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Residues Depletion of Doxycycline in Rabbit Tissues Using HPLC

Ahmed A. Said[1], Sameh M. El-Nabtity[1], Elham A. Mobarez[2], Eslam E. Hamed[3] and Maha S. Abdel-Hafeez[2*]

[1]Pharmacology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Egypt
[2]Chemistry Department, Animal Health Research Institute, Dokki, Giza, Egypt
[3]Central Laboratory, Faculty of Veterinary Medicine, Zagazig University

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Abstract

This work was performed to quantitatively determine doxycycline residues in different tissues of rabbits (kidneys, spleen, liver, muscles, heart and lungs) and sera following multiple oral doses of the drug using High Performance Liquid Chromatography. Moreover, the study aimed to estimate the withdrawal time of this drug in rabbit tissues. Twenty five healthy male New Zealand rabbits ranging from 2-2.5 kg body weight were used. Twenty one rabbits were given doxycycline directly into the stomach at a dosage of 10 mg/kg BW once daily for five successive days. Samples were analyzed at 1st, 3rd, 5th, 7th, 9th, 15th and 21st day after last oral dose. The results indicated a widespread distribution of doxycycline in the samples, which remained within the detectable limit till the 3rd day in most tested tissues. While in kidneys, spleen and liver, doxycycline remained till the 5th day following the last oral administration of the drug. Therefore, it is recommended that rabbits treated with doxycycline must be slaughtered after the fifth day of drug administration to be safe for human consumption.

Keywords: Residues, Depletion, Doxycycline, Rabbits, HPLC

Introduction

Tetracyclines are wide spectrum antibacterials, active against G+ve, G-ve bacteria and *Mycoplasma* [1-9]. They prevent the synthesis of bacterial protein by blocking the attachment of t-RNA with the bacterial ribosome [10,11]. However, the use of tetracyclines results in high concentrations of residues in different animal tissues which may cause allergy in hypersensitive people. Low doses of antibiotics in feed stuffs can lead to problems such as spread of drug-resistant micro-organisms if consumed for long periods [12].

The European regulation number 2377/90 sets maximum residue limit (MRL) of tetracyclines in different edible tissues [13]. The MRLs of tetracyclines in rabbit tissues are (300 µg/kg for liver, 600 µg/kg for kidneys and 100 µg/kg for muscle) [14]. Therefore, the current study was conducted to quantitatively determine doxycycline residues in different tissues of rabbits following multiple oral doses of this drug using High Performance liquid chromatography. Moreover, the study aimed to estimate the withdrawal time of this drug in rabbit tissues.

Materials and Methods

Experimental design

Doxycycline (Doxy 40 H.C.®) was obtained from Arab Company for medical Products-Cairo- Egypt. The molecular formula is $C_{22}H_{24}N_2O_8$•HCl•½ C_2H_6O•½ H_2O and the molecular weight is 512.9. Twenty five healthy male New Zealand rabbits ranging from 2- 2.5 kg body weight were used. Four rabbits were used as controls. 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.

***Corresponding author e-mail: (mohammedsaleh85_doctor@msn.com), Chemistry Department, Animal Health Research Institute, Dokki, Giza, Egypt.**

Twenty one rabbits were given doxycycline directly into the stomach through the feeding tube orally at a dosage of 10 mg/kg BW once daily for five successive days [15]. Three rabbits were slaughtered at 1st, 3rd, 5th, 7th, 9th, 15th and 21st day after last oral dose. Samples from kidneys, spleen, liver, muscles, serum, heart and lungs were preserved at -20°C until analysis using HPLC for doxycycline residues' determination.

Analytical procedures

Preparation of the 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 High Performance Liquid chromatography (HPLC) at the Central Laboratory, Faculty of Veterinary Medicine, Zagazig University. At the time of assay, frozen rabbit tissue samples were partially thawed at room temperature (23°C) 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°C until analyzed within 30 days.

Extraction and determination of drug residues

Extraction of the drug residues from the samples was carried out according to Cinquina *et al*. [16]. Five grams of the tissue were accurately weighted and placed in a polypropylene centrifuge tube. Two ml of 20% trichloroacetic acid (TCA) were added and then the sample was vortexed for few seconds. Twenty ml of McIlvaine buffer (11.8 gram of citric acid monohydrate, 13.72 gram of disodium hydrogen phosphate dihydrate and 33.62 gram of ethylenediaminetetraacetic acid disodium salt diluted in 1 liter of water 0.01 M) were added and the mixture was centrifuged at 4000 rpm/20 min. The clear supernatant was cleaned up with SPE HLB C18 columns using the following steps:

- Activation of columns with 3 ml methanol then 2 ml water.
- Loading of the samples then columns were washed with 2 ml methanol 5% in water. The eluent was then eluted with 3 ml methanol.
- Evaporation using nitrogen evaporator then the residues were reconstituted in 1 ml methanol. Finally, filtration was performed using 0.45 µm nylon syringe filter.

Liquid chromatography operating conditions

Liquid chromatography operating conditions included doxycycline injection volume of 20 µl, flow rate: 1 ml/min., column temperature: not controlled, UV- Detector: 364 nm and the mobile phase: 0.01 M oxalic acid: methanol: acetonitrile (60:25:15) according to Cinquina *et al*. [16].

Quantification

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

Method validation

It is the procedure by which the performance characteristics of the method meet 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 doxycycline standard solutions. Acceptance criteria: RSD is < 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 doxycycline standard. Those samples were analyzed against standard solutions of the same concentrations. The accuracy is then calculated from the test results as a percentage recovery according to Senyuva *et al*. [17].

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 sample at different conditions, such as different personnel and different days. Acceptance criteria: pooled RSD is < 6% in every change item.

Robustness

It was determined by detecting how a method stands up to slight variations in normal operating conditions. Acceptance criteria: pooled RSD is < 6% in every change item.

Results

Method validation

The HPLC system was found precise as the RSD of five replicates of the toluene standard solution is 0.002%. High correlation coefficient was obtained indicating linearity (r^2 = 0.99941). The method for doxycycline separation is precise as the RSD of five replicates of the doxycycline standard solution was 0.41%. There was no interference between the pure standard and peaks of any impurities or extracted solvents. The retention time (R.T.) of doxycycline was 14.052 minutes (Figure 1).

Table 1: Concentrations of doxycycline standard (µg/ml) and their corresponding peak response automatically using HPLC chromatogram system

RT	Level	Amount (µg/ml)	Area
14.052	1	0.010	2.310
	2	0.020	4.754
	3	0.050	9.586
	4	0.100	23.804
	5	0.200	39.820
	6	0.500	87.281
	7	1.000	178.990
	8	2.000	377.690

*RT: Retention Time

The percentage recovery of doxycycline spiked samples ranged from 95-98%. The LOD for doxycycline was 0.0025 µg/ml, while, LOQ was 0.01 µg/ml. The pooled RSD for doxycycline was 4.2% for ruggedness and the Pooled RSD for robustness was 2.3%.

Standard curve preparation

Doxycycline standard concentrations of 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1 and 2 µg/ml and their corresponding peak responses (area under peak) are illustrated in Table (1) and shown in Figure (2). The calibration curve was calculated by linear regression equation method as y = 186.412094 x + 0.1063125

where y symbol indicated area under peak and x symbol indicated concentrations of doxycycline. Linearity existed within the range of 0.05 and 10 µg/ml with a correlation coefficient (r^2 = 0.99941).

Table 2: The concentrations of doxycycline in tissues of slaughtered rabbits at various intervals following the last oral administration determined automatically using HPLC chromatogram system

Tissue Intervals	The concentration (µg/gm) Mean ± SE						
	1st	3rd	5th	7h	9th	15th	21th
Liver	0.134 ± 0.003	0.073 ± 0.002	0.055 ± 0.004	ND	ND	ND	ND
Kidneys	0.165 ± 0.004	0.136 ± 0.001	0.089 ± 0.001	ND	ND	ND	ND
Muscle	0.080 ± 0.007	0.055 ± 0.002	ND	ND	ND	ND	ND
Lungs	0.088 ± 0.007	0.061 ± 0.004	ND	ND	ND	ND	ND
Spleen	0.143 ± 0.002	0.081 ± 0.002	0.060 ± 0.001	ND	ND	ND	ND
Serum	0.227 ± 0.006	0.072 ± 0.003	ND	ND	ND	ND	ND
Heart	0.049 ± 0.002	0.050 ± 0.002	ND	ND	ND	ND	ND

ND: Not Detected

Tissue residues

Doxycycline distribution in both serum and tissues of normal healthy rabbits after oral administration (10 mg/kg BW / 5 days) was examined and the obtained results are presented in Table (2). The data represented in the table emphasized a widespread distribution of the drug in the examined samples (kidneys, spleen, liver, muscle, serum, heart and lungs).

The doxycycline tissue concentrations were (0.165 ± 0.008, 0.141 ± 0.004, 0.131 ± 0.007, 0.0898 ± 0.009, 0.082 ± 0.007, 1.138 ± 0.048 and 0.048 ± 0.003 µg/gm) at the first day after the last oral dosage in kidneys, spleen, liver, muscle, lungs, serum and heart, respectively (Figure 3). Doxycycline remained within the detectable level till the 3rd day in all tested tissues, while in liver, kidneys and spleen it remained till the 5th day following the last oral administration of the drug (Table 2).

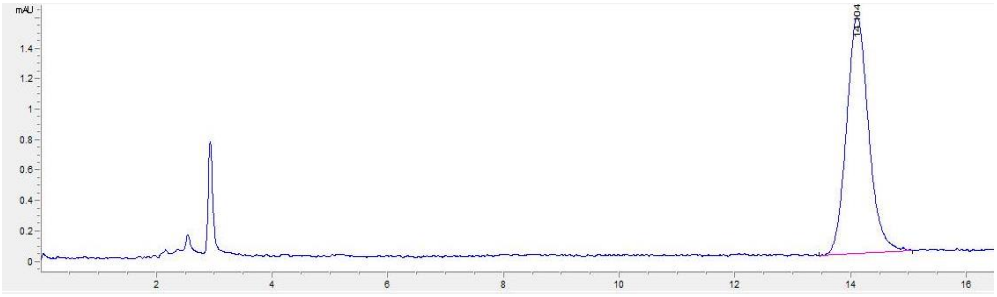

Figure 1: Chromatograms of doxycycline standard (0.2µg/ml) determined automatically using HPLC chromatogram system

Discussion

High concentration of drug residues in edible animal tissues is a consequence of extra-label use of drugs or non-compliance withdrawal period [18]. The control of the 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 [18,19]. In most cases, doxycycline residue causes benign intracranial hypertension resulting in different clinical signs such as loss of vision, vomiting, nausea, diarrhea, dysphagia, entero-colitis, inflammatory lesions with monilial overgrowth in the genital region, esophagitis and esophageal ulcerations [18-20].

The current study revealed that doxycycline was highly distributed in different rabbit tissues (Table 2). The drug was detected in all tested tissues. The highest doxycycline concentration was determined in kidneys (0.165 ± 0.004 µg/gm), spleen (0.143 ± 0.002

µg/gm), liver (0.134 ± 0.003 µg/gm) and lungs (0.088 ± 0.007 µg/gm). These results were supported by Anadon *et al.* [23] who reported that doxycycline was distributed in all examined tissues (liver, kidneys, lungs, muscle) and serum, and high amounts were found after oral treatment of 30 chickens (20 mg/kg/4 days). The results showed that doxycycline was cleared slowly and became below the accepted permissible limit at the 5th day after dosing.

From the obtained results, doxycycline concentrations in the examined organs were lower than the concentration in the serum at the 1st day after treatment (Table 2). This finding is not compatible with that mentioned by Cars and Ryan [15] who detected that the doxycycline levels in rabbit muscles were much higher than the corresponding serum level. This could be attributed to different degrees of tissue penetration of doxycycline in different species. The results agreed with Anadon *et al.* [23] who found that the levels of doxycycline residues in the examined tissues were less than the synchronous plasma levels at 12 h post treatment in chickens.

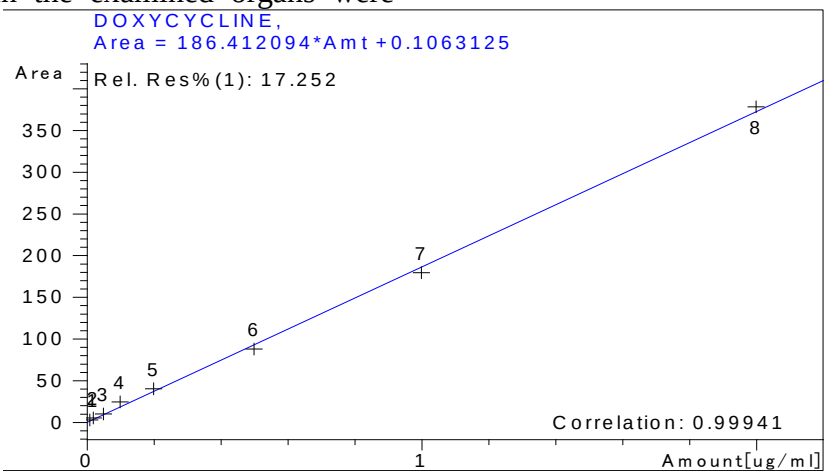

Figure 2: Standard curve of doxycycline determined automatically using HPLC chromatogram system

Doxycycline is effective against respiratory pathogens in avian medicine, as well as in other domestic species, because it penetrates well into respiratory tissues [22,24-26]. By injecting long acting doxycycline (Dox-LA), this feature seems to be boosted and is longer-lasting compared with a single bolus of aqueous Dox (Dox-PO) [27]. This is likely to be beneficial when treating susceptible pathogens such as *Mycoplasma* spp, *E. coli* and others. Additionally, the gastrointestinal system is one of the main routes for elimination of doxycycline, which is therefore effective against *colibacillosis* and other enterobacterial infections [27].

In the present study, the levels of doxycycline after oral treatment (10 mg/kg BW daily/5 consecutive days) revealed that the concentration in muscles (0.080 ± 0.007 µg/gm) < lungs (0.088 ± 0.007 µg/gm) < liver (0.134 ± 0.003 µg/gm) < kidneys (0.165 ± 0.004 µg/gm) at the first day after treatment. The obtained results are supported by Ismail and El-Kattan [26] who detected that the arrangement of tissue concentrations of doxycycline following repeated oral administration in different tissues were: kidneys > liver > lungs > muscle. Doxycycline was detected in liver, kidneys and spleen in substantial concentrations on the 5th day after treatment (Table 2). However, on the 7th day, doxycycline concentration in all other tissues was lower than the limit of detection of the used method.

In contrast to the present findings, Crivineanu *et al.* [28] reported that after the therapeutic use of doxycycline in pigs, the withdrawal period was eight days for meat, seven days for liver and four days for kidneys. This could be attributed to differences in the dose, species and administration route.

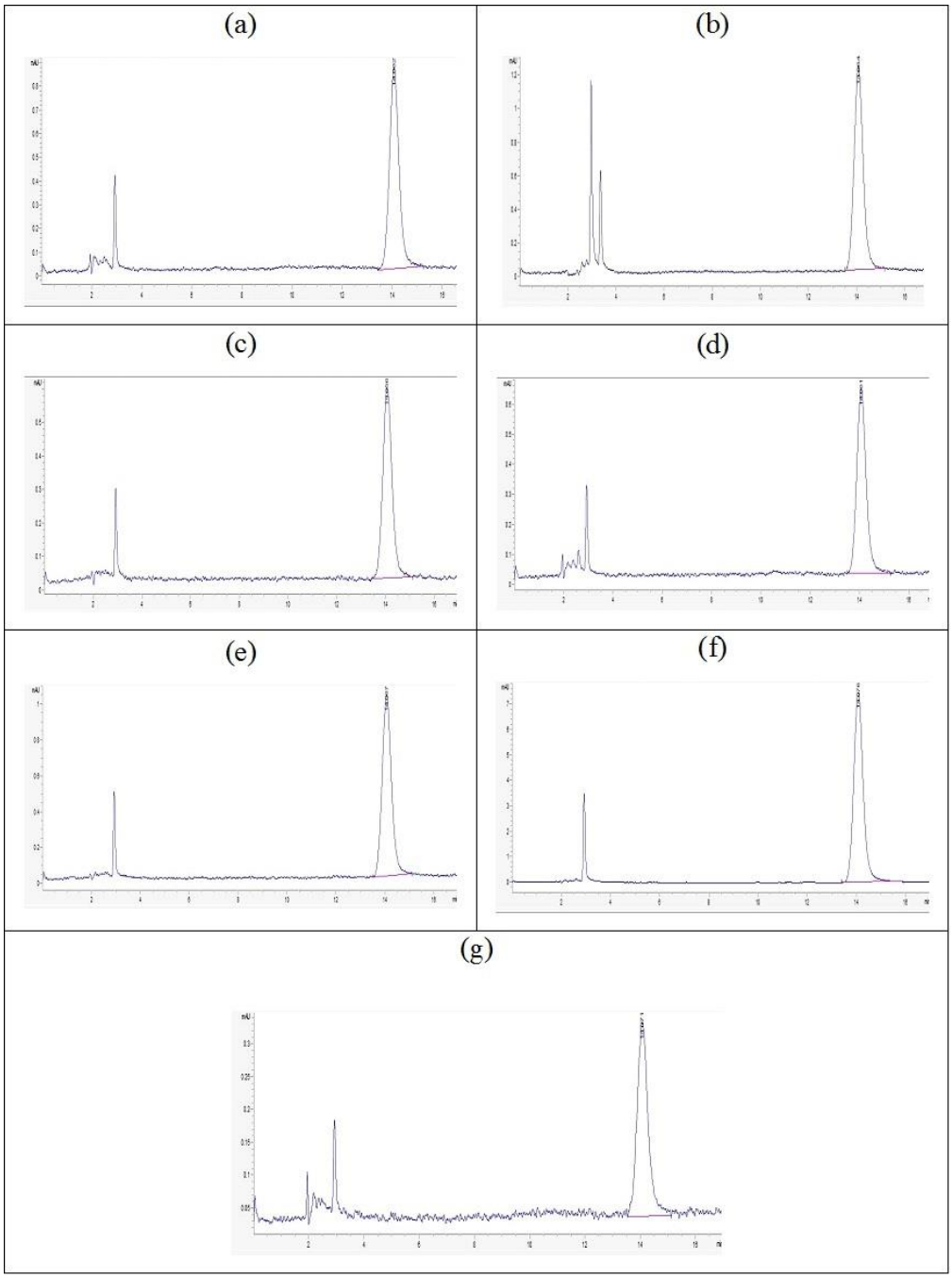

Figure 3: Chromatograms of doxycycline extract of rabbit liver (a), kidneys (b), muscles (c), lungs (d), spleen (e),serum (f) and heart (g) at 1st day following the last oral dose (10 mg/kg BW) determined automatically using HPLC chromatogram system

Identical MRLs have been developed in rabbits (100, 300 and 600 µg/kg for muscles, liver and kidneys, respectively) [29]. According to EMEA [29] the microbiological ADI is 3 µg/kg BW (i.e. 210 µg/person) for doxycycline. According to the established MRL of doxycycline 100 µg/kg for muscle, 300 µg/kg for liver and 600 µg/kg for kidneys, the obtained results revealed that rabbit tissues are lower than MRL at the 1th day after treatment. The present findings disagree with Bacchetta *et al.* [30] who stated that doxycycline residues concentrations were below the MRLs three days after the cessation of the treatment after its administration orally at the dose of 40 mg/kg BW. Such different results might be contributed to differences in the selected dosage, drug metabolism and analytical procedures.

Yoshimura *et al*. [31] reported that the withdrawal time for doxycycline after oral treatment of laying hens at a dose of 0.5 g/liter for seven consecutive days was six days. In addition, Anadon *et al.* [23] reported that the withdrawal time for doxycycline after oral treatment (20 mg/kg/4 days) in chickens was five days. Moreover, Croubels *et al.* [32] recorded that the withdrawal time for liver and muscle tissue were 12 days and 17 days, respectively in turkeys following its administration at a dosage of 25 mg/kg BW. Atef *et al.* [25] recorded that the doxycycline residue concentrations in the examined tissues was below the MRL six days after oral or intra-muscular treatment with 15 mg/kg BW. twice daily for five successive days in healthy chickens. Ismail and El-Kattan [26] found that the withdrawal time for doxycycline after oral dose of 20 mg/kg given twice daily for five successive days in diseased chickens was seven days, whereas, its levels in all tissues was lower than the sensitivity limit of the used method. Finally, Wang *et al*. [33] mentioned that the withdrawal period should not be less than 16 days after an intra-muscular injection of doxycycline HCl once a day at dose of 2.5 mg/kg BW for four days. These differences could be related to the used dose, species and age variations which could affect the degree of protein binding of the drug and/or the difference in the method selected for the assessment of the drug.

Conclusion

According to the established MRL of doxycycline, the obtained results revealed that doxycycline concentrations in the examined organs were lower than the recommended MRL at the 1st day post treatment. Rabbits treated with doxycycline must be slaughtered after the fifth day of drug administration to be safe for human consumption.

Conflict of interest

None of the authors have any conflict of interest to declare

Acknowledgment

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الملخص العربي

سحب بقايا الدوكسيسيكلين فى أنسجة الأرانب باستخدام جهاز الفصل الكروماتوجرافى

احمد عبده سعيد[١]، سامح محمد النبتيتى[١]، الهام احمد مبارز[٢]، اسلام السيد حامد[٣] ، مها صبرى عبد الحفيظ[٢*]
[١]قسم الفارماكولوجيا- كلية الطب البيطرى-جامعة الزقازيق-مصر
[٢]معهد بحوث صحة الحيوان- الدقى- الجيزة-مصر
[٣]المعمل المركزي- كلية الطب البيطرى-جامعة الزقازيق-مصر

استهدفت هذه الدراسة قياس بقايا المضاد الحيوي الدوكسيسيكلين فى أنسجة الأرانب المختلفة (الكبد، الكلى، العضلات، الطحال، الرئة، القلب و الدم) بعد اعطاء عدد٢١ أرنب الدوكسيسيكلين عن طريق الفم بجرعة ١٠مجم/ كجم من وزن الأرانب لمدة ٥ أيام متتالية؛ والقاء الضوء على مدة سحب الدواء 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 هذا المضاد الحيوي فى عينات المصل والأنسجة المختلفة وذلك بواسطة جهاز الفصل الكروماتوجرافى السائل العالى الأداء. و من هذه النتائج نستنتج وجود بقايا لهذا الدواء فى أنسجة الأرانب المختلفة (الكلى، الطحال ، الكبد،العضلات، الرئة، القلب و المصل). وقد تبين وجود الدوكسيسيكلين فى الأنسجة المختلفة حتى اليوم الثالث من إنتهاء العلاج للدواء بينما ظل متواجدا فى الكلى، الطحال والكبد حتى اليوم الخامس فقط بعد إنتهاء العلاج. لذا ننصح بذبح الأرانب التي تم معالجتها بالدوكسيسيكلين بعد اليوم الخامس من توقف التجريع لتصبح صالحة للاستهلاك الأدمي.