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Residues of Ciprofloxacin in Rabbit Tissues by HPLC

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Abstract

The current study aimed to determine residues of ciprofloxacin in different rabbit tissues (liver, muscles, kidneys, spleen, heart and lungs) and sera following administration of multiple oral doses. Twenty five rabbits were given the drug at a dose of 5 mg/kg BW for five successive days and then samples were collected at 1st, 3rd, 5th, 7th, 9th, 15th and 21st day after last oral dose. The results indicated a widespread distribution of ciprofloxacin in the tested tissues except in the heart. The drug remained within the detectable limit till the 3rd day in most tested tissues, while in kidneys it remained till the 5th day following the last oral administration of the drug. Therefore, muscles of rabbits could be eaten safely in the 3rd day post treatment, while liver and kidneys could be eaten safely in the 5th day after treatment without any hazards on consumers.

Keywords: Residues, Ciprofloxacin, Rabbits, HPLC

Introduction

High concentrations of drug residues in edible animal tissues might result from the extra-label use of drug or non-compliance with the withdrawal period [1]. The control of drug residues is a significant point to obtain safe food for human consumption, therefore, maximum residue limits (MRL) of drugs have been set for edible animal tissues [1,2].

Ciprofloxacin is a fluorinated quinolone carboxylic acid derivative; it exhibits a wide spectrum of antimicrobial activity, including some G +ve, G -ve bacteria and *Mycoplasma* [3-7]. It prevents the bacterial DNA replication and synthesis via the inhibition of the A subunit of the bacterial DNA gyrase, this synthetic drug act as bactericidal at relatively low concentration [8]. The use of fluoroquinolones in animals has been discussed recently due to the development of resistant micro-organisms among humans. Therefore, fluoroquinolones became a part of highly risk antimicrobial drugs [9,10].

The World Health Organization and Office International des Epizooties have defined quinolones as "critically important antimicrobials" for both human and animal health [11].

The current study aimed to determine residues of ciprofloxacin in different rabbit tissues and sera following multiple oral doses of this drug using High Performance Liquid Chromatography (HPLC). Moreover, the estimation of the withdrawal time of the drug in rabbit tissues was carried out.

Material and Methods

Experimental design

Ciprofloxacin (Ciproxin 10%®) was obtained as an oral suspension (10%) from the Arab Company for the Manufacture of Pesticides and Veterinary Medicines, Animal Health Division, Jordan.

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The molecular formula is: $C_{17}H_{18}FN_3O_3 \bullet HC_l \bullet H_2O$ and the molecular weight is 385.8. Twenty five healthy male New Zealand rabbits ranging from 2-2.5 kg body weight were used including four control rabbits. The animals were housed in the Experimental Animals Research Unit (EARU) at the Faculty of Veterinary Medicine, Zagazig University.

The control rabbits were used for the preparation of blank and spiked samples for method validation. Twenty one rabbits were given ciprofloxacin directly into the stomach through the feeding tube orally at a dosage of 5 mg/kg B.W once daily for 5 successive days [12]. Three rabbits were slaughtered at 1^{st}, 3^{rd}, 5^{th}, 7^{th}, 9^{th}, 15^{th} and 21^{st} day after last oral dose. Samples from blood for separation of serum, heart, lungs, liver, spleen, muscles and kidneys were taken from slaughtered rabbits for the determination of ciprofloxacin residues.

Analytical procedures

Preparation of samples for analysis

The collected blood samples in centrifuge tubes were left to coagulate and were centrifuged at 3000 rpm for 15 minutes to obtain clear serum. The serum was then transferred immediately to sterile tubes and stored at -20°C until analysis using HPLC at the Central Laboratory, Faculty of Veterinary Medicine, Zagazig University. At the time of the assay, frozen rabbit tissue samples were partially thawed at room temperature (23^oC) for 30 min and were blended in a food processor four times for 20–30 sec at high speed. The material after each intermittent blending were subjected to stirring to obtain a uniform paste-like consistency, and the samples were then stored at -70^oC until analyzed within 30 days.

Extraction and determination of drug residues

Extraction of the drug residues from the samples was carried out according to Stoilova [13]. Frozen samples were thawed in centrifuge tubes at room temperature (23°C) and then 1 gm was accurately weighted into a polypropylene centrifuge tube. Ten ml of acetonitrile were added and shaken for 1min; the sample was then shaken for 10 min and centrifuged for 10 min at 9500 rpm.

The supernatant was evaporated under a nitrogen stream at 50°C, and the extraction was repeated using acetonitrile with the sample residues. The additional supernatant was added to the initial one and evaporated under a nitrogen stream at 50°C. The residue was then dissolved in 5 ml of 0.02 M ammonium acetate pH=9 then vortexed for 1 min. The extract was then applied to SPE C18 cartridge using the following steps:

- SPE cartridge was previously activated with 3 ml acetonitrile and 3 ml 0.02 M ammonium acetate pH=3.0.
- After sample loading, the cartridge was washed with 2 ml water, and then dried for 3 min.
- The analyte was eluted with 10 ml 0.2% formic acid in acetonitrile.

  The sample was evaporated to dryness and dissolved in to 1 ml mobile phase. Finally, filtration was performed using 0.45 µm nylon syringe filter.

Liquid chromatography operating conditions

Liquid chromatography operating conditions included injection volume of 20 µl, flow rate: 1 ml/min, column temperature: 50^oC, UV- detector: 280 nm and the mobile phase: 50 mL/L acetic acid: acetonitrile: methanol (900:50:50) according to Kamberie *et al*. [14].

Quantification

Quantification of residues in the samples was obtained and calculated from area under curves extrapolated automatically by the software.

Method validation

The validation was established by laboratory studies, that the performance characteristics of the method met the requirements for the intended analytical application.

System Precision

It was conducted using five replicates of the toluene standard solution. Acceptance criteria: Relative standard deviation (RSD) ≤ 1% according to International conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH).

Linearity and range

Linearity was performed by preparing a minimum of five different concentrations of drug standard at squared correlation coefficient of 0.99 (r^2) according to ICH.

Method Precision

It was conducted using five replicates of ciprofloxacin standard solutions. Acceptance criteria: RSD ≤ 1% according to ICH.

Selectivity and specificity

Verification of selectivity was conducted by evaluating the spiked standard response following extraction from different rabbit tissues. Acceptance criteria: there is no interference between the pure standard and peaks of any impurities or extracted solvents according to ICH.

Accuracy and recovery

The tissue samples of rabbits were spiked by adding known quantities of ciprofloxacin. Those samples were analyzed against standard solutions of same concentrations. The accuracy was then calculated from the test results as a percentage recovery Senyuva *et al*. [15].

Limit of detection (LOD)

It is the concentration which gives signal to noise ratio 3:1 according to (ICH).

Limit of quantification (LOQ):

It is the concentration which gives signal to noise ratio 10:1 according to (ICH).

Ruggedness

It was conducted by the analysis of the same samples under different conditions, such as different personnel and different times. Acceptance criteria: pooled RSD is not more than 6% in every change item.

Robustness

It was determined by observing how a method stands up to slight variations in normal operating parameters. Acceptance criteria: pooled RSD is not more than 6% in every change item.

Table 1: The concentrations of ciprofloxacin standard (µg/ml) and their corresponding peak response determined automatically using HPLC chromatogram system

*RT	Level	Amount (µg/ml)	Area
11.215	1	0.050	2.425
	2	0.100	4.333
	3	0.500	28.850
	4	1.000	44.377
	5	2.000	73.224
	6	4.000	243.770
	7	5.000	286.800
	8	10.000	546.540

*RT: Retention Time

Results

Method validation

The HPLC system was found precise as the Relative Standard Deviation (RSD) of five replicates of the toluene standard solution was 0.002%. High correlation coefficient was obtained indicating linearity (r^2 = 0.9968). The method for ciprofloxacin separation was precise as the RSD of five replicates of the ciprofloxacin standard solution was 0.23%. There was no interference between the pure standard and peaks of any impurities or

extracted solvents. The retention time (R.T.) of ciprofloxacin was 11.215 minutes (Figure 1).

The percentage recovery of ciprofloxacin spiked samples ranged from 98-100%. The LOD for ciprofloxacin was 0.002 µg/ml, while, LOQ was 0.025 µg/ml. The pooled RSD for ciprofloxacin was 3.5% for ruggedness and the pooled RSD for robustness was 1.4%.

Standard curve preparation

Ciprofloxacin standard concentrations of 0.05, 0.1, 0.5, 1, 2, 4, 5 and 10 µg/ml and their corresponding peak responses are illustrated in Table (1) and Figure (2). The calibration curve was calculated by linear regression equation method as y = 55.8367493x – 3.8199805 where y symbol indicated the area under peak and x symbol indicated concentrations of ciprofloxacin. Linearity existed witin the range of 0.05 and 10 µg/ml with a correlation coefficient (r^2 = 0.9968).

Table 2: The concentrations of ciprofloxacin residues in tissues of slaughtered rabbits at various intervals after treatment (5 mg/kg BW once daily for 5 consecutive days) (n=3) determined automatically using HPLC chromatogram system

Tissue	The concentration (µg/gm) Mean ± SE						
	1st	3rd	5th	7th	9th	15th	21th
Liver	0.657 ± 0.013	0.313 ± 0.012	ND	ND	ND	ND	ND
Kidneys	0.746 ± 0.014	0.402 ± 0.026	0.215 ± 0.001	ND	ND	ND	ND
Muscles	0.129 ± 0.001	ND	ND	ND	ND	ND	ND
Lungs	0.702 ± 0.036	0.340 ± 0.005	ND	ND	ND	ND	ND
Spleen	0.524 ± 0.048	0.157 ± 0.006	ND	ND	ND	ND	ND
Serum	0.134 ± 0.01	ND	ND	ND	ND	ND	ND
Heart	ND	ND	ND	ND	ND	ND	ND

*ND: Not Detected

Tissue residues

Tissue distribution of ciprofloxacin is represented in Table (2). The data represented emphasized a widespread distribution of the drug in tested tissues (liver, kidneys, muscles, lungs, spleen, serum and heart). Ciprofloxacin concentrations were 0.657 ± 0.013, 0.746 ± 0.014, 0.129 ± 0.001, 0.702 ± 0.036, 0.524 ± 0.048 and 0.134 ± 0.01 µg/gm at the 1st day post last oral dosage in liver, kidneys, muscles, lungs, spleen and serum, respectively while it was not detected in the heart.

Ciprofloxacin remained within the detectable limit till the 3rd day in most tested tissues. While in kidneys, it remained till the 5th day after treatment of the drug (Table 2).

Discussion

Ciprofloxacin is a fluorinated quinolone carboxylic acid derivative that exhibits a wide spectrum of antimicrobial activity, including some Gram +ve, Gram -ve bacteria and *Mycoplasma* [3-7]. It prevents the bacterial DNA replication and synthesis via the inhibition of the A subunit of the bacterial DNA gyrase, this synthetic drug act as bactericidal and antimicrobial at relatively low concentration [8]. It was reported that very low amounts of veterinary drugs remain in animal products as drug residues [16]. A number of possible adverse effects of veterinary drug residues have been suggested, such as; allergy, antibiotic resistance, disruption of intestinal flora and chronic toxic effects with prolonged administration.

The use of enrofloxacin and Ciprofloxacin became a dangerous problem, as their residues in the tissues may be directly toxic or causing bacterial resistance and may cause allergic hypersensitivity reactions in humans [17]. It was mentioned that fluoroquinolones have health hazards as they causes gastro-intestinal toxicity, photoirritation, and developmental alteration beside joints inflammation [18].

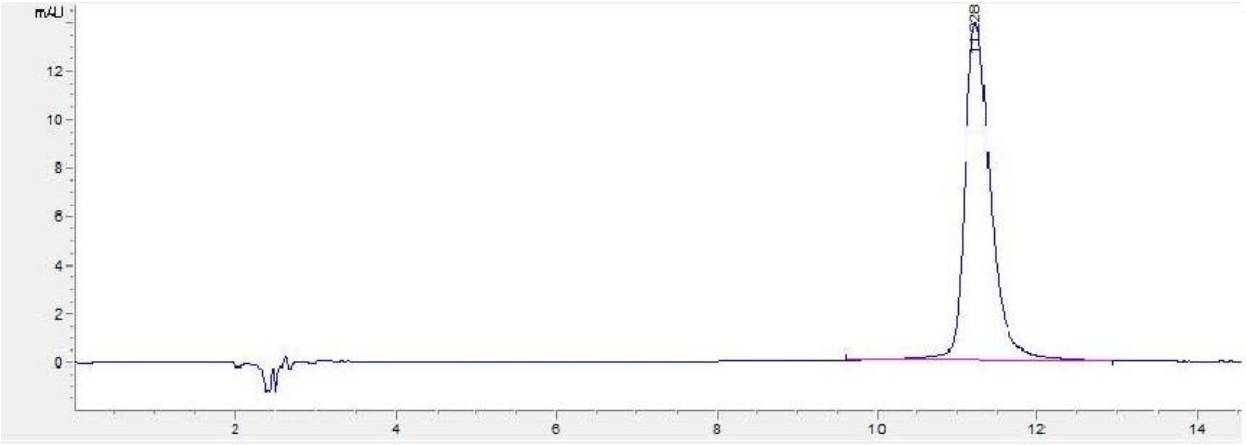

Figure 1: Chromatograms of ciprofloxacin standard (5µg/ml) determined automatically using HPLC chromatogram system

Due to lack of previous studies about ciprofloxacin residues, we compared the current study with the other valuable members of fluoroquinolones group. The present study revealed that ciprofloxacin was highly distributed in different body tissues. The drug was detected in all tested organs and tissues except the heart.

The obtained high ciprofloxacin concentrations in kidneys, lungs and liver at the 1st day after treatment are in agreement with those reported by Anadón *et al*. [19] who found that the residues of enrofloxacin and its metabolite ciprofloxacin were highly distributed in liver, kidneys, muscles, lungs, fat, and skin of slaughtered chickens treated orally with 10 mg/kg once daily for four days. Moreover, the results were in accordance with those reported by Widiastuti [20] who mentioned that enrofloxacin and ciprofloxacin residues were distributed in breast, thigh and liver of chickens received enrofloxacin orally at a dose of 50 mg/kg BW daily for nine days consecutively.

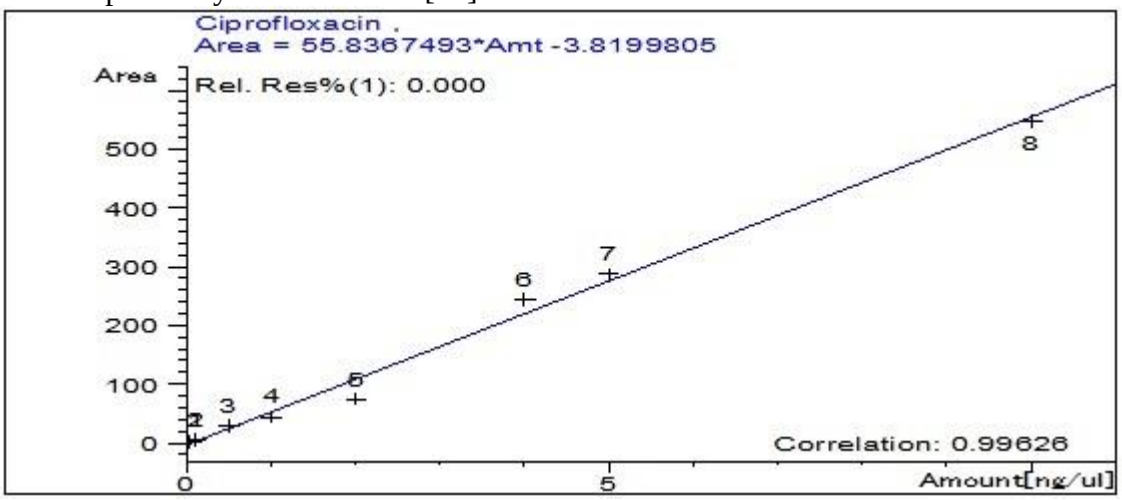

Figure 2: Standard curve of ciprofloxacin determined automatically using HPLC chromatogram system

Ciprofloxacin remained within the detectable limit till the 3rd day in most tested tissues, while in kidneys, it remained till the 5th day following last oral administration of the drug. Finally, the results showed that the withdrawal time of ciprofloxacin was seven days after the last oral administration (Table 2). The obtained results are supported by Anadón *et al.* [21] who detected that the withdrawal time of ciprofloxacin was five days after the last oral dose of ciprofloxacin to chickens (8 mg/kg/day on 3 successive days).

The drug concentration in muscles was 0.129 ± 0.001 µg/gm at the 1st day only then it was not detected in the following days (Table 2). This finding is in agreement with Jelena *et*

al. [22] who reported that ciprofloxacin was not detected in broiler muscles after 2 days of oral administration at a dose of 10 mg/kg BW/day.

A progressive order of ciprofloxacin levels in the muscles, liver and kidneys, respectively, with increasing time was observed in the current study. This is equally reflected by the increasing concentrations in the MRLs recommended by EMEA [23] as 100 µg/kg, 200 µg/kg and 300 µg/kg in muscles, liver and kidneys, respectively.

The organs with high levels of residues in the first day were kidneys (0.746 ± 0.014 µg/g), liver (0.657 ± 0.013 µg/g) then muscles (0.129 ± 0.001 µg/g) (Table 2). In the third day of slaughter, the residues disappeared from breast muscles only and they were minimized in all organs (Table 2). Moreover, in the 5th day post treatment, the residues disappeared from all the examined organs while were still found in kidneys with a concentration of 0.215 ± 0.001 µg/g. Finally, ciprofloxacin residues were lower than MRL at the 5th day after treatment. In accordance, another study reported that ciprofloxacin was distributed in all tissues tested at high levels until 7 days post-administration after oral treatment of broilers with an enrofloxacin formulation at 10 mg/kg/5 days [24]. In contrary, Anadón *et al*. [19] reported that enrofloxacin and ciprofloxacin residues were decreased slowly fat, kidney, liver, lungs, muscles and skin of chickens. The metabolite ciprofloxacin continued until 12 days in post oral administration of enrofloxacin (10 mg/kg/4 days).

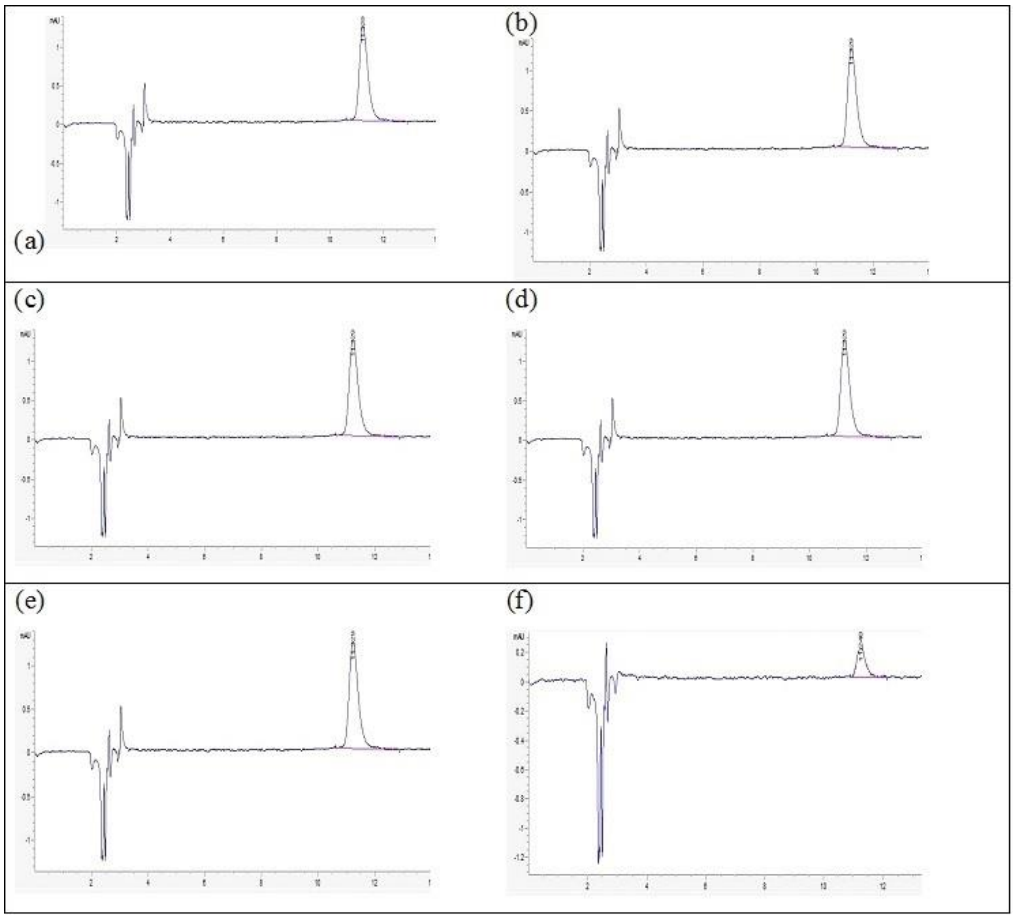

Figure 3: Chromatograms of ciprofloxacin extract of rabbit liver (a), kidneys (b), muscles (c), lungs (d), spleen (e) and serum (f) at 1st day following last oral dose (5 mg/kg B.W) determined automatically using HPLC chromatogram system

It had been reported that the withdrawal time for ciprofloxacin in laying hens was five days after administering ciprofloxacin orally at a dose of 5 mg/kg/day for five days [25].

While, Anadón *et al*. [17] reported that the withdrawal period of ciprofloxacin in pigs was 10 days after intra-muscular administration of enrofloxacin at 2.5 mg/kg for 3 days. The withdrawal period for pork meat was 6-8 days, depending on the pharmaceutical form and the concentration of the drug [26].

According to EMEA [23] a microbiological acceptable daily intake (ADI) of 6.2 µg/kg BW × 70 kg (standard body weight of human according FAO/WHO [27]) = 434 µg/person can be ingested by human over a life time without appreciable risk.

Conclusion

In conclusion, only muscle samples of rabbits at the 3rd day post treatment contained ciprofloxacin residues below the recommended MRL, while liver and kidneys at the 3rd day post treatment contained ciprofloxacin residues above the recommended MRL. Therefore, muscles of rabbits could be eaten safely in the 3rd day post treatment, while liver and kidneys of rabbits could be eaten safely in the 5th day after treatment without any hazards on consumers.

Conflict of interest

None of the authors have any conflict of interest to declare

Acknowledgment

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الملخص العربي

البقايا الدوائية للسيبروفلوكساسين فى الأرانب

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استهدفت هذه الدراسة قياس بقايا السيبروفلوكساسين فى أنسجة الأرانب المختلفة (الكبد، الكلى، العضلات، الطحال، الرئة، القلب و الدم بعد اعطاء عدد ٢١ أرنب السيبروفلوكساسين عن طريق الفم بجرعة ٥ مجم/ كجم من وزن الأرانب لمدة ٥ أيام متتالية ؛ والقاء الضوء على مدة سحب الأدوية من الأنسجة المختلفة لتصبح امنة للاستهلاك الأدمى. وقد تم استخدام عدد ٤ أرانب (المجموعة الضابطة). تم ذبح عدد ٣ أرانب عند اليوم الأول، الثالث، الخامس، السابع، التاسع، الخامس عشر و الحادى و العشرين بعد آخر جرعة و أخذ الأنسجة المختلفة (الكبد، الكلى، العضلات، الطحال، الرئة، القلب و الدم) ثم فحصها و قياس مستوى هذه المضادات فى عينات الدم والأنسجة المختلفة وذلك بواسطة جهاز الفصل الكروماتوجرافى السائل العالى الأداء و من هذه النتائج نستنتج انتشار الدواء انتشارا واسعا فى أنسجة الأرانب المختلفة (الكبد، الكلى، العضلات، الطحال، الرئة، القلب و الدم). قد تلاحظ وجود السيبروفلوكساسين فى الأنسجة المختلفة حتى اليوم الثالث من إعطاء الجرعة النهائية فيما عدا الكلي استمر وجود الدواء حتى اليوم الخامس من إعطاء الجرعة النهائية.