PHARMACOKINETICS OF DIFLOXACIN IN NORMAL AND EXPERIMENTALLY ESCHERICHIA COLI INFECTED GOATS.

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A B S T R A C T

The pharmacokinetic behaviour of difloxacin following intravenous (IV) and intramuscular (IM) and repeated intramuscular (IM) administration in normal healthy and *Escherichia coli* infected goats were investigated. Following a single intravenous injection of 5 mg difloxacin /kg.b.wt., difloxacin could be detected in a therapeutic concentration 24 hours post intravenous dose with value equal to 0.18 µg/ml. The plasma concentration time curve of difloxacin following intravenous injection showed that the drug obeyed a two-compartments open mode. Difloxacin after intravenous dose revealed a rapid distribution phase (α = 0.689 h^{-1}) with a distribution half-life ($t_{0.5(\alpha)}$ = 1.00 h). The volume of distribution to central compartment (V^{1}_{c} = 335.82 ml/kg), whereas the calculated body distribution by extrapolation [$V_{d(\beta)}$], area [$V_{d(area)}$] and steady state [$V_{(dss)}$] methods were 841.97, 833.15 and 590.83 ml/kg respectively. Difloxacin was eliminated after intravenous injection with a half-life [$t_{0.5(\beta}$)] value of 5.30 hours and cleared by all clearance processes in the body at a rate of 2.04 ml/kg./min. Following a single intramuscular injection of 5 mg difloxacin/kg.b.wt. in normal goats, the drug reached its maximum plasma concentrations after 1 hours of injection with value equal to 2.77 µg/ml. difloxacin could be detected in a therapeutic concentration 24 hours post intramuscular dose with value equal to 0.22 µg/ml. The absorption half-life [$t_{0.5(ab)}$] was 0.482 hours, apparent elimination half-life $t_{0.5(\beta)}$ was 5.86 hours and difloxacin was cleared by all clearance processes (cl_{tot}) with rate equal to 2.99 ml/kg/min. it was concluded that difloxacin is a drug of choice for coliseptcemia.

Key Words: Difloxacin; *Escherichia coli*; Coliseptcemia; Goats.

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1. INTRODUCTION

Difloxacin is a water soluble synthetic antimicrobial agent of the fluroquinolones class. Similarly, to that of other fluoroquinolones, the bactericidal activity of difloxacin is mediated by inhibition of subunit A of DNA topoisomerases II (gyrase), an enzyme that is essential for DNA synthesis and repair [1], [2]. Difloxacin has high antimicrobial activity *in-vitro* against a wide variety of Gram-negative and Gram-positive bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella spp.*, *Salmonella spp.*, and *mycoplasma* [3], [4], [5], [6]. In veterinary medicine, difloxacin seemed to have a great potential for treating infections caused by bacteria [7]**.** With its broad spectrum of antibacterial activity and good distribution in most tissues and body fluids as well as low incidence of adverse effects, difloxacin might be used in many types of infection [8]. The aim of the study were to determine the pharmacokinetics and bioavailability of

difloxacin in goats following intramuscular administration.

2. MATERIALS AND METHODS

2.1. Drug.

Difloxacin was obtained from Savco for veterinary medicine company, Damascus, Syria. Under trade name **Over active®.** .

2.2. Experimental design:

Eight clinically normal lactating baladi and four experimentally *Escherichia coli* infected lactating goats were used in this study. The body weight and age of the tested goats ranged from 20-27 kg and from 2 to 3 years old (for normal goats) and from 22 – 31 kg and from 2.5 to 3.5 years old (for experimentally *Escherichia coli* infected goats). Goats were housed in hygienic stable fed on barseem, drawa and Concentrate and water was provided *ad-libitum.*

Grouping of goats:
Group (1):
It included 4 normal post-partum lactating goats. Each goat was injected intravenously into the left jugular vein with 5 mg difloxacin per kilogram body weight[9]. These goats were left for 15 days after the intravenous injection to ensure complete excretion of difloxacin from goat's body. Then, each goat was injected intramuscularly into the gluteus medius muscle with 5 mg difloxacin /kg b.wt. The aim of a single intramuscular injection to calculate the bioavailability of difloxacin in normal goats.

Group (2):

It included 4 post-partum lactating goats. Each goat was injected intramuscularly into the gluteus medius muscle with 5 mg difloxacin /kg b.wt., once daily for five consecutive days.

Group (3):

It included 4 experimentally *Escherichia coli* infected post-partum lactating goats. Each goat was injected intramuscularly into the gluteus medius muscle with 5 mg difloxacin /kg b.wt, fourty eight hours after experimental infection with *Escherichia coli,* once daily for five consecutive days.

2.3. Collection of samples.

2.3.1. Blood samples.

Blood samples were collected after 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours of administration. Blood samples following the second, third, fourth and fifth intramuscular doses were collected at 0.50, 1, 2, 4, 8, 12 and 24 hours post injection. Blood samples taken from goats were treated with anticoagulant and the plasma was separated by centrifugation.

2.3.2. Urine samples.

Urine samples were taken after 0.25, 0.50, 1, 2, 4, 8, 12 and 24 hours of administrations. Urine samples taken at 0.25 hour were discarded. Urine samples were measured using graduated cylinder. After the end of each experiment, the urinary bladder was irrigated with 15 milliliters potassium permanganate solution 1: 5000 as antiseptic agent.

2.3.3. Milk samples:

Milk samples were taken after 0.50, 1, 2, 4, 8, 12 and 24 hours of administrations, milk samples taken at 0.25 hour were discarded. The udder of each goat in all groups was completely evacuated before drug administration and after each milk samples.

2.4. Analytical procedures:

Difloxacin was assayed in plasma, sulphoric acid and milk using modified spectrophotometric method.

2.5. Assay of tissue samples:

The stock solution of difloxacin was prepared; 3 ml of 5% w/v ammonium

vanadate solution was added in a 10 ml volumetric flask followed by 2 ml of concentrated sulphouric acid. The mixture was mixed well and boiled gently for 20 minutes in water bath, then cooled and diluted to volume with bidistilled water. The absorbance of each sample was measured at wavelength 766 nm against blank.

3. RESULTS

3.1. Following a single intravenous injection of 5 mg difloxacin/kg b.wt. in normal goats, difloxacin could be detected therapeutically for 24 hours post intravenous injection (Table 1 and figure 1).

3. 2. The plasma concentration – time curve of difloxacin following intravenous injection showed that the drug obeyed a two compartments open model. Following a single intramuscular injection of 5 mg difloxacin/ kg. b.wt. the drug reached its maximum plasma concentrations after 1 hours of injection (2.77 ± 0.011 µg/ml). Difloxacin could be detected in plasma in a therapeutic level for 24 hours (Table 2) and Figure (2).

3.3. The pharmacokinetic parameters following a single intramuscular injection of difoxacin were recorded in table (3).

Table (1): Plasma concentrations of difloxacin (µg/ml) in normal goats following a single intravenous injection of 5 mg/kg.b.wt. in normal goats (n=4).

Time after administration (h)	Goats				$\overline{X}$ ± S.E.
	Goat (1)	Goat (2)	Goat (3)	Goat (4)	
0.083	13.45	13.51	13.59	13.46	13.50 ± 0.032
0.167	12.77	12.86	13.01	12.97	12.90 ± 0.054
0.25	11.42	11.38	11.37	11.43	11.40 ± 0.015
0.5	11.03	10.99	11.00	10.98	11.00 ± 0.011
1	9.06	9.04	8.98	9.01	9.00 ± 0.018
2	5.78	5.83	5.81	5.79	5.80 ± 0.011
4	2.41	2.39	2.38	2.42	2.40 ± 0.009
6	1.80	1.77	1.81	1.82	1.80 ± 0.011
12	0.88	0.91	0.92	0.89	0.90 ± 0.009
24	0.18	0.19	0.18	0.17	0.18 ± 0.004

Table (2): Pharmacokinetic parameters of difloxacin in normal goats following a single intravenous injection of 5 mg/kg.b.wt. in normal goats (n=4).

Parameter	Unit	Goat (1)	Goat (2)	Goat (3)	Goat (4)	$\overline{X}$ ± S.E.
C^{o}	µg/ml	14.94	15.00	14.66	14.96	14.89 ± 0.078
A	µg/ml	11.03	11.13	10.63	10.87	10.92 ± 0.109
A	h^{-1}	0.692	0.683	0.677	0.702	0.689 ± 0.006
$t_{0.5(\alpha)}$	H	1.00	1.01	1.02	0.986	1.00 ± 0.007
$V^{1}c$	ml/kg	333.33	334.67	341.06	334.22	335.82 ± 1.77
$V_{d(\beta)}$	ml/kg	795.04	882.99	867.35	822.49	841.97 ± 20.23
$V_{d(area)}$	ml/kg	796.18	882.99	829.99	823.45	833.15 ± 18.15
V_{dss}	ml/kg	554.77	597.31	607.29	603.94	590.83 ± 12.20
K_{12}	h^{-1}	0.210	0.190	0.217	0.230	0.212 ± 0.008
K_{21}	h^{-1}	0.292	0.286	0.278	0.285	0.285 ± 0.003
B	µg/ml	3.91	3.87	4.03	4.09	3.98 ± 0.051
B	h^{-1}	0.130	0.138	0.127	0.128	0.131 ± 0.003
$t_{0.5(\beta)}$	H	5.33	5.02	5.45	5.41	5.30 ± 0.097
K_{13}	h^{-1}	0.318	0.353	0.449	0.315	0.359 ± 0.031
Cl_{tot}	ml/kg/min	1.87	1.96	2.55	1.76	2.04 ± 0.177

Table (3): Plasma concentrations of difloxacin (µg/ml) in normal goats following a single intramuscular injection of 5 mg/kg.b.wt. in goats previously given the same dose by a single intravenous injection (n=4).

Time after administration (h)	Goat				$\overline{X}$± S.E.
	Goat (1)	Goat (2)	Goat (3)	Goat (4)	
0.083	0.015	0.016	0.016	0.017	0.016 ± 0.001
0.167	0.07	0.09	0.06	0.09	0.08 ± 0.008
0.25	0.25	0.28	0.29	0.26	0.27 ± 0.009
0.5	1.31	1.26	1.32	1.31	1.30 ± 0.014
1	2.79	2.78	2.74	2.76	2.77 ± 0.011
2	2.53	2.47	2.51	2.49	2.50 ± 0.013
4	1.99	1.97	2.01	2.03	2.00 ± 0.013
6	1.52	1.50	1.51	1.48	1.50 ± 0.009
12	0.73	0.76	0.77	0.74	0.75 ± 0.009
24	0.23	0.19	0.21	0.25	0.22 ± 0.013

Table (3): Pharmacokinetic parameters of difloxacin in normal goats following a single intramuscular injection of 5 mg difloxacin /kg.b.wt. in goats previously given the same dose by a single intravenous injection (n=4).

Parameter	Unit	Goat (1)	Goat (2)	Goat (3)	Goat (4)	$\overline{X}$± S.E.
A	µg/ml	3.21	3.47	3.42	3.58	3.42 ± 0.078
K_{ab}	h^{-1}	1.28	1.48	1.42	1.60	1.45 ± 0.067
$t_{0.5(ab)}$	H	0.540	0.468	0.487	0.433	0.482 ± 0.022
$t_{max\ (cal.)}$	H	2.06	1.88	1.91	1.73	1.90 ± 0.068
$C_{max\ (cal.)}$	µg/ml	2.61	2.49	2.54	2.17	2.45 ± 0.097
$\bar{C}_{max}$	µg/ml	2.79	2.60	2.79	2.34	2.63 ± 0.107
$\bar{C}_{min}$	µg/ml	0.208	0.203	0.214	0.207	0.208 ± 0.002
B	µg/ml	3.32	3.09	3.18	3.94	3.38 ± 0.192
K_{el}	h^{-1}	0.117	0.119	0.118	0.125	0.120 ± 0.002
$t_{0.5(\beta)}$	H	5.95	6.03	5.90	5.55	5.86 ± 0.106
Cl_{tot}	ml/kg/min	2.94	3.10	3.09	2.84	2.99 ± 0.063

Table (4): Bioavailability of difloxacin in normal goats following a single intramuscular injection of 5 mg /kg.b.wt. in goats previously given the same dose by a single intravenous injection (n=4).

Goats Number	AUC (Intramuscular) (µg/ml/h)	AUC (Intravenous) (µg/ml/h)	Bioavailability percent (%)
(1)	27.91	51.12	51.12
(2)	27.83	52.16	52.16
(3)	27.72	52.04	53.27
(4)	27.56	52.92	52.08
$\overline{X}$ ± S.E.	27.76 ± 0.076	52.06 ± 0.369	52.16 ± 0.440

Figure (1): Semilogarithmic graph depicting the time course of difloxacin in plasma of normal goats following a single intravenous injection of 5mg/kg bwt. (n=4).

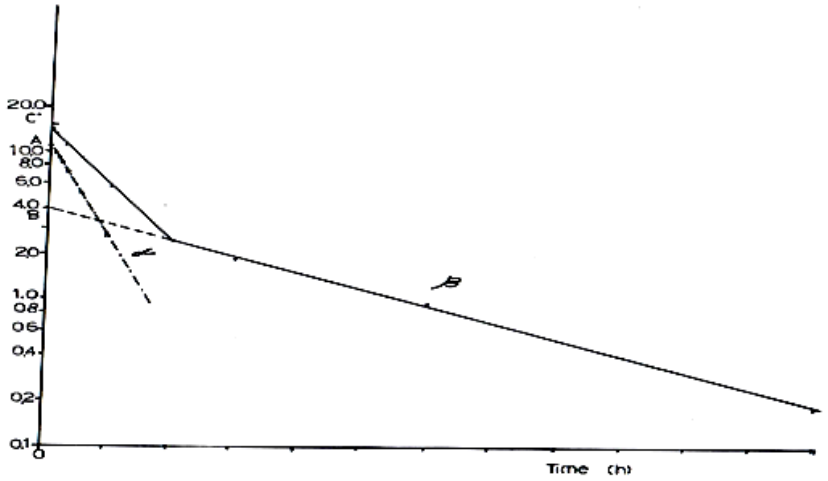
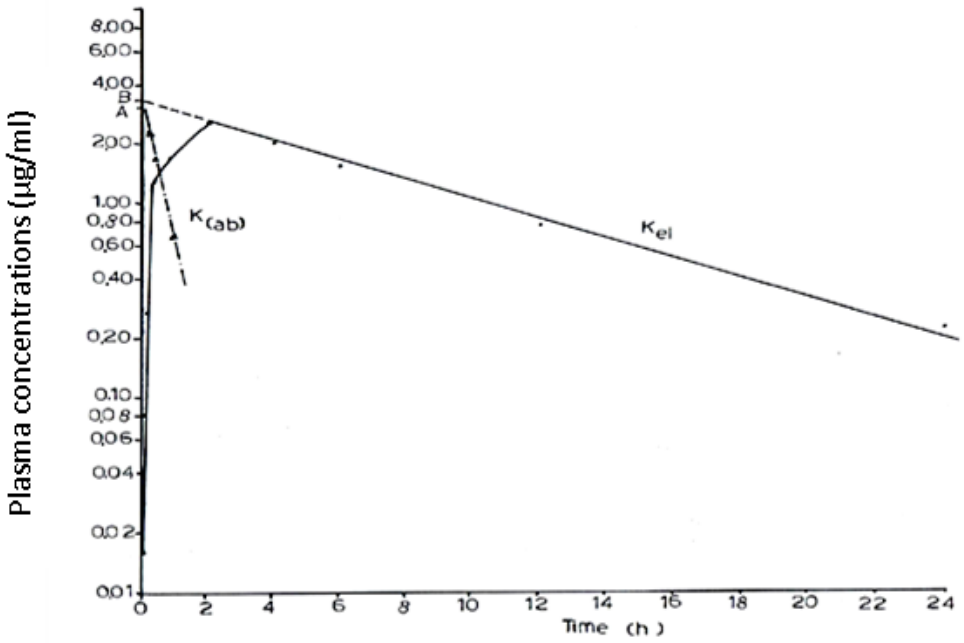


Figure (2): Semilogarithmic graph depicting the time course of difloxacin in plasma of normal goats following a single intramuscular injection of 5mg/kg bwt. (n=4).



4. DISCUSSION

Following a single intravenous injection of 5 mg difloxacin /kg.b.wt. in normal goats, the drug showed high serum level (13.50 µg/ml) at 5 minutes post-injection, then its concentration decreased gradually till reached its minimum level at 24 hours post-injection (0.18 µg/ml).

The pharmacokinetic interpretation revealed that the volume of distribution of difloxacin calculated by extrapolation [$V_{d(\beta)}$], area [$V_{d(area)}$] and steady-state [V_{dss}] methods were 0.841, 0.833 and 0.590 L/kg. respectively. These results were lower than those previously investigated for difloxacin in goats which showed that, the volume of distribution for difloxacin in goats (V_{dss} = 1.1 L/kg), [10], and in calves (1.12 L/kg), [11] and in camels (1.02 L/kg), [12].

The elimination half-life [$t_{0.5(\beta)}$] of difloxacin following a single intravenous injection was equal to 5.30 h. This observation agreed with the data reported after intravenous administration of difloxacin in calves [$t_{0.5(\beta)}$ =5.56 h], [13]. On contrast this value was longer than those recorded in other species as rabbits (3.25 h), [14], goat kids (3.57 h) and lambs (2.63 h), [15]. On the other hand, it was shorter than those showed in goats (6.3 h), [16], pigs (17.14 h) and broilers (6.11 h), [17], The elimination half-lives were apparently sufficiently long to maintain the drug in tissues at concentrations considerably higher than in blood.

The rate of total body clearance of difloxacin following intravenous injection was 2.04 ml/kg/min. This observation agreed with the data reported after intravenous administration of difloxacin in calves (2.19 ml/min/kg), [18]. In contrast the clearance values in goats were 0.13 L/kg/h [19], in rabbit was 0.59 L/kg/h [20], in sheep 0.21 L/kg/h [21], in goat kids and in lambs were 0.12 L/kg/h, 0.11 L/kg/h respectively [22]. These differences in total body clearance might be attributed to the specific interspecies variations [23].

Following a single intramuscular injection of 5 mg difloxacin/kg.b.wt, the drug reached its maximum plasma concentrations after 2 hours of injection with value of 2.50 µg/ml. Difloxacin could be detected in serum in a therapeutic level (0.22 µg/ml) at 24 hours. On contrast, these results were differed than those reported by [24] in goats, who observed that, the maximum serum concentration after intramuscular administration (C_{max}) was 4.1 µg/ml at (t_{max}) equal to 1 hours. [25] found that, after intramuscular administration of 5 mg difloxacin /kg.b.wt.in rabbit, the (C_{max}) were 3.85 µg/ml, at (t_{max}) equal to 1.61 hours. [26] stated that, the maximum serum concentration of difloxacin after intramuscular administration in calves (C_{max}) was 3.38 µg/ml at (t_{max}) equal to 1.22 hours. [27] found that, the maximum serum concentration after intramuscular administration of difloxacin in sheep (C_{max}) was 1.89 µg/ml at (t_{max}) equal to 2.42 hours. [28] stated that, the maximum serum concentration of difloxacin after intramuscular administration in goat kids and lambs (C_{max}) was 4.95 µg/ml and 4.25 µg/ml respectively at (t_{max}) equal to 1.85 hours and 1.31 hours respectively.

The absorption rate constant (K_{ab}) after a single intramuscular administration in normal goats was equal to 1.45 h^{-1}. The mean peak serum concentrations of difloxacin (C_{max}) was achived at maximum time (t_{max} = 1.90 h). The reported (t_{max}) was nearly similar to that reported in rabbit (1.61 h) [29], and in goat kids (1.85 h) [30], and differed with that recorded in sheep (2.42 h) [31] and in calves (1.22 h) [32] and in lambs (1.31 h)[33] and in camels (1.42 h)[34].

In the present study difloxacin was rapidly absorbed from the site of injection after single intramuscular administration with a short absorbtion half-life [$t_{0.5(ab)}$ = 0.482 h]. This value was nearly similar to that reported by [35] after intramuscular administration of difloxacin in goats [$t_{0.5(ab)}$ = 0.37 h], and to that reported by [36] after intramuscular administration of difloxacin in calves [$t_{0.5(ab)}$ = 0.38 h]. The elimination half-life [$t_{0.5(\beta)}$] following single intramuscular administration was 5.86 hours. This value was lower than that reported by [37] after intramuscular administration of difloxacin in calves [$t_{0.5(\beta)}$ = 6.12 h].

The bioavailability of difloxacin in normal goats, which estimated the rate and extent of the dose entered the systemic circulation after intramuscular injection was 52.16 %. This value was lower than the bioavailabilities recorded for difloxacin in goats (95.4 %) [38] and in camels (93.51) [39] and in pigs (105.7 %) [40] and in goat kids and lambs (97.5 % and 97.1 % respectively) [41] and for difloxacin in broiler chickens (97.11 %).

Finally it is concluded that plasma concentration of difloxacin in normal and *Escherichia coli* infected goats could be detected in a therapeutic level for 24 hours following intravenous and repeated intramuscular administration and exceeded the MIC' of *Escherichia coli* 0.025 µg/ml a factor indicating that difloxacin is a drug of choice for coliseptcemia.

The highest concentrations of difloxacin in the urine, suggest that difloxacin is suitable for treatment of urinary tract infections caused by *Escherichia coli* in goats.

The highest milk concentrations of difloxacin in lactating goats suggested that difloxacin could be used for treatment of mastitis caused by *Escherichia coli* in lactating goats.

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حركية عقار الدايفلوكساسين فى الماعز السليمة والمصابة تجريبيا

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الملخص العربي

فى هذه الدراسة تم دراسة الجوانب الفارماكوكينيتيكية للعقار على الماعز السليمة و الأخرى المصابة، ومن جهة أخرى استهدفت هذه الدراسة تنقية عقار الدايفلوكساسين، كما تم حساب معدل طرح الكرياتينين. وتم مقارنة معدل طرح العقار على حدة بمعدل طرح الكرياتينين. و تم دراسة معدل الاستفادة من العقار بعد الحقن العضلي و قد أوضحت النتائج الاتي: بعد حقن الحيوانات السليمة فى الوريد مرة واحدة بمعدل 5 مجم دايفلوكساسين / كجم من وزن الجسم فقد تبين أن فترة نصف العمر لمرحلة ألفا [$t_{0.5(\alpha)}$] كانت 1.00 ساعة و قد وجد أن معدل الانتشار الظاهرى لعقار الدايفلوكساسين بطريقة [$V_{d(\beta)}$] ، [$V_{d(area)}$] ، [$V_{(dss)}$] هى 841.97 ، 833.15 ، 590.83 ملجم / كجم على الترتيب. وفترة نصف العمر لإفراز الدايفلوكساسين [$t_{0.5(\beta)}$] هى 5.30 ساعات. وقد وصل أعلى تركيز للدواء فى البول بعد ساعتين من الحقن بمقدار 104.99 ميكروجرام/مللى. بينما وصل أعلى تركيز للدواء فى اللبن بعد ساعتين من الحقن بمقدار 1.30 ميكروجرام/مللي. بعد حقن الحيوانات السليمة بجرعة واحدة فى العضل بمعدل 5 مجم دايفلوكساسين / كجم من وزن الماعز (نفس الماعز التي سبق حقنها فى الوريد). وصل أعلى تركيز للدواء فى الدم بعد ساعة من الحقن بمقدار 2.77 ميكروجرام/مللي. وقد تبين أن فترة نصف عمر امتصاص الدواء [$t_{0.5(ab)}$] كانت 0.482 ساعة. وقد وصل أعلى تركيز للدواء فى البول بعد ساعتين من الحقن بمقدار 29.95 ميكروجرام/مللى. بينما وصل أعلى تركيز للدواء فى اللبن بعد ساعتين من الحقن بمقدار 0.63 ميكروجرام/مللى. وكان معدل استفادة الجسم للحيوانات السليمة بعد الحقن العضلي للدايفلوكساسين هي 52.16 % وهذه النسبة تعبر عن امتصاص جيد لعقار الدايفلوكساسين بعد الحقن فى العضل. من هذه الرسالة يتضح أن تركيز الدايفلوكساسين فى الدم يستمر لمدة 24 ساعة بعد الحقن فى الوريد أو العضل. كما ينصح باستخدام الدايفلوكساسين فى علاج أمراض الجهاز البولي وكذلك التهاب الضرع.

(مجلة بنها للعلوم الطبية البيطرية: عدد 25(1):124-134, سبتمبر 2013)