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The Physiological and Biochemical Evaluation of Tulathromycin Premix in Pigs

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Abstract: The aim of the study was to investigated the influence of dietary inclusion of tulathromycin at 5 mg kg^{-1} die on haematological to provide an experiment support for the clinical use of this drug. Eighteen pigs were randomly allocated to three treatment groups. A further six pigs were left untreated as controls (group NTXL). Tulathromycin was administered twice by the oral route administrations of 5, 15, 25 mg kg^{-1} B.W. in three treatment groups on the 1st and the 4th day, respectively. Blood samples were taken from all animals on days 1, 17, 14 for serum chemical and hematology evaluation. Weight and temperature were measured from all animals at the same time. Comparisons of mean physical examination parameters between treatment and control groups over the 14 day study period revealed no significant differences ($p>0.05$). All pigs did not show any signs of discomfort after Premix. Hematology evaluation indicated that comparisons of RBC, WBC, HGB, HCT, MCV, MCH, MCHC and PLT between treatment and control groups also revealed no significant differences ($p>0.05$). AST, ALT, ALP, ALB, BUN were significantly higher in treated groups when compared with the control group ($p<0.05$) post-treatment. No significant differences as time goes on suggesting that a slight effect of injury on liver was caused by tulathromycin. The safety of tulathromycin Premix in target animal swine indicated that pigs were administered of 5-25 mg kg^{-1} B.W. via the oral route satisfied clinicians' demands.

Key words: Tulathromycin, physiological indexes, biochemical indexes, safety evaluation, oral, pig

INTRODUCTION

Tulathromycin is a member of the triamilide subclass of macrolide antibiotics which is used for the treatment of bacterial respiratory diseases in cattle and swine. In aqueous media, the active form of tulathromycin is a stable equilibrated mixture of 2 macrocycles, a 13 membered ring azalide (10%) and a 15 membered ring azalide (90%) which differ by the formation of a lactone bond at C11 and C13 of an otherwise identical molecule (Nowakowski *et al*., 2004; Benchaoui *et al*., 2004). Despite the unique structural features of tulathromycin, its principal mechanism of action against bacteria is the same as that of other macrolides which involves the direct inhibition of essential protein biosynthesis by selective binding to the bacterial 50S ribosomal subunit and stimulation of the dissociation of peptidyl-tRNA from the ribosome during the translocation process (Wellman and O'Connor, 2007; Kilgore *et al*., 2005; Giguere *et al*., 2004; Venner *et al*., 2007). The pneumonic form of pasteurellosis is regarded as one of the most important bacterial diseases of sheep and pigs (Martin, 1996; Kanwar *et al*., 1998). Both Pasteurella (Mannheimia) haemolytica and *Pasteurella multocida* have been implicated as primary pathogens (Cutlip *et al*., 1998) and various species of Mycoplasma have been shown to cause significant respiratory disease as well (Rahman and Singh, 1990; Alley *et al*., 1999).

Tulathromycin is a newly introduced triamilide antimicrobial labeled for the treatment of respiratory disease in cattle and swine. Because of tulathromycin's efficacy in cattle against the same bacteria commonly isolated from pigs (Godinho, 2008; McKelvie *et al*., 2005; Hellman *et al*., 2008; Icen *et al*., 2009; Simsek *et al*., 2009; Ragbetli *et al*., 2009; Skogerboe *et al*., 2005), its efficacy against Mycoplasma (Pfizer Animal Health, 2006) and its long-acting properties (Nowakowski *et al*., 2004), it may provide an effective tool in the treatment of caprine respiratory disease. The safety of tulathromycin administration in pigs and cattle were studied; physical and laboratory parameters between treatment and control groups prior to treatment yielded no significant differences (Washburn *et al*., 2007; Radaelli *et al*., 2008). The pharmacokinetics of tulathromycin following subcutaneous administration in meat goats were also researched (Young *et al*., 2011). However, the researchers are unaware of any target animal safety studies demonstrating its safety in this species.

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The objectives of this study were to evaluate effects of tulathromycin on haematological and serum biochemical status and growth and carcass performance of pigs.

MATERIALS AND METHODS

Animal feeding and housing: Twenty-fouth crossbred (Landrace x Yorkshire) pigs with an average age of 2 months and an average body weight of 24 kg were enrolled in the study. Eighteen pigs were randomly allocated to three treatment groups (TB1, TB2 and TB3). A further six pigs were left untreated as controls (group NTXL). Each group contained three gilts and three castrated males. Pigs from control group were fed the basal diets and the three treatment groups were fed basal diets with 5, 15 and 25 mg kg^{-1} added tulathromycin in 3 days. About 21 days prior to treatment, all animals were identified by ear tag, housed individually and randomly assigned to treatment or control groups containing five animals each. Treatment and control subjects received identical nutritional support throughout the study. The basal diets mainly based on corn, barley and soybean meal were formulated according to the nutrient requirements for pigs (Table 1). All pigs had free access to water from a nipple adjacent to the feeder. Animals in each study were loose-housed as a group with straw bedding in a single room with a minimum floor area of 1.5 m^2 per animal. The pigs were maintained on a 12 h/12 hight/dark cycle, in a controlled environment (temperature range 16-27°C; humidity 32-84%).

Parameter measured: About 1 day prior to treatment, feed intake, body weight, temperature, heart rate, blood samples for haematological analyses were assessed and recorded as baseline values and subsequently examined daily until the end of the study. EDTA dipotassium salt was used as an anticoagulant and noncoagulated blood was analysed for White Blood Cell (WBC), Red Blood Cell (RBC), Hemoglobin (HGB), Packed Red Cell Volume (HCT), Erythrocyte Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH) and Blood Platelet Count (PLT). Biochemical and physiological index were tested by serum including of Albumin (ALB), Alkali Phosphatase (ALP), Alkaline Aminotransferase (ALT), Aspartate Aminotransferase (AST), Bilirubin (BIL), Blood Urea Nitrogen (BUN), Creatinine (CRE), Gamma Glutamyl Transferase (GGT), Glucose (GLU) and so on. All haematological index in noncoagulated blood were measured with Sysmex Coulter HmX automatic blood analyzer (Beckman, America). Serum physio-biochemical indices in the blood serum were detected by automatic biochemistry analyzer (Beckman coulter Synchron CX4 PRO, America). Urine routine were tested by Miditron Junior II automated urine analyzer (German). Pathological slices were analyzed by biomicroscope.

Table 1: Ingredients and chemical composition of basal diets

Ingredients	Rate (%)	Nutrients	Level
Corn	58.00	Digestible Energy (DE/MJkg)	15.20
Soybean meal	18.00	Crude Protein (CP/%)	19.00
Extruded soybean	6.00	Crude Fiber (CF/%)	6.00
Fish meal	5.00	Crude Ash (Ash/%)	8.00
Whey powder	6.00	Calcium (Ca/%)	0.80
Fat powder	1.00	Available Phosphorus (AP/%)	0.40
Stone powder	2.00	Salt (NaCl/%)	0.35
Calcium hydrogen phosphate	0.80	Methionine (Met/%)	0.30
Salt	1.10	Lysine (Lys%)	1.15
Lysine	0.35		
Premix[a]	1.50		
Total	100.00		

[a]Premix provided per kilogram of diet: vitamin A20,000 IU vitamin D2000 IU, vitamin E60 IU, Vitamin K 2mg, Vitamin B_1 2 mg, Riboflavin 10 mg, Pantothenic acid 20 mg, Niacin 40 mg, Vitamin B_6 5 mg, Vitamin B_{12} 40 μg, folic acid 1.5 mg, Vitamin C 200 mg; Choline chloride 600 mg; Manganese 75 mg; Zinc 120 mg, Iron 140 mg, Copper 8 mg, Iodine 0.4 mg, Selenium 0.3 mg

The pigs were observed postadmistrated for 2, 4, 6, 8 and 12 h by one of the researchers (Zhao) and any adverse reactions were recorded. Subsequently, two of the researchers (Hao and Guo) blinded to treatment and side effect observed each pig at 1, 7 and 14 days postadmistrated and then daily for 14 days post-treatment for survival, general condition.

Blood and urine samples were taken from all pigs on days 1, 7 and 14 for serum chemical, hematology and urinalysis evaluation. Comparisons were made between pretreatment values and post-treatment values over a 14 day period.

All pigs were humanely killed 14 days post-treatment and gross and histologic evaluations were performed to assess changes potentially attributable to tulathromycin administration. Pathologists were blinded to treatment and stomach. Additionally, tissues submitted for histologic evaluation included heart, lung, aorta, liver and kidney.

Statistical analysis: All results were espressed as mean±Standard Error (SE). Comparisons were made between study groups using Mann-Whitney U-test. Results from study days 1, 7 and 14 were evaluated for differences between treatment and placebo groups using repeated measures ANOVA. Data from individual time points were compared using Student's t-test. Commercially available software (SPSS Version 16.0; SPSS Inc., Chicago, IL, USA) was used for all analyses. Statistical comparisons were considered to be significant at $p<0.05$.

RESULTS AND DISCUSSION

Tempreture parameters of pigs are shown in Table 2 and weight parameters of pigs are shown in Table 3.

Results of haematological and serum physio-biochemical parameters are shown in Table 4 and 5. Effects of urine routine are shown in Table 6. Hematology evaluation indicated that comparisons of RBC, WBC, HGB, HCT, MCV, MCH, MCHC and PLT between treatment and control groups also revealed no significant differences ($p>0.05$). ALT, ALB, TP, Na+ and P were significantly higher in treated groups when compared with the control group ($p<0.05$) post-treatment. However, other serum chemical parameters such as CREA, AST, GGT, GLU, TB, BUN, UA, LDH, ALP, CK, TG, Na+, P revealed no significant differences ($p>0.05$). Also, There were no obvious abnormal changes in cerebrum, lymph node, heart, kidney, spleen, lung, liver and stomach.

Dates shown in Table 2 and 3 show the mean tempreture and weight was higher for the treatment group when compared with the control, however, comparisons of mean physical examination parameters between treatment and control groups over the 14 days study period revealed no significant differences ($p>0.05$). All pigs did not show any signs of discomfort after dietary treatment. Low dose (10-100 mg kg^{-1}) of macrolide drugs with antibacterial effect and promoting animal growth such as 30 mg kg^{-1} tylosin add in pig feed can improve the 2.1-7.9% gain and on pig blood biochemical composition and morphology without adverse effects. Tulathromycin belonging to the treatment of drug, it has not been reported on piglets growth. The experimental results show that with different doses of tulathromycin premix on piglets have a certain role in promoting, performed in the average daily gain of control group 11.5-17.57% but there is no significant difference between ($p>0.05$).

Administration process driven, capture will cause certain animal stress response, effects of animal body growth, to breed production losses. Antibacterial drugs by the oral route of administration in modern intensive livestock farming has play a decisive role status, treatment and prevention of diseases of livestock and poultry are the main measures (Buckham Sporer *et al*., 2007). The

Table 2: Tempreture parameters of pigs which treated with tulathromycin and pigs of control group over a 14 day study period ($\bar{X}$±SE, n = 6)

	Days after treatment			
Groups	-1	1	7	14
Control (0 mg kg^{-1})	39.93±0.49	39.82±0.59	39.53±0.42	39.82±0.25
Low dosage (5 mg kg^{-1})	39.95±0.34	39.83±0.62	39.70±0.32	$39.42±0.34^{a}$
Middle dosage (15 mg kg^{-1})	$40.52±0.69^{B}$	40.05±0.67	$39.48±0.29^{A}$	$40.07±0.33^{b}$
High dosage (25 mg kg^{-1})	39.95±0.41	$39.52±0.26^{A}$	$39.43±0.49^{A}$	$40.03±0.72^{b}$

Table 3: Weight parameters of pigs which treated with tulathromycin and pigs of control group over a 14 days study period ($\bar{X}$±SE, n = 6)

	Days after treatment			
Groups	-1	1	7	14
Control (0 mg kg^{-1})	$20.13±3.18^{E}$	$21.07±3.38^{E}$	25.37±3.42	$29.40±4.27^{A}$
Low dosage (5 mg kg^{-1})	$20.23±0.97^{F}$	$20.93±1.86^{F}$	24.73±1.48	$29.53±2.27^{B}$
Middle dosage (15 mg kg^{-1})	$20.80±1.42^{G}$	$21.53±1.89^{G}$	25.57±2.52	$29.30±3.34^{C}$
High dosage (25 mg kg^{-1})	$20.43±1.15^{H}$	$21.10±1.65^{H}$	24.97±1.86	$29.27±3.75^{D}$

Different uppercases in the same row do significantly ($p<0.05$) and different lowercases in the same column do significantly ($p<0.05$) in all the tables in this very study

Table 4: Hematology parameters of pigs treated with tulathromycin and pigs of control group over a 14 days study period ($\bar{X}$±SE, n = 6)

		Hematology indexes						
Dosage (mg kg^{-1})	Days after treatment	WBC (10^{9} L^{-1})	RBC (10^{12} L^{-1})	HGB (g L^{-1})	HCT (%)	MCV (fl)	MCH (pg)	PLT (10^{9} L^{-1})
0	-1	18.73±4.67	6.38±0.39	128.00±9.51	37.12±1.55	58.68±2.06	20.62±0.65	453.83±28.27
	1	19.28±1.19	5.77±0.17	119.20±5.49	33.32±2.84	58.12±1.16	20.38±0.67	433.83±22.96
	7	21.80±2.26	5.97±0.17	115.33±4.10	33.18±0.87	55.68±1.10	19.33±0.55	497.67±55.87
	14	23.85±1.07	6.23±0.14	122.00±3.21	35.57±0.65	57.17±1.28	19.62±0.66	395.83±61.67
5	-1	23.00±4.37	6.56±0.26	136.33±8.50	36.32±1.58	56.80±3.53	19.70±0.93	449.17±17.08
	1	18.62±1.44	5.82±0.12	112.00±7.23	31.50±2.27	56.98±1.43	19.97±0.39	446.17±54.21
	7	19.65±1.74	5.79±0.07	114.00±3.19	32.12±0.94	55.50±1.48	19.77±0.42	405.00±28.73
	14	20.43±2.86	5.81±0.07	112.17±4.19	32.90±1.04	56.60±1.56	18.90±2.44	349.67±42.17
15	-1	19.68±1.89	6.63±0.21	131.83±4.53	38.00±1.15	57.12±1.61	19.87±0.64	460.00±24.56
	1	19.13±0.80	5.81±0.08	118.00±7.61	33.85±2.19	56.68±2.58	19.97±0.52	457.83±39.98
	7	19.13±1.46	5.83±0.06	116.17±2.60	32.45±0.57	55.65±0.67	19.90±0.30	541.67±40.61
	14	19.25±1.11	5.92±0.11	116.67±2.55	33.47±0.83	56.53±0.81	19.70±0.25	387.00±73.57
25	-1	19.76±4.11	6.45±0.16	133.00±7.62	38.36±2.20	56.90±2.46	19.72±0.75	480.83±47.57
	1	18.17±2.58	5.77±0.12	115.83±3.71	33.62±0.78	56.78±2.35	20.05±0.46	519.67±64.22
	7	15.22±0.87	6.05±0.15	119.17±1.35	34.03±0.42	56.25±1.06	19.50±0.37	503.83±50.94
	14	17.95±1.43	5.98±0.19	115.33±3.64	33.63±0.94	56.30±1.11	19.30±0.39	414.33±88.54

Table 5: Biochemical parameters of pigs treated with tulathromycin and pigs of control group over a 14 days study period ($\bar{X}$±SE, n = 6)

		Biochemical indexes									
Dosage (mg kg^{-1})	Days after treatment	AST (U L^{-1})	ALT (U L^{-1})	ALP (U L^{-1})	ALB (g L^{-1})	BUN (mmol L^{-1})	CREA (μmol L^{-1})	GLU (mmol L^{-1})	TP (mmol L^{-1})	Na+	P
0	-1	73.35±17.75^{A}	33.66±7.930^{A}	211.15±87.36^{A}	42.34±1.20^{A}	3.50±0.85	368.52±55.77	5.53±0.59	2.38±0.85	94.35±6.12	2.52±0.27
	1	72.69±13.41	35.13±7.350	160.10±48.36	36.67±3.14	3.33±0.78	324.25±68.88	4.29±0.27	2.86±0.50	93.32±5.52^{A}	2.15±0.32^{A}
	7	89.81±15.75	31.90±6.260	138.18±55.74	34.89±3.51	3.91±0.86	334.22±28.63	3.16±0.38	3.99±0.56	95.82±4.58	2.45±0.39
	14	86.65±7.170	36.65±3.460	151.40±24.06	29.61±3.00	5.37±0.83	233.56±70.37	3.71±0.43	3.01±0.97	96.15±7.10	2.77±0.21
5	-1	80.10±14.98^{A}	41.56±12.42^{A}	266.85±79.15^{A}	42.78±1.98^{A}	3.34±0.57	432.12±25.74	5.18±0.65	2.63±0.49	94.52±6.25	2.68±0.41
	1	77.07±12.31	47.97±9.190^{B}	186.98±51.49	35.72±1.87	3.62±0.81	449.52±71.24	4.46±0.67	3.48±0.26	93.89±8.43^{A}	2.31±0.26^{A}
	7	94.66±13.22	40.49±7.790	190.93±64.99	35.99±3.12	3.86±1.15	369.18±86.64	3.84±0.61	3.03±0.34	95.57±3.89	2.92±0.38
	14	87.66±8.290	35.46±4.230	159.77±48.25	28.94±4.35	5.79±0.81	232.30±80.19	3.54±0.76	2.73±0.54	95.24±4.65	2.74±0.39
15	-1	86.91±16.73^{A}	39.59±2.390^{A}	246.13±82.82^{A}	42.41±1.08^{A}	3.30±0.84	398.55±60.51	5.26±0.89	2.67±0.32	96.85±6.81	2.78±0.13
	1	126.08±25.19^{B}	42.67±7.040	204.88±44.19	40.17±2.78^{B}	3.42±1.16	400.97±72.10	4.82±0.91	3.33±0.43	100.17±1.88^{B}	2.56±0.54^{B}
	7	81.20±12.27	36.10±7.150	166.02±54.33	36.98±2.77	3.78±1.27	356.10±69.87	3.45±0.77	3.90±0.52	99.25±8.14	3.38±0.40
	14	84.66±12.13	33.76±6.340	141.69±29.79	30.29±3.59	5.52±0.84	279.68±99.57	3.59±0.82	2.06±0.41	94.25±9.12	2.51±0.31
25	-1	87.12±7.980^{A}	33.62±10.32^{A}	268.81±46.61^{A}	43.03±1.52^{A}	3.76±1.48	389.63±63.70	5.52±0.71	2.66±0.26	95.32±6.22	2.45±0.23
	1	127.93±33.73^{B}	56.88±4.090^{B}	198.60±56.94	39.59±2.51^{B}	4.87±1.15	301.33±59.18	5.04±0.48	3.26±0.52	117.52±7.96^{B}	2.87±0.35^{B}
	7	86.60±21.95	38.67±7.370	216.50±56.10	38.77±2.70	5.07±1.23	348.28±79.51	4.54±0.72	3.60±0.31	98.27±5.89	3.24±0.93
	14	86.21±10.80	35.80±4.700	163.59±58.22	31.37±5.00	6.25±1.51	217.32±80.72	3.88±0.72	2.88±0.82	96.15±6.20	2.66±0.18

Table 6: Urine parameters of pigs treated with tulathromycin and pigs of control group over a 14 day study period

		Urine indexes						
Dosage (mg kg^{-1})	Days after treatment	UBG	PH	PRO	ERY	XII	NIT	SG
0	-1	-	8.1±0.8	-	-	-	+	1.0120±0.00158
	1	-	8.0±0.0	-	-	-	+	1.0215±0.00250
	7	-	7.9±1.1	-	-	-	+	1.0086±0.00210
	14	-	8.2±0.3	-	-	-	+	1.0125±0.00240
5	-1	-	7.7±0.5	-	-	-	+	1.0300±0.00150
	1	-	7.6±1.2	-	-	-	+	1.0233±0.00240
	7	-	7.8±0.8	-	-	-	+	1.0158±0.00160
	14	-	7.7±0.6	-	-	-	+	1.0220±0.00140
15	-1	-	8.0±0.8	-	-	-	+	1.0200±0.00170
	1	-	7.9±0.3	-	-	-	+	1.0205±0.00240
	7	-	8.1±1.0	-	-	-	+	1.0004±0.00280
	14	-	8.0±0.9	-	-	-	+	1.0154±0.00200
25	-1	-	±	-	-	-	+	1.0200±0.00380
	1	-	11.58±0.0	-	-	-	+	1.0220±0.00400
	7	-	±	-	-	-	+	1.0254±0.00340
	14	-	±	-	-	-	+	1.0186±0.00180

UBG = Urobilinogen, PRO = Protein; ERY = Erythrocyte; XII = Ketone Bodies II; NIT = Nitrites; SG = Specific Gravity; +: positive, -: negative

current clinical veterinary approved the use of macrolides in general need repeated administration to research. Tulathromycin by oral medication, the dosage is reduced to the minimum to maximum compliance, thereby reducing animal stress response. So, tulathromycin premix in veterinary clinical has the widespread application prospect.

RBC, HGB, HCT, MCV and MCH are used to determine the type of anemia anemia and differential. In all kinds of anemia because the red cell hemoglobin concentration, red blood cells and hemoglobin two reduction degree can be inconsistent, therefore in the anemia of judgement in anemia, discrimination, in addition to the use of the HGB criterion of anemia but also refer to the RBC such as the two scale is maladjusted, need further reference MCV, MCH and MCHC. The number of platelets and coagulation mechanism closely related.

Under normal circumstances the platelets are involved in physiological hemostasis, coagulation, promote the maintenance of capillary wall integrity (Sporer *et al*., 2008). The Platelet count (PLT) can be used as a viral disease, sepsis, aplastic anemia, drug allergic reaction and malignant tumor diagnosis index. The test results show, all the test animal red blood cells and hemoglobin before and after administration of good relationship are within the normal range, HCT, MCV, MCH, MCHC and PLT results page within the normal range, the treatment group and blank group at the same time have no significant difference ($p>0.05$). Therefore, tulathromycin premix on the above indexes and influence.

The change of serum biochemical indicators of physiological condition is changed and the body function changes (Kozlov *et al*., 1987). Animal liver, kidney and myocardium functional status can be through in the serum of some biochemical indices. AST, ALT, ALP, ALB, TP and GGT commonly used liver functional indices; AST, LDH and CK as the index of heart function; in the present experiment, after administration of the dose groups of TP, GGT, GLU, Na+ and P average values compared with the blank group there was a significant difference ($p<0.05$), however, after the administration of 14 day, each group TP, GGT, GLU, Na+ and P levels were within normal reference ranges by day 14 and compared with blank control group with no significant difference ($p>0.05$). Thus, Tulathromycin premix on the target animal pig liver with slight loss function.

CONCLUSION

Tulathromycin is a new type of semi synthetic beasts special macrolide antibiotics, the study based on pig 3 days oral administration and clinical symptoms, blood physiological and biochemical indexes of comparative analysis and delivery compared to before, all the animal after administration of feed and actions are often respiration and excretion also showed no abnormalities, the clinical manifestations were normal. In 5-25 mg kg^{-1} body weight dose range with the passage of time, comparisons of mean physical and laboratory parameters between treatment and control groups prior to treatment yielded no significant differences. At present there is that tulathromycin premix in clinical use by the oral delivery, every kg weight, pig 5 mg dosage, safety without any adverse reaction.

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