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PHARMACOKINETICS, BIOAVILABILITY AND TISSUE RESIDUES OF APRAMYCIN IN NORMAL CHICKENS AND ESCHERICHIA COLI INFECTED BROILER CHICKENS

EL. Sayed*, M.G.A. EL-Komy, A.A.A. and Soliman, A. Asmaa

Department of Pharmacology, Faculty of Veterinary Medicine, Benha University, EGYPT.

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***Corresponding Author**
EL. Sayed
Department of Pharmacology, Faculty of Veterinary Medicine. Benha University, EGYPT.

ABSTRACT

The pharmacokinetics (after single intravenous, and oral administration) and tissue residues after repeated oral (daily for five days) administration of apramycin were investigated in normal and experimentally *Escherichia coli* infected chickens. Apramycin was administered at a dose level of 25 mg/kg b. wt. (for oral administration) and at 10 mg/kg b. wt. for intravenous injection. Fourty six clinically normal Hubbard chicken of four weeks of age weighting about 1500 to 2000 grams were used in the current study. The maximum plasma concentrations of apramycin were achieved 0.705 µg/ml at 0.5 hour after oral administration and 35.09 µg/ml at 0.083 hours after intravenous injection. The systemic bioavailability was 1.31% after oral administration indicating poor absorption of apramycin. After intravenous injection, the pharmacokinetics of apramycin was best described by a three-compartment open model with at $t_{1/2\alpha}$ of 0.113 hour, $t_{1/2\beta}$ of 0.999 hour, $t_{0.5(s)}$ of 4.56 hour, V_{dss} of 1460.19 ml/kg. The plasma protein binding of apramycin was 7.13 ± 0.444 %. oral administration of 25 mg apramycin per kilogram body weight three times daily for five consecutive days in normal and *Escherichia coli* infected chickens revealed a lower significant serum apramycin concentration in *Escherichia coli* infected chickens compared with normal chickens. The highest tissue concentrations of apramycin were present in the kidneys and liver.

KEYWORDS: Apramycin; Pharmacokinetics; Bioavailability; Residues; Broiler chickens.

INTRODUCTION

Apramycin is an important aminocyclitol class of antibacterial agents. Apramycin acts by irreversible binding to the 30 S ribosomal subunit there by inhibiting protein synthesis.

Apramycin is a broad spectrum antibacterial used for treatment of systemic and enteric infections in avariety of species of animals.[1] It is generally not well absorbed from gastrointestinal tract of animals.[2]

The aim of the present work was undertaken to study the pharmacokinetic parameters of apramycin after intravenous and oral administration in normal and experimentally *Escherichia coli* infected chickens. Also bioavailability of apramycin will be calculated in normal chicken. The disposition kinetics as well as the tissue residues after repeated oral administrations of apramycin in normal and experimentally *Escherichia coli* infected chickens will be studied.

MATERIALS AND METHODS

Drug (apramycin)

Apramycin was used in this study under trade name (Apracolin®). It was obtained from ATCO pharma for pharmaceutical industries, Qusina, EGYPT. It is used for oral administration. Each 100 gm of patent preprartion contains 86.548 gm of apramycin sulphate (eq. to 59.524 gm apramycin base).

Experimental animals

Fourty six clinically normal Hubbard chicken of four weeks of age weighting about 1500 to 2000 grams were chosen randomly from poultry farm in Qalubia governorate, EGYPT. Chickens were fed on a balanced ration free from antibiotics.The ration was obtained from Al-Qaed feed,Mansoura,Egypt. Chicken were left for two weeks to withdraw any antibiotic residues. The dose of administration was 25 mg apramycin for oral route and 10 mg for intravenous route in chickens according to drug manufacturing instructions.

Grouping of chicken

Group (1)

It included six normal chicken, which were administered intravenously in to the wing vein with single dose of 10 mg apramycin per kilogram body weight.

These chickens were left for 15 day after the intravenous injection to ensure complete elimination of apramycin from their bodies and then administered orally with 25 mg apramycin per kilogram body weight, to determine the bioavailability of apramycin in normal chicken.

Group (2)

It included twenty normal chickens were orally administered 25 mg apramycin per kilogram body-weight three daily for five consecutive days, to determine pharmacokinetics and at the end of fifth day of administration, three chickens were slaughtered after 1,3,5,7,9 and 11 days to determine tissue residue of apramycin.

Group (3)

It include twenty experimentally *E.coli* infected chickens were orally administered single dose of 25 mg apramycin per kilogram body-weight three times daily for five consecutive days after the appearance of the symptoms, 48 hours after experimental infection with *E.coli* to determine pharmacokinetics and tissue residue of apramycin.

Collection of samples

Blood samples

About one milliliter of blood was taken from the right wing vein, following administration of the drug. Blood samples were collected at 5,10,25,30 minutes, 1,2,4,6,8,12, 24 hours after single intravenous and oral administration of apramycin. Blood samples following repeated oral administration of apramycin in normal and experimentally infected chicken for 5 consecutive days were collected at 10,15,30 minutes, 1,2,4,6 hours and before, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth,and thriteenth doses.

All blood samples were collected in sterilized centrifugated tubes and allowed to clot. Serum was separated by centrifugation for 15 minutes at 3000 revolution per minutes. Sera were kept frozen until assayed.

Tissue samples

At the end of fifth day of repeated oral administration of apramycin, three chicken were slaughtered from group (2) and group (3). From each slaughtered chicken, samples of brain, heart, spleen, liver, kidney, breast muscle, thigh muscle, intestine, fat and skin were taken for assaying of residues of apramycin at 1,3,5,7,9 and 11 days. Sample were frozen and stored at -20^0c until assayed.

Analytical procedures

The concentration of apramycin in serum samples was estimated by a standard microbiological assay using *Bacillus subtilis* ATCC 6633 as test micro-organism. The

medium was prepared by dissolving 9.5 g Mueller–Hinton agar in 250 ml distilled water in a 0.5 l flat-bottomed flask, which was autoclaved for 20 min. After cooling to 50^{o}C in a water bath, 0.4 ml of the diluted suspension of reference organism was added to the media. Six wells, 8 mm in diameter were cut at equal distances in standard Petri dishes containing 25 ml seeded agar. The wells were filled with 100 µl of either the test samples or apramycin standards. The plates were kept at room temperature for 2 hours before being incubated at 37^{o}C for 18 hours. Zones of inhibition were measured using micrometers, and the apramycin concentrations in the test samples were calculated from the standard curve. Negative control samples showed no bacterial inhibition, indicating no intrinsic antibacterial activity of the samples. For assay of tissue samples, two grams of tissue were homogenized by automatic homogenizer with 2 ml of distilled water. Mixtures were centrifuged at 3000 revolution per minutes. for 10 minutes and supernatant fluid of each sample was obtained and directly assayed microbiologically for apramycin concentration.

Pharmacokinetic analysis

Pharmacokinetic parameter calculated by winnonlin program, version1.2. and other parameters according to[3] and.[4-5]

Statistical Analysis

Data were expressed as mean ± S.E. The obtained data were statistically analyzed using Student's *t*–test to express the differences between groups.[6]

RESULTS

Following a single intravenous injection of 10 mg apramycin/kg b.wt.in normal chicken, apramycin could be detected therapeutically in serum till-12 hours post intravenous injection**.**The plasma concentration – time curve of apramycin following intravenous injection showed that the drug obeyed a three compartment opem model. The disposition kinetics of apramycin following a single intravenous and oral administration were showed in figure (1) and recorded in (table1).

Oral administration of 25 mg apramycin / kg b.wt. three times daily for five consecutive days in normal and *E-coli* infected chickens revealed a lower significant apramycin concentrations at all times sampling in E-coli infected chickens than in normal chickens. The pharmacokinetic parameters of apramycin after repeated oral administration in normal chickens were compered to those in *E-coli* infected chickens(table 2).

Tissue samples from liver, kidney, lung, heart, breast muscle, thigh muscle, skin, and blood were taken for assaying of residues of apramycin at 1,3,5,7,9 and 11 days after the last oral administration of 25 mg/kg b.wt. from normal chickens were compared to those in *E-coli* infected chickens(table 3).

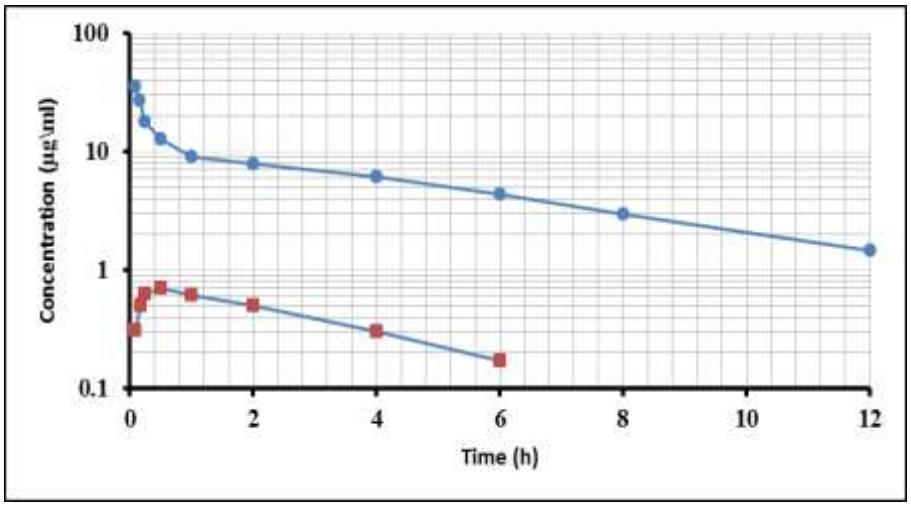

Figure (1): Semilogharithmic graph depicting the time course of apramycin concentration in normal chickens following a single oral administration of 25 mg/ kg.b.wt. (■——■)and 10 mg/ kg.b.wt. of single intravenous(●——●)in chickens.(n=6).

Table 1: pharmacokinetic parameters of apramycin in following a single intravenous injection of 10 mg/kg b.wt. and oral administration of 25 mg/kg b.wt in normal chickens(n=6).

Parameter	Unite	Intravenous	Oral
C^0	µg/ml	1.29±0.006	1.29±0.006
A	µg/ml	40.84 ±0.265	0.474 ± 0.005
α	h^{-1}	6.08 ± 0.048	-
B	µg/ml	0.530 ±0.006	0.814 ± 0.001
β	h^{-1}	0.693± 0.004	-
$t_{0.5(\beta)}$	h	0.999 ± 0.006	-
C	µg/ml	10.54 ± 0.205	-
ɤ	h^{-1}	0.152 ± 0.002	-
$t_{0.5(\gamma)}$	h	4.56±0.079	-
K_{12}	h^{-1}	3.89 ±0.025	-
K_{21}	h^{-1}	1.44 ± 0.015	-
K_{13}	h^{-1}	0.212 ±0.002	-
K_{31}	h^{-1}	0.650± 0.013	-
V_1	ml/kg	384.61±2.33	-
V_2	ml/kg	1032.24± 15.01	-
V_3	ml/kg	120.69±1.86	-
V_{dss}	ml/kg	1460.19 ± 82.24	-
K_{10}	h^{-1}	0.672 ± 0.004	-

$CL_{(tot)}$	ml/min	0.257± 0.002	0.170±0.0004
AUMC	µg.h2/hr	464.88± 2.69	-
$t_{0.5(Kel)}$	h	-	1.90 ± 0.164
T_{max}	h	-	0.524 ± 0.006
C_{max}	µg/ml	-	0.712 ±0.002
$T_{0.5(k10)}$	H	-	1.31±0.009
AUC	(µg/ml/h)	2.54±0.023	77.43±0.0363

A, B and c Zero time serum drug concentration intercepts of biphasic intravenous disposition curve. The coefficient B is based on the terminal exponential phase (µg/ml). α & β**,** Hybrid rate constant of biphasic intravenous disposition curve values of α and β are related to the slopes of distribution and elimination phase respectively, of biexponential drug disposition curve (h^{-1}); AUC, Total area under the serum drug concentration versus time curve from t=0 to t=α after administration of single dose (µg/ml); C^0, Drug concentration in the serum at zero time immediately after single intravenous injection (µg/ml); C_{max}, Maximum serum concentration of drug in blood after extra vascular administration (µg/ml); CL_{tot}, The total clearance of a drug, which represents the sum of all clearance processes in the body (ml/kg/min); K_{21}, First – order transfer rate constant for drug distribution from peripheral to central compartment (h^{-1}). K_{13}, First –order elimination rate constant for disappearance of drug from central compartment(h^{-1}**);** $t_{0.5(\alpha)}$, Distribution half – life (h); $t_{0.5(\beta)}$, Elimination half – life (h); $t_{0.5(\gamma)}$, the terminal phase (h); t_{max}, The time at which the maximum concentration of drug was reached after extravascular administration (h); V_{1c}**,** the apparent volume of central compartment(ml/kg); $V_{d(B)}$, The apparent volume of distribution which calculated by extrapolation method(ml/kg); $V_{d(area)}$, The apparent volume of distribution which was calculated by the area method (ml/kg); V_{dss}: The apparent volume of distribution which calculated by steady – state method (ml/kg).

Table 2: Pharmacokinetic parameters of apramycin in normal (N) and experimentally *E.coli* infected chickens (I) during repeated oral administrations of 25 mg/kg b.wt. three times daily for 5 consecutive days (n=6).

arameter	Unit	1st dose		4rd dose		7th dose		10th dose		13th dose	
		_ N (X ± S.E.)	_ I (X ± S.E.)	_ N (X ± S.E.)	_ I (X ± S.E.)	_ N (X ± S.E.)	_ I (X ± S.E.)	_ N (X ± S.E.)	_ I (X ± S.E.)	_ N (X ± S.E.)	_ I (X ± S.E.)
C^0	µg/ml	**1.29**±0.009	**1.42±0.036**	**1.75**±0.005	**1.71**±0.045	**1.76**±0.003	**1.57**±0.039	**3.12**±0.004	**2.32**±0.058	**5.21±0.078**	**3.60±0.09**
A	µg/ml	**0.474±0.005**	**0.563±0.014**	**0.721±0.004**	**0.827±0.020**	**0.701±0.004**	**0.609±0.014**	**1.49±0.013**	**1.04±0.025**	**2.85±0.037**	**1.98±0.046**
K_{ab}	h^{-1}	**5.68**±0.074	**0.160*****±0.211	4.32±0.056	9.02***±0.189	5.65±0.048	11.20***±0.258	8.34±0.125	10.84*±0.260	10.81±0.129	9.08±0.209
$t_{0.5(ab)}$	H	1.22±0.001	0.076±0.002	0.160±0.002	0.078±0.002	0123±0.004	0.062±0.002	0.083±0.001	0.064±0.002	0.064±0.001	0.076±0.002
T_{max}	H	0.524±0.006	0.797±0.019	0.443±0.007	0.833±0.017	0.476±0.005	0.797±0.019	0.503±0.007	0.782±0.019	0.521±0.007	0.774±0.019
C_{max}	µg/ml	0.712±0.002	0.765±0.018	0.939±0.003	0.855±0.018	0.952±0.003	0.999±0.025	1.43±0.018	1.21±0.029	1.97±0.029	1.44±0.033
B	µg/ml	**0.814±0.0001**	**0.8**52±**0.020**	1.03±**0.012**	0.879±**0.021**	**1.06±0.016**	**0.963±0.022**	**1.63±0.024**	**1.28±0.031**	**2.36±0.035**	**1.62±0.039**
K_{el}	h^{-1}	0.333±0.002	1.25±0.030	0.285±0.003	1.20±0.028	0.254±0.003	**1.25**±0.030	0.296±0.004	1.26±0.030	0.342±0.004	1. 29±0.031
$t_{0.5(Kel)}$	H	1.90±0.164	0.553±0.013	2.43±0.081	**0.577***±0.014	**2.73**±0.068	0.553±0.013	2.34±0.033	0.549±0.013	2.03±0.028	0.537±0.013
CL_{tot}	µg/mL/h	0.107±0.0016	0.368±0.009	0.068±0.001	0.293±0.007	0.060±0.001	0.265±0.006	0.040±0.001	0.226±0.005	0.027±0.0004	0.149±0.0004
AUC	hr/µg/mL	2.54±0.023	1.66±0.040	2.82±0.029	1.94±0.045	2.36±0.035	2.17±0.052	3.29±0.049	2.61±0.063	**4.36±0.057**	**3.03±0.073**

***P<0.05 **p<0.01 ***p<0.001.**

Table 3: Tissue concentrations of apramycin (µg/ml) in normal (N) and experimentally *E.coli* infected chickens during repeated oral administration of 25 mg/kg b.wt. three times daily for 5 consecutive days (n=3).

Tissue	After 1 day		After 3 day		After 5 day		After 7 day		After 9 day		After 11 day	
	N _(X ± S.E.)	I _(X ± S.E.)	N _(X ± S.E.)	I _(X ± S.E.)	N _(X ± S.E.)	I _(X ± S.E.)	N _(X ± S.E.)	I _(X ± S.E.)	N _(X ± S.E.)	I _(X ± S.E.)	N _(X ± S.E.)	I _(X ± S.E.)
Heart	-	-	-	-	-	-	-	-	-	-	-	-
Liver	0.373± 0.008	0.330**± 0.011	0.300± 0.150	0.263**± 0.008	0.190± 0.005	-	-	-	-	-	-	-
Intestine	0.330± 0.005	0.290*± 0.006	0.310± 0.011	0.250**± 0.005	0.183± 0.008	-	-	-	-	-	-	-
Kidney	1.60± 0.115	1.20**± 0.057	1.40± 0.088	0.910***± 0.003	1.00± 0.005	-	-	-	-	-	-	-
Lung	0.356± 0.008	0.250***± 0.005	0.183± 0.003	-	-	-	-	-	-	-	-	-
Brain	0.210± 0.005	0.173***± 0.003	0.170± 0.008	-	-	-	-	-	-	-	-	-
Breast muscle	0.250± 0.012	0.200**± 0.008	0.180± 0.014	0.150**± 0.005	0.106± 0.012	-	-	-	-	-	-	-

(*) Represents the significance in comparison with 1st dose.

***P<0.05 **p<0.01 ***p<0.001**

DISCUSSION

In the present investigation intravenous injection of 10 mg apramycin /kg b.wt. in normal chickens showed that the disposition best fitted a three compartments open model. The obtained result was disagreed with those reported previously for apramycin in normal chickens given apramycin at a dose of 75 mg /kg b.wt.[7]

The V_{dss} is a clearance-independent volume of distribution that is used to calculate the drug amount in the body under equilibrium conditions**.** The V_{dss} for apramycin was 1.46.19±82.24 L/kg, this obtained value lower than the data reported after intravenous administration of apramycin (4.82 ± 0.08 L/kg).[7] On the other hand, the volume of distribution was higher than those recorded for apramycin in adult chicken (0.182±0.021)**[8]** goats (0.26 ± 0.038 L/kg)[9] turkey (0.292±0.05 L/kg)**[10]** sheep (0,167±0.008), rabbits (0.284±0.035) and pigeons (0.077±0.001)[8] and also in calves (0.71 L/kg).[1]

Apramycin was transferred from central to peripheral compartment at a faster rate (K_{12} = 3.89 ± 0.0251h^{-1}) than its passage from peripheral compartment to central compartment (K_{21} = 1.44 ± 0.151h^{-1}).These values were lower to that reported for apramycin in broiler chickens (K_{12} = 4.124±1.432 h^{-1}) and (K_{21} = 2.215±0.487 h^{-1}) by[9] On the other hand, these values were higher than these reported for apramycin in chickens (K_{12} = 0.01h^{-1}) and (K_{21} = 0.39h^{-1}) by[10] gentamycin in goats (K_{12} = 1.1614h^{-1}) and (K_{21} = 1.584h^{-1}), amikacin (K_{12} = 2.138h^{-1}) and(K_{21} = 1.4293h^{-1}) by.[9]

The elimination half-life[$t_{0.5(\beta)}$] of apramycin following a single intravenous injection of 10 mg/kg b.wt. was equal to 0.999±0.006h. This observation lower than those reported after intravenous administration of apramycin in chickens (2.10 h)**[7]** calves (4.4h)[1] goats (1.32±0.09), gentamycin in goots(1.81±0.85), amikacin(2.42±0.8), tobramycin (1.82±0.5), kanamycin (2.06±0.5884)[9] amikacin in broiler chicken (4.48)[11] and also in foals (5.07 and 5.2)[12] This value was higher than apramycin in Japanese quails (0.50±0.02 h)**.[13]**

The rate of total body clearance[CL_{tot}] of apramycin following intravenous injection was 0.257±0.002 L/kg/hr.This value was nearly similar to amikacin in dogs(0.24 L/kg/hr)**[14]** cats(1.46±0.26 L/kg/hr)**[15]** chickens (0.109±0.017 L/kg/hr)[16] This value was lower than apramycin in calves(0.447 L/kg/hr)**[17]** This value was higher than these values reported in the aminoglycosides as amikacin in broiler chicken (0.08 L/kg/hr)**[11]** lactating goats(0.05 L/kg/hr).**[18]**

Following a single oral administration of 25 mg/kg b.wt. the drug reached its maximum concentration (0.705±.027 µg/ml) at 0.5 hours and could be detected in serum in a level 0.173±0.007 µg/ml for 6 hours.The mean peak serum concentration of apramycin (C_{max}) was(0.712 ± 0.002 µg/ml) achieved at (t_{max}) (0.524 ±0.006 hours). These value were nearly similar to those recorded (C_{max})(0.790 ± 0.020µg/ml) and (t_{max}) (0.200 ± 0.010 hours)[7] The (C_{max}) value were higher than to these recorded(C_{max}) (0.23 ±0.12 µg/ml)[19] On other hand these value is lower than amikacin in broiler chickens (C_{max})(15.25 ± 0.020µg/ml) and (t_{max}) (1.89 ± 0.010 hours)[11] and also amikacin in sheep(C_{max}) (16.97 µg/ml).[10]

The bioavailability of apramycin in normal chickens was 1.31%. Similar results were reported and found that apramycin is normally not well absorbed from the intestinal tract of broiler chickens.[2-20] This percent indicated a low absorption of apramycin after oral administration. This value was lower than the bioavailability recorded for apramycin in broiler chickens(2.03%)[7] On the other hand, this value was lower than the bioavailabilities recorded for other species, by diferent routes other than the oral route in pneumonic calves (61.98%)[17] in lactating cows, ewes and goats(60-70 %)[1] Japanese quails (56%)[13] and in turkey roosters (97.2%)[12] gentamycin in goats(96.3)[21] broiler chicken (79%)[22] amikacin in broiler chickens (95.2%)[11] and(91.2 ±17.6%)[16] dogs (91.3%)[19] cats(95± 20%)[15] sheep (87%) and calves(99%)[31] and in lactating goats(98.27%)[18] and neomycin in sheep(74-85%).[24]

Protein binding has long been considered one of the most important physicochemical characteristics of drugs, playing a potential role in distribution, excretion, and therapeutic effectiveness as a low protein binding generally enables a rapid and extensive distribution into the intracellular and extracellular space[7] In this study, the *in vitro* plasma protein binding experiment showed that apramycin displayed a low level of binding to plasma proteins (7.13%) to broiler chicken plasma.Similar results of gentamycin in broiler chickens (6.46%)[22] is recorded. This value was lower to these reported value of 26.0% for apramycin in broiler chicken[7] in lactating cows, ewes and goats (<22.5%)[1] amikacin in broiler chickens(11.57%)[11] On contrast this value was higher that those reported values of apramycin in pneumonic calves (2.29%).[17]

The study showed that the blood concentrations of apramycin in *Escherichia coli* infected chickens were significantly lower than those in normal chickens following repeated oral administrations. These lower blood concentrations in infected chickens might attributed to

higher penetrating power of drug to the diseased tissues[24] This phenomenon agreed with the data recorded by[10] who found that apramycin concentrations in plasma of infected birds were lower than those of healthy ones by[25] proved that, the serum concentrations of amikacin following intravenous administration on 10 mg/kg. b.wt. in normal goats (afebrile) were significantly higher than *E. Coli* infected goats(febrile),and also by[11] reported that the blood concentration of amikacin in *Escherichia coli* infected chickens were significantly lower than those in normal chickens following repeated intramuscular administrations.

=In contrast,[17] was reported that the serum concentrations of apramycin following intramuscular administration on 20 mg/kg. b.wt. two times daily for five consecutive days, apramycin peaked in serum 2 hours after each intramuscular dose with higher significant values recorded in pneumonic calves than in normal calves.

Repeated oral administrations of 25 mg apramycin /kg b.wt.three times daily for five consecutive days in normal and experimently *E.Coli* infected chickens revealed that kidney and liver contained the highest drug concentrations. Apramycin was detected in kidneys, liver, intestine and breast muscle till 5 days post last dose in normal chickens and till 3 days post last dose in *E-coli* infected chickens. And lung, brain till 3 days post last dose in normal chickens and till 1 day post last dose in *E-coli* infected chickens. This result slightly agreed with that recorded for apramycin in chickens by[7] who found the highest concentration was in kidney and liver.

CONCLUSION

Oral bioavailability of apramycin was low, which indicated low oral absorption, so it is recommended to be used against enteric infectious diseases caused be *Salmonella species and E.coli*. Reapted oral administrations of 25 mg apramycin /kg b.wt three times daily for five consecutive days would provide an effective concentration against enteric infectious diseases in broiler chickens. Treated chickens must not be slaughtered before 3 days from last dose of repeated administration of apramycin to withdraw the drug residues from all tissues of treated chickens.

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