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ROLE OF OXYTETRACYCLINE IN LIVER DYSFUNCTION OF EGYPTIAN BUFFALO CALVES

(With 3 Tables)

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دور الأوكسيتتراسيكلين فى خلل وظائف الكبد فى عجول الجاموس

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اجرى هذا البحث على عدد ١٢ عجل جاموس (عمر ١-٢ شهرا) سليم اكلينيكيا حيث قسمت العجول الى مجموعتين متساويتين . المجموعة الاولى كانت المجموعة التجريبية التى حقنت بجرعة قدرها ٢٠٠ مليجرام من الأوكسيتتراسيكلين لكل ١٠ كجم من الوزن الحى بالحقن العضلى مرة واحدة والمجموعة الثانية لم تحقن سوى محلول الملح الفسيولوجى واستعلمت كمجموعة ضابطة.هذا وقد اتضح ان حقن عجول الجاموس بجرعة علاجية من عقار الأوكسيتتراسيكلين تؤدى الى زيادة معنوية فى مستوى أنزيمى الترانس أمينيز . وأنزيم الفوسفاتيز القاعدى . الدهون الكلية , الكوليسترول , وكذلك فى مستوى نسبة البيلروبين الكلى. وهذه التغيرات وجد أنها تستمر لمدة اسبوعين . وعلى نفس المستوى , وجد ان عقار الاوكسيتتراسيكلين قد أحدث زيادة فى انزيم الارجينيز والتى استمرت لمدة اسبوع. وفى اطار نفس التجربة اظهرت المجموعة المعالجة بعقار الأوكسيتتراسيكلين ارتفاعا معنويا فى مستوى جلوكوز الدم لمدة اسبوع بعد المعالجة . وعلى النقيض ، أحدث الحقن بعقار الأوكسيتتراسيكلين فى عجول الجاموس انخفاضا معنويا فى مستوى البروتين الكلى والجلوبيولين وذلك لمدة اسبوعين بينما لم يحدث اى تغيرات معنوية فى مستوى الالبيومن .

SUMMERY

This work was carried on 12 clinically healthy buffalo calves (1-2 month old) devided into 2 eequal groups. The first group was the expermintal group where single intramuscular ingection of 20 mg oxytetracycline base /kg body weight was given to each animal. The scond group usded as control and was injected on normal physiological saline solution. In buffalo calves of the first group single intramuscular injection dose of oxytetracycline evoked a significant increase ($P < 0.05$) in blood serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline phosphatase (ALP) activities , total lipids , total cholesterol and serum total bilirubin levels. The previous changes lasted for two weeks. On the similar grounds, oxytetracycline administration induced an elevation of serum arginase activity that lasted for one week In keeping with this line, oxytetracycline treated group displayed

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a significant increase (P<0.05) of blood serum glucose level for one week pos treatment. Conversely, oxytetracycline injection produced a significant declin (P<0.05) of blood serum total protein and globulin levels for two weeks . Meanwhile oxytetracycline induced non significant changes in blood serum albumin levels in th treated buffalo calves .

Kaywords: *Role, oxytetracyline, liver dysfunction, Egyptian buffalo-calves*

INTRODUCTION

Oxytetracycline is a member of a group of antibiotics produced by a strain of Streptomyces rinosus and belongs to the tetracycline group . It is a broad spectrum antibiotic used for treatment of both gram positive and gram negative bacterial infections in animals. The drug is used against mycoplasma, rickttsia and clamidia diseases *(SANDE and MANDELL, 1991)*. The use of tetracyclines is now discouraged due to problems of bacteria resistance *(TROLLE-NIER, 1980 and HARVEY, 1980)*. Toxic effect induced on different organs of the body, especially the liver and kidneys in camel *(EL-ATRASH, 1983)* and in goat *(AZOOZ, 1994)* were also established .

The present study was carried out to investigate the possible adverse effects, if any, of oxy-tetracycline treatment in buffalo calves. eventually to address the validity of the promising future use of this drug in calves.

MATERIAL and METHODS

1-Drug: Oxytetracycline dihydrate (Terramycin/LA®- Pfizer Egypt) equivalent to 200 mg. oxytetracycline base/ml as mag-nesium complex in an aqueous solution, was used in this study.

2- Animals: Twelve, 1-2 month old buffalo calves were expermented These animals proved to be clinicall healthy by cili-nical examination laboratory findings which ascertained that such animals were free from both internal and exeternal parasites. Case history of these animals indecated tha they were not subjected to medica- ments for at least 35 days before the present expermentation. Animals were then randomly classified into two equal groups. The first group was intramuscularly injected with one dose of 200mg oxytetracycline/10 Kg body weight (1Ml./10 Kg body weight). The 2nd group was kept as control and injected with normal saline .

3- Sampling: Blood samples were collected from the jugular vein 1/2 hour (h.). before treatment, 2h., 6 h., 12 h., 24 h., 3 days, one week, 2 weeks and 3 weeks post treatment. The samples were left to clot and centrifuged at 3000 r.p.m. for 15 minutes. The separated serum samples were stored at -20°C for bio-chemical analysis.

4- Biochemical analysis: Blood serum samples were analyzed for aspartate amino transferase (AST); alanine amino transferase (ALT) activities;

alkaline phosphatase activity *(REJ and HORDER, 1983)*, total bilirubin *(MALLORY and EVELYN, 1937)*; glucose *(DUBOWSKI, 1962)*; total cholesterol *(WATSON, 1960)*; total lipids *(ZOLLNER and KIRSCH, 1962)*; total proteins *(KING and WOOTTON, 1959)*; albumin; globulins levels *(rEINHOLD, 1953)* and arginase activity *(MIA and KOGER, 1978)*.

5- ***Statistical analysis:*** The results are represented as the mean ± S.E.. Statistical significance was determined by Student's (t) test for paired observations according to *SNEDECOR (1971)*.

RESULTS

Data presented in table (1) revealed that 6 hours post oxy-tetracycline injection evoked a significant increase ($P<0.05$) in ALT, AST and ALP activites was recorded. The previous increases lasted for two weeks, achieving nearily the normal control levels after the 3rd. week post injection. Arginase activity displayed a significant elevation, 2 hours post treatment, that persisted so till the 1st. week but declined thereafter to reach nearly the normal control level at the 2nd. week post injection when compared with the control group.

Table (2) showed that oxytetracycline induced a marked augmentation ($P<0.05$) of total lipids, total cholesterol, and total bilirubin levels for two weeks post treatment. Elevated glucose level persisted till one week post treatment.

Oxytetracycline treated group exhibited a significant ($P<0.05$) reduction of serum total proteins and globulins levels after 3 days, that was clearly prevailed through the 2nd. week. On the 3rd week, the previous changes restored nearily its normal control level values. On the other hand, oxy-tetracycline evoked no significant changes in albumin levels as com-pared with respective control values (Table 3).

DISCUSSION

In the present study, it has been found that in buffalo calves, single injection of oxytetracycline elici-ted a significant increase in ALT, AST, Alkaline phosphatase activities, Total Cholesterol, Total lipids , Total bilirubin and Glucose values with a significant decrease ($P<0.05$) in serum total protein and globulins levels.

Unfortunately, our data don't provide us with a ready explanation for the previous changes, nevertheless, a number of proposal worth discussion could be stated.

Serum alkaline phosphatase activity is of some value in the diagnosis of bile duct obstruction in both cats and dogs. Alkaline phosphatase activity level increases in early hepatic damage and is particularly valuable in the fatty liver change associated with diabetes militus *(DOXEY, 1983)*. Values also increased when the liver was congested or exposed to toxin *(CORNELIUS, 1989)*. In chronic active hepatitis and hepatocellular carcinoma, the levels also increases *(STRO-MBECK, 1978 and STROMBECK and GRIBBLE, 1978)*.

High serum levels are seen in cases of acute hepatic damage *(TROMBECK and GRIBBLE, 1978)*. Serum alkaline phosphatase activity levels are elevated in cases of acute pancreatitis *(SCHAER, 1979)*. The enzyme level tend to rise in association with increase osteoblast activity but the increase seen in bone disorder is not specific for any particular disorder *(DOXEY, 1983)*. Alkaline phospatase enzyme is excreted in the bile and so circulating value will increase in cases of liver damage particularly of biliary or intrahepatic obstructive types as well as in instances of excessive bone activities *(FREEDLAND et al., 1965)*.

It is proposed that increased serum AST activity is shown following muscular damage, liver damage, myocardial infarction and exposure to various chemicals and drugs *(KANEKO, 1989)*. Another possible explanation is cellular destruction in several extrahepatic tissues and thus elevated serum AST activity level is shown to be non specific for hepatic tissue damage *(VARELY et al., 1980)*.

In dogs, cardiac damage of an acute nature results in a marked rise in serum activity levels of ALT. However, similar results are obtained with muscular or liver damage. Most cases of acute pancreatitis exhibit high level of serum ALT activity *(DOXEY, 1983)*.

Arginase serum level will rise rapidly following acute hepatic damage *(SODIKOFF, 1980)*.

In hyperlipimia there appear to be excessive fat mobilization, which iris in free fatty acids levels, with evidence of liver damage *(DOXEY, 1983)*.

Hypercholesteremia, is found in nephrotic syndrome, nephritis, obstructive jaundice, diabetes mel-litus, acidosis, hepatocellular da-mage, hyperthyroidism and pancreatitis *(VARELY et al., 1980)*.

Hypoproteinemia occurs in failure of parenchymal synthesis of serum amino acids, portal cirrho-sis, renal diseases (Glomerulonepheritis), nephrotic syndrome, pancreatic hypoplasia or atrophy, diabetes mellitus and increase protein breakdown for gluconeogenisis *(BENJAMIN, 1979)*.

Serum bilirubin levels increase in any forms of jaundice and hepatocellular damage *(SOVA, 1965)*.

Given this framework, how our data can be interpreted?. It is tempting to suggest that the forementioned alterations are imp-utable, at least in part, to a pro-posed adverse effect of oxytet-racycline exerted exclusively on hepatic tissues.

In support of the previous concept, is the fact that oxytetra-cycline dose inhibit liver mitochondrial oxidative phosphoralyation *(Dubuy and Showacare, 1961)*. On similar grounds, it is proposed that inhibition of protein synthesis is the initial step in pathogenesis of tetracyclines inducing fatty changes in hepatocyts *(YEH and SHILS, 1966 and ZIA and PRICE, 1976)*. Needless to say, our data reinforced those previously documented with oxytetracycline treatment in camels *(EL-ATRASH, 1983)* and goats *(AZOOZ, 1994)*.

The hypoproteinemia and hypo-globulinamia observed in this study could be viewed in the light of significant inhibitory effect of oxy-tetracycline on the protein syn-thesis of mammalian cells and reduction of β cell activity and ultimately antibody reduction *(BANCKS and FORSGREN, 1979 and HASSAN, 1994).*

Summing up our observations, it could be concluded that this study represented a further image of the hazardous effect of oxytetracycline therapy in buffalo calves that would ultimately be mirrored as liver dysfunction. In keeping with this line, the present study imposes much weight on the argument against the fact that oxytetracycline is the drug of choice in bacterial infection of buffalo calves .

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Table (1) : Effect of oxytetracycline treatment on the level of blood serum AST , ALT , Alkaline phosphatase (AL.P) and Arginase in buffalo calves .

(U / Lit.) (n = 6 / group) (Mean ± S.E.)

TIME POST TREATMENT	CONTROL GROUP				TREATED GROUP			
	AST	*ALT*	*ALP.*	*ARGINASE*	*AST*	*ALT*	*ALP.*	*ARGINASE*
pretreatment	90.80 ± 9.62	22.28 ± 2.93	63.4 ± 5.6	5.13 ± 0.12	83.64 ± 11.82	23.81 ± 3.71	67.2 ± 10.6	6.72 ± 0.88
2h.	81.72 ± 7.30	21.98 ± 3.32	64.2 ± 7.2	4.35 ± 0.72	105.42 ± 15.22	22.39 ±2 .93	76.0 ± 12.4	8.73 ± 1.10 *
6h.	97.16 ± 9.81	22.40 ± 2.28	60.2± 9.2	6.18 ± 0.45	133.26 ± 9.32*	32.66 ± 1.33*	178.4 ± 19.8*	9.83 ± 1.02 *
12h.	94.96 ± 8.50	23.82 ± 2.50	69.0 ± 4.6	4.52 ± 0.63	157.2 ± 11.00*	31.33 ± 2.23*	146.4 ± 8.4*	13.65 ± 0.52*
24h.	90.88 ± 6.66	21.73 ± 2.39	60.4 ± 7.6	5.32 ± 0.56	161.8 ± 15.34*	35.16 ± 3.56*	171.2 ± 21.3*	13.12 ± 0.83*
3days	101.2 ± 9.62	23.11 ± 3.33	64.6 ± 8.4	5.86 ± 0.51	178.07 ± 14.8*	33.33 ± 1.44*	177.0 ± 16.7*	13.51 ± 0.33*
one week	104.0± 6.42	20.22 ± 2.56	72.4 ± 7.9	6.21 ± 0.32	169.13 ± 11.3*	36.65 ± 2.32*	172.6 ± 26.8*	15.72 ± 0.85*
two weeks	86.73 ± 6.22	22.31 ± 2.88	71.8 ± 6.4	5.68 ± 0.47	163.41 ±10.8*	34.51 ± 3.37*	148.0 ± 18.5*	8.02 ± 1.73
three weeks	97.32 ± 7.84	24.56 ± 3.97	68.7 ± 7.8	4.72 ± 0.45	120.62 ± 20.2	30.36 ± 3.33	105.2 ± 26.1	6.11 ± 0.68

* : Significant at $P < 0.05$

Table (2) : Effect of oxytetracycline treatment on the level of blood serum Total lipids (T.Lipids) ,Total cholesterol (T.Cholest.), Glucose and Total bilirubin (T.bil.) in buffalo calves . (mg / 100 ml) *(n = 6 / group)* *(Mean ± S.E.)*

TIME POST TREATMENT	**CONTROL GROUP**				**TREATED GROUP**			
	T. LIPIDS	*CHOLEST.*	*GLUCOSE*	*T.BIL.*	*T.LIPIDS*		*GLUCOSE*	*T.BiL*
pretreatment	633 ± 52.1	105 ± 16.2	111 ± 12	0.37 ± 0.05	605 ± 41	113 ± 21	107 ± 12	0.45 ± 0.06
2h.	640 ± 61	113 ± 10.2	95 ± 6.5	0.32 ± 0.03	657 ± 82	115 ± 12.5	100 ± 18	0.51 ± 0 .15
6h.	621 ± 65	102 ± 7.6	104 ± 8.6	0.35 ± 0.05	673 ± 65	128 ± 12.9	134 ± 12.5	0.73 ± 012*
12h.	635 ± 72	114 ± 8.8	97 ± 7.7	0.38 ± 0.01	685 ± 61	132 ± 14.8	145 ± 11.3*	1.52 ± 0.09*
24h.	505 ± 67	100 ± 12.0	123 ± 11. 5	0.31 ± 0.07	788 ± 33*	182 ± 7.5*	176 ± 8.3*	1.62 ± 0.11*
3days	515 ± 58	98 ± 8.5	115 ± 10.3	0.29 ± 0.06	819 ± 57*	172 ± 15.8*	182 ± 10.7*	1.36 ± 0.07*
one week	676 ± 72	121 ± 16.3	106 ± 8.6	0.37 ± 0.03	925 ± 59*	180 ± 8.7*	187 ± 11.5*	1.07 ± 0.15*
two weeks	613 ± 29	104 ± 7.3	126 ± 13.2	0.40 ± 0.02	882 ± 72*	161 ± 7.5*	115 ± 18.3	1.38 ± 0.17*
three weeks	588 ± 67	109 ± 13.8	118 ± 16.5	0.35 ± 0.09	761 ± 55	125 ± 14.3	135 ± 28.6	0.56 ± 0.13

* : Significant at $P < 0.05$

Table (3) : Effect of oxytetracycline treatment on the level of blood serum total proteins (T.P.) , albumin (Alb.)and globulins (Glb.) in buffalo calves .

(gm / 100 ml.) *(n = 6 / group)* *(Mean ± S.E.)*

TIME POST TREATMENT	Control Group			Traeted Group		
	T.P.	ALB.	GLB.	T.P	ALB.	GLB.
pretreatment	7.62 ± 1.03	3.35 ± 0.62	3.65 ± 0.27	6.89 ± 0.47	3.29 ± 0.25	3.58 ± 041
2h.	7.53 ± 0.82	3.15 ± 0.32	3.58 ± 0.28	7.02 ± 0.52	3.31± 0.36	3.71± 0.23
6h.	7.77± 0.65	3.72 ± 0.25	4.02 ± 0.35	6.88 ± 0.60	3.41± 0.51	3.50 ± 058
12h.	6.81 ± 0.75	2.66 ± 0.30	4.15 ± 0.47	6.42 ± 0.33	3.32 ± 0.30	3.36 ± 0.43
24h.	6.74 ± 0.42	2.85 ± 0.28	4.10 ± 0.35	5.62 ± 0.63	3.05 ± 0.42	2.46 ± 0.83
3 days	6.96 ± 0.58	2.93 ± 0.31	3.04 ± 0.21	5.11± 0.06*	3.15 ± 0.16	2.09 ± 0.22*
one week	7.23 ± 0.81	3.33 ± 0.27	4.09 ± 0.17	5.20 ± 0.11*	3.26 ± 0.47	2.11 ± 0.05*
two weeks	6.58 ± 0.72	2.92 ± 0.32	3.88 ± 0.45	5.01 ± 0.03*	3.15 ± 0.38	2.03 ± 0.06*
three weeks	7.35 ± 1.31	3.38 ± 0.45	3.96 ± 0.23	6.33 ± 0.71	3.16 ± 0.52	3.33 ± 0.47

* : Significant at $P < 0.05$