Colistin susceptibility, pharmacokinetics, and residues in b and laying hens.

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Abstract

One hundred and twenty four Escherichia coli isolates were obtained fr autopsied chickens showing lesions of avian colibacillosis in Egy Antibiograms showed that the majority of E. coli isolates were hig susceptible to colistin sulphate (65.3%) and neomycin (54.8%) Opposite all isolates were resistant to oxytetracycline and amoxicillin (10 resistance).

After single i.v. (1 mg/kg) or oral (5 mg/kg b.w.) administration of colis sulphate to broiler and laying hens, colistin could be detected in bro plasma longer than in laying hen plasma. Following i.v. injection of colis sulphate, elimination half-lives (t0.5 β) were 1.82 and 2.61 hours in broil and laying hens, respectively. Total body clearances (Cltot) were 0.21 a 0.18 L/h.kg in broiler and laying hens respectively. Areas under curv (AUC) were 2.93 and 2.75 µg/ml.h in broiler and laying hens respective After oral administration of colistin sulphate to broiler and laying he absorption have-lives (t0.5 ab) and elimination half-lives (t0.5 β) were 0. and 0.41, &1.19 and 1.21 hours respectively. Oral bioavailabilities (Fo were 11.48 and 10.29% in broiler and laying hens respectively. detectable levels of colistin could be measured in muscles or eggs a single oral administration of colistin.

Key words: *chicken, colistin, Escherichia coli, pharmacokinetic, residu susceptibility.*

Introduction:

Colistin, also known as polymyxin E, is polypeptide antibiotic that was first in Japan from Bacillus colistinus in 1947, and became available for clinical use The bactericidal action of colistin takes place through its binding to m phospholipid of Gram-negative bacteria such as Escherichia coli, Pseud aeruginosa, Salmonella, and Hemophilus, leading to leak out of bacterial cell (Rastogi et al. 1987; and Li et al. 2005).

Colistin is widely used in many countries for treatment of Gram-negative infections (mainly Colibacillosis and Salmonellosis) in broilers and layin Because colistin was introduced into clinical practice over 45 years ago, it w subject to the regulations those modern drugs are subject to. Therefore, neither standardized dosing of colistin nor detailed pharmacokinetics inform chickens. Furthermore, there are no confirmed data about colistin oral bioava chicken; especially that colistin has shown no virtual systemic absorption a administration in most of mammalian species (Escoula et al. 1981; and Men al. 1997). Moreover, the prolonged and massive use of colistin in chicken far increase bacterial resistance against it.

The objective of the present study was to study the susceptibility of virule to colistin, to examine the pharmacokinetic of colistin in chickens, and to deter possible residues of colistin in chicken's meat and eggs after its oral administra

Materials and methods

Drugs:

1) Antibiotic disks: oxytetracycline (OT30) lot 410988, doxcycline hydr (Do30) lot 391249, amoxicillin (AML10) lot 371513, neomycin (N30), colistin (CT25) lot 370571, enrofloxacin (ENR5), ciprofloxacin (CIP5) lot 416 spiramycin (SP100) lot 404338 were purchased from Oxoid Ltd (Bas Hampshire, England).

2) Colistin sulphate: obtained from Sigma Chemicals (St. Louis, Mo.), witl of 19,740 IU/mg. Drug was dissolved in sterile pyrogen-free saline for i.v. water for oral administration.

Bacterial isolates:

One hundred and twenty four isolates of Escherichia coli were obtaine commercial broiler flocks located in Egypt (Ismailia governorate) throughout from July to November, 2006. Specimens were isolated from heart and liver chicken (2-6 weeks age) those had died from Colisepticemia. Specimens wer on McConkey and EMB agar, the suspected E. coli colonies were ide standard biochemical methods according to Cruickshank et al. (1979). Fifty E. coli were isolated and identified; then the antibiograms of the isolated E antimicrobial agents were performed using the disk diffusion method describ and Luther (1980).

Birds for pharmacokinetics and residues study:

Experiments were conducted using 2 commercial breeds of female chick acres broilers (22 birds) and white leghorn laying hens (15 birds). Every 5 la were kept in individual wire cage, while broilers were housed on deep litter m2). The animal house temperature was maintained at 25 ± 3 °C and humi 70%. All birds were fed on antibacterial-free commercial diet and had a free drinking water. The birds were allowed to settle one week before starti experiment. At the start of experiment, ages and body weights of broilers hens were 6 and 56 weeks, 1948 ± 56 and 2374 ± 49 gm, respectively.

Experiments design, grouping of animals and sample collection:

Chickens were randomly grouped into 6 groups and treated as follow: (broiler, n=5) and 2 (layers, n=5) were used to study colistin dispositior administration. Groups 3 (broiler, n=5) and 4 (layers, n=5) were used for th of colistin pharmacokinetic after oral administration, while groups 5 (broiler, 6 (layers, n=5) were used for estimating colistin residues in meat respectively after oral administration of colistin.

In order to study colistin disposition after i.v. administration, chickens o and 2 were administered single i.v. dose of 0.25% watery solution of colisti in a dose of 1mg/kg body weight. Drug was injected in the left cutaneous using 1-ml plastic syringe with 26G needle. Blood samples (not more than both groups were collected from the right cutaneous ulnar vein at 0.17, 0. 1.5, 2, 2.5, 3, 3.5, 4, and 5 hours after dosing.

For studying of colistin pharmacokinetics after oral administration, chi groups 3 and 4 were administered colistin sulphate in a single oral dose colistin sulphate/kg body weight(equivalent to 98,700 IU/kg) as 1% watery Drug was administered directly into chicken crop using flexible rubber tub samples from both groups were collected from the cutaneous ulnar vein at 0.2 2, 3, 4, 5 and 6 hours after dosing.

All blood samples were collected using heparinized 1-ml plastic syringe needle, blood sample was immediately transferred to 1.5-ml Eppendorf tube refrigerator for 1 hour, then centrifuged at 2600 g (relative centrifugation forc minutes, the clear plasma was collected and stored at -20 °C until assaying.

In order to estimate colistin residues in chicken's meat and eggs, single oral colistin sulphate was administered to groups 5 and 6 in the same route and d group 3. Four birds from group 5 were slaughtered 1, 2, and 3 days after col administration. Ten gm from right breast muscle of each slaughtered homogenized with 10 ml of extraction solvent (4 volume methanol 50% / 1 trichloroacetic acid 25%) using Polytron ® homogenizer (Kinematica, Switzerla homogenized sample was centrifuged (4000 g for 10 minutes at room temp pH was adjusted to 6.0, diluted with phosphate buffers and re-centrifuged. 1 supernatant aseptically separated in clean screw-capped tube, and stored at - assaying. For assaying of colistin residues in eggs, 4 eggs (from group collected daily for 3 successive days after colistin oral administration, albumin of each egg were homogenized with equal amount of phosphate buffer solu 6.0) using Polytron ® homogenizer. Sample was heated to 70 °C for 20 mi eliminate the inhibitory effect of egg albumin on the test microorganism, 5 ml supernatant fluids was collected and centrifuged at 4000 g for 10 minutes, 1 supernatant aseptically separated in screw-capped tube, and stored at -2 assaying (Roudaut 1989).

Quantitative assay of colistin:

Colistin concentrations were assayed microbiologically with agar diffusion using nutrient meat-peptone agar media and E. coli ATCC 25922 as microorganism (Lin et al. 2005). Colistin sulphate standard solutions were pre plasma from untreated chickens as a reference. The detection limit of the as 0.05 µg/ml. The standard curve showed linear relationship over the range of µg colistin sulphate/ml with correlation coefficient (r) of 0.991. Intra- and int coefficients of precision were 3.6% and 5.2%, respectively. Similarly, coli assayed in meat and eggs with sensitivity limit of 1µg/gm and 2µg/gm and percent of 76 and 68%, respectively. Intra- and inter-assay coefficients of were 5.8% and 7.3%, respectively.

Pharmacokinetical and statistical analysis:

Compartmental analysis of colistin in plasma was performed using a regression analysis program WinNonlin (Version1.1, Pharsight Inc., NC Classical pharmacokinetic parameters were calculated using standard e (Gibaldi and Perrier 1982).

For statistical analysis of pharmacokinetic parameters, data of broilers and lay were initially analyzed for homogeneity of variance using Bartlett's test (S Rohlf 1981). If there were no significant variances (homogeneity) at P = 0. Dunnett's multiple comparison procedure was used (Dunnett 1964). If varia significant (heterogeneity), data were analyzed using the nonparametric Krusk

test. P value less than 0.05 was considered significant. The arithmetic m standard deviation were calculated for all parameters except for half-live value harmonic mean values and standard deviation were calculated according to L (1985).

Results

1) Antimicrobial susceptibility study:

The in vitro antibiograms of isolated E. coli against 7 commonly used anti agents (Table 1 and Fig. 1) showed that, the majority of strains were highly su to colistin sulphate (65.3%) and neomycin (54.8%). On the other hand, isolates were resistant to oxytetracycline and amoxicillin. Concerning othe antimicrobial agents, E. coli isolates showed moderately to low susceptib prevalence of resistance was: amoxicillin and oxytetracycline (100%), doxcyc enrofloxacin (50%), neomycin, ciprofloxacin and colistin (< 5%).

2) Pharmacokinetics and residues study:

Colistin plasma concentrations following single intravenous administration i of 1mg/kg b.w. in broilers and laying hens are shown in Figure 2, the concentrations decreased biexponentially suggesting two-compartmental ope In four chickens out of five in each group, colistin could be detected in plasm and 4 hours in case of broilers and laying hens, respectively.

The pharmacokinetic parameters describing colistin disposition after i.v. administration are listed in Tables 2 and 3, respectively. Rapid distribution p achieved in broilers and laying hens ($t_{0.5}\alpha$ = 0.40 ± 0.09 and 0.34 ± 0.0 respectively) after i.v. administration of colistin. Elimination half-lives ($t_{0.5}\beta$) i and laying hens were 1.82 ± 0.29 and 2.61 ± 0.42 hours, respectively. Th state distribution volumes (Vss) were 0.88 ± 0.16 and 0.78 ± 0.12 L/kg, while body clearances (Cltot) were 0.21 ± 0.04 and 0.18 ± 0.03 L/h.kg in broilers a hens, respectively. Pharmacokinetic analysis of colistin after i.v. admi showed no significant difference ($P \leq 0.05$) between broilers and laying hens.

After single oral administration of colistin sulphate (5 mg/kg b.w.) in b laying hens, colistin plasma concentrations versus time were best descri single-compartment open model with a first order absorption (Fig. 3). Agai could be detected in broiler plasma longer than in laying hen plasma (6 an respectively). In 2 laying hens out of 5, colistin was detectable up to 4 hou contrast, in one broiler chicken, colistin could be detected in plasma up to 7 h

After oral administration of colistin sulphate in broilers and laying hens, plasma concentrations (Cmax) of 0.66 ± 0.12 and 0.50 ± 0.09 µg/ml, were a time of maximum concentrations (Tmax) of 1.18 ± 0.07 and 0.86 ± 0. respectively. Tmax was significantly ($P \leq 0.05$) shorter in laying hens than Except for Tmax, no significant difference were found between broilers and l in colistin pharmacokinetic after oral administration. Interestingly, colistin sh bioavailability of 11.48 and 10.29% after oral administration in broilers and la respectively.

Concerning colistin residues in chicken's muscles and eggs after administration, all samples were free from any detectable concentrations of c

Discussion

1) Antimicrobial susceptibility study:

In this study, the majority of E. coli isolates (65.3%) were highly susceptible resistance (2.4%) to colistin, similar results were recorded by Gyurov (19 studied the susceptibility of 223 strains of Escherichia coli (isolated from organs and bone marrow of birds died of colisepticaemia) to therapeutic age author found that, the highest number of strains (96.06%) were sensitive to cc other study, Orden et al. (2000) found the most of E. coli strains isolat diarrhoeic calves were highly susceptible (99–100 %) to polymyxin. In more study, Kilonzo-Nthenge et al. (2008) who studied the incidence of antibiotic re in microorganisms isolated from chickens and guinea fowl, stated that, E. coli were sensitive to colistin. Although colistin is widely used for treatment of colib in chickens as one of the first choice antibiotics, resistance against colistin is acquired (Catchpole et al. 1997).

Also, the antibiograms showed that, all of the E. coli isolates were resi oxytetracycline and amoxicillin. Concerning oxytetracycline, Cloud et al. Gyurov (1985), and Kilonzo-Nthenge et al. (2008) reported that, E. coli isolat resistant to oxytetracycline. Inconsistent with our results, Gyurov (1985) Ghamdi et al. (1999) found most of E. coli isolates were sensitive to amoxi more recent study, Diarrassouba et al. (2007) reported that, 55 out of 74 isolates were resistant to amoxicillin. Moreover, Oteo et al. (2008) recorded in amoxicillin-clavulanic acid resistance in E. coli isolated from human blood in S Egypt, oxytetracycline and amoxicillin had been extensively used in poultry far many years, which may explain the development of resistant against the antibiotics in our study. These results suggest that universal susceptibility amoxicillin should not be assumed, particularly for E. coli.

Regarding to the other tested antimicrobials, antibiogram results are in ag with most other researchers. The presented antibiogram pattern can be us adequate selection of antimicrobial agents for treatment of colibacillosis in ch sensitivity test can't be done.

2) Pharmacokinetics and residues study:

Following single intravenous administration of colistin in a dose of 1mg/ rapid distribution was achieved in broilers and laying hens (t0.5 α = 0.40 ± 0 0.34 ± 0.03 hour, respectively), similar short distribution half-life (0.3 ho recorded in pig by Mengelers et al. (1997). Elimination half-lives (t0.5 β) sho significant difference (P≤ 0.05) between broilers and laying hens (1.82 ± 0.29 a ± 0.42 hours, respectively). Compared with pigs and calves, colistin half-life in was similar to that reported in pigs (2.2 hours) and about half of that recorded i (4.5 hours) by Mengelers et al. (1997) and Ziv et al. (1982), respectively. Matc parameters with those obtained in calves by Ziv et al. (1982), colistin to clearance (Cltot) in chicken was similar to that registered in calves (0.20 Meanwhile, volume of distribution (Vss) of colistin in chicken (0.88 and 0.78 broilers and layers, respectively) was about two thirds of that listed in calves (1 and about four fifths of that reported in pigs (1.02 L/kg). Volume of distribution than 0.7 L/kg could be due to wide colistin distribution into total body fluids, hig binding, or both. As residual study revealed no detectable level of colistin in c muscles, it could be suggested that, the high volume of distribution of colistin to high drug distribution in chicken body fluids.

After oral administration of colistin in broilers and laying hens, maximum concentrations (Cmax) of 0.66 ± 0.12 and 0.50 ± 0.09 µg/ml, were achieved a 1.18 ± 0.07 and 0.86 ± 0.05 hours, respectively. Tmax was significantly (shorter in laying hens than in broiler; comparable differences in pharma between broilers and layers were recorded by other investigators and attribut laying process (Bintvihok et al. 2002; and Pirard & De Pauw, 2006).
Interestingly, colistin showed oral bioavailability of 11.48 and 10.29% a administration in broilers and laying hens, respectively. That oral absorption colistin blood concentrations over the MIC50 for E. coli (0.1µg/ml) up to 6 and in case of broiler and layers, respectively. Although these oral bioavailabili indicate limited oral absorption of colistin in chicken, still colistin oral abso chicken is much higher than that in mammals; which showed no virtual absorption of colistin after oral administration (Escoula et al. 1981; and Men al. 1997). Compared with mammals, similar relatively high oral drug abso chicken was reported by other researchers who estimated apramy bioavailability in chickens and calves (Shikha, 1987; Afifi and Ramadan,1997).
Concerning colistin residues in muscles and eggs, all chicken samples were any detectable concentrations of colistin. These data are in agreement reported by Roudaut (1989) who found no detectable colistin residue in eggs administration of 90,000 IU colistin/kg b.w. for 5 days.

Conclusion: *Although colistin sulphate was used in Egypt and ma countries for several decades for treatment of Colibacillosis and Salmon poultry farms, most of E. coli isolates were either highly or moderately susc colistin, which indicated low resistance of E. coli against colistin. On the ot while colistin sulphate is an effective and safe drug for oral and topical use ir veterinarian must draw attention not to exceed the recommended therapeutic chickens, as about 10% of the administered oral dose could be absorbed. that the systemic use of colistin was associated with considerable toxici nephrotoxicity and neurotoxicity, including neuromuscular blockade (Walla 2008).*

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Table 1 Comparative efficacy of 7 antimicrobials against Escheri isolated from chicken showing lesions of avian colibacillosis (n=12

Antibiotic	Disk potency	Degree of susceptibility Number (%)			
		+++	++	+	R
Oxytetracycline (OT 30)	30 µg	0 (0)	0 (0)	0 (0)	124 (100)
Doxcycline (Do 30)	30 µg	32 (25.8)	16 (12.9)	16 (12.9)	60 (48.
Amoxicillin (AML 10)	10 µg	0 (0)	0 (0)	0 (0)	124 (100)
Neomycin (N 30)	30 µg	68 (54.8)	48 (38.7)	4 (3.2)	4 (3.2)
Colistin Sulphate (CT 25)	25 µg	81 (65.3)	28 (22.6)	12 (9.7)	3 (2.4)
Enrofloxacin (ENR 5)	5 µg	12 (9.7)	32 (25.8)	20 (16.1)	60 (48
Ciprofloxacin (CIP 5)	5 µg	44 (35.5)	56 (45.2)	20 (16.1)	4 (3.2)

+++ = high susceptible, ++ = moderate susceptible, + = low suscepti resistant..

Table 2 Pharmacokinetic parameters of colistin following single intrav administration of 1mg colistin sulphate/kg body weight in broilers and hens.

Parameter	Unit	Mean ± SE	
		Broiler chickens	Laying hens
A	µg/ml	1.33 ± 0.43	2.64 ± 0.53
α	h-1	2.03 ± 0.41	2.14 ± 0.21
t0.5 (α)	h	0.40 ± 0.09	0.34 ± 0.03
B	µg/ml	0.82 ± 0.22	0.47 ± 0.08
β	h-1	0.38 ± 0.05	0.34 ± 0.04
t0.5 (β)	h	1.82 ± 0.29	2.61 ± 0.42
K12	h-1	0.58 ± 0.20	0.70 ± 0.11
K21	h-1	1.09 ± 0.27	0.64 ± 0.09
Kel	h-1	0.74 ± 0.08	1.15 ± 0.12
Cl tot	L/h.kg	0.21 ± 0.04	0.18 ± 0.03
MRT	h	2.20 ± 0.17	1.99 ± 0.37
Vss	L/kg	0.88 ± 0.16	0.78 ± 0.12
AUC	µg/ml.h	2.93 ± 0.66	2.75 ± 0.57
AUMC	(µg/ml)h2	6.57 ± 1.60	6.07 ± 2.37

A & B = zero-time plasma drug concentration intercepts of biphasic disp curve; α & β = distribution and elimination rate constants respectively; t0. t 0.5 (β)= distribution and elimination half-lives respectively; K12 & diffusion rate constant from the central compartment to the peri compartment and vice versa; Cl tot = total body clearance; MRT = residence time of drug molecules in chicken body; Vdss = volume of distri at steady state; AUC & AUMC = area under the drug plasma concentratio curve and area under the moment curve, respectively

Table 3 Pharmacokinetic parameters of colistin after single oral admir of 5 mg colistin sulphate/kg body weight in broilers and laying hens. indicates significant difference at $P \leq 0.05$.

Parameter	Unit	Mean ± SE	
		Broiler chickens	Laying hens
Cmax	µg/ml	0.66 ± 0.12	0.50 ± 0.09
Tmax	h	1.18 ± 0.07	0.86 ± 0.05*
t0.5 (ab)	h	0.60 ± 0.08	0.41 ± 0.10
t0.5 (β)	h	1.19 ± 0.13	1.21 ± 0.25
Kab	h-1	1.25 ± 0.17	2.18 ± 0.46
Kel	h-1	0.58 ± 0.08	0.65 ± 0.15
AUC	µg/ml/h	1.74 ± 0.24	1.39 ± 0.26
Foral	(%)	11.48 ± 3.23	10.29 ± 3.28

Cmax = maximum drug concentration; Tmax = time at which wa achieved; t0.5 (ab) & t 0.5(β)= absorption and elimination half-lives res Kab & kel = absorption and elimination rate constants, respectively; A under the drug plasma concentration-time curve; Foral = oral bioavailab

Fig. 1 Comparative efficacy of 8 antimicrobials against Escherichia co from chicken showing lesions of avian colibacillosis (n=124).

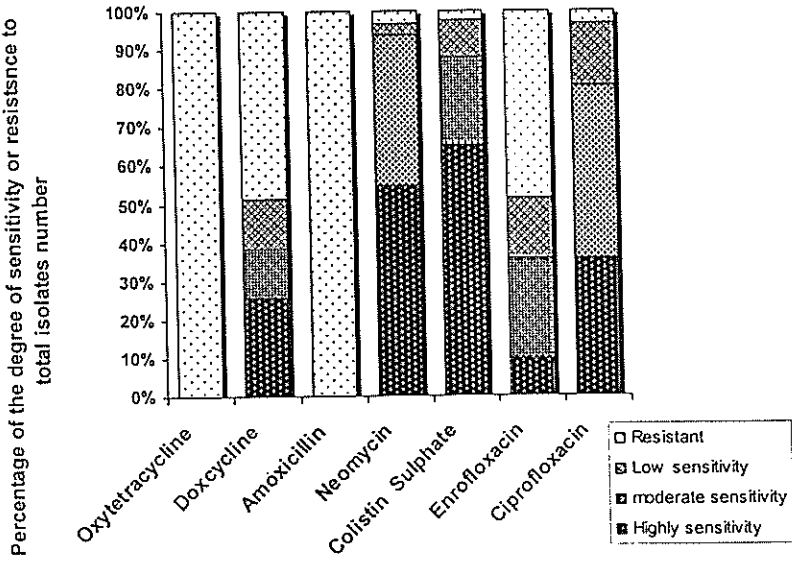
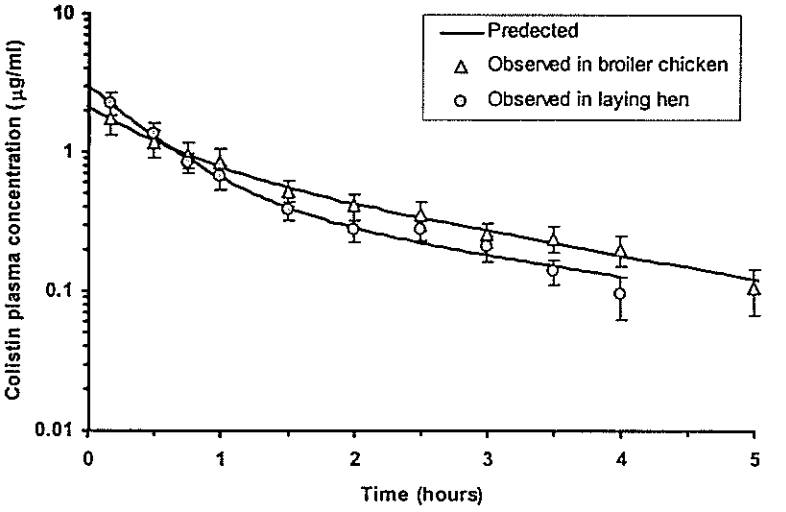


Fig. 2 Semilogarithmic plot of colistin concentrations in plasma after sing intravenous administration of 1mg colistin sulphate/kg body weight in br and laying hens..



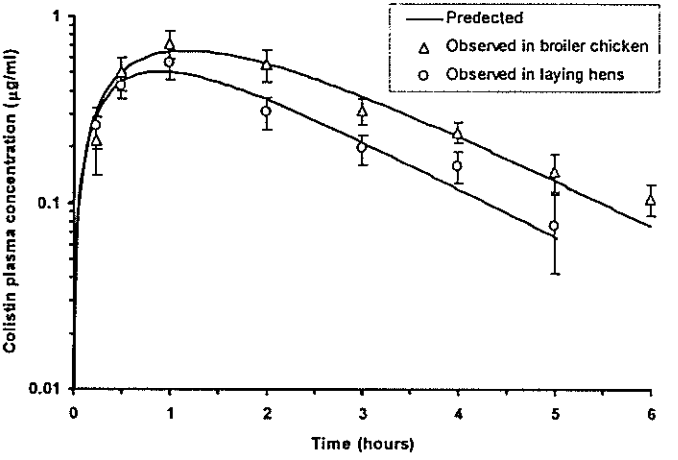


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Fig.3Semilogarithmic plot of colistin concentrations in plasma following oral administration of 5 mg colistin sulphate/kg body weight in broilers a laying hens.

العربى

حساسية والحركة الدوائية والبقايا الدوائية لدواء الكولستين في دجاج اللحم البياض

خليل١ و داليا حامد منصور.٢
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جميع عدد ١٢٤ عينة من دجاج نافق نتيجة عدوي الميكروب القولوني (إشيرشيا كولاى) في سماعيلية. و عند إختبار حساسية الميكروب القولوني المعزول من الدجاج لسبعة مضادات رت النتائج أن ٦٥,٣% من العينات كانت شديدة الحساسية للكولستين و أن ٥٤,٨% من ت شديدة الحساسية نيومايسين، في حين أن كل العينات كانت مقاومة للاوكسيتتراسيكلين و لين.

كولستين وريدياً (بجرعة ١ مليجرام لكل كجم من وزن الجسم) أو إعطاءه عن طريق الفم مليجرام لكل كجم من وزن الجسم)، إستمر وجود الكولستين في بلازما دجاج اللحم لفترة جوده في بلازما الدجاج البياض. فعند حقن الكولستين وريدياً، كانت فترة عمر النصف في دجاج اللحم ١,٨٢ ساعة و في الدجاج البياض ٢,٦١ ساعة. كما قدر ت المساحة تحت المنحنى (AUC) بـ ٢,٩٣ و ٢,٧٥ ميكروجرام لكل مليلتر في الساعة في كل من و البياض على التوالي.

لكولستين عن طريق الفم، كانت فترة عمر النصف لمرحلتيّ الأمتصاص و الإخراج (t0.5 ab) ٠,٦ و ١,١٩ ساعة في دجاج اللحم و ٠,٤١ و ١,٢١ ساعة في الدجاج البياض على سجلت الدراسة معدل إتاحة حيوية فمية تراوحت من ١١,٤٨% (في دجاج اللحم) إلى في الدجاج البياض). في حين لم يتم قياس أي بقايا دوائية في عضلات أو بيض الدجاج بعد ستين عن طريق الفم في جرعة ٥ مليجرام لكل كجم من وزن الجسم.