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Original Article

Pharmacokinetical Interactions of Amoxicillin and Amprolium in Broiler Chickens

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Abstract

Bioavailability of amoxicillin following a single intravenous and oral administrations as well as tissue residues were determined in broiler chickens. Effect of amprolium on the disposition kinetics and tissue residues of amoxicillin following repeated oral administrations was also investigated. Following a single intravenous injection of amoxicillin, 20 mg/kg.b.wt., in normal broiler chickens , plasma concentration-time curve was best described by a three - compartments open model with elimination half-life $t_{0.5\delta}$ = 9.78 ± 0.43 h, volume of distribution V_{dss} = 1012.06 ml/kg and total clearance of the drug CL_{tot} =0.090 ml/kg/min. Following a single oral dosing, the maximum plasma concentration was 12.54 ± 0.140 μg/ml, reached at T_{max} =1.05 ± 0.042 h. The mean systemic bioavailability following oral administration was 67.33%. Following repeated oral administration in normal chickens, highest plasma concentration peaked after one hour of each oral dose. Amoxicillin showed accumulative behavior in plasma of broiler chickens. Amprolium resulted in a significant decrease in maximum plasma concentration of amoxicillin C_{max} = 12.36 ± 0.506 μg/ml compared with amoxicillin alone C_{max} = 14.38 ± 0.373 μg/ml. Amprolium resulted in a significant increase in total drug clearance Cltot = 1.43 ± 0.089 L/kg compared with amoxicillin alone (Cltot = 1.20 ± 0.028 L/kg). Amprolium resulted in a significant decrease in amoxicillin residues concentrations in all assayed tissues. It is concluded that the administration of amprolium before amoxicillin would altered its pharmacokinetic profile.

Keywords: Pharmacokinetics, interaction, amoxicillin, amprolium, chickens.

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Introduction

Pharmacokinetic drug interactions are of great clinical importance in veterinary practice. Drugs have the same metabolic pathway usually show drug interactions in its concomitant administration. Amoxicillin is a semisynthetic penicillin belonging to aminopenicillin group, it is bactericidal β-lactam antibiotic with extended antibacterial spectrum against wide range of Gram-negative and Gram-positive pathogens. Amoxicillin is a widely used in human and veterinary medicine for the treatment and prevention of respiratory, gastrointestinal, urinary and skin bacterial infections. It is usually the drug of choice because it is better absorbed, following oral administration, than other β-lactam antibiotics.

Amprolium is a thiamine analogue used in treatment and prevention of coccidiosis in poultry and rabbits. It is usually added to poultry rations as a feed additive, which may interact with any administered drugs. The aim of this study is to investigate the effect of amprolium pretreatment on the pharmacokinetics and tissue residues of amoxicillin in broiler chickens. The pharmacokinetic profiles of the amoxicillin, following a single intravenous and oral administration in normal chickens were determined. Bioavailability of amoxicillin in normal chickens was calculated. The pharmacokinetic profiles as well as tissue residues of amoxicillin following repeated oral administrations in normal chickens and in chickens previously given amprolium were performed.

Materials and Methods

Drugs

Amoxicillin: (E-MOX)®

It was obtained as powder from Egyptian International Pharmaceutical Industries Co. (E.I.P.I.Co.), Cairo, Egypt, under trade name of E-MOX®.

Amprolium: (Amprolium 20%)®

samples were taken from either right or left wing vein of chickens were collected after 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after a single intravenous and oral (single & repeated) administrations in all groups. All plasma samples were frozen at –20°C until assay.

Tissue Samples

After the end of the repeated oral administration of amoxicillin in normal chickens (group 2), and in chickens pre-treated with amprolium (group 3), three chickens were slaughtered after 24, 48, 72, and 96 hours. Tissue samples from brain, lung, heart, gizzard, liver, spleen, kidney, breast muscles, thigh muscles, fat and skin were taken from each slaughtered bird for amoxicillin assay. Samples were frozen and stored at –20°C until assayed.

Analytical Procedures

Amoxicillin was assayed in plasma and tissues of chickens by modified spectrophotometric method of by using a double beam UV- visible spectrophotometer (T60U, United Kingdom) in the central lab., that follow Center of Excellence for Scientific Research (CESR) , faculty of veterinary medicine- Benha University. The pharmacokinetic parameters were calculated by WinNonlin® program, version 1.1 and some parameters according to El-barawy *et al.,* and Gehan 2013. All statistical analysis was carried out according to El-Sayed *et al.,* and Gehan 2013.

Assay of Blood Samples

According to El-barawy *et al.,* and Gehan 2013, half milliliter of plasma sample was mixed with 4 ml of distilled water and 0.5 ml of 70 % perchloric acid was added to precipitate plasma protein. The mixture was shaken for 5 minutes, and then centrifuged for 40 minutes at 2500 rpm. The supernatant was collected and read at 235 nm by modified spectrophotometric method using a double beam UV- visible spectrophotometer (T60U, United Kingdom), in the central lab., that follow Center of Excellence for Scientific Research (CESR), faculty of veterinary medicine - Benha University. Concentrations of the drug at different time intervals were obtained from the standard curve prepared previously and expressed as µg/ ml of the plasma.

Assay of Tissue Samples

Three milliliters of distilled water were added to one gram of the obtained tissue sample and homogenized in a porcelain mortar by the aid of sterile sand. The homogenate was left in the refrigerator overnight then centrifuged. The supernatant was taken and subjected to the same procedures for assay in plasma samples. Concentrations of the drug at different time intervals were obtained from the standard curve of amoxicillin in distillated water prepared previously and expressed as µg/gm of the tissue.

Results

The semilogarithmic plasma concentration-time curve of amoxicillin in normal broilers, after a single intravenous injection of 20 mg/kg b.wt. (Fig. 1) showed that the drug obeyed a three compartments open model. Amoxicillin could be detected for 24 hours post intravenous injection. The corresponding kinetic parameters are described in table (1).

Table 1: Pharmacokinetic parameters of amoxicillin in plasma following a single intravenous injection of 20 mg/ kg b.wt., in normal chickens (n=7).

Parameter	Unit	($\bar{X}$ ±S.E.)	Parameter	Unit	($\bar{X}$ ±S.E.)
Body weight	kg	1.85±0.063	C	µg/ml	12.11 ± 0.292
C^o	µg/ml	94.88 ± 0.583	δ	h^{-1}	0.072 ± 0.003
A	µg/ml	64.15 ± 0.520	$t_{0.5\delta}$	h	9.780 ± 0.430
α	h^{-1}	5.56 ± 0.288	K_{10}	h^{-1}	0.443 ± 0.011
$t_{0.5\alpha}$	h	0.126 ±0.006	V_1	ml/kg	210.86±1.299
K_{12}	h^{-1}	2.672 ± 0.111	V_2	ml/kg	260.96±8.082
K_{21}	h^{-1}	2.177 ± 0.129	V_3	ml/kg	540.24±56.95
B	µg/ml	18.62 ± 0.564	Vdss	ml/kg	1012.0±657.01

β	h^{-1}	0.619 ± 0.056	CL_{tot}	ml/kg/min	0.090±0.002
$t_{0.5\beta}$	h	1.160 ± 0.087	AUMC	µg.h/ml	2508.38±17.28
K_{13}	h^{-1}	0.678 ± 0.042	$_{MRT}$	h	11.30±0.593
K_{31}	h^{-1}	0.235±0.005	-	-	-

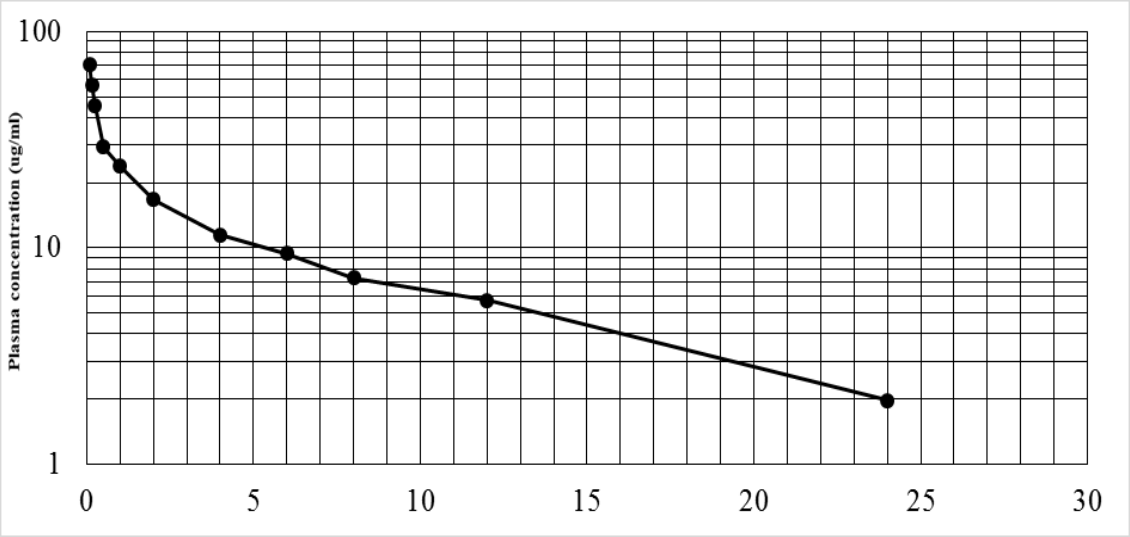

Fig. 1: Semi-logarithmic graph depicting the time course of amoxicillin (µg /ml) in plasma of normal broiler chickens following a single intravenous injection of 20 mg/kg b.wt. (n=7).

The semi logarithmic plasma concentration-time curve of amoxicillin in normal broilers, after a single oral administration of 20 mg/kg.b.wt. is depicted in (fig. 2). The corresponding kinetic parameters are described in table (2).

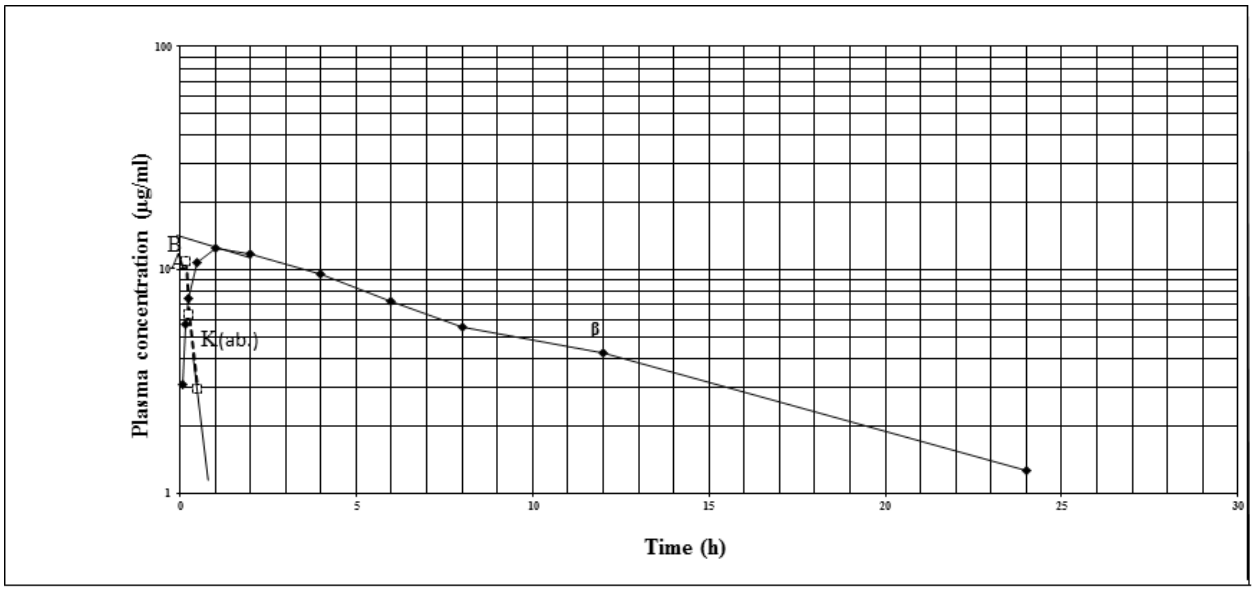

Fig. 2: Semi-logarithmic graph depicting the time course of amoxicillin in plasma of normal chickens following a single oral administration of 20 mg/kg.b.wt. (n=7).

Table 2: Pharmacokinetic parameters of amoxicillin in plasma following a single oral administration of 20 mg /kg b. wt. in normal chickens previously given the same dose by a single intravenous injection (n=7).

Parameter	Unit	($\bar{X}$ ± S.E.)
Body weight	Kg	1.971±0.065
A	µg/ml	12.16±0.582
K_{ab}	h^{-1}	3.48±0.210
$t_{0.5\ (ab.)}$	h	0.203±0.011
B	µg/ml	13.92±0.197
K_{el}	h^{-1}	0.099±0.002
$t_{0.5(\beta)}$	h	7.01±0.119
C^o	µg/ml	26.07±0.446
C_{max}	µg/ml	12.54±0.140
t_{max}	h	1.05±0.04
CL_{tot}	ML/kg/min	1.27±0.033

Plasma concentrations of amoxicillin following repeated oral administration of 20 mg/kg b.wt twice daily for five consecutive days in normal chickens and in that previously given amprolium 30 mg/kg.b.wt. once daily for 5 consecutive days revealed a highly significant decrease in plasma concentrations of amoxicillin in chickens previously given amprolium when compared with normal chickens at most times of sampling (Figures 3&4). The pharmacokinetic parameters of amoxicillin as well as tissue residues after repeated oral administration in normal chickens were compared to that previously given amprolium (Tables 3&4).

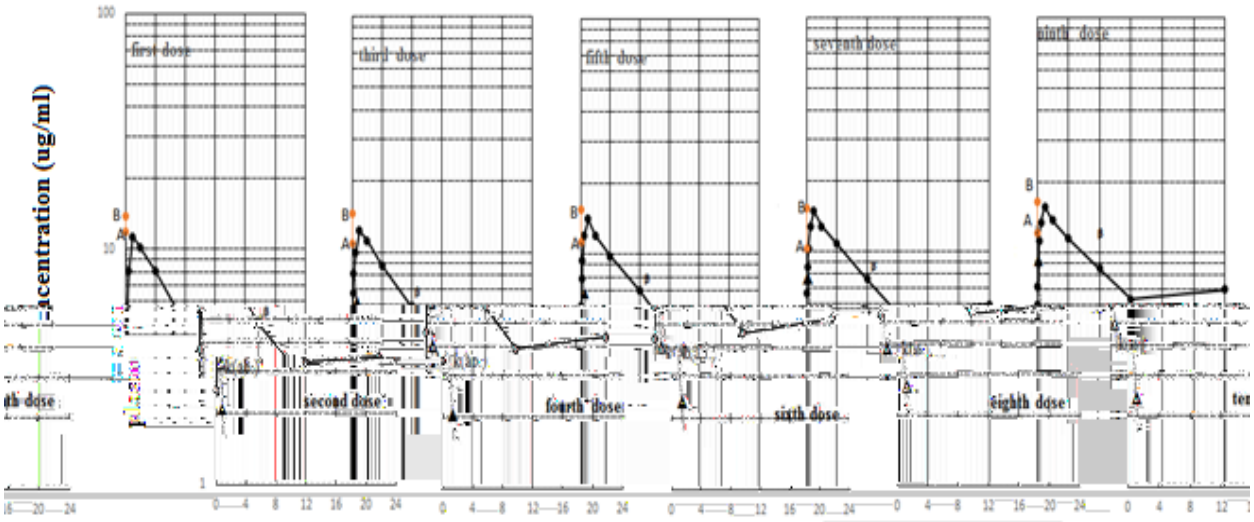

Fig. 3: Semi-logarithmic graph depicting the time course of amoxicillin (µg/ml) in plasma of normal chickens following repeated oral administration of 20 mg/kg b. wt. twice daily for 5 consecutive days. (n=7).

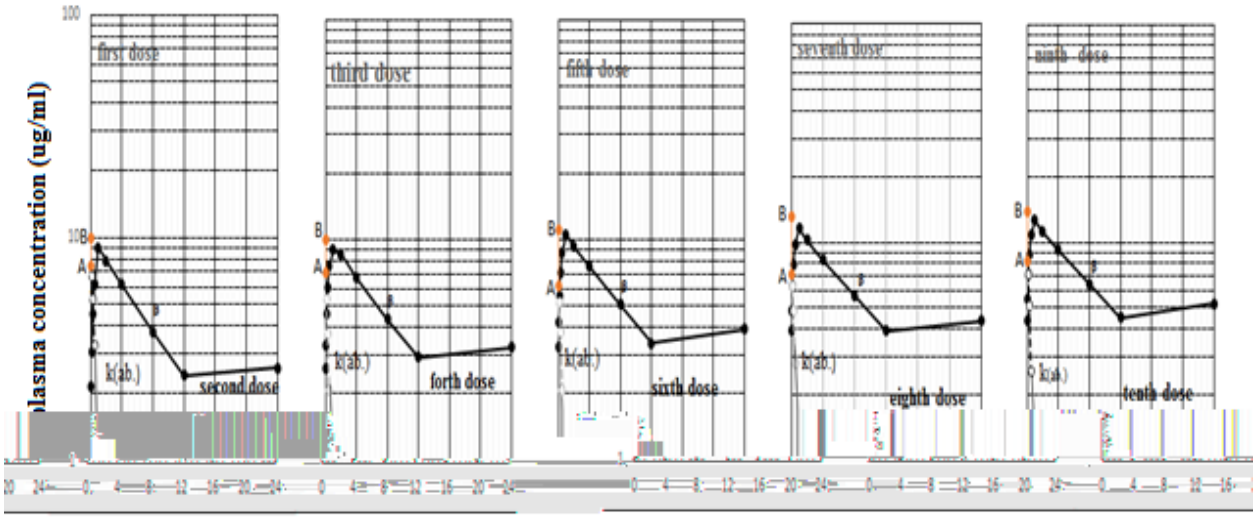

Fig. 4: Semi-logarithmic graph depicting the time course of amoxicillin (µg/ml) following repeated oral administration of 20 mg/kg b. wt. twice daily for 5 consecutive days in chickens previously given amprolium 30 mg/kg b. wt. once daily for 5 consecutive days (n=7).

Table 3: Pharmacokinetic parameters of amoxicillin (µg/ml) following repeated oral administration of 20 mg/kg b. wt. twice daily for consecutive 5 days in normal chickens and in chickens previously given amprolium 30 mg/kg b.wt. once daily for 5 consecutive days (n=7).

		First dose		Third dose		Fifth dose		Seventh dose		Ninth dose	
Param-eter	Unit	amox. ($\bar{x}$±SE)	amox.+amp. ($\bar{x}$±SE)	amox. ($\bar{x}$±SE)	amox.+amp. ($\bar{x}$±SE)	amox. ($\bar{x}$±SE)	amox.+amp. ($\bar{x}$±SE)	amox. ($\bar{x}$±SE)	amox.+amp. ($\bar{x}$±SE)	amox. ($\bar{x}$±SE)	amox.+amp. ($\bar{x}$±SE)
A	µg/ml	11.80± 0.367	7.43± 0.314***	10.94± 0.337	7.05± 0.254***	11.17± 0.288	6.18± 0.260***	10.24± 0.381	7.09± 0.305***	12.02± 0.695	8.19± 0.343***
K_{ab}	h^{-1}	1.64± 0.130	1.88± 0.068	1.74± 0.041	2.36± 0.099***	2.75± 0.154	2.41± 0.111***	2.39± 0.119	2.20± 0.090***	2.59± 0.152	2.78± 0.103***
$t_{0.5\ (ab.)}$	h	0.451± 0.032	0.369±0 .014	0.4± 0.010	0.294± 0.012**	0.257± 0.152	0.288± 0. 013	0.294± 0.015	0.315± 0.013***	0.275± 0.021	0.249± 0.009***
B	µg/ml	13.84± 0.403	9.97± 0.518***	14.5± 0.319	10.08± 0.38***	15.47± 0.335	11.19± 0.436***	15.29± 0.328	13.04± 0.469***	16.5± 0.343	13.93± 0.543***
K_{el}	h^{-1}	0.129± 0.05	0.121± 0.006	0.127± 0.003	0.101± 0.004	0.114± 0.001	0.103± 0.004	0.088± 0.002	0.101± 0.004**	0.086± 0.002	0.095± 0.004**
$t_{0.5\beta}$	h	5.41± 0.189	5.75± 0.259	5.47± 0.124	6.84± 0.294**	6.09± 0.0617	6.76± 0.250**	7.87± 0.169	6.84± 0.315***	8.12± 0.186	7.29± 0.299***
C^o	µg/ml	25.63± 0.721	17.40± 0.68***	25.73 ±0.668	17.13± 0.74***	26.64± 0.553	17.37± 0.75***	25.53± 0.365	20.13± 0.825***	28.52± 0.652	22.12± 0.907***
$C_{max.}$	µg/ml	11.51± 0.255	8.26± 0.380***	11.95± 0.220	8.75± 0.40***	13.57± 0.203	9.73± 0.418***	13.58± 0.249	11.24± 0.427***	14.38± 0.373	12.36± 0.506***
t_{max}	h	1.72± 0.077	1.56± 0.059*	1.67± 0.053	1.40± 0.060*	1.30± 0.069	1.35± 0.062	1.26± 0.085	1.47± 0.053**	1.27± 0.039	1.26± 0.063
CL_{tot}	ml /kg /min	1.5± 0.049	2.31± 0.118***	1.58± 0.045	1.97± 0.091**	1.34 ± 0.0189	1.98± 0.091***	1.23± 0.065	1.67± 0.067**	1.20± 0.028	1.43± 0.089**

*P<0.05, ** P<0.01, *** P<0.001.
amox. = amoxicillin, amp. = amprolium.

Table 4: Plasma (μg/ml) and tissue concentrations (μg/g) of amoxicillin following repeated oral administration of 20 mg/kg b. wt. twice daily for 5 consecutive days in normal chickens and in chickens previously given amprolium 30 mg/kg b. wt. once daily for 5 consecutive days (n=3).

Tissue	After 24 hours		After 48 hours		After 72 hours	
	amox. ($\bar{x}$ ±S.E.)	amox.+amp. ($\bar{x}$ ±S.E.)	amox. ($\bar{x}$ ±S.E.)	amox.+amp. ($\bar{x}$ ±S.E.)	amox. ($\bar{x}$ ±S.E.)	amox.+amp. ($\bar{x}$ ±S.E.)
Plasma	2.89±0.177	2.15±0.23***	1.32±0.211	1.08±0.22***	-	-
Brain	1.047±0.065	0.717±0.073***	0.523±0.318	0.393±0.049***	-	-
Heart	2.53±0.064	1.88±0.14***	0.761±0.090	0.58±0.99***	-	-
liver	2.88±0.152	2.31±0.18***	1.083±0.099	0.89±0.12***	0.358±0.032	-
kidney	7.19±0.222	4.81±0.39***	3.34±0.183	2.16±0.19***		

The calculated systemic oral bioavailability percent was 67.33 ± 0.72%. This percent was nearly equal to that in horses (67%) and in broiler chickens (63.00 ± 4.58%). While it was higher than the bioavailability percent in goats (27%) and in ducks (34.67 ± 5.06%). On the other hand, this oral bioavailability was lower than that in dogs (76.8 ± 16.7%). The relatively high bioavailability of amoxicillin in this study (67.33 ± 0.72%) indicated high absorption of the drug from chicken's gut.

The obtained plasma levels following repeated oral administration of amoxicillin in chickens previously given amprolium were significally lower than those in normal chickens. This result was in agree with that recorded in chickens as they recorded that the mean serum concentrations of levofloxacin were significantly lower in amprolium pretreated broilers compared to control broilers. Similar findings were previously reported for amprolium with enrofloxacin in broilers who reported that, coccidia infected birds pretreated with amprolium exhibit a lower serum enrofloxacin concentration if compared with control birds. While these results were differ from another study in chickens who recorded that ampicillin concentration following repeated oral co-administrations with amprolium revealed a significant increase in serum drug concentration when compared with ampicillin alone.

The pharmacokinetic parameters of amoxicillin during repeated oral administration in chickens previously given amprolium revealed significant increase in the apparent first order absorption rate constant (2.78 ± 0.103 h-1) in chickens previously given amprolium, than in normal chickens (2.59 ± 0.152 h-1). The absorption half- life was significantly lowered (0.249 ± 0.009 h) in chickens previously given amprolium if compared with normal chickens (0.275 ± 0.021 h). The lower calculated Cmax for amoxicillin (12.36 ± 0.506 μg/ml) in chickens pretreated with amprolium compared with normal chickens (14.38 ± 0.373 μg/ml) was associated with shorter ($t_{0.5\beta}$) of amoxicillin in chickens pretreated with amprolium (7.29 ± 0.299 h) if compared with normal chickens (8.12 ± 0.186 h). This observation could be attributed to the rapid elimination rate constant in this study (0.095 ± 0.004 h-1) in chickens pretreated with amprolium if compared with normal chickens (0.086 ± 0.002 h-1). This might be agreed with pharmacological interaction previously recorded for salinomycin in broiler chickens who found that serum concentration of amoxicillin (Cmax) was significantly lower in salinomycin treated chickens. In the current study, the lower Cmax of amoxicillin when pretreated with amprolium in broilers could be explained on the basis of the effect of amprolium on microsomal enzymes of liver. Similar observation was previously reported in goats, on co-administration of enrofloxacin with albendazole. Both albendazole and toltrazuril are highly metabolized to sulphone in liver, a phenomenon explaining the probability of both drugs in inducing CYP 450 enzymes in animals and birds and consequently the rapid biotransformation and lower Cmax of amoxicillin. Pretreatment of chickens with amprolium five days before amoxicillin administration was enough time to induce liver microsomal CYP 450 enzymes, although found that a single dose of albendazole was sufficient to induce such induction in goats. While these results were, differ in broiler chickens, who reported that the kinetic parameters of ampicillin following repeated oral co-administrations with amprolium revealed a significant increase when compared with ampicillin alone.

Tissue residues (μg/g) of amoxicillin following repeated oral administration, revealed wide distribution of the drug in the tested tissues, (brain, lung, heart, gizzard, liver, spleen, kidney, breast muscles, thigh muscles, fat and skin). High concentrations were found in the kidney (4.81 ± 0.390 μg/g), 24 hours after the last dose followed by liver (2.31 ± 0.180 μg/g) while the lowest concentrations were determined in fat and skin. Amoxicillin residues could not be detected in all examined tissues after 48 hours of the last dose. There was a significant decrease in the tissue concentrations of amoxicillin in chickens previously given amprolium when compared with normal chickens. Similar findings were previously reported for broiler chickens as they mentioned that, lower tissues concentration of the drug at different time interval after stopping dosage regimen in amprolium-pretreated chickens as compared with values recorded in control birds.

On the other hand, these findings are different from broiler chickens, who found that the anticoccidials (diclazuril and halofuginone), prolonged the withdrawal time of the tested antibiotics (tylosin and doxycycline), and who recorded that amprolium resulted in a significant increase of ampicillin concentrations in serum and different tested tissues when compared with ampicillin alone. The lower tissues concentration of amoxicillin at different time intervals in chickens previously given amprolium as compared with values recorded in normal chickens could be attributed to the inducing effect of amprolium on liver microsomal enzymes. Similar observation was previously reported.

Conclusion

Administration of the anticoccidial drug, amprolium, before amoxicillin in broiler chickens would altered its kinetic profiles as well as tissue residues. Therefore, under this condition, the dose of amoxicillin administration by oral route needs to be carefully adjusted.

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