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INFLUENCE OF SUBCHRONIC LEAD INTOXICATION ON THE PHARMACOKINETIC PROFILE OF OXYTETRACYCLINE IN BROILER CHICKENS

(With 4 Tables & 2 Fig.)

By

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أثر التسمم تحت المزمن بالرصاص على المسار الحركى لدواء الأوكسى تتراسيكلين فى دجاج التسمين

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تم فى هذا البحث دراسة أثر التسمم تحت المزمن بالرصاص على المسار الحركى للأوكسى تتراسيكلين فى دجاج التسمين وذلك بعد أعطاء جرعة واحدة من هذا الدواء (١٠ مجم/ كجم من الوزن) عن طريقى الحقن الوريدى والفم ، وكذا تم دراسة انتشار هذا الدواء فى الدجاج السليم والدجاج المسمم معملياً بالرصاص ، بالإضافه إلى دراسة تأثير هذا التسمم على فترة تخلص الجسم من بقايا الاوكسى تتراسيكلين. وأشارت النتائج إلى أن التسمم بالرصاص يؤدى إلى حدوث نقص معنوى فى تركيز الاوكسى تتراسيكلين فى دم الدجاج وكذلك فى الفتره المحسوبه بين الجرعتين وفى معدل إستفادة الجسم من هذا الدواء. كما أظهرت النتائج أن الفتره اللازمه للتخلص من بقايا دواء الاوكسى تتراسيكلين الموجوده بأنسجة الدجاج السليم والدجاج المسمم معملياً بالرصاص كانت ٣ ، ٢٠ يوم على التوالى.

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SUMMARY

The pharmacokinetic profile of oxytetracycline in healthy and experimentally lead intoxicated broiler chickens following its single oral and intravenous administration (10 mg/Kg b.wt) was studied. Tissue distribution and residue - depletion following its oral administration for 5 successive days was investigated. Lead acetate solution was given orally in a subtoxic dose of 4.2 mg/Kg b.wt/day for 8 successive weeks prior to oxytetracyline administration. Oxytetracycline reached its maximum concentration at 1 hr following its oral administration in healthy and lead-intoxicated chickens with a mean serum level of 0.73 and 0.47 µg/ml and absorption half-life ($t_{0.5(ab)}$) of 9.89 and 13.08 minutes and elimination half-life ($t_{0.s(B)}$) 2.12 and 1.97 hrs, respectively. A short interval between doses of the drug was calculated for intoxicated group as compared with healthy one. Following intravenous injection, oxytetracycline was fitted to follow one compartment model in healthy as well as in intoxicated group with $t_{0.5}$ of 2.18 and 2.56 hrs, volume of distribution (VD) of 9.22 and 8.79 L/Kg and total body clearance of 28.91 and 32.58 mg/Kg/min., respectively. A decreased value for systemic bioavailablity (F %) of the drug was recorded for lead-intoxicated group (54.05%) as compared with healthy one (78.85%) after its oral administration indicating lower extent of drug absorption from intestinal tract of intoxicated chickens than healthy ones. Following oral adminsitration of oxytetracycline (10 mg/Kg b.wt) for 5 successive days, the drug was detected in edible tissues (liver, lung, kidney and muscles) of healthy and intoxicated chickens on the first day after its discontinuation with residual levels lower than 0.25 ppm and completely deplete from tissues after the third and second day in healthy and lead-intoxicated chickens, respectively.

INTRODUCTION

The residues of some environmental pollutants in animal tissues particularly heavy metals may impair the therapeutic

effectiveness of some antibacterial agents (e.g. sulphonamides) as they affect pharamacokinetic pattern *(GOEDE & KUHNERT, 1986 and ATEF et al., 1992).* The extensive use of oxytetracycline for treatment of bacterial infections in poultry and the problems caused by heavy metal intoxication as result of food and/or feed contamination have necessitate the study of influence of heavy metals on the pharmacokinetic profile of common used antibacterials.

The pharmacokinetic aspect of oxytetracycline have been extensively investigated in different animal species by many investigators *(PILLOUD, 1973; IMMELMANN, 1977; NOUWS & ZIV, 1977 and LARSON & STOWE, 1981; BRADLEY et al., 1982; EL-GENDI et al. 1982 and VARMA & PAUL, 1983)*, but less was recorded for avian species *(HINZ et al., 1972; BLACK, 1977 and ATEF et al., 1986).*

The present study was therefore, disgnated to describe the influence of subchronic lead intoxication on the dispoistion Kinetic of oxytetracycline in broiler chickens.

MATERIAL and METHODS

Drug:

Oxytetracycline (Terravet)$^{(R)}$, was obtained from Virbac-France as vial (each 1 ml contains 50 mg oxytetracycline Hcl).

Birds:

Thirty apparantly healthy and 30 subchronically lead intoxicated hybred native broiler chickens of both sexes and aged 60-70 days old were used. Birds were housed in groups of 10 birds in each cage, fed on antibacterials free balanced ration and water was offered *ad libitum.*

Experimental lead intoxication:

Lead acetate was given to one day old chick orally in subtoxic dose of 4.3 mg/Kg.b.wt/day for 8 successive weeks via drinking water according to *BABAN (1980).*

Experiments:

Pharmacokinetic profile:

1) Single dose study: Two groups of 10 healthy and 10 lead intoxicated broiler chickens were injected intravenously with a single dose of oxytetracycline (10 mg/Kg.b.wt) into the left wing vein. Blood samples were collected from right wing vein at different and percise time intervals of 10, 20, 30 min, 1,2,4,6 and 8 hours. Two weeks latter, the drug was given orally to each bird in both groups at the same dosage level. Blood

samples were collected at the same time intervals following intravenous administration for determination of drug concentration in blood and its bioavailability after intravenous and oral administration routes.

2) Multiple dose study: This study was performed in 2 groups of broiler chickens, apparantly healthy and lead intoxicated (each of 20 birds). All birds were given orally oxytetracycline in a dose of 10 mg/Kg.b.wt. twich daily for 5 successive days. Blood samples were taken at different time intervals of 24, 48, 72 and 120 hours following the first dose from each bird in both tested groups. Five chickens from each group were slaughtered, one hour following the last dose then daily till the disappearance of the drug from the tissues of the tested birds. Blood and tissue samples were taken from the slaughtered birds for determining of oxytetracycline residual levels.

Analytical procedures:

Estimation of oxytetracycline concentration in blood and tested tissue samples was carried out by using microbiological assay technique described by *ARRET et al. (1971)* using *Bacillus subtlis* as a tested organism *(LEVETZOW, 1971).*

Protein binding:

The percent of protein binding tendency of the drug was performed as described by *LORIAN (1980).*

Statistical calculation:

The pharmacokinetic parameters were calculated according to *BAGGOT (1978)* whereas statistical analysis was calculated according to *SNEDECOR and COCHRAN (1976).*

RESULTS

1. Single dose study:

The mean ± S.E. serum concentrations of oxytetracycline in healthy and experimentaly lead intoxicated broiler chickens following single oral and intravenous administration of 18 mg/Kg.b.wt. are incorporated in table 1.

Values for kinetic constants describing the absorption and disposition of oxytetracycline in normal and intoxicated birds are recorded in tables 2 and 3 and illustrated in Fig. 1 and 2.

Following the intravenous injection of the drug in healthy and intoxicated birds, the serum concentration revealed a monoexponential decline curve that can be described as one compartment open model. In addition, the drug was rapidly

distributed and eliminated by the first order process with a mean half-life of 2.18 ± 0.002 and 2.56 ± 0.050 hours in healthy and intoxicated birds, respectively. This indicates the shorter elimination half life in normal as compared with intoxicated ones. The total body clearance (Cl_{tot}), 32.58 ± 0.53 ml/Kg/min. in intoxicated chickens was faster than that recorded for healthy birds (28.91 ± 0.2 ml/Kg/min). Higher volume of distribution of the drug more than one litter per Kg indicated the higher distribution in tissues than in blood of healthy and intoxicated birds.

The peak serum concentration of oxytetracycline (0.73 ± 0.01 and 0.47 ± 0.03 µg/ml) following a single oral adminsitration of 10 mg/Kg..b.wt. was achieved at one hour. In addition, the calculated maximum concentration ($C_{max.}$, 0.83 ± 0.01 µg/ml for healthy and 0.5 ± 0.02 µg/ml for intoxicated birds) was reached at 0.66 ± 0.02 and 0..83 ± 0.05 hr. after the oral route of administration, respectively (Table 3 and Fig. 2).

The systemic bioavailability (F%) of oxytetracycline following the oral adminsitration in healthy (78.85 ± 1.42%) and lead intoxicated (54.05 ± 1.65%) chickens indicated that the extent of the drug absorption in healthy birds was higher than that in the intoxicated ones.

2. Multiple dose study:

The mean concentrations of oxytetracycline in serum and tissue of slaughtered healthy and intoxicated birds after oral administration of 10 mg/Kg.b.Wt. twic daily for 5 successive days are presented in table 4. The drug was detected one day after slaughtering in serum and all tested tissues (except brain) of healthy and intoxicated birds and only detected in liver, kidney, lung and spleen of healthy birds at the 2nd day. However, oxytetracycline was detected in a significant concentrations in liver, kidney, lung and spleen of tested healthy chickens which slaughtered 2 days after stopping of drug administration. The drug could not be detected in either serum or tissues of both tested birds after the 3rd day of discontinuation of the drug medication.

The *In vitro* tendency of oxytetracycline to bind with plasma protein in healthy and intoxicated chickens was 25.34 ± 0.411%.

DISCUSSION

The present investigation has demonstrated that higher serum concentration was observed in lead intoxicated birds as

compared with healthy ones following the intravenous injection of oxytetracycline in a single dose of 10 mg/Kg b.wt. This might be refered to decrease the protein binding tendency with the intestinal mucosal cells as a result of the ability of lead to cause denaturation of protein *(GOEDE and KUHNERT, 1986)*. Following the intravenous injection of a single dose of the drug in healthy and intoxicated chickens resulted in a high blood level which declined to very low level (0.097 and 0.12 µg/ml, respetively) at 8 hours. This could be described by monoexponential decline of the drug (one compartment open model) as it has been previously observed by *ATEF* et al. (1986) for oxytetracycline in broiler chickens.

Our investigation have demonstrated that the absorption rate of oxytetracycline given orally was slower in intoxicated birds as compared with healthy ones (to.5(ab)9.89 ± 0.57 *hin normal and 13.08* ±0.47 hours in intoxicated birds(with a peak serum concentration of 0.73 ± 0.01 µg/ml in normal and 0.03 µg/ml in intoxicated birds attained a 1 hour and decreased to 0.071 ± 0.003 and 0.036 ± 0.006 µg/ml at 8 hours in healthy and intoxicated birds, respectively. This is consistant with that value previously recorded by *ATEF* et al. *(1986)* who noticed that peak serum concentration of oxytetracycline (6 mg/Kg b.wt.) in healthy chickens was 0.63 ± 0.001 µg/ml attained at 1 hour and decreased to 0.05 µg/ml at 8 hours. *BRANDER and PUGH (1977)* decleared that blood level of 0.5 to 1 µg/ml oxytetracyline has been accepted as adequate for most purposes in treatment of intected man and animals. Accordingly, effective serum levels of the drug were achieved for 2 hours following oral and intravenous adminstration in healthy birds. In addition, the obtained data showed that serum concentration of the drug in intoxicated birds was lower than values recorded in healthy ones when the drug given via oral administration. This change may be attributed to the ability of lead to chelate the oxytetracycline and/or protein denaturating effect which may influnce the permeability of the intestinal mucosa and accordingly a decreament in the rate of absorption of the drug from the gastrointestinal tract was achieved. In this respect, *GOEDE and KUHNERT (1986)* recorded that, the intestinal absorption of sulphacetamide in rats was clearly affected by protein denaturating and permeability reducing action of heavy metals following oral administration beside ability of lead to act as chelating agent. Furthermore, *LINDKAER-JENSEN and NELLEMANN SORENSEN (1976)* added that copper sulphate was able to reduce the absorption of therapeutic dose of salicylates and lithium carbonate in rats and refered this phenomena to the

synthesis of chelating compounds from copper with salicylates and lithium carbonate.

The obtained data showed the faster disappearance of oxytetracycline (shorter elimination half-life) from the serum of lead intoxicated chickens ($t_{0.5}\beta$' 1.97 ± 0.01 hr.)than in healthy ones ($t_{0.5}\beta$ 2.12 ± 0.04 hr.) after oral adminstration. These values are similar to that recorded in chickens (1.94 ± 0.27 h, *ATEF et al., 1986)* but much shorter than in calves (7.07 h, *SCHIFFERLI et al., 1982)*, horse (10.5 h, *PILLOUD, 1973)*, cows and goats (9.1 h, *PILLOUD, 1973)*, dogs (6.0 h, *BAGGOT, 1977)* and camel (7.0 h, *EL-GENDI et al., 1982).* The faster elimination of the drug from chickens body than animals could be explained on the basis of its weak alkalinity and the urine is highly acidic in poultry. This was also supported by *HUBER (1971) and ROBBELEE & CLANDININ (1964) and BLACK (1977)* who denoted that the loss of tetracyclines from the blood serum of laying hens after termination of treatment was rapid and has been eliminated 24 hours from the with-drawal of the antibiotic. They added that the period of persistence of serum concentrations of oxytetracycline was approximatly half that observed in cattle and swine and the drug is rapidly metabolised in poultry than other mammals. In addition, shorter interval between doses observed in intoxicated birds (8.97 ± 0.33 h) than that observed with values recorded for healthy ones (11.41 ± 0.41 h) confirm our explanation. These values are also consistant with the shorter elimination half life noticed with intoxicated birds as compared with healthy ones. Similar values are previously recorded in chickens after oral administration of the drug (10.74, hr *ATEF et al., 1986)* but shorter than those recorded after intramuscular dosage in cattle and pigs (48 and 24 hr. respectively, *BAGGOT, 1983).*

The obtained data have demonstrated that higher apparent volume of distribution value of oxytetracycline (9.22 + 0.05 and 8.79 ± 0.1 L/Kg) in healthy and intoxicated chickens, respectively following its intravenous dosage, indicated that higher distribution of the drug in tissues than in serum. In this respect, previous studies showed much less values except chickens and calves, e.g. 1.83 L/Kg in camel *(EL-GENDI et al., 1982)*, 1.508 L/Kg in dogs *(BAGGOT, 1978)*, 7.16 L/Kg in calves *(SCHIFFERLI et al., 1982)* and 5.58 L/Kg in chickens *(ATEF et al., 1986).* The higher distribution of oxytetracycline in tissues than in serum was anticipated, since the drug is a lipophilic compound and can diffuse readily through cell membrane *(BAGGOT, 1983(.*

The recorded systemic bioavailability of oxytetracycline in healthy chickens (F%, 78.85 ± 1.42) was higher than lead

intoxicated ones (F%, 54.05 ± 1.65) after a single oral dosage of 10 mg/Kg b.wt. This indicates that the extent of absorption of the drug from the site of adminsitration was higher in healthy than intoxicated chickens. Similar values were previously recorded in healthy chickens (F%, 75.26, *ATEF, et al., 1986)* but these values are much lower than that recorded in claves (F %, 46,35; *SCHIFFERLI et al., 1982).*

The tendancy of oxytetracycline to bind with serum protein in chickens was 25.34 ± 0.41. This finding provides evidence that oxytetracycline is not being extensively bound to serum protein in chickens. In addition,. this value is within the range as it previously recorded in chickens (28.88%, *ATEF et al., 1986)* and for human (24.64%, *KUNIN, 1967)* but lower than in horse and cows (50%, *PILLOUD, 1973).*

Oxytetracycline was found to be rapidly distributed in all tissues except brain following its oral administration twice daily for 5 days in chickens and high concentrations were detected in tissue of healthy birds as compared with level detected in intoxicated ones. This finding was correlated with the lower serum concentration in intoxicated birds than healthy ones. The drug was found to be concentrated in lung, kidney and spleen and can not be detected after 72 and 48 hours in tissues of healthy and lead intoxicated birds, respectively. These results could be explained by the shorter elimination half life of the drug determined in our study and that of the ability of oxytetracycline to undergo a considerable enterohepatic cycle and its elimination through the bile and the urine is nearly the same *(BAGGOT, 1983).* The preslaughter withdrawal time recorded here was nearly similar to that recorded in healthy chickens (24 h, *ATEF et al., 1986)* after oral dosage (6 mg/Kg for 5 days) while much shorter than in cows (28 days) reported by *BAGGOT (1983).*

Conclusively, subchronic lead intoxication may impair the therapeutic efficacy of oxytetracycline as well as therapeutic dosage regimens in tested chickens. Therefore, attention should be paid towards feed or water contaminated with lead in order to minimize the therapeutic failure of antibacterials used for treatment of infectous diseases either in animals or poultry.

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Table (1): Serum concentration of oxytetracycline in healthy and lead intoxicated broiler chickens following a single oral and intravenous administration of 10 mg/kg b.wt. (n = 10).

Time of sampling	Oral		Intravenous	
	N	L.I.	N	L.I.
10 min.	-	-	1.08±0.007	1.11±0.003
20 min.	0.102±0.007	0.071±0.002**	0.99±0.002	1.02±0.009**
30 min.	0.35±0.002	0.21 ±0.01**	0.92±0.002	0.94±0.004**
1 hr.	0.73±0.01	0.47 ±0.03**	0.79±0.001	0.82±0.006**
2 hr.	0.55±0.008	0.316±0.01**	0.57±0.01	0.60±0.007*
4 hr.	0.28±0.002	0.166±0.005**	0.29±0.01	0.32±0.006*
6 hr.	0.13±0.007	0.079±0.004**	0.18±0.001	0.21±0.008**
8 hr.	0.071±0.003	0.036±0.006**	0.097±0.009	0.21±0.006

N: Normal

L.I.: Lead intoxicated

-: - Undetectable

Significant at:

* P > 0.05

** P > 0.01

Table (2): Pharmacokinetic parameters of oxytetracycline in healthy and lead intoxicated broiler chickens following a single intravenous injection of 10 mg/kg b.wt. (n = 10)

Parameter	Unit	Healthy	Lead intoxicated
C°	ug/ml	1.09±0.004	1.14±0.01**
Kel	h^{-1}	0.32±0.005	0.27±0.006**
$t_{0.5}$	h	2.18±0.002	2.56±0.05**
Vd	L/Kg	9.22±0.05	8.79±0.1**
$Cl_{(tot)}$	ml/kg/min.	28.91±0.20	32.58±0.53**

Significant at :

** P > 0.01

Table (3): Pharmacokinetic parameters of oxytetracycline in healthy and experimentally lead intoxicated broiler chickens following a single oral administration of 10 mg/kg b.wt. (n = 10)

Parameter	Unit	Healthy	Lead intoxicated
Body weight	Kg	1.34±0.04	0.98±0.03**
A	ug/ml	1.88±0.02	0.90±0.09**
Kab	h^{-1}	4.26±0.24	3.07±0.23**
$t_{0.5\ (ab)}$	min.	9.89±0.57	13.08±0.47**
B	ug/ml	1.03±0.01	0.66±0.03**
K_{el}	h^{-1}	0.33±0.009	0.35±0.01
$t_{0.5(\beta)}$	h	2.12±0.04	1.97±0.01**
$C_{max\ (cal.)}$	ug/ml	0.83±0.01	0.50±0.02**
$t_{max\ (cal.)}$	h	0.66±0.02	0.83±0.05*
Interval between doses	h	11.41±0.4	8.91±0.33**
F %	%	78.85±1.42	54.02±1.65**

F % = systemic bioavailability

* = $P < 0.05$

** = $P < 0.01$

Cal. = Calculated

Table (4): Tissue concentrations of oxytetracycline (µg/gm) in healthy and experimentally lead intoxicated broiler chickens after oral administration of 10 mg/kg b.wt. twice daily for 5 successive days (n = 5)

	Time of slaughter after							
	1 hour		1st day		2nd day		3rd day	
	N	L.I.	N.	L.I.	N.	L.I.	N.	L.I.
Serum	0.74±0.01	0.43±0.004	0.11±0.001	-	-	-	-	-
Liver	0.57±0.03	0.165±0.001	0.21±0.002	0.1±0.001	0.09±0.002	-	-	-
Kidney	0.65±0.021	0.30±0.011	0.31±0.01	0.12±0.001	0.12±0.002	-	-	-
Lung	0.96±0.013	0.41±0.003	0.32±0.01	0.21±0.001	0.15±0.001	-	-	-
Spleen	0.75±0.09	0.10±0.001	0.10±0.001	0.07±0.001	0.03±0.001	-	-	-
Brain	-	-	-	-	-	-	-	-
Thigh muscle	0.41±0.008	0.13±0.002	0.20±0.009	0.01±0.001	-	-	-	-
Breast muscle	0.47±0.003	0.21±0.001	0.23±0.001	0.015±0.005	-	-	-	-
Bile Intestine	0.48±0.001	0.30±0.002	0.16±0.008	0.11 ±0.0003	0.05±0.001	-	-	-

N: Normal

L.I.: Lead intoxicated

- : Undetectable

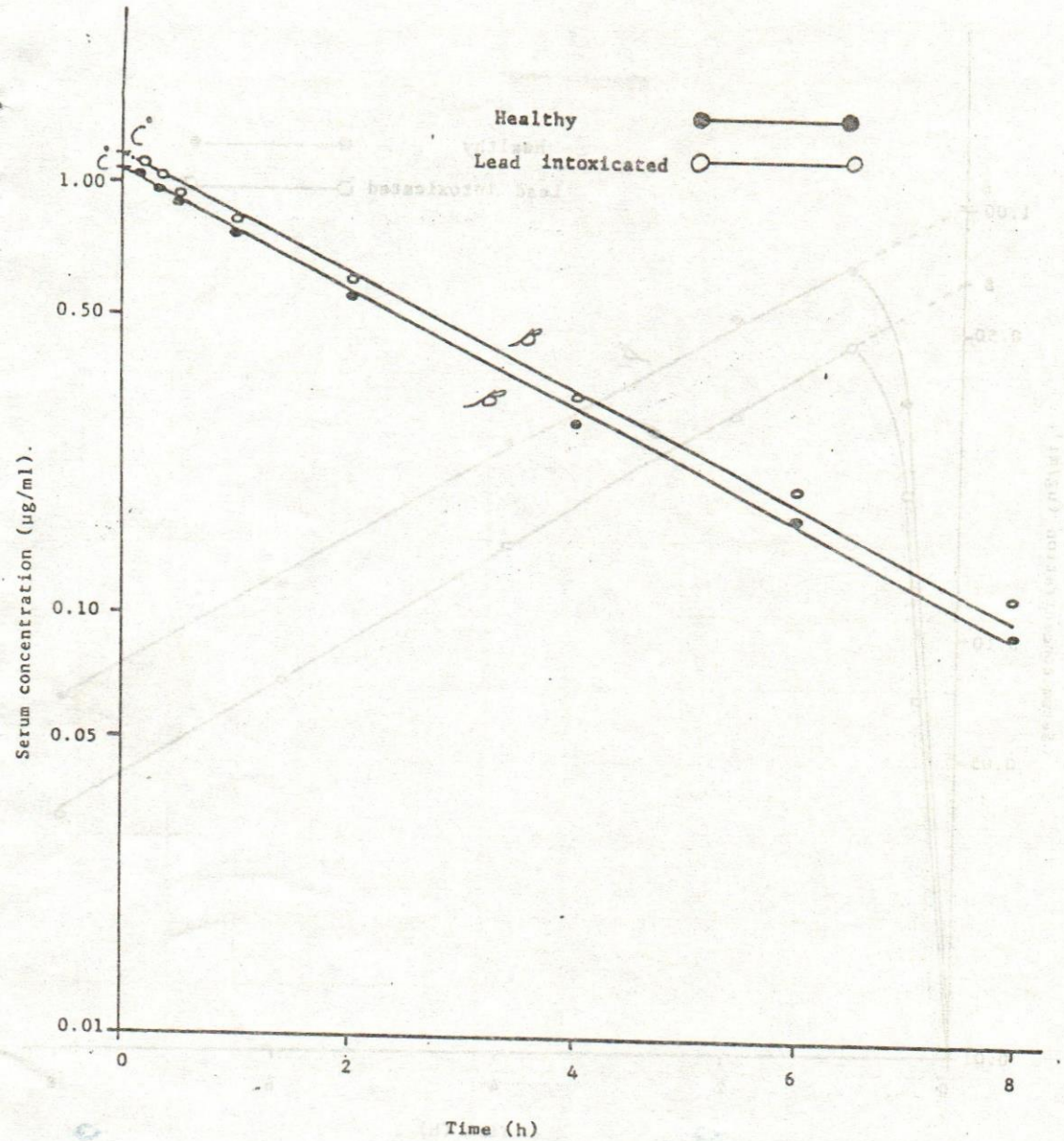

Fig. (1): Semilogarithmic graph depicting the time course of oxytetracycline in serum of healthy and lead intoxicated broiler chickens after single intravenous injection of 10 mg/kg b. wt.

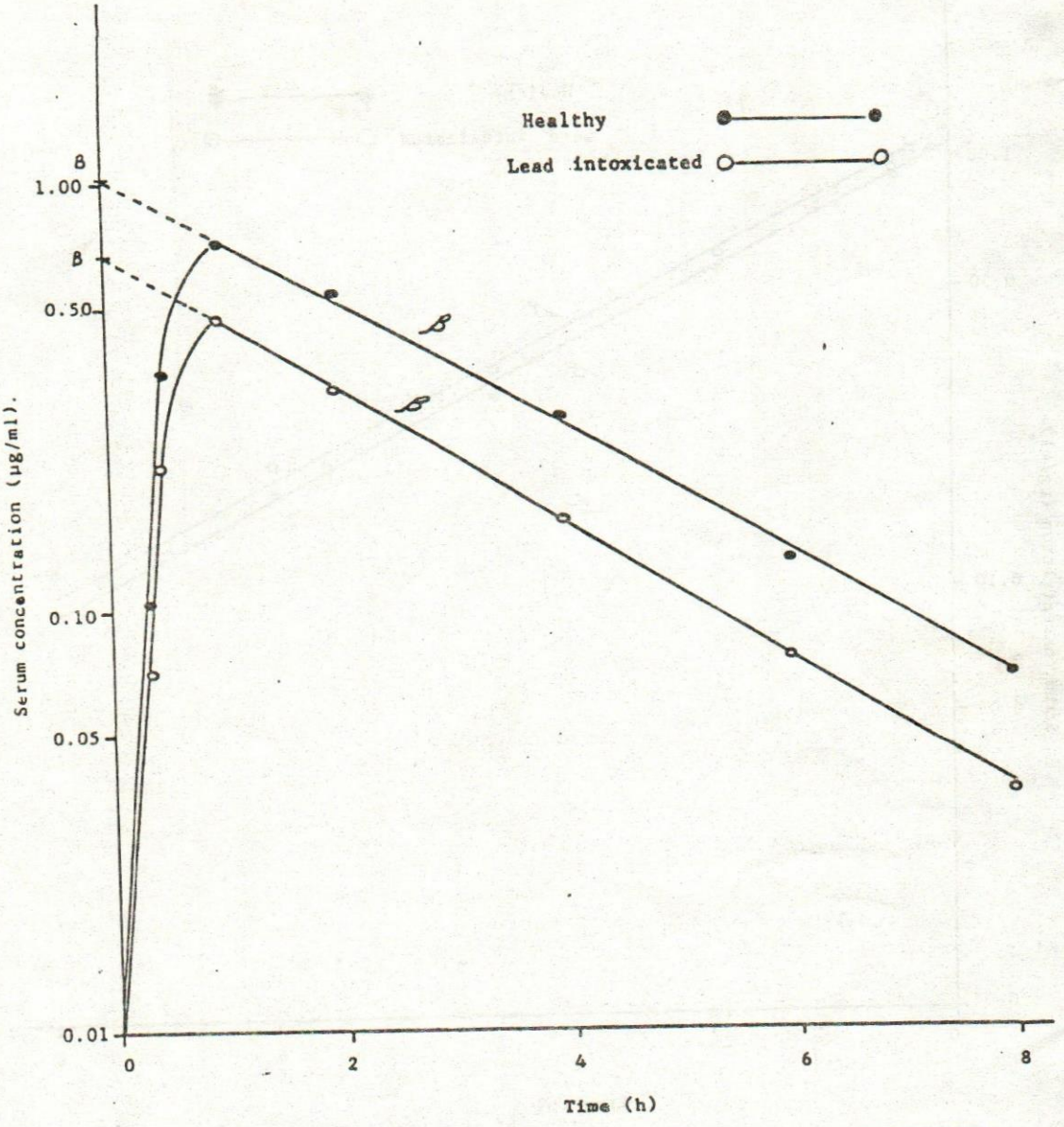

Fig. (2): Semilogarithmic graph depicting the time course of oxytetracycline in serum of healthy and lead intoxicated broiler chickens after a single oral administration of 10 mg/kg b.wt.