabbit model ,tissue residue profile using a microbiological assay with bacillus subtilis as the test organism revealed that the tissue level concentrations were highest in kidneys, and decreased in the following order: liver> heart> muscles and plasma. No ceftazidim residues were detected in tissues and plasma after 72h. In addition, **Beconi-Barker et al.,(1996)** reported that after I/M injection of ceftiofur at a dose of 2.45mg /kg for 5 successive days to six cattle(3 male, 3 female), In females, average total residues measured in edible tissues at 12 hours after the final injection were : kidney, (7.91 mg/kg); liver (1.60 mg/kg); muscle, (0.28 mg/kg); and fat , (0.24 mg/kg). While in males , average total residues in edible tissue collected at 12 hrs after the final injection were: kidney, (6.82 mg/kg); liver,(1.34 mg/kg); muscle, (0.21mg/kg); and fat (0.40 mg/kg).

The result also revealed that , Cefotaxime sodium residues were highest in kidney tissues and lowest in muscle of rabbits. The observed high concentration of the drug in kidney could be attributed to renal route of cefotaxime excretion **.** On the same ground **Riviere and Papich,(2009)** reported that the route of elimination of cephalosporins is

primarily renal and concentration in urine are usually high , this feature make cephalosporins good choice for treatment of urinary tract infections.

Concerning the effect of cooking on the level of cefotaxime sodium in rabbit tissues(kidney ,liver, muscle), it was found that cefotaxime concentration were significantly decreased to 25±0.41&3.13±0.21&1.1±0.13µg/gm in raw kidney, liver, muscle, respectively, while were declined up to 19.3±1.02&2.02±0.21& 0.66±0.15µg/gm in cooked kidney, liver, muscle, respectively, in the 1st day post last dose. The obtained results were not previously discussed by any author ,so more studies on the effect of cooking on the residues of cephalosporins in edible tissues must be performed.

Table (1): The corrected reading of inhibition zones (mm) for the standard curve of ciprofloxacin in serum and tissues of rabbits

Concentration (µg/ml)	Inhibition Zone(mm)		
	Liver	Kidney	Muscle
50	30	30	28
25	23	22	21
12.50	21	21	20
6.25	18	18	18
3.12	15	16	12
1.5	14	13	11
0.78	10	9	10

Table(2): Concentration of ciprofloxacin in kidney of rabbit(µg/gm)after oral administration 0f 20mg/kgb.wt. for 5 successive days.

Mean±S.E. n=6

Kidney Sample	Time of sampling					
	1st day	2nd Day	4th day	6th day	7th day	14th day
Raw sample	12.88 ± 0.48	4.46 ± 0.24	1.28 ± 0.08	ND	ND	ND
Cooked Sample	10.02 ± 1.09*	3.25 ± 0.25*	0.8 ± 0.1*	ND	ND	ND

*Significant at P<0.05

Table(3): Concentration of ciprofloxacin(µg/gm) in raw and cooked liver of treated rabbit(µg/gm)after oral administration of 20mg/kgb.wt. for 5 successive days. Mean±S.E. n=6

liver sample	Time of sampling					
	1st day	2nd Day	4th day	6th day	7th day	14th day
Raw sample	11.41 ± 0.39	2.89 ± 0.24	0.6 ± 0.05	ND	ND	ND
Cooked sample	5.4 ± 0.19*	1.17 ± 0.17*	ND*	ND	ND	ND

***Significant at P<0.05.**

Table(4): Concentration of ciprofloxacin(µg/gm) in raw and cooked muscle of treated rabbit after oral administration at 20mg/kgb.wt. for 5 successive days.

Mean±S.E. n=6

muscle sample	**Time of sampling**					
	1st day	**2nd Day**	**4th day**	**6th day**	**7th day**	**14th day**
Raw sample	5.75 ± 0.24	1.41 ± 0.13	ND	ND	ND	ND
Cooked Sample	2.6 ± 0.25*	0.38 ± 0.015*	ND	ND	ND	ND

*** Significant at P<0.05.**

Table (5): The corrected reading of inhibition zones (mm) for the standard curve of cefotaxime sodium in serum and tissues of rabbits

Concentrations (µg/ml)	**Inhibition Zone(mm)**		
	liver	Kidney	Muscle
50	26	22	27
25	19	19	20
12.5	16	15	19
6.25	14	12	16
3.12	12	10	14
1.5	10	9	12
0.78	7	5	7

Table (6): Concentration of cefotaxime sodium in raw and cooked kidney of rabbits (µg/gm) after I.M injection of 50 mg/kgb.wt,/day for 3 successive days:

Mean±S.E n=6

kidney sample	Time of sampling					
	1st day	2nd Day	4th day	6th day	7th day	14th day
Raw sample	25.41 ± 0.41	8.4 ± 0.51	3.55 ± 0.34	1.016 ± 0.07	ND	ND
Cooked Sample	19.3 ± 1.02*	5.5 ± 0.57*	2.36 ± 0.22*	0.75 ± 0.08*	ND	ND

* Significant at P<0.05.

Table(7): Concentration of cefotaxime sodium(µg/gm) in raw and cooked liver of rabbits after I.M injection of 50mg/kg/day for 3 successive days.

Mean±S.E n=6

Liver Sample	Time of sampling					
	1st day	2nd day	4th day	6th day	7th day	14th day
Raw sample	3.13 ± 0.21	0.9 ± 0.01	ND	ND	ND	ND
Cooked Sample	2.02 ± 0.21*	ND*	ND	ND	ND	ND

***Significant at P<0.05.**

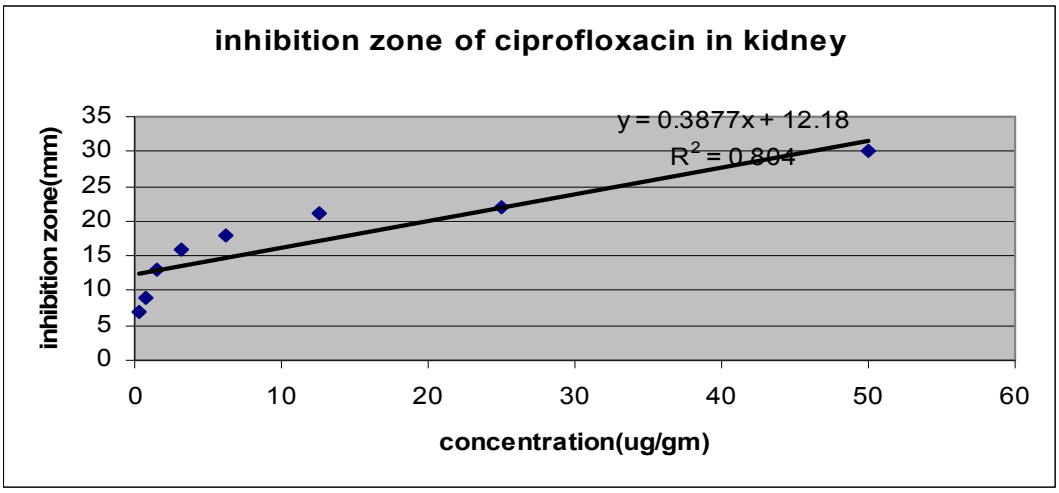
Table(8): Concentration of cefotaxime sodium(µg/gm) in raw and cooked muscle of rabbits after I.M injection of 50mg/kg/day for 3 successive days.

Mean±S.E n=6

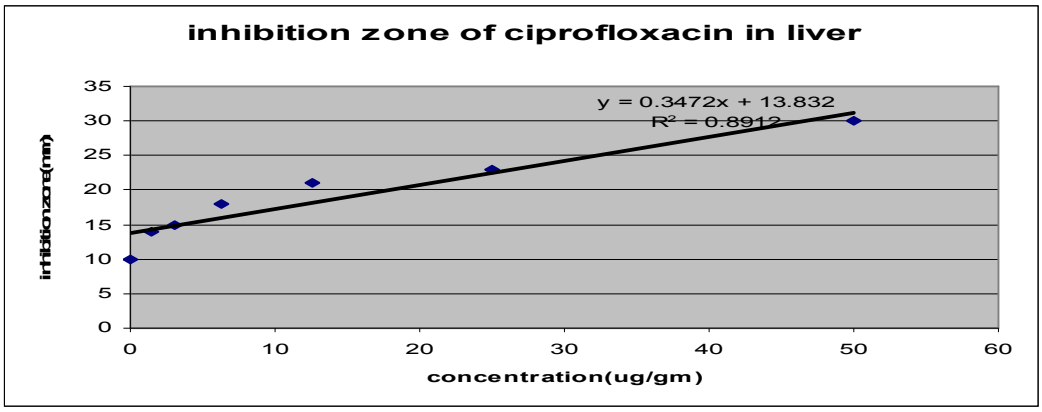
Muscle sample	Time of sampling					
	1st day	2nd day	4th day	6th day	7th day	14th day
Raw sample	1.1 ± 0.13	0.16 ± 0.01	ND	ND	ND	ND
Cooked Sample	0.66 ± 0.05*	ND	ND	ND	ND	ND

*** Significant at P<0.05.**

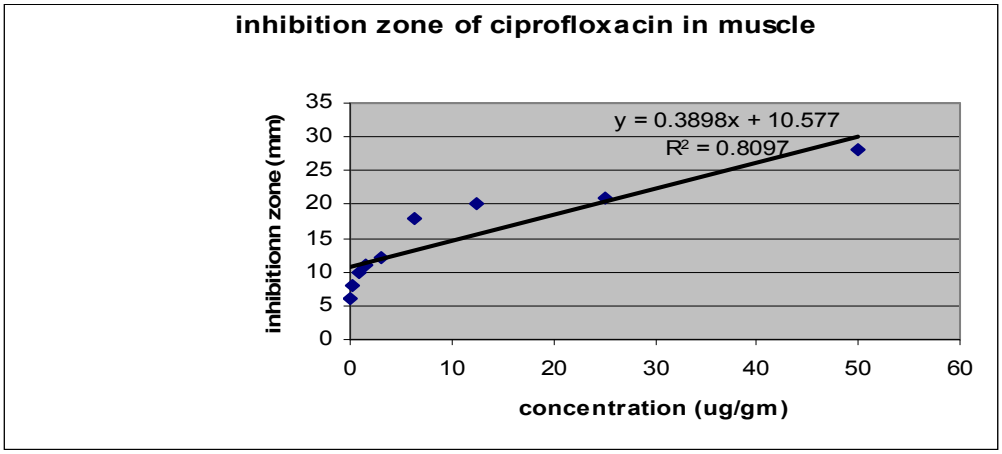
Fig(1): The corrected readings of inhibiton zones (mm) for standard curve of ciprofloxacin in rabbits kidney



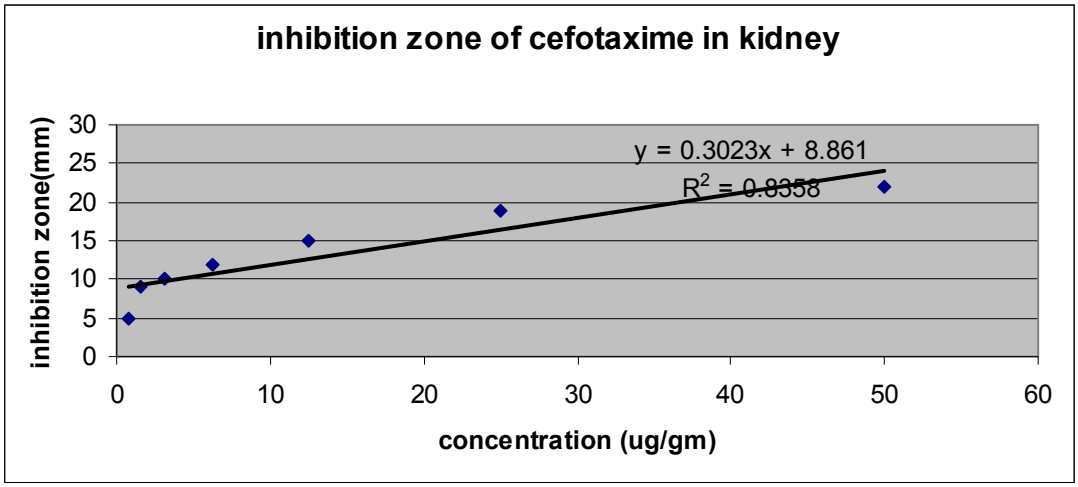
Fig(2): The corrected readings of inhibiton zones (mm) for standard curve of ciprofloxacin in rabbits liver



Fig(3): The corrected readings of inhibiton zones(mm) of ciprofloxacin in rabbits muscle



Fig(4): The corrected readings of inhibition zones (mm) for standard curve of cefotaxime sodium **i**n rabbits kidney



Fig(5): The corrected readings of inhibition zones (mm) for standard curve of cefotaxime sodium in rabbits liver

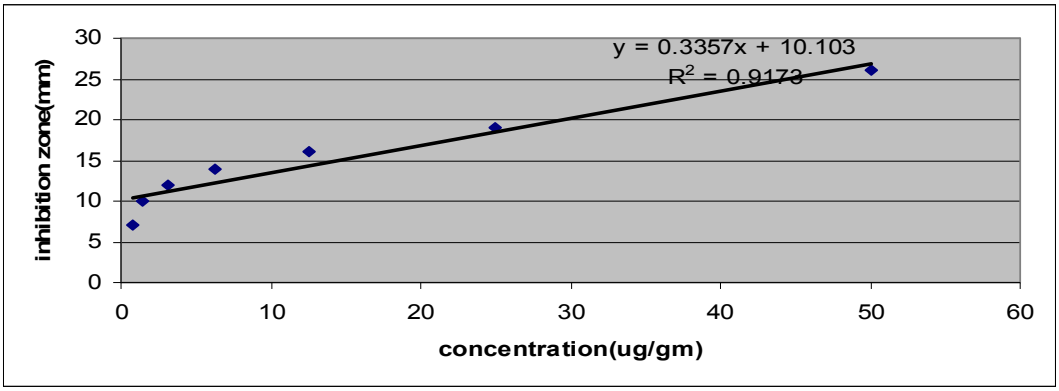
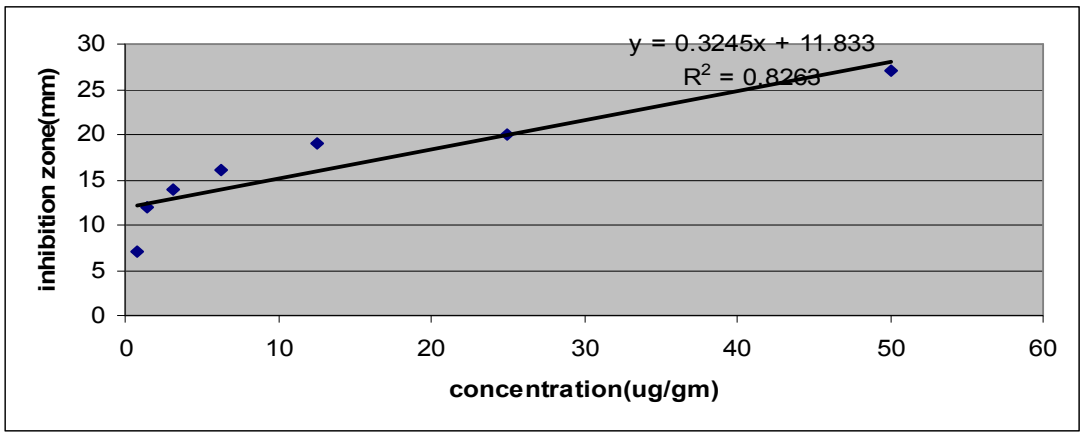


Fig (6): The corrected readings (mm) of inhibition zones for standard curve of cefotaxime sodium in rabbits muscle**.**



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الملخص العربى

بقايا السيبروفلوكساسين والسيفوتاكسيم صوديوم فى انسجة الارانب المعالجة

أ.د/ مجدى صلاح عامر أ.د/ محمد جبرالسيد سارة طة العزب

قسم الادوية- كلية الطب البيطرى- جامعة المنصورة

اجريت هذة الدراسة على عدد ٨٢ ارنب لدراسة بقايا السيبروفلوكساسين والسيفوتاكسيم صوديوم فى الانسجة (الكلى والكبدو العضلات) بطريقة القياس الميكربيولوجى . وقد قسمت الارانب الى ثلاثة مجاميع على النحو التالى:

المجموعة الأولى:(١٠أرانب) المجموعة الظابطة بدون علاج.

المجموعة الثانية: (٣٦أرنب) أعطيت هذة المجموعة عقار السيبروفلوكساسين بالفم بجرعة علاجية قدرها ٢٠مجم/كجم من وزن الجسم لمدة خمسة أيام.

المجموعة الثالثة: (٣٦أرنب) تم حقنها عضليا بعقار السيفوتاكسيم صوديوم بجرعة علاجية قدرها٥٠ مجم/كجم من وزن الجسم لمدة ثلاثة أيام متتالية.

تم جمع عينات من الكبد،الكلى والعضلات من كل أرنب (بواقع٦ أرانب من كل مجموعة) بعد يوم، يومين، و٤ أيام، و ٦أيام و ٧ أيام ، ١٤ يوم من انتهاء الجرعة العلاجية. هذا وقد قسمت كل عينة الى جزئين، الاول ترك نيئ وتم طهى الجزء الآخر، وذلك لقياس بقايا الأدوية بهم.

اوضحت النتائج ان بقايا عقار السيبروفلوكساسين فى الانسجة النيئة قد أظهرت تفاوت بعد خمسة ايام علاج متتالية حيث وجد فى انسجة الكلى اعلى تركيز بالنسبة لعقار السيبروفلوكساسين (١٢,٨٨±٤٨, ٠ميكروجرام/جرام) ثم الكبد(١١,٤١±٠,٣٩ميكروجرام/جرام) واقلهم العضلات(٥,٧٥±٠,٢٤ ٠ميكروجرام /جرام) فى الارانب المعالجة بعد ٢٤ ساعة من ايقاف العلاج. هذة النتائج قلت تدريجيا الى ان اختفى العقار من انسجة الكلى والكبد فى اليوم السادس من انتهاء العلاج ومن العضلات فى اليوم الرابع من انتهاء العلاج. وقد اوضحت الدراسة ايضا ان معاملة انسجة الكبد والكلى والعضلات بالطهى قد احدث انخفاضا معنويا لبقايا عقار السيبروفلوكساسين مقارنة بالانسجة الطازجة حيث سجلت تركيزات٢٥,±٦, ٢ &١٩, ± ٥,٤&٠٩, ١±٠٢, ١٠ فى العضلات والكبد والكلى وذلك عند اليوم الاول بعد ايقاف العلاجز

كما اوضحت النتائج ان بقايا عقار السيفوتاكسيم صوديوم فى الانسجة النيئة بعد ثلاثة ايام علاج متتالية كانت عالية فى انسجة الكلى (٤١و٢٥±٤١و ميكروجرام/جرام) ثم الكبد(٣,١٣±٢١,ميكروجرام/جرام) ثم العضلات(١,١±١٣, ميكروجرام /جرام) فى الارانب المعالجة بعد ٢٤ ساعة من ايقاف العلاج. هذة النتائج قلت تدريجيا الى ان اختفى العقار من انسجة الكلى فى اليوم السابع من انتهاء العلاج ومن الكبد و العضلات فى اليوم الرابع من انتهاء العلاج. وقد اوضحت الدراسة ان معاملة انسجة الكبد والكلى والعضلات بالطهى قد احدث انخفاضا معنويا لبقايا عقار السيبروفلوكساسين مقارنة بالانسجة الطازجة فقد اصبحت٠٥,±٦٦,&٢١, ±٢,٠٢&١,٠٢±٣, ١٩ فى العضلات والكبد والكلى وذلك عند اليوم الاول بعد ايقاف العلاج.