Pathological and Biochemical Studies on The Adverse Effects of Phenylbutazone Administration in Draft Horses

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ABSTRACT

Phenylbutazone (PBZ) is the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs) in equine. Despite its beneficial effects, its misuse can result in deleterious findings including gastric and colonic ulceration and renal failure. The present study describes the lesions, hematological findings and biochemical profile in draft horses suffering orthopedic diseases and injected with PBZ. Fifty-five native breed draft horses of both sexes (forty diseased and fifteen control) were clinically investigated during the period from October 2006 to December 2008. The treated horses were categorized into survivors gp.1 and nonsurvivors gp.2. Anemia, increased ALT, AST, urea and creatinine levels were noticed in both groups. The oxidative stress markers showed significantly elevated MDA and NO. Meanwhile, the GSH and SOD levels were significantly decreased. Macroscopically, gp.2 showed gastrointestinal ulceration and erosion particularly in the right dorsal colon with thrombotic and necrotic blood vessels. Pulmonary congestion and hepatocytic degeneration were also observed, besides necrotic renal papillae. It could be concluded that the injected PBZ induced severe gastrointestinal, hepatic and renal lesions. Moreover, the use of PBZ should be under strict medical care.

INTRODUCTION

The nonsteroidal anti-inflammatory drugs(NSAIDs) are used for treatment of many painful conditions in horses; including arthritis, laminitis and colic *(1-3)*. Phenylbutazone (PBZ) is a potent NSAID that has been recommended for treatment of equine colic, musculoskeletal pain, endotoxic shock and secretory diarrhea *(4,5)*. PBZ inhibits the cyclooxygenase-enzyme system, which is responsible for synthesis of prostanoids such as PGE2. Despite its beneficial effects for many disease conditions, its misuse can result in deleterious effects including gastric and colonic ulcerations and renal failure even when used at appropriate dose *(6-8)*. The toxic effects are mainly seen in the gastrointestinal tract in the form of ulcers in the gastric glandular mucosa, and necrotizing protein-losing colitis *(9-11)*. The risk of gastric and colonic ulcerations or renal failure is exacerbated by dehydration, hypovolemia and pre-existing gastrointestinal or renal injury *(7,12)*. PBZ at a dose greater than that recommended by the manufacturer results in toxic effects especially if maintained for more than a few days *(13)*. Right dorsal colitis (RDC), and acute necrotizing colitis have been documented in horses treated with PBZ *(14,15)*.

The pathogenesis of RDC is unknown, however it could be induced by local and systemic factors *(16,17)*. Colitis is associated with liberation of oxygen free radicals which further damage the colonic mucosal epithelium and potentiate the activity of the proteolytic enzymes released by phagocytic cells during the inflammatory process *(18)*. Little work has been done on the association of the right dorsal colitis, caused by PBZ, with the oxidative stress markers and antioxidants in draft horses *(8)*. The present study was designed to investigate the adverse effects of injectable PBZ in draft horses and to evaluate the associated oxidative damage. .

MATERIAL AND METHODS

Animals and Medical Records

Forty native breed draft horses of both sexes (26 females and 14 males), aged between one to four years, were sporadically investigated during the period from October 2006 to December 2008.in the Clinic of Faculty of Vet. Med., Mansoura University, Mansoura, Egypt. Moreover, fifteen apparently healthy horses of both sexes (10 females and 5 males of the same age-range), were randomly selected to be the control group. The clinical study was performed at The Veterinary Teaching Hospital, Faculty of

Veterinary Medicine, Mansoura University, Mansoura, Egypt. The examined horses were suffering chronic musculo-skeletal painful conditions (myositis, septic arthritis, laminitis and joint dislocation). They were treated with multiple doses of PBZ. Complete medical record for each horse depended upon the case history and signs. The selected horses were divided into 3 groups. Gp. 1 comprised 25 survivors.. Gp.2 comprised 15 non-survivor horses. Gp. 3 contain15 control horses.

Blood Samples

Two blood samples (ten ml each) were collected from the jugular vein.. The first was collected in centrifuge tube containing 5mg EDTA for hematological study (erythrocytic, leukocytic and differential leukocytic cell counts, besides the packed cell volume, (PCV %) *(19)*.The second was left to coagulate, then centrifuged at 2000 rpm. The serum was separated and frozen till biochemically analyzed [AST, GGT, MDA, SOD, uric acid, reduced glutathione (GSH), nitric oxide (NO), urea and creatinine]. Spectrophotometer and commercial test kits (supplied by Randox Laboratories, Emapole Poland, Bio Diagnostic Egypt, ABC Diagnostics, Bio Diagnostic Egypt, Bio Diagnostic Egypt, Spinreact, Bio Diagnostics Egypt, Bio Diagnostics Egypt, Bio Diagnostics Egypt, Boehringer Mannheim, ABC Diagnostics, Biodiagnostic Egypt and ABC Diagnostics, respectively according to the methods described in the enclosed pamphlets) were used.

Postmortem and histopathological examination

Fifteen horses (gp.2) failed to respond to medical treatment and died after 6-11 days from the start of treatment. Necropsy was performed *(20)* and specimens were collected from stomach, cecum, colon, liver, lungs, spleen and kidneys and immediately fixed in 10% neutral buffered formalin solution. Five-micron thick paraffin sections were prepared, stained with hematoxylin and eosin *(21)* and examined microscopically.

Statistical analysis

The collected data were subjected to statistical analysis using statistical software program (SPSS for Windows, version 15, SPSS Inc. Chicago, USA). Means and standard deviation for each variable were estimated. Differences between the means were carried out using one way ANOVA with Duncan *post-hoc* multiple comparison test. At $P < 0.05$, results were considered significant *(22)*. Kaplan-Meier survival analysis 17 was performed to analyze the association of melena and colic status with measured outcomes. Start point was defined as onset of clinical signs. The outcome was defined as conservative survival time (time to death whatever the cause).

RESULTS

History and clinical signs

History of PBZ treatment, clinical signs and survival curve of horses were recorded in Table 1, Fig. 1 and Table 2 respectively. Intermittent colic, poor appetite, progressive weight loss, pale mucous membrane, ventral abdominal edema and diarrhea were the main complaints.

Pathological Finding

Macroscopically, congestion, petechial hemorrhages, erosion and ulceration were the most prominent lesions in glandular stomach and RDC. The gastric mucosa and serosa were severely congested (Fig. 2). Sometimes the nonglandular stomach was eroded. The luminal surface of the glandular stomach, particularly in pyloric region, was severely congested and showed erosions and ulcerations (Fig. 3). The base of these ulcers was hemorrhagic and dark red in color with raised borders. The small intestine showed thickened wall and congested serosa, besides congested and eroded mucosa. The obvious lesions were seen in RDC which were represented by severe congestion, petechial and ecchymotic hemorrhages and superficial or deep hemorrhagic ulcerations along its entire length or even intestinal perforation (Fig. 4). Moreover, similar but less severe lesions were observed in the large colon (Fig. 5). The liver was slightly enlarged and mottled gray. The heart showed congestion of coronary blood vessels and petechial hemorrhages on the adipose tissue of the coronary grooves (Fig. 6). The kidneys were swollen and dark in color with congested cortex and medulla (Fig. 7). The lungs were pale and voluminous, meanwhile the spleen was congested.

Microscopically, the nonglandular gastric mucosa showed pre-erosive lesions represented by acanthosis, spongiosis and vesiculation (Fig. 8). The lamina propria was infiltrated with neutrophils and few macrophages ,besides congested and thrombosed blood vessels. The glandular gastric mucosa showed coagulative necrosis and ulcerations. The latter extended into the submucosa but rarely beyond the musculosa (Figs 9-13). Bluish granular materials (dystrophic calcification) were seen on the tips of necrotic epithelium of pits and glands (Figs. 14&15). The underlying tissue showed serofibrinous exudate entrapping huge number of neutrophils, lymphocytes and macrophages ,besides congested and thrombosed blood vessels (Fig. 16). Desquamation and erosion of the small intestinal epithelial lining were observed ,besides congestion and infiltration of the lamina propria with neutrophils and few lymphocytes. The large intestine, particularly the dorsal right colon (DRC), showed more severe ulcerative and necrotic lesions. The DRC showed necrosis of the whole mucosa and submucosa with the base of ulcer located on the tunica muscularis (Fig. 17-22). The necrotic mucosa and submucosa presented thrombosis and numerous inflammatory cells particularly neutrophils. The liver was congested with vacuolation of some hepatocytes (Figs.23 & 24) The renal cortex showed congested glomerular tufts and intertubular capillaries (Fig. 25). Hemorrhages were seen, particularly under the renal capsule and in medulla (Fig. 26). The renal tubular epithelium was vacuolated and necrotic, particularly near medulla and involving renal papillae (Fig. 27). The pulmonary tissue showed congested peribronchial and interalveolar vasculature ,besides plugging of some alveoli with pale eosinophilic material, meanwhile other alveoli showed compensatory emphysema (Figs. 28 & 29). Spleen showed severe depletion of lymphocytes from the white pulp, besides congested red pulp. Moreover hemosiderosis was seen. The walls of central arterioles were hyalinized (Figs.30&31).

Table 1. History of PBZ treatment in gps. (1&2).

Groups	Survivors (n = 25)		Non-survivors (n = 15)	
	(mean± SD)	Range	(mean ±SD)	Range
IV daily dose of PBZ (mg/kg B. Wt/day) at which toxicity signs appeared..	4.90 ± 1.37	2.5 – 8.0	9.40 ± 2.54	5.0– 15.0
Duration in days of PBZ administration.	5.80 ± 1.03	4.0– 7.0	4.70 ± 0.67	4.0 – 6.0
Time in days of appearance of signs of toxicity from SOT with PBZ	6.40 ± 1.07	5.0 – 8.0	5.30 ± 0.82	4.0 – 7.0
Duration of illness in days from the onset of toxicity signs till recovery or death.	15.30 ± 6.87	8.0 – 31.0	8.00 ± 1.30	6.0 – 11.0

Table 2. Clinical findings of the examined horses treated with PBZ.

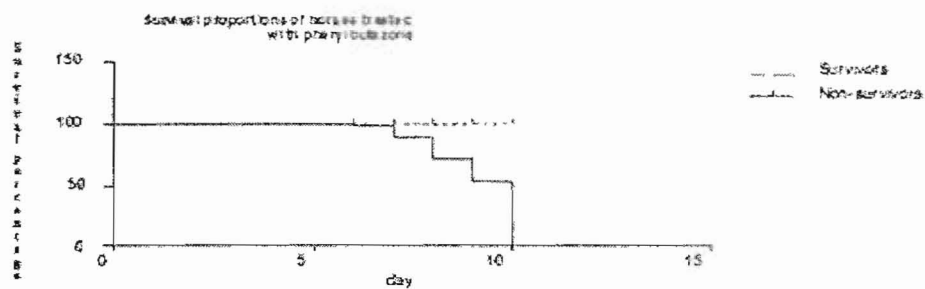|	Appetite	Visible color of mucous membrane	Severity of Abdominal pain	Abdominal auscultation Cecum/colon
Survivors (*n* = 25)	Inappetence (13/25) Anorexia (12/25)	Pale (18/25) Rosy red (7/25)	Mild intermittent	Hypomotile (15/25) Stasis (10/25)
Nonsurvivors (n=15)	Anorexia	Pale (9/15) Icteric (6/15)	Mild intermittent (10/15) Moderate (5/15)	stasis stasis

Fig.-(1)Survival percentage curve of investigated horses.
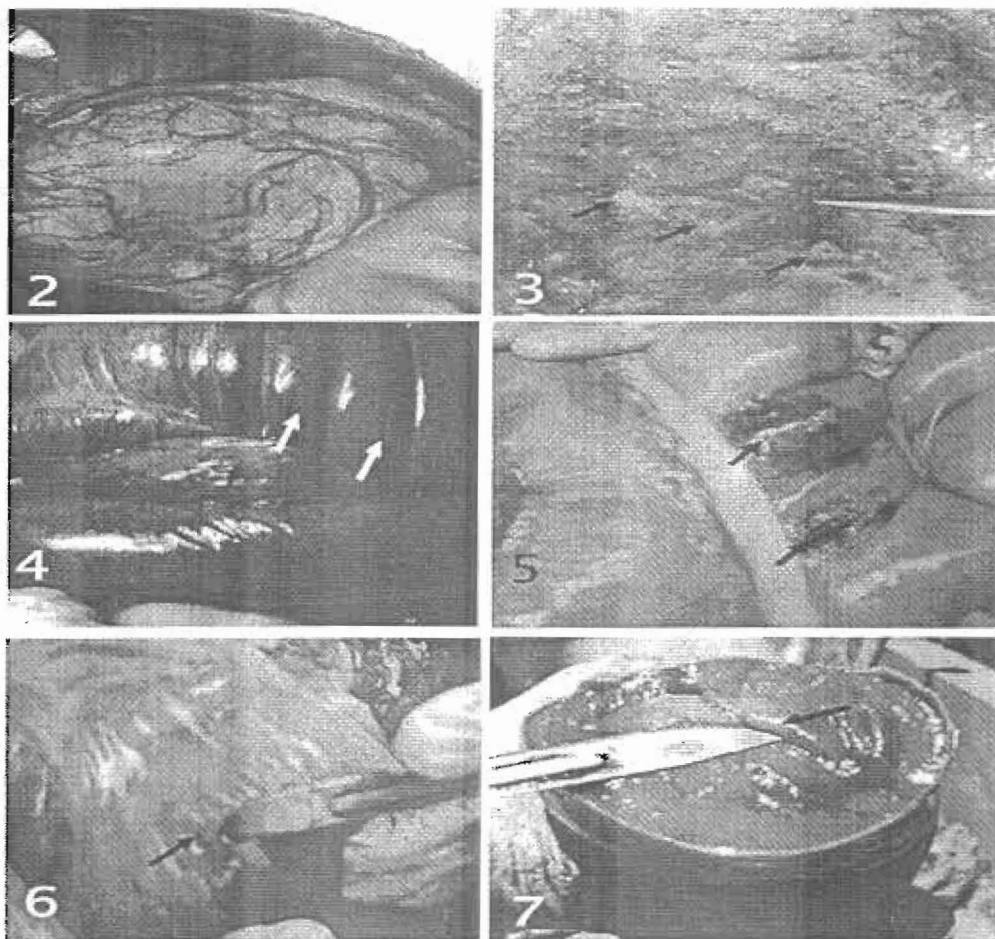
Figs. 2-7, gp.2, fig.2. Severely congested gastric serrosa. 3-Congested and ulcerated (arrow) gastric mucosa. 4. Congestion, hemorrhage and ulceration along the whole RDC-serosa. 5-*Large colon* with multiple circumscribed ulcerations and hemorrhages (arrows). 6-Heart with congested adipose tissue of the coronary grooves (arrow). 7-Congestion and hemorrhagic renal cortex and medulla (arrow).
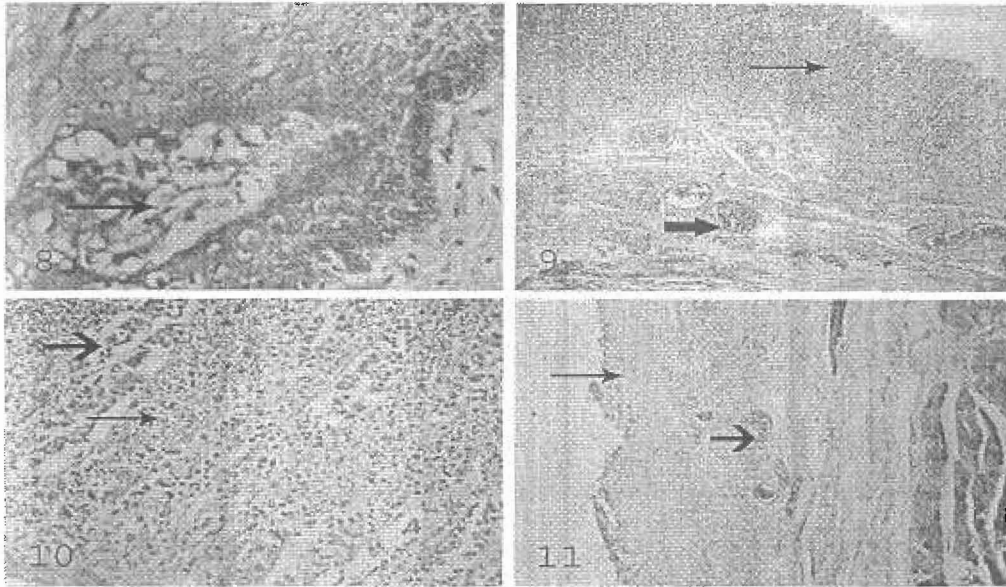
Figs 8-11: gp.2, fig 8: Nonglandular gastric mucosa showing spongiosis and vesiculation (arrow). (H&E., x520). Fig 9: Glandular gastric mucosa showing necrotic glandular epithelium (thin arrow) and thrombotic submucosa (thick arrow). (H&E., x300). Fig 10: High power for fig 9 to show coagulative necrosis of gastric glands(thick arrow) besides congestion and hemorrhages(thin arrow). (H&E., x520) Fig 11: Glandular stomach showing diffusely necrotic gastric mucosa (Thin arrow) and thrombosed submucosa (thick arrow). (H&E., x130).
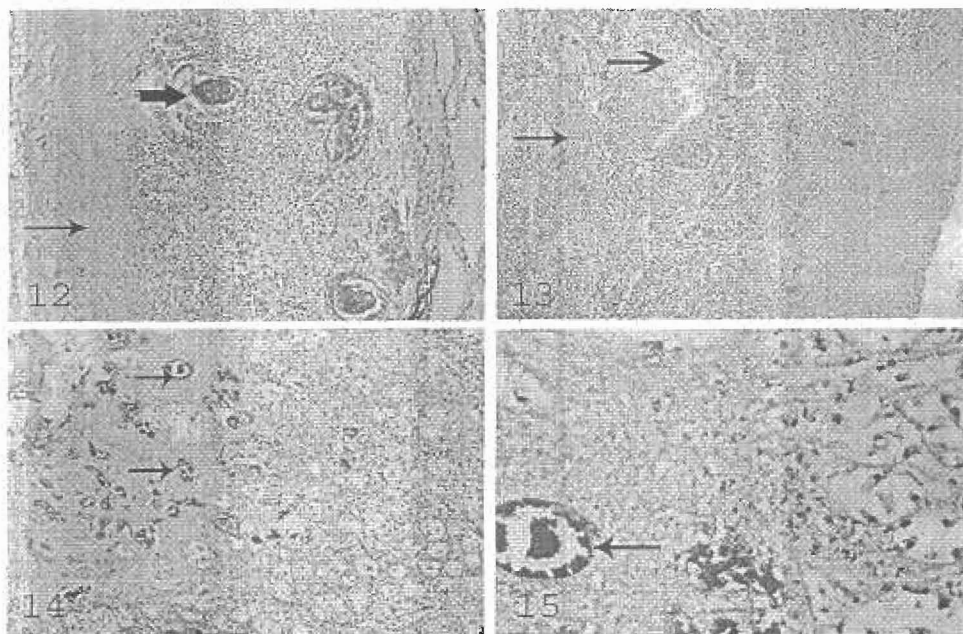

Figs 12-15: gp 2, fig 12: High power for fig. 11 to show necrotic mucosa (thin arrow) , besides round cell infiltration and thrombotic submucosa. (H&E., x520) Fig 13: Glandular gastric mucosa infiltrated with round cells and thorombotic submucosa. (H&E., x300). Fig 14: Necrotic and focally calcified gastric mucosa. (H&E., x300). Fig 15: Magnification of fig. 14 to show necrotic and calcified gastric glands. (H&E., x520)
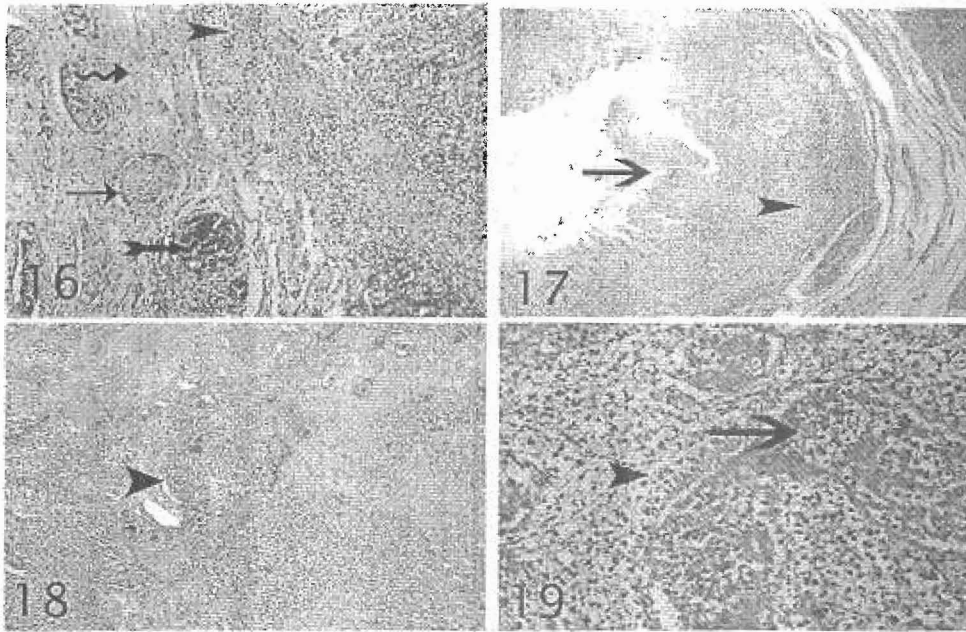
Figs 16-19: gp. 2, fig 16: Glandular gastric mucosa showing serofibrinous inflammation (arrowhead and corrugated arrow) and congested submucosa (arrrow) besides thrombosis (bitailed arrow). (H&E., x300). Fig 17: RDC showing necrotic mucosa (arrow), besides mucosal round cell infiltration and edema (arrowhead). (H&E., x130). Fig 18: RDC-mucosa showing recent thrombus (arrowhead) and round cell infiltration. (H&E., x300). Fig 19: High power of fig. 18 to show recent thrombus (arrow) and round cells infiltration (arrowhead). (H&E., x520)
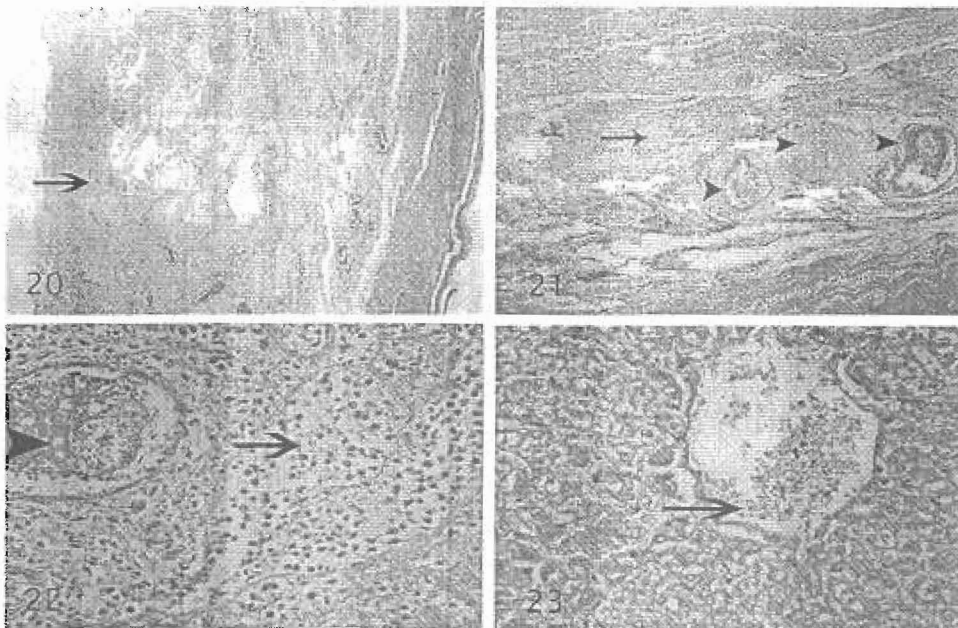
Figs 20-23: gp. 2, fig 20: RDC showing necrotic mucosa (arrow). (H&E., x130). Fig 21: RDC- mucosa showing serofibrinous inflammation (arrow) and congested blood vessels, besides thrombosis (arrowheads). (H&E., x300). Fig 22: Magnification of fig. 21 to show recent thrombus (arrowhead) and mucosal round cell infiltration (arrow). (H&E., x520) Fig 23: Liver showing congested central vein and hepatic sinusoids. (H&E., x520).
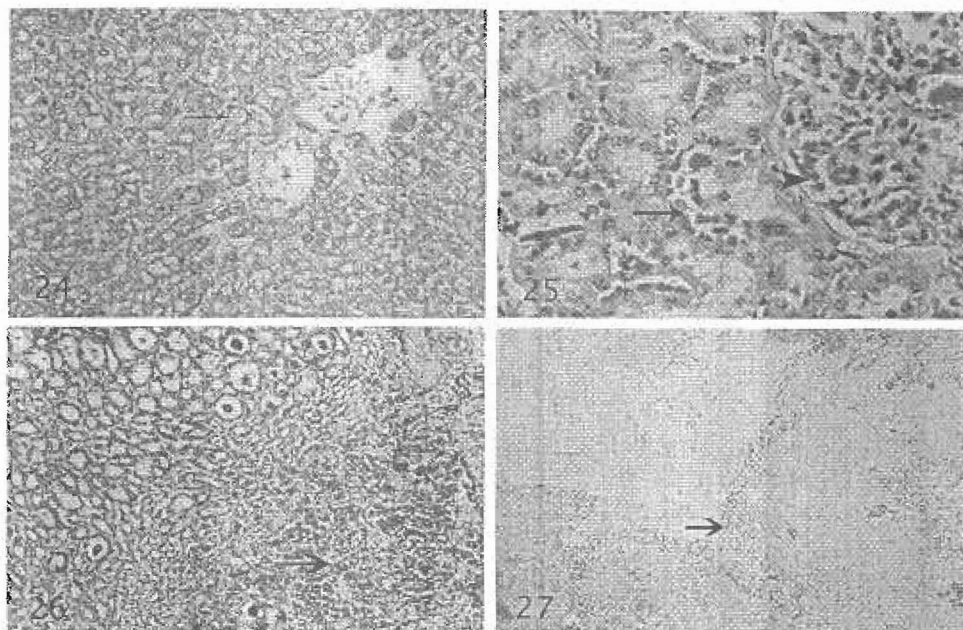
Figs 24-27: gp. 2, Fig 24: Vacuolated hepatocytes. (H&E., x520). Fig 25: Congested intertubular capillaries (arrows) and glomerular tufts. (H&E., x520). Fig 26: Renal medullary hemorrhage (arrow). (H&E., x300). Fig. 27: Renal papillary necrosis (arrow). (H&E., x130).
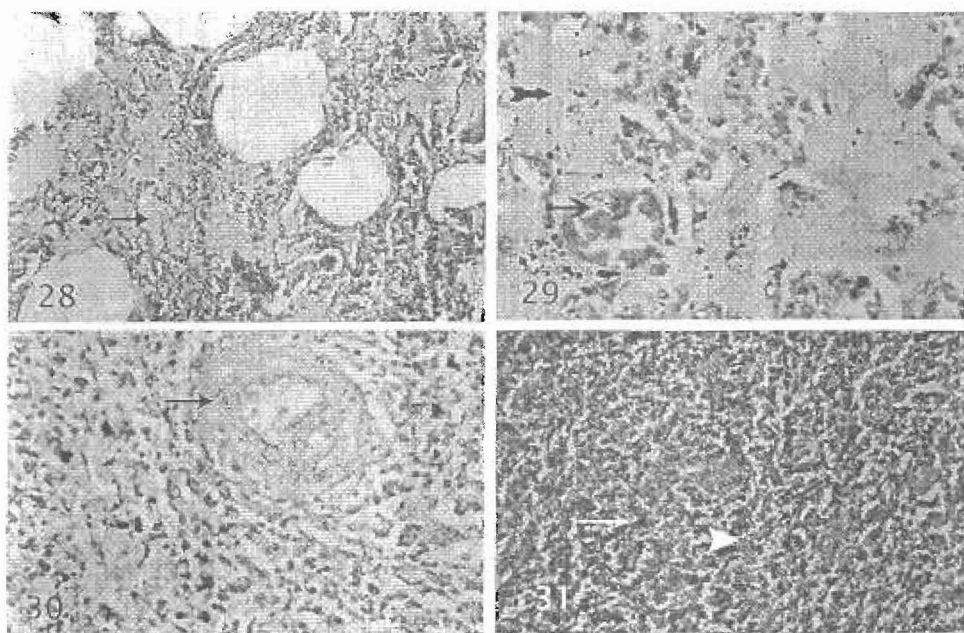
Figs 28-31: gp. 2, fig 28: Lung showing passive congestion and compensatory focal alveolar emphysema. (H&E., x300). Fig 29: Magnification of fig. 28 to show pulmonary alveoli filled with pale eosinophilic fluid (bitailed arrow) besides congested blood vessels(arrow) and dark brown pigments. (H&E., x520) Fig 30: Hyalinized splenic arterial wall (arrow) and depleted white pulp. (H&E., x520) Fig 31: Spleen showing congested red pulp (arrowhead) and hemosiderosis (arrow). (H&E., x520)

Blood profile

Table 3 shows the hematological parameters(RBC and WBC-counts, besides PCV- value). Gps. 1&2 suffered anemia (6.71 ± 0.70 and 5.53 ± 0.78 respectively). Moreover, PCV % was significantly decreased in gp.1 (27.00 ± 4.21) and gp.2 (25.00 ± 2.32).Gp. 1 showed a significant increase in the total leukocytic counts (10.17 ± 1.26 x 103) with insignificant change in the differential leukocytic counts. Gp. 2 exhibited leukopenia (5.71 ± 1.44 x 103) with significant increase in the band cells % (4.54 ± 1.29).

Biochemical profile

Gps. 1&2 showed a significantly increased activities of AST, GGT and SD (P < 0.05) when compared with the control group (Table 4). Meanwhile, the AST activity differed significantly between gp 1 (١٩٤,٩٨ ± 12.65) and gp.2 (221.17±27.68). Moreover, urea and creatinine levels were significantly increased in gp. 2 when compared with gp. 3. Moreover the MDA, NO and uric acid were significantly increased (P<0.05) in gps.(1&2). On the other hand, the SOD and GSH were significantly decreased in gp. 2when compared with gps. 1&3 as shown in table 5.

Table 3. Total erythrocytic counts ($\times 10^6$), packed cell volume (PCV %), total and differential leukocytic count (mean values ± SD) in clinically healthy draft horses and in those treated with phenylbutazone.

		Gp.(3),control (n = 15)	Gp.1(survived) (n = 25)	Gp.(2)non-survived (n = 15)
Total Erythrocytic Counts	$X10^6$	9.80 ± 1.73^a	6.71 ± 0.70^b	5.53 ± 0.78^c
PCV	%	34.7 ± 2.31^a	27.00 ± 4.21^b	25.00 ± 2.32^b
TLC	$X10^3$	8.80 ± 1.57^a	10.17 ± 1.26^b	5.71 ± 1.44^c
Neutrophils	%	49.90 ± 9.94^a	53.80 ± 4.98^a	48.36 ± 3.35^a
Band Cells	%	0.00^a	0.00^a	4.54 ± 1.29^b
Lymphocytes	%	47.50 ± 9.42^a	45.55 ± 4.71^a	45.63 ± 1.56^a
Eosinophils	%	0.56 ± 0.43^a	0.55 ± 0.32^a	0.54 ± 0.31^a
Monocytes	%	1.50 ± 0.80^a	1.20 ± 0.91^a	1.00 ± 0.63^a

[a, b, c]: Variables with different superscript in the same raw are significantly different at p < 0.05

Table 4. AST (IU/L), GGT (IU/L), SD (IU/L) (mean values ± SD) in clinically healthy draft horses and in those treated with phenylbutazone.

	AST (IU/L)	GGT (IU/L)	SD (IU/L)
Control (n = 15)	177.24 ± 11.84^a	10.52 ± 1.02^a	18.78 ± 1.49^a
Survivors (n = 25)	194.98 ± 12.65^b	24.24 ± 5.26^b	31.30 ± 4.67^b
Non-survivors (n = 15)	221.17 ± 27.68^c	25.67 ± 5.34^b	36.44 ± 13.06^b

[a, b, c]: Variables with different superscript in the same column are significantly different at p < 0.05

Table 5. Oxidative stress markers and anti-oxidant parameters (mean values ± SD) in clinically healthy draft horses and in those treated with phenylbutazone.

	MDA (μmol/L)	SOD (u/ml)	Uric acid (mg/dl)	GHS (mg/dL)	NO (μmol/L)
Control (n = 15)	3.40 ± 1.17[a]	3015 ± 600[a]	0.08 ± 0.04[a]	4.24 ± 0.66[a]	6.66 ± 0.43[a]
Survived (n = 25)	12.40 ± 5.27[b]	٢٢٩٤ ± 359[b]	0.83 ± 0.52[a]	2.95 ± 0.57[b]	3.94 ± 0.70[b]
Non-survived (n = 15)	15.50 ±11.37[b]	٥٠٤٥ ± 3205[b]	3.47 ± 1.5[b]	2.60 ± 0.51[b]	3.00 ± 0.41[c]

[a, b, c]: Variables with different superscript in the same column are significantly different at p < 0.05

DISCUSSION

The present study was designed to determine the pathogenesis, pathological changes and laboratory finding particularly oxidative stress in draft horse associated with PBZ administration. The administration of PBZ is very common in equine medicine. However, clinical findings due to its toxicity have been well documented in horses, after either oral or intravenous administration *(13, 23,24)*. PBZ has a narrow therapeutic index in the horse. If the administered dose is greater than recommended by the manufacturer, toxic effects may be produced, especially if high dose is maintained for more than a few days **(5)**. In the present study, the estimated doses of PBZ required to produce toxicity under field conditions were 4.90 ± 1.37 and 9.40 ± 2.54 mg/kg B.W/day for 5.80 ± 1.03 and 4.70 ± 0.67 (days) in survivor and non-survivor horses, respectively. Nearly similar results were previously obtained *(25-28)*.

Depressed appetite (13/25) to anorexia (12/25), were recorded in gp. 1, whereas, gp. 2 showed anorexia (n = 15). The changes in appetite could be attributed to pain which caused an inhibitory effect on the gastrointestinal motility *(29)*. Depression, melena, diarrhea, weight loss, ventral abdominal edema and death were also recorded. The melena and diarrhea could be attributed to gastrointestinal ulceration and hemorrhage. Moreover, the ventral abdominal edema could be due to anemia and hypoproteinemia associated with intestinal hemorrhage. Such clinical findings are in agreement with previous work *(8, 23, 27, 30)*.

The visible mucous membranes, in the affected horses, were pale in the survivors(18/25) and nonsurvivors (9/15); however, icteric mucous membranes were found in the nonsurvivors(6/15). The pale colored mucous membranes could be attributed to anemia resulting from blood losses through the ulcerated gastric mucosa and right dorsal colon *(31,30)* whereas, the icteric mucosa could result from anorexia and liver damage *(32,33)*.

The development of gastric ulceration is a common finding of NSAID toxicity, specially when administered orally *(10, 25,27)*. The ulcerogenic effect of PBZ in the gastric glandular mucosa is related to systemic and local effects *(13)*. The systemic effect is induced with overdoses, and it is mediated by nonspecific COX inhibition. The local effect is unrelated to COX inhibition and it is specially induced when the oral route is used, because of the rapid diffusion of NSAIDs into mucosal cells, inside which they stay trapped and lead to damage of the surface epithelial cells *(34, 35)*. The current study showed degenerative changes in the nonglandular stomach with infiltration of the lamina propria with inflammatory cells. The glandular portion showed eroded and ulcerated mucosa, besides serofibrinous inflammation and thrombosis. Moreover, The ulcers and erosions could be induced by thrombosis of the microcirculation. Our results are in line with others *(28)* who recorded that PBZ initially causes a microvascular ultrastructural lesion characterized by swelling, lysis, and necrosis of the microvascular endothelial cells. Damage to the endothelium results in micro-hemorrhage,

stasis, and thrombosis. Necrosis and sloughing of the surrounding tissue follows swelling and lyses of the endothelial lining of the capillaries and postcapillary venules of lamina propria of glandular stomach. Diffuse typhlo-colitis with mononuclear cell infiltration and vasculitis with fibrinoid necrosis were induced in horses with phenylbutazone toxicity *(8, 9, 26, 28)*. Our results showed similar lesions represented by superficial and deep ulceration, besides hemorrhages, fibrinous inflammation and diffuse leukocytic infiltration. Moreover, the gastrointestinal mucosal injury by phenylbutazone has been attributed to reduced mucus and/or bicarbonate production,besides ischemia due to thromboses and neutrophil plugging of capillaries together with impaired healing *(8,36)*.

The AST, GGT and SD activities were significantly increased in gps 1&2 when compared with the control group. Such increase of liver enzyme-activities could result from hepatic injury, indicating hepatic oxidative damage caused by phenylbutazone toxicity *(37)*.

The MDA and SOD levels were significantly increased in gp. 1 when compared with the control group. Such increase in MDA levels could be attributed to oxidative damage resulting from free radical production *(38, 39)*. On the other hand, the increased values of SOD could be attributed to the compensatory response against the increased oxidative stress to counteract the effect of free radicals. These findings are in agreement with previous investigations *(40, 41)* and disagree with others *(42, 43)* who found decreased erythrocytic SOD activity in rats exposed to oxidative stress by NSAID treatment.

The reduced glutathione (GSH) level was insignificantly decreased in gps 1&2 when compared with the control group. This finding is in accordance with previous studies *(42, 44)* who described biphasic response of GSH to oxidant injury. The GSH was initially decreased as the available GSH was oxidized followed by an increase as hepatic stores are mobilized. Depletion of GSH precedes cell injury by several toxic oxidants and oxidative stress.

Nitric Oxide levels showed a significant decrease in gp. (1)- when compared with the control. Such decrease in NO levels could be attributed to the decreased antioxidant defenses by increased oxidative stress induced with NSAID treatment *(45)*. This finding is in concurrence with others *(46)*.

Conclusion and Clinical Relevance

It could be concluded that dosing of phenylbutazone should follow the instructions when treating horses with orthopedic diseases. Owners should be aware of the drug side-effects, even when given according to the instructions. Other factors, particularly dehydration, should alert the veterinarians to be especially cautious about administration of even low doses of phenylbutazone. Moreover, antioxidants may be used as ancillary treatment in cases with right dorsal colitis caused by phenylbutazone administration as oxidative stress was documented in such clinical conditions.

REFERENCES

1. *Higgins AJ and Lees P (1984):* The acute inflammatory process, arachidonic acid metabolism and the mode of action of anti-inflammatory drugs. Equine Vet J.; 16: 140–141

2. *O'Banion MK, Sadowski HB and Winn VA (1991):* serum and glucocorticoid-regulated n4-kilobase mRNA encodes a cyclooxygenase related protein. J Biol. Chem.; 266: 23261–23267.

3. *Caron JP (2000):* Non-steroidal Anti-inflammatory Drugs. In depth medication. Reprinted in the IVIS website with the permission of AAEP.; 46: 243-249

4. *Owens JG, Kamerling SG, Stanton SR (1996):* Effects of pretreatment with ketoprofen and phenylbutazone on experimentally induced synovitis in horses. Am J Vet Res; 57: 866–874

5. *Tobin T, Chay S, Kamerling S, Woods W, Weckman T, and Lees P (2008):* Phenylbutazone in the horse: a review . Journal of Veterinary Pharmacology and Therapeutics; 9: 1 - 25

6. **Lees MS (1996):** Nonsteroidal anti-inflammatory drugs. In: McIlwraith CW, 3rd ed. Joint Disease in the Horse. Philadelphia: W.B. Saunders; 223–237

7. **Baker CK (2005):** NSAIDS in Equine Medicine. The North American Veterinary Conference, Orlando, Florida. Published in IVIS with the permission of the NAVC: 206-208

8. **McCcnnico RS, Morgan TW, Williams CC, Hubert JD and Moore RM (2008):** Pathophysiologic effects of phenylbutazone on the right dorsal colon in horses. Am J Vet Res.; 69: 1496-1505.

9. **Hough M, Steel CM, Bolton JR, Yovich, JV (1999):** Ulceration and stricture of the right dorsal colon after phenylbutazone administration in four horses. Australian Veterinary Journal; 77: 785–788.

10. **Monreal L, Sabate D, Segura D, Mayos I and Homedes J (2004):** Lower gastric ulcerogenic effect of suxibuzone compared to phenylbutazone when administered orally to horses. Research in Veterinary Science; 76: 145–149

11. **Martineau H, Thompson H and Taylor D (2009):** Pathology of gastritis and gastric ulceration in the horse. Part 1: range of lesions present in 21 mature individuals. Equine Vet J.; 41: 638-44.

12. **Jones SL (2006):** Update on Anti-inflammatory Therapy. In: NAVA Proceeding, North American Veterinary Conference. Publisher: NAVC.

13. **Snow DH (1987):** Phenylbutazone toxicity. In: Robinson, N.E., Current Therapy In Equine Medicine, 2nd Ed . W.B. Saunders Co, Philadelphia, pp. 118–119.

14. **Karcher LF, Dill SG, Anderson WI and King JM (1990):** Right dorsal colitis. Journal of Veterinary Internal Medicine; 4: 247–253

15. **Keegan K, Messer N, Wilson D and Kramer J (2008):** Effectiveness of administration of phenylbutazone alone or concurrent administration of phenylbutazone

and flunixin meglumine to alleviate lameness in horses. American Journal of Veterinary Research, 69: 167-173.

16. **McCarthy DM (1995):** Mechanisms of mucosal injury and healing: the role of nonsteroidal anti-inflammatory drugs. Scand. J. Gastroenterol.; 30: 24- 29

17. **Cohen, ND (2002):** Right dorsal colitis. Equine Vet Educ.; 14: 212-219.

18. **Jones SL and Spier SJ (1998):** Pathophysiology of colonic inflammation and diarrhea, In: Equine Internal Medicine Philadelphia, WB Saunders: 660- 663

19. **Coles EH (1986):** Veterinary Clinical Pathology. 4th Ed., W.B Saunders company, Philadelphia, London and Toronto.

20. **Tayler FG and Hillyer MH (1997):** Diagnostic Techniques in Equine Medicine. WB Saunders Company Ltd. London, Philadelphia, Toronto, Sydney and Tokyo: 191-200

21. **Bancroff JP, Stevenes A and Turner DR (1990):** Theory and Practice of histopathological techniques 3rd ed. Clurcchill, Livingston, Edinburgh, London.

22. **Ihler CF, Larsen JV and Eystein S (2004):** Evaluation of clinical and laboratory variables as prognostic indicators in hospitalized gastrointestinal colic horses. Acta. Vet. Scand.; 45: 109-118

23. **MacAllister C , Morgan J, and Pollet A (1993):** Comparison of adverse effects of phenylbutazone, flunixin meglumine, and ketoprofen in horses. J. Am. Vet. Med. Assoc.; 1: 71-73

24. **Goodrich LR, Furr MO, Robertson JL, Warnick LD (1998):** A toxicity study of eltenac, a nonsteroidal anti-inflammatory drug, in horses. J Vet Pharmacol. Ther.; 2: 24-33.

25. **Snow DH, Douglas TA, Thompson H, Parkins JJ and Holmes PH (1981):** Phenylbutazone toxicosis in equidae: A biochemical and pathophysiological study. Am. J. Vet. Res.; 42: 1754-1759

26. **MacKay JR, French TW Nguyen HT and Mayhew GI (1983):** Effects of large doses of phenylbutazone administration to horses. Am. J. Vet Res.; 5: 774-780

27. **Collines LG and Tyler DE (1984):** Phenylbutazone toxicosis in the horse: a clinical study.J. Am. Vet. Med. Assoc.; 6: 699-703.

28. **Meschter CL, Gilbert M, Krook L, Maylin G and Corradino R (1990):** The effects of phenylbutazone on the intestinal mucosa of the horse: a morphological, ultrasructural and biochemical study. Equine Veterinary Journal.; 22: 255-263

29. **Radostits OM, Gay CC, Hinchliff K W, Constable PD (2007):** Veterinary Medicine. A textbook of the diseases of cattle, horses, sheep, pigs and goats 10th Ed. Saunders El Sevier printed in Spain.

30. **Cohen ND (2003):** Right Dorsal Colitis in Horses In: 8th Congress on Equine Medicine and Surgery. Publisher: International Veterinary Information Service, Ithaca, New York, USA.

31. **Davis EG (2005):** Right Dorsal Colitis and Dietary Management. Manhattan, Kansas Proceeding of the NAVC. North American Veterinary Conference, Orlando, Florida: 8-12.

32. **Kaneko JJ (1997):** Clinical Biochemistry of Domestic Animals 5th Ed. Academic press , U. S.A.

33. **Susan CE and Denise IB (1997):** Laboratory profiles of equine diseases. Department of Large Animal Medicine and Pathology. College of Vet. Med. University of Georgia, Athens, Georgia.

34. **Scheiman JM (1994):** NSAID-induced peptic ulcer disease: a critical review of pathogenesis and management. Dig Dis; 2: 210-22.

35. **Rodriguez-Tellez, M, Arguelles, F, Herrer_ias Jr, J.M., Ledro, D. (2001):** Antiinflamatory agents less dangerous for gastrointestinal tract. Curr Pharm Des.;7: 951-76.

36. **Wallace JL (1997):** Nonsteroidal anti-inflammatory drugs and gastroenteropathy: the second hundred years. Gastroenterology; 112: 1000

37. **Ellison RS, Jacobs RM (1990):** The isoelectric focusing properties of serum alkaline phosphatase in disease and following prednisolone and phenylbutazone administration in the horse. Can J Vet Res.; 54: 126-31.

38. **Williams CA, Kronfeld DS, Hess TM, Saker KE, Waldron JE, Crandell KM and Harri PA (2005):** Comparison of oxidative stress and antioxidant status in endurance horses in three 80 km races. Equine Comparative Exercise and Physiology; 2: 153–157.

39. **Azzi A (2007):** Oxidative stress: A dead end or a laboratory hypothesis. Biochemical and Biophysical Research Communications; 362, 230–232

40. **Frankiewicz-Jozko and Szarska E (2000):** Anti-oxidant level to exercise in the blood of endurance horses. Biology of Sport.; 17: 217–227

41. **Afanas IB (2006):** Competition between superoxide and hydrogen peroxide signaling in heterolytic enzymatic processes. Medical Hypotheses; 66: 1125–1128

42. **De Moffarts B, Kirschvink N, Art T, Pincemail J and Lekeux P (2005):** Assessment of the oxidant-antioxidant blood balance in a field exercise test in Standardbred and eventing horses. Equine and Comparative Exercise Physiology; 2: 253-261

43. **Odabasoglu F, Cakir A, Suleyman H, Aslan A, Bayir Y, Halici M, Kazaz C (2006):** Gastroprotective and antioxidant effects of usnic acid on indomethacin-induced gastric ulcer in rats. J Ethnopharmacol.; 3: 59-65

44. **Marlin DJ, Fenn K, Smith N, Deaton CD, Roberts CA, Harris PA, Dunster C and Kelly FJ (2002):** Changes in circulatory antioxidant status in horses during prolonged

exercise. The Journal of Nutrition; 132: 1622–1627

45. *Motawi TK, Abd Elgawad HM, Shahin NN (2008):* Gastroprotective effect of leptin in indomethacin-induced gastric injury. J Biomed Sci.;15(3):405-12.

46. *Sala R, Moriggi E, Corvasce G and Morelli D (1993):* Protection by N-acetylcysteine against pulmonary endothelial cell damage induced by oxidant injury. European Respiratory Journal.; 6: 440 – 446.

الملخص العربى

دراسات باثولوجية وبيوكيميانية على التأثير السيئ لاستخدام الفينايل بيوتازون في خيول الجر

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تمت هذه الدراسة على عدد (٤٠) من خيول الجر فى الفترة بين أكتوبر ٢٠٠٦ إلى أكتوبر ٢٠٠٨ م تراوحت أعمارها بين سنة وأربع سنوات كانت جميعا تعانى من العرج والتهابات المفاصل والتهابات الحافر والالتهاب العضلي وكانت السمة المشتركة بين هذه الخيول هو تلقيها لجرعات عالية من الفينايل بيوتازون كمضاد للالتهاب لفترات طويلة مما أدى إلى ظهور علامات المغص المتقطع وفقدان الشهية ونقص حاد في الوزن القائم واسهالات وتورم أسفل البطن وحول السرة بالإضافة إلى تلون البراز باللون الأسود .

تم فحص هذه الخيول إكلينيكيا ومعمليا وإجراء الصفة التشريحية بعد النفوق لهذه الخيول لدراسة وإيضاح مدى تأثر هذه الخيول إكلينيكيا ومعمليا بهذه الجرعات العالية من الفينايل بيوتازون وأيضا دراسة العلاقة بين الشوارد الحرة ومضادات الأكسدة في مثل هذه الحالات . هذا بالإضافة إلى عدد (١٥) من خيول الجر السليمة ظاهريا تم اختيارها عشوائيا واعتبرت كمجموعة ضابطة .

خلصت هذه الدراسة إلى أن الجرعات العالية من الفينايل بيوتازون ولفترات طويلة قد تؤدى إلى تقرحات متعددة في الجهاز الهضمي وبخاصة المعدة والاثنى عشر والأعور والقولون الكبير هذا بالإضافة إلى فشل في وظائف الكبد والكلى واحتقان عام في كافة أعضاء الحيوان وزيادة نسبة الشوارد الحرة ونقص حاد فى مضادات الأكسدة مما يؤدى إلى تلف الأنسجة ونفوق هذه الخيول لذا توصى الدراسة بإتباع الجرعات المقررة من قبل الشركات المنتجة أو باستخدام مضادات الالتهابات المضادة لـ COX2 تفاديا للآثار الجانبية التي تحدثها مضادات الالتهابات التي تؤثر على كلا من COX1, COX2.