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Phenylbutazone Administration in Arabian Horses and its Digestive and Cardiac Injuries (Biochemical, Hematological and Endoscopic Findings)

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Abstract: The present study was conducted To evaluate of hematological, biochemical and endoscopic findings in horse following long period use of Phenylbutazone. 24 heads male Arab horses were divided to 2 groups consisted of 12 horses with an identical feeding, management and activity conditions. Physiological serum, 2 mg/kg phenylbutazone were injected intra muscular for 10 days, respectively, for groups 1 and 2. On zero time (before injection), days 2,4,6,8 and 10 of blood sampling was done from the horses' vena cava and the samples' serum was separated and frozen. Hematologic tests and some of biochemical tests were done on serum samples followed by endoscopic tests on horses for evaluating gastric viscera and gastric ulcers. Hematologic changes such as red and white blood cells count and haematocrit percentage were not meaningful in group 2. In group2 the average level of total protein, albumin, creatinine and urea serum levels demonstrated a meaningful increase with increasing of drug using period ($P<0.05$). The average level of CK, ALP, ALT, AST and GGT enzymes serum concentration in understudying horses had a meaningful increase by increasing the period of the used drug ($P<0.05$). Based on endoscopic findings all horses of group one had healthy gastric viscera after 10^{th} day but 5 horses in group two had healthy gastric viscera, 2 horses suffered from grade I gastric ulcer and 3 horse suffered from grade II gastric ulcer and 2 horses with grade III gastric ulcer, respectively. The result is that the use of phenylbutazone for long time lead to increase total protein, albumin, creatinine, urea, heart troponin and CK, ALP, ALT, AST, GGT but there is no meaningful change in hematologic findings and causes to horse gastric viscera injury. Therefore, liver, renal and digestive injuries are some of long term influences of the drugs on horse.

Key words: Horse · Phenylbutazone · Biochemical · Hematological · Endoscopic

INTRODUCTION

The advantage of non steroid anti-inflammatory drugs compared with corticosteroids is due to glucocorticoids. Because of the many side effects in human this issue has e especial importance in human medicine. Most of non steroid anti-inflammatory applied their effects by controlling cyclooxygenase activity followed by controlling the production of prostaglandins. Although most of non steroid anti-inflammatory percent locotrins formation, some of them, ketoprofen and ibuprofen, control lipooxygenase and prevent locotrin production. Non steroid anti-inflammatory decrease the pain caused by inflammation but considered as inefficient analgesics and unable to relieve the visceral pain like stomachache or sever body pain like bone fracture and hurt pain [1-5].The role of non steroid anti-inflammatory increating of gastric ulcer has been well known [6-9]. The role and place of these kinds of drugs in producing gastric ulcers is so clear that researchers sometimes enjoy these drugs in creating experimental ulcers. Phenylbutazone, for instance, have a proved role in creating gastric ulcers beside its side effects like aplastic anemia [10]. The other drug of this group is flunixin meglomin which has some roles in creating gastric ulcer in ponies which received 1.5 mg/kg per 8 hours for 6 days or 1.1 mg/kg per 8 hours for 7 days [10,11]. It must be noted that the prescription of these drugs, orally or injection, can cause gastric ulcer. Furthermore, other problems such as epithelial necrosis and intestine epithelium inflation have been attributed to these drugs [10]. Long term use of non steroid anti-inflammatory ay have some effects on cardiac function

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[12,13]. The present study examines this issue by evaluating cardiac and digestive enzymes. The study aiming at evaluating hematological, biochemical and endoscopic findings following long term use of phenylbutazone in Arabian horse which examines mainly their effects on cardiac and digestive functions.

MATERIALS AND METHODS

The present study is an experimental- interventional one which was conducted on 24 male Arabian horses of Tabriz stableswhich were divided into 2 groups of 12 horses each with an identical feeding, management and activity conditions. dietary Feeding of all groups consisted of alfalfa, hay, bran and barley. Normal saline, 2 mg/kg phenylbutazone were injected Intramuscularly for 10 days for groups 1 and 2 respectively [14]. On zero day (before injection), days of 2,4,6,8 and 10 the blood sampling was Withdrawn from the horses' vena cava and the samples' serum was separated by centrifugation; then the serum were frozen until used for biochemical tests.. Two blood samples were obtained; one of them with anti-coagulant for hematologic tests and another one without anti-coagulant for biochemical tests. Hematologic tests consisted of red and white blood cells count and haematocrit percentage as well as biochemical tests Which included of total protein, albumin, CK, ALP, ALT, AST and GGT enzymes serum concentration, creatinine, urea and cardiac troponin. All of serum levels were measured by biochemical kits and cardiac troponin was measured by ELISA kit at Sina laboratory. Finally, the average level of the mentioned metabolites was calculated on the mentioned times. All horses were endoscoped for examining gastric epithelium and gastric ulcer.

Statistical Analysis: For analyzing the data were used of $SPSS_{13}$ and for comparison of means between groups and between different days of ANOVA test were used.

RESULTS

Hematologic findings of two groups: normal saline (group 1) and phenylbutazone (group 2) has been given in table 1. The changes in red blood cells count in control group are not meaningful from zero to 10th day. Besides, these changes were not meaningful in group 2. On the other hand, the differences among two groups isn't meaningful on any of sampling days. The average level difference of white blood cells and haematocrit was not meaningful from zero to 10th day as well and the observed changes aren't significant.

Table 1: Hematological effects of saline (group 1) and Phenylbutazone (group 2) administration in Arabian horses during different times of sampling (M±SE)

		Group	
Factors	Day of Sampling	Saline (Mean±SE)	Phenylbutazone (Mean±SE)
RBC(×10⁶/µl)	0	8.4±0.92 Aa	8.2±1.00 Aa
	2	8.1±1.04 Aa	8.5±0.97 Aa
	4	8.5±0.65 Aa	7.9±0.76 Aa
	6	8.0±0.74 Aa	7.6±1.03 Aa
	8	7.9±0.34 Aa	8.0±0.89 Aa
	10	8.4±1.11 Aa	7.5±0.98 Aa
WBC(×10³/µl)	0	6.8±0.33 Aa	6.6±1.03 Aa
	2	6.6±0.65 Aa	6.8±0.88 Aa
	4	6.7±0.98 Aa	7.0±0.75 Aa
	6	6.8±0.56 Aa	7.3±1.02 Aa
	8	7.0±0.75 Aa	7.6±1.11 Aa
	10	7.1±0.77 Aa	8.1±0.96Ba
PCV (%)	0	45.31±4.23 Aa	45.54±7.6 Aa 4
	2	44.53±6.87 Aa	47.54±5.58 Aa
	4	46.76±6.08 Aa	49.64±6.60 Aa
	6	44.64±5.50 Aa	50.62±3.68 Aa
	8	43.97±7.18 Aa	50.05±7.34 Aa
	10	44.69±3.28 Aa	48.94±4.86 Aa

a,b,c,…: In each row, only those means with different letters are significantly different (p<0.05)

A,B,C,…: In each column, only those means with different letters are significantly different (p<0.05)

RBC red blood cell, WBC white blood cell, PCV packed cell volume, SE standard error

The average level of total protein serum had no meaningful difference from zero to 10th day in group 1 but it was increased on the mentioned days in group 2 such that from 6th day afterwards the increase was significant (P<0.05). Furthermore, the average difference among two roups was meaningful on the zero and second days. The difference of phenylbutazone was not significant and the averages difference among two groups was meaningful on 6th, 8th, 10th days (P<0.05). The average level of serum albumin in group 1 was not Significantly different difference among various days but has meaningful difference in group 2 from 8th day afterwards (P<0.05). The average difference among groups was not meaningful on zero and 2nd days but it was meaningful on the other days (P<0.05). The average of serum creatinine in group 1 had not meaningful difference on various days but it was different from 8th day afterwards in group 2 (P<0.05). The difference of the averages among groups on zero, 2nd and 4th days was not meaningful but it

Table 2: Some biochemical effects of saline (group 1) and phenylbutazone (group 2) administration in Arabian horses during different times of sampling (M±SE)

Factors	Day of Sampling	Group: Saline (Mean±SE)	Group: Phenylbutazone (Mean±SE)
Total protein(g/dl)	0	6.91±1.07^{Aa}	6.95±0.97^{Aa}
	2	7.04±1.11^{Aa}	7.08±1.11^{Aa}
	4	7.12±0.89^{Aa}	7.91±1.05^{Aa}
	6	6.86±1.04^{Aa}	9.57±1.13^{Bb}
	8	7.00±0.86^{Aa}	11.44±1.03^{Bb}
	10	7.23±0.45^{Aa}	11.69±1.20^{Bb}
Albumin (g/dl)	0	3.01±0.23^{Aa}	3.10±0.05^{Aa}
	2	3.15±0.54^{Aa}	3.22±0.10^{Aa}
	4	2.97±0.44^{Aa}	3.53±0.21^{Ab}
	6	2.88±0.21^{Aa}	4.14±0.31^{Ab}
	8	3.07±0.45^{Aa}	4.88±0.51^{Bb}
	10	3.10±0.55^{Aa}	5.03±0.33^{Bb}
Creatinine (mg/dl)	0	0.87±0.04^{Aa}	0.86±0.11^{Aa}
	2	0.79±0.03^{Aa}	0.97±0.10^{Aa}
	4	0.88±0.10^{Aa}	1.12±0.07^{Ab}
	6	0.86±0.04^{Aa}	1.05±0.30^{Ab}
	8	0.91±0.04^{Aa}	1.29±0.41^{Bb}
	10	0.86±0.11^{Aa}	1.98±0.65^{Bb}
Blood urea nitrogen (mg/dl)	0	17.81±2.17^{Aa}	20.15±3.17^{Aa}
	2	18.92±3.08^{Aa}	19.53±2.86^{Aa}
	4	20.05±3.65^{Aa}	21.63±2.75^{Aa}
	6	19.54±4.18^{Aa}	33.17±3.06^{Bb}
	8	18.76±3.85^{Aa}	37.63±3.86^{Bb}
	10	17.65±5.01^{Aa}	39.60±2.85^{Bc}
Cardiac troponin (mg/ml)	0	0.078±0.01^{Aa}	0.077±0.00^{Aa}
	2	0.065±0.00^{Aa}	0.069±0.01^{Aa}
	4	0.066±0.01^{Aa}	0.088±0.00^{Aa}
	6	0.081±0.03^{Aa}	0.11±0.02^{Bb}
	8	0.082±0.00^{Aa}	0.54±0.11^{Bb}
	10	0.076±0.00^{Aa}	2.06±0.27^{Cb}

a,b,c,…: In each row, only those means with different letters are significantly different ($p<0.05$)

A,B,C,…: In each column, only those means with different letters are significantly different ($p<0.05$)

was significant on the other days ($P<0.05$). The average level of blood urea wasn't meaningful in group 1 on various days but it was meaningful in group 2 from 6th day afterwards ($P<0.05$). The difference of the average among all groups wasn't meaningful on zero, 2nd and 4th days but it was significant on the other days ($P<0.05$).

The average level of cardiac troponin serum was not meaningful in group 1 on various days but it was meaningful in group 2 from 6th day afterwards ($P<0.05$) such that the increase was significant on 10th day. The difference of the average among groups was not meaningful on zero, 2nd and 4th days but it was meaningful on the other days ($P<0.05$).

Table 3: Some enzyme effects of saline (group 1) and phenylbutazone (group 2) administration in Arabian horses during different times of sampling (M±SE)

Factors	Day of Sampling	Group: Saline (Mean±SE)	Group: Phenylbutazone (Mean±SE)
CK(U/L)	0	217.64±12.29^{Aa}	222.43±11.76^{Aa}
	2	220.76±11.65^{Aa}	237.64±20.52^{Aa}
	4	224.54±13.76^{Aa}	230.49±12.54^{Aa}
	6	216.65±5.97^{Aa}	259.44±16.94^{Bb}
	8	219.98±11.75^{Aa}	278.93±15.40^{Bb}
	10	223.45±13.24^{Aa}	305.33±19.54^{Bb}
ALP(U/L)	0	387.23±24.29^{Aa}	395.64±12.96^{Aa}
	2	396.54±31.09^{Aa}	402.66±24.60^{Aa}
	4	376.64±16.76^{Aa}	419.43±17.56^{Aa}
	6	384.73±25.87^{Aa}	423.55±24.06^{Ab}
	8	392.87±19.13^{Aa}	479.84±19.63^{Bb}
	10	390.43±13.65^{Aa}	531.57±22.34^{Bb}
ALT(U/L)	0	9.27±1.14^{Aa}	9.77±3.12^{Aa}
	2	9.05±1.65^{Aa}	9.43±1.04^{Aa}
	4	9.54±0.87^{Aa}	8.95±0.88^{Aa}
	6	8.95±1.58^{Aa}	10.13±1.11^{Bb}
	8	9.33±2.06^{Aa}	14.80±1.23^{Bb}
	10	9.24±1.10^{Aa}	17.23±1.65^{Cb}
AST(U/L)	0	314.36±9.23^{Aa}	316.54±10.41^{Aa}
	2	320.14±10.13^{Aa}	321.76±11.05^{Aa}
	4	308.64±7.67^{Aa}	319.75±21.65^{Aa}
	6	311.34±11.18^{Aa}	330.64±18.26^{Aa}
	8	316.45±9.67^{Aa}	397.65±20.15^{Bb}
	10	310.65±17.65^{Aa}	496.53±22.74^{Bb}
GGT(U/L)	0	26.39±2.17^{Aa}	24.76±2.98^{Aa}
	2	25.61±3.85^{Aa}	29.54±3.07^{Aa}
	4	29.02±4.62^{Aa}	30.66±4.16^{Aa}
	6	25.75±1.64^{Aa}	47.61±2.69^{Bb}
	8	26.08±4.11^{Aa}	46.59±3.76^{Bb}
	10	27.92±3.05^{Aa}	53.66±4.38^{Bb}

a,b,c,…: In each row, only those means with different letters are significantly different ($p<0.05$)

A,B,C,…: In each column, only those means with different letters are significantly different ($p<0.05$)

CK creatine kinase, ALP alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, GGT γ glutamyl transferase, SE standard error

Table 4: The number of horses affected with different grades of gastric ulcer through endoscopic survey in three groups

Group	Grade of gastric ulcer: 0	I	II	III	IV
Saline	12	-	-	-	-
Phenylbutazone	5	2	3	2	-

The average level of of serum keratin kinase enzyme was not significantly different in group 1 along various days but it was different meaningfully in group 2 from 6th day afterwards (P<0.05). The difference of the average among all groups was not meaningful on zero and 2nd days but it was meaningful on the other days (P<0.05). The average of serum alkaline phosphatase enzyme was not different meaningfully in group 1 on various days but it was meaningful in group 2 from 8th day afterwards (P<0.05). The difference of the average among all groups was not meaningful on zero and 2nd days but it was meaningful on the other days (P<0.05).The average of serum alanine transferase was not meaningfully different in group 1 along various days but it was different meaningfully in group 2 from 8th day afterwards (P<0.05). The difference of the groups' average was not meaningful on zero, 2nd and 4th days but it was meaningful on the other days (P<0.05). The average of serum aspartate amino transferase was not meaningfully different in group 1 on various days but it was different meaningfully in group 2 from 8th day afterwards (P<0.05). The difference of the groups' average was not meaningful on zero, 2nd days but it was meaningful on the other days (P<0.05). The average of serum γ glutamyl transferase was not meaningfully different in group 1 on various days but it was different meaningfully in group 2 from 6th day afterwards (P<0.05). The difference of the groups' average was not meaningful on zero, 2nd and 4th days but it was meaningful on the other days (P<0.05).

Based on endoscopic findings all horses of group one had healthy gastric viscera after 10th day but 5 horses in group two had healthy gastric viscera, 2 horses suffered from I grade gastric ulcer and 3 horse suffered from II grade gastric ulcer and 2 horse suffered from III grade gastric ulcer.

DISCUSSION

Nowadays, non-steroidal anti inflammatory drugs have a high use in veterinary which are used in equine treatment as well. The present study aiming at evaluating the hematological, biochemical and endoscopic findings in horse following long term use of non-steroidal anti inflammatory. The average of red blood cells count in group 2 decreased from zero to 10th days but the decrease was not significant. Furthermore, the decrease of the haematocrit percentage was not significant. The average of white blood cell count in both groups increase with increasing the injection days which was not significant. The difference of hematologic parameters among three groups was not meaningful on any sampling days. The decrease of red blood cell count and haematocrit may associate with anemia caused by gastric ulcers in groups 2 [15]. Lees *et al.* in 1989 reported an anemia in horse caused by gastric ulcer. Although the increase of white blood cells was not meaningful but it can be due to inflation caused by gastric epithelium injuries because of long term use of non-steroidal anti inflammatory drugs [16]. It was characterized in the present study by endoscopic examinations that there were various degrees of gastric ulcer in epithelium after 10th day of the drugs using; 7 horses of group 2. The role and place of these kinds of drugs in producing gastric ulcers is so clear that researchers sometimes cases these drugs in creating experimental ulcers. Phenylbutazone, for instance, have a proved role in creating gastric ulcers beside its side effects like aplastic anemia [10]. The other drug of this group is flunixin meglumine which has some roles in creating gastric ulcer in ponies which received 1.5 mg/kg per 8 hours for 6 days or 1.1 mg/kg per 8 hours for 7 days [10, 17]. In another study by Morris *et al.* the negative influence of Phenylbutazone on thyroidal hormones serum level has been proved; the thyroidal hormones of these horses increased immediately by Phenylbutazone injection [4]. Goodrich *et al.* In 1998 and Traub *et al.* in 1988 has reported high gastric ulcer following the long term use of non steroidal anti inflammatory like Phenylbutazone and flunixin meglomin [18]. Long term uses of non steroidal anti inflammatory disable protective mechanisms of gastric epithelium against gastric juice due to limit the PGE_2 synthesis and decrease the blood circulation in gastric epithelium [19]. Our findings confirm the to findings of Goodrich *et al.* in 1998 and Traub *et al.* in 1988 [18, 20]. Lack of appetite resulted from long term use of the drugs has been reported in 6 horses which is caused by gastric epithelium injuries [17]. It was characterized in this study that the average level of serum total protein and albumin was increased meaningfully in group 2 from 6th afterwards. These changes can be resulted of gastroenteropathy. Gastric epithelium injury and gastric ulcer followed by increasing the serum level of total protein and albumin have been reported in a study conducted by MacAlister *et al.* [17].In another study by Meschter *et al.* in 1990 it was reported that horses with gastric ulcer suffered from hypoproteinemia and hypocalcaemia. The meaningful increase of blood creatinine and urea average level in group 2 with increasing of using period of the drug can be resulted of renal injury which needs more evaluation [21]. In the study conducted by Mozaffari *et al.* on goats and Snow *et al.* on ponies the issue has been confirmed and it has been mentioned that long term use of non

steroidal anti inflamatorys resulted in renal injury and increasing blood urea and serum level of alkaline phosphatase and creatinine [5, 22] . It was characterized in this study that cardiac troponin serum level had a meaningful increase in group 2 since 6th day, which was tenfold in group 2 on 10th day. Nowadays, the increase of cardiac troponin level is as a standard biochemical criterion for identifying myocardial injury and severs myocardial infarctions [23, 24]. Cardiac troponin serum level increase can be resulted from long term use of the drugs followed by cardiac myocardial. Cornelisse *et al.* in a study reported that a horse with arterial rupture and ventricular tachycardia the cTnl serum level was 5.9 mg/ml on referral day and 4.3 mg/ml five days afterwards [25]. Schwarzwald *et al.* in 2003 showed the increased level of troponin in a horse with ventricular tachycardia and myocardial necrosis. Phiilips *et al.* in 2003 demonstrated in a study that cTnl serum level in competition horses was not meaningfully different compared with pasture horses [24, 26]. The average level of cTnl in both groups was 0.047 ± 0.085 mg/ml. Begg *et al.* in 2006 estimated by ADVIA the normal level of cTnl in Thoroughbred horses lower than 0/15 ìg/ml [27]. It was shown in 2007 that in equine piroplasmosis the increase of cTnl serum level was associated with tachycardia and early complexes of ventricular polymorphism. CTnl level was estimated at 0.27 mg/ml in horses suffered from piroplasmosis and at 0.1- 0.03 mg/ml in healthy horses [28]. Hostell and Haggstrom in 2008 showed that the horses had troponin lower than 0.022 ìg/l but it was decreased 1-2 hours after competition like 10 to 14 hours after that time [29]. The average level of serum concentration of CK, ALP, ALT, AST and GGT enzymes in understudying horses of group 2 showed a meaningful increase with increasing the using period of the drug. The increase of these enzymes can be resulted of liver injury which was mentioned by other researchers as well [4,30]. The increase of GGT following the use of Phenylbutazone past has been reported by lees *et al.* in 1987 [16].

CONCLUSION

The conclusion is that phenylbutazone Treatment increased the total protein, albumin, creatinine, urea and cardiac troponin enzymes, CK, ALP, ALT, AST and GGT but cause no meaningful change in hematologic findings as well as cause the gastric epithelium injury in horse. So, liver, renal and digestive injuries are long term results of the drug in horse.

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