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Evaluation of clinical and laboratory variables as diagnostic indicators of phenylbutazone toxicity in Egyptian draft horses

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SUMMARY

To the best of the author's knowledge, this is the first report describing the diagnostic significance of clinical as well as various biochemical variables to predict the clinical outcome of phenylbutazone **(PBZ)** toxicity in Egyptian draft horses. Horses with PBZ toxicity were tentatively diagnosed based on competent case history and physical examination findings as well and post-mortem findings in non-survived cases. According to the clinical outcome, diseased horses were categorized into survivors (n = 21) and non-survivors (n = 17). Clinically, there was a significant association between non-survivors and anorexia ($p < 0.01$), stasis of intestinal motility ($p < 0.01$), melena ($p < 0.01$), and diarrhoea ($p < 0.001$). Biochemically, malondialdehyde **(MDA)**, nitric oxide **(NO)**, aspartate amino transferase **(AST)**, gamma glutamyl transferase **(GGT)**, sorbitol dehydrogenase **(SD)**, total bilirubin, urea and creatinine showed a significant increase ($p < 0.05$) in non-survivors compared to survivors; meanwhile, superoxide dismutase activities **(SOD)**, total plasma protein and albumin levels were significantly decreased ($p < 0.05$). To predict the clinical outcome of PBZ toxicity in examined horses, receiver operating characteristic curve **(ROC)** was applied for all tested biochemical variables. Analysis of **ROC** curve showed high sensitivity and specificity of total leucocytic count **(TLC)**, neutrophils, band cells as well as blood urea, creatinine, total plasma protein, AST, MDA, NO, SOD and vitamin C **(Vit. C)** levels. It could be concluded that clinical and biochemical investigations could provide valuable diagnostic information about the adverse effects of PBZ in draft horses. Our findings

also suggest that estimation of these biochemical variables might help predict the outcomes of PBZ toxicity in Egyptian draft horses.

Keywords: Phenylbutazone toxicity; Clinical; Laboratory; Horses; Diagnosis.

INTRODUCTION

Non-steroidal anti-inflammatory medications (NSAIDs) are a class of agents best recognized for anti-inflammatory and analgesic (pain suppression) properties. An important clinical use of this class of medication is to improve patient status and minimize pain. (Higgins and Lees, 1984; O'Banion et al. 1991 and Caron, 2000). Most non-steroidal anti-inflammatory drugs are inhibitors of one or more of the cyclooxygenase enzymes. In general, it has been shown that COX-1 is responsible for producing prostaglandins that regulate normal body functions such as protection of the gastrointestinal tract from injury, whereas COX-2 is typically not present in most tissues, including the gut and joints, unless there is inflammation. Today, most COX inhibitors, including PBZ, are non-selective COX inhibitors meaning that they inhibit both COX-1 and COX-2 at therapeutic concentrations achieved in patients (Jones, 2006). Although PBZ is one of the most popular and economical agent used in horses and its clinical efficacy appears to compare favourably with other NSAIDs (Owens et al 1996), its clearance from acidic (inflamed) tissues is slower than plasma elimination, indicating that its therapeutic effects may persist in tissues after plasma levels have decreased to negligible levels (Lees, 1996). Despite its beneficial effects for many disease conditions, its overuse and misuse can results in deleterious findings and a high incidence of side effects (Baker, 2005). Its common side effects include gastric and colonic ulceration and renal failure even when used at appropriate doses (Lees, 1996). The risk of gastric and colonic ulceration or renal failure is exacerbated in dehydrated or hypovolemic horses, horses with hypotensive shock, or those with pre-existing gastrointestinal or renal injury (Kallings, 1993; Baker, 2005; Jones, 2006). To our knowledge, the diagnostic importance of clinical as well as laboratory variables in horses with PBZ toxicity has not been previously discussed. Therefore, the present study was carried out to assess the diagnostic significance of clinical as well as various biochemical variables to predict the clinical outcome of PBZ toxicity in Egyptian draft horses under the field condition.

MATERIALS AND METHODS

Animals and Medical Records

Medical records of thirty eight Egyptian draft horses (twenty six females; twelve

males), at 3-4 years of age were retrospectively reviewed. All horses had a history of musculo-skeletal painful conditions and were treated with variable daily doses of injectible PBZ. Foals less than two years of age and adult horses received NSAIDs other than PBZ were excluded from the study. On admission, clinical signs of intermittent colic, poor appetite, progressive weight loss, melena, ventral oedema and diarrhoea were considered as the chief complaints. Complete medical record for each horse was recorded depending on the competent history and clinical signs. Sufficient follow-up information was defined as at least one clinical examination or contact with owners or referring veterinarians regarding the status of the horses after the completion of a prescribed course of treatment. The clinical study was performed at The Veterinary Teaching Hospital, Faculty of Veterinary Medicine, Mansoura University, Mansoura, Egypt between October 2006 and March 2009. Cases were either admitted directly to the hospital or from referring veterinarians. Final diagnosis of such clinical cases was achieved by competent case history, clinical findings, laboratory investigations and results of post-mortem finding. According to the clinical outcome, horses with PBZ toxicity were categorized into survivors (n = 21) and non-survivors (n = 17). For comparison, fifteen apparently health Egyptian draft horses of both sexes (ten females and five males) were randomly selected and considered as a control group.

Blood Samples and laboratory analysis

Two blood samples (ten ml for each) were collected via jugular vein puncture from each horse; the first blood sample was added to 5mg of sodium ethylene diamine tetra acetic acid (EDTA) as anticoagulant for haematological examination (Feildman et al., 2000), whereas the second blood sample was collected into heparinised syringe. After collection, the blood sample was immediately centrifuged at 2500 x g for 5 minutes for separation of blood plasma and red blood cells (RBCs). RBCs were washed with ice-cold saline solution and divided into aliquots. RBCs and plasma aliquots were then frozen and stored at -20 °C until further analysis. RBCs hemolysate were used for SOD estimation, whereas plasma aliquots were used for biochemical analyses of AST, GGT, SD, total bilirubin, MDA, activity of reduced glutathione (GSH), Vit. C, NO, total protein, albumin, urea and creatinine. Biochemical variables were spectrophotometrically measured using commercial test kits according to the standard protocols of the suppliers. For AST, GGT, SD, total bilirubin, commercial test kits supplied by Randox (Randox Laboratories Ltd, UK) were used. However, for MDA, SOD, GSH, Vit. C and NO, commercial test kits supplied by Bio Diagnostic (Bio Diagnostic, Cairo, Egypt) were used. But, commercial test kits supplied

by Spinreact (Spinreact, Barcelona, Spain) were used for measurement of total protein, albumin, urea and creatinine.

Treatment trials

Horses with PBZ toxicity were initially managed by discontinuation of PBZ administration and dietary modification to easily laxative food (bran mashes). For each case, the following drugs were administered; Sucralfait (Gastrofait; Egyptian International Pharmaceutical Company, Egypt) at a dose rate of 20 mg kg^{-1} orally, Ranitidine (Ranitidine; Medical Union pharmaceutical company, Egypt) at a dose rate of 1.5 mg kg^{-1} intravenously twice daily and also orally at a dose rate of 6.6 mg kg^{-1} q 8 hours, Metronidazole (Flagyl; Alexanderia Company for Chemical and Pharmaceutical) at a dose rate of 15 mg kg^{-1} orally twice daily; Al/Mg hydroxide (Mucogel; Egyptian Pharmaceutical International Company, Egypt) at a dose rate of 0.5 mg kg^{-1} orally q 6 hours, and Xylazine (Xylaject; Egyptian company for chemical and pharmaceutical) at a dose rate of 1.0 mg kg^{-1} intravenously when needed to control abdominal pain. Fluid therapy was also given through I/V dribbling according to degree of dehydration.

Postmortem examination

Necropsy procedures were applied to non survived horses and post-mortem findings were recorded according to the method described by Bancroff et al. (1990).

Statistical analysis

Data were statistically analyzed using statistical software program (**Graph Pad prism version 5.0, Graph Pad software Inc., USA**). Chi-square (χ^2) analysis test was used to study the possible association between the survival and the variables of clinical findings. For those variables with more than two categories, chi-square for trend was used and the results were considered to be significant at $p < 0.05$. For haematological and biochemical parameters, data were tested for normality of distribution using D'Agostino and Pearson Omnibus normality test. Mean and standard deviation for each variable was estimated. Differences between groups were assessed by one-way ANOVA with *Duncan* test. ROC analysis was used to assess the sensitivity and specificity of estimated parameters to predict the clinical outcome of the affection under investigation. Differences were considered significant at p value ≤ 0.05.

RESULTS

The clinical and laboratory variables in horses with PBZ toxicity were summarized in Table 1, 2, 3, 4 and 5. Clinically, heart rate, respiratory rate and rectal temperature were elevated ($p < 0.05$) in non- survivors compared to survivors. Their values were (75.0 ± 7.2 vs. 60.8 ± 1.9 beat/min.), (18.6 ± 1.1 vs. 15.8 ± 0.8 cycle/min.), (39.3 ± 0.3 vs.

38.0 ± 0.6 C), respectively. Biochemically, MDA and NO levels showed a significant increase ($p < 0.05$) in non-survivors compared to survivors, whereas SOD activities showed a significant decrease ($p < 0.05$). GSH reduced and Vit. C showed a significant decrease ($p < 0.05$) in survivors and non survivors compared to control group (Table 2). Total plasma protein and albumin levels showed a significant decrease ($p < 0.05$) in non-survivors compared to survivors. However, there was a significant increase ($p < 0.05$) of plasma AST and SD activities as well as urea and creatinine ($p < 0.05$) levels in non-survivors compared to survivors (Table 3). Haematologically, total leucocytic count, neutrophils and lymphocytes were significantly decreased ($p < 0.05$) in non-survivors compared to survivors. However, band cells and monocytes showed a significant increase (Table 4). Additionally, total erythrocytic counts showed a significant decrease in survived and non survived horses compared to control group. Analysis of ROC curve showed high sensitivity and specificity of TLC, neutrophils, band cells as well as blood urea, creatinine, total plasma protein, AST, MDA, NO, SOD and vit. C levels to predict the clinical outcome of PBZ toxicity in diseased horses (Table 5).

Out of the 38 diseased horses, 17 died (12 females, 5 males). Post-mortem examinations showed hemorrhagic and ulcerative inflammation of the entire right dorsal colon and cecum with varying degrees in all cases (Figure 1A&B). Congestion with presence of non hemorrhagic ulcerations in the glandular portion of the stomach was also recorded (Figure 1C&D).

Table 1: Clinical findings of phenylbutazone toxicity in draft horses ($n = 38$).

Variable	Survivors ($n = 21$)	Non-survivors ($n = 17$)
Appetite		
Inappetance	11/21	0/17
Anorexia	10/21	17/17
Visible mucous membrane color		
Rosy red	5/21	0/17
Pale	16/21	10/17
Icteric	0/21	7/17
Severity of Abdominal pain		
Mild intermittent	21/21	10/17
Moderate	0/21	7/17
Abdominal auscultation Cecum/Colon		
Hypomotile	13/21	0/17
Stasis	8/21	17/17
Occult blood in the feces	1/21	17/17
Diarrhea	3/21	17/17
Weight loss	18/21	17/17
Ventral edema	19/21	17/17

Table 2: Oxidative stress level and anti-oxidant parameters (mean ± SD) in clinically healthy horses and in those with phenylbutazone toxicity ($n = 38$).

Groups	MDA (µmol/L)	NO (µmol/L)	SOD (x10³ IU/gHb)	GSH (mg/dL)	Vit. C (mg/L)
Control ($n = 15$)	3.4 ±1.1[a]	3.0 ±0.4[a]	2.80 ± 0.21[a]	4.2 ±0.6[a]	77.8 ± 2.5[a]
Survivors ($n = 21$)	11.9 ± 1.6[b]	3.9 ±0.7[b]	2.51 ± 0.13[b]	2.9 ±0.5[b]	64.8±2.2[b]
Non-survivors ($n = 17$)	15.3 ±0.9[c]	6.5 ±0.7[c]	2.16 ± 0.18[c]	2.6 ±0.5[b]	62.0 ±2.7[b]

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

Table 3: Mean values ± SD of some plasma biochemical variables in clinically healthy horses and those with phenylbutazone toxicity ($n = 38$).

Groups	Total protein (g/L)	Albumin (g/L)	AST (IU/L)	GGT (IU/L)	SD (IU/L)	T.Bilirubin (µmol/L)	Urea (mmol/L)	Creatinine (µmol/L)
Control ($n = 15$)	73.0 ± 4.74[a]	37.4 ± 3.2[a]	177.2 ± 11.8[a]	10.5 ± 1.0[a]	18.7 ± 1.4[a]	1.7 ± 0.0[a]	7.2 ± 1.0[a]	96.35 ± 16[a]
Survivors ($n = 21$)	58.0 ± 4.5[b]	26.3 ± 3.5[b]	194.9 ± 12.6[b]	24.2 ± 5.2[b]	31.3 ± 4.6[b]	8.8 ± 0.2[b]	8.2 ± 3.7[b]	141.4 ± 14[a]
Non-survivors ($n = 17$)	48.2 ± 5.8[c]	22.4 ± 5.9[c]	221.1 ± 13.6[c]	25.6 ± 5.3[b]	36.4 ± 5.0[c]	11.6 ± 0.3[b]	17.8 ±1.2[c]	247.5± 93.7[b]

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

Table 4: Mean values ± SD of haematological parameters in clinically healthy horses and those with phenylbutazone toxicity ($n = 38$).

Groups	Erythrocytes (x10⁶)	Leucocytes (x10³)	Neutrophils (Cell/µl) x10³	Band Cells (Cell/µl)	Lymphocytes (Cell/µl) x10³	Eosinophils (Cell/µl)	Monocytes (Cell/µl)
Control ($n = 15$)	9.8 ± 1.7[a]	8.8 ± 1.5[a]	4.3 ± 0.8[a]	0.0[a]	4.1 ± 0.8[a]	49.2 ± 37.8[a]	132.0 ± 70.4[a]
Survivors ($n = 21$)	5.7 ± 0.7[b]	10.1 ± 1.2[b]	5.4 ± 0.5[b]	0.0[a]	4.6 ± 0.4[b]	55.9 ± 32.5[a]	122.0 ± 92.5[a]
Non-survivors ($n = 17$)	4.5 ± 0.7[b]	5.7 ± 1.4[c]	2.6 ± 0.1[c]	259.0 ± 23.0[b]	2.6 ± 0.8[c]	30.8 ± 17.7[a]	157.1 ± 35.9[b]

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

Table 5: Analysis of ROC curve of selected biochemical variables of phenylbutazone toxicity in draft horses ($n = 38$).

Variables	Area under the curve	Cutoff point	P value	95 % CI	Sensitivity %	Specivicity %	Likelihood ratio
TLC	0.986	< 8.20	< 0.0001	0.94-1.02	91	100	9.09
Neutrophils	0.836	< 4 x10³	< 0.009	0.66-1.006	81	70	2.73
Band Cells	1.0	> 123	< 0.0001	1.0-1.0	100	100	-
Total protein	0.775	< 52.5	< 0.024	0.58 – 0.96	71	80	3.57
Urea	0.871	> 69.0	< 0.0002	0.72-1.0	78	80	3.93
Creatinine	0.967	> 163.5	< 0.0001	0.9-1.0	93	90	9.29
MDA	0.977	>13.5	< 0.001	1-1.20	100	88	8.33
NO	0.985	> 5.5	< 0.001	0.9-1.014	94	96	23.44
SOD	1.0	< 2.34 x10³	< 0.006	1.0-1.0	100	100	5
Vitamin C	0.778	< 63.5	< 0.022	0.577-0.97	78	80	3.93
AST	0.785	> 205	< 0.01	0.60-0.96	80	71	2.80

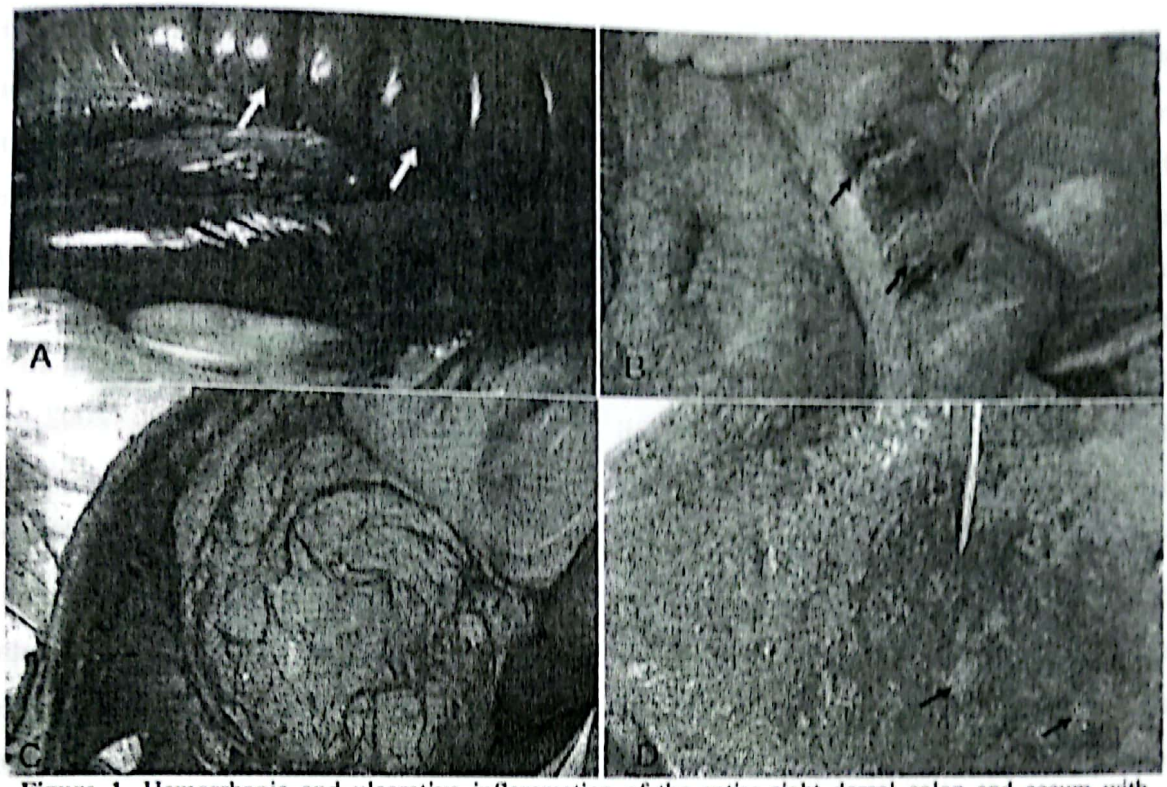

Figure 1. Hemorrhagic and ulcerative inflammation of the entire right dorsal colon and cecum with varying degrees **(A&B).** Congestion with presence of non hemorrhagic ulcerations in the glandular portion of the stomach **(C&D).**

DISCUSSION

Based on the data retrieved from the medical records, it has been found that the only therapeutic medicament given to all 38 horses was PBZ. The duration of illness from the onset of appearance of signs till recovery or death in survivors and non-survivors was 8 – 31 and 6 – 11 days, respectively. It has been previously found that the dose of PBZ required to induce ulcerative colitis was 8-10 mg kg^{-1} for several days and doses of 15 mg kg^{-1} or greater, when given on multiple days were found to be lethal, with death occurring as early as day 4 of treatment (Meschter et al. 1990; MacAllister 1983). On the contrary, Collins and Tyler (1984) reported that horses receiving less than or equal to 8.8 mg kg^{-1}/day for less than or equal to 4 days or 2 - 4 mg kg^{-1}/day for up to 50 days remained clinically normal. It is suggested that the toxic side effects of PBZ varies from horse to another. The clinical findings reported in this study were coincided with previous reports (Meschter et al. 1990; MacAllister et al. 1993; Galvin et al. 2004; McConnico et al. 2008).

Our findings showed that there was a significant association between non-survivors and anorexia ($p < 0.01$), stasis of intestinal motility ($p < 0.01$), melena ($p < 0.01$), and diarrhoea ($p < 0.001$). However, there was no significant association with weight loss ($p = 0.1630$) and presence of ventral oedema ($p = 0.1025$). Similarly, previous studies

established the role of clinical parameters to predict the outcomes of horses with colic (Sutton et al. 2009; Smith et al. 2010). It has been hypothesized that gastro-intestinal mucosal injury caused by PBZ toxicities is attributable to reduced mucus and/or bicarbonate production, ischemia results from thromboses of the blood vessels, neutrophil plugging of capillaries and impaired healing (Wallace, 1997). The importance of blood flow may explain why toxicity is most frequently noted in hypovolemic patients. However, toxic effects of the PBZ in the colon have also been noted in normovolemic horses given therapeutic dosages suggesting as yet unidentified non-vascular mechanisms involved in the pathogenesis of right dorsal colitis (Cohen et al., 1995).

To our knowledge, this is the first report describing the changes of oxidative stress levels and antioxidant variables as well as their predictive value in horses with PBZ toxicity under field condition. Interestingly, MDA and NO levels were significantly increased in non-survivors compared to survivors, whereas SOD activities were significantly decreased. On the other hand, GSH reduced and Vit. C levels were significantly decreased in diseased horses as compared to control group. The changes of MDA, NO, SOD, GSH and Vit. C levels were probably attributed to oxidative damage resulting from free radicals production. Similar findings were reported by Odabasoglu et al. (2005) and (Motawi et al., 2008) for MDA, SOD and NO, respectively in rats following NSAIDs treatment. On the contrary, McConnico et al. (2008) mentioned that there was no significant difference of MDA levels in horses experimentally treated with PBZ for 21 days compared to control group. Similarly, Tung et al. (2002) reported that there was insignificant expression of nitric oxide production in horse chondrocytes treated with PBZ.

It has been found that TLC, neutrophils, band cells as well as total plasma protein, blood urea, creatinine, MDA, NO, SOD, vit. C, and AST levels provided high sensitivity and specificity to predict the clinical outcomes of PBZ toxicity in draft horses, suggesting their clinical diagnostic usefulness. The cutoff point for these variables are < 8.20 $x10^3$, < 4 $x10^3$, > 123 Cell/µL, < 52.5 g/L, > 69.0 mmol/L, > 163.5 µmol/L, >13.5 µmol/L, > 5.5 µmol/L, < 2.34 $x10^3$ IU/gHb, < 63.5 mg/L, and > 205 IU/L, respectively. Similarly, in horses with peritonitis, MDA has been found to have prognostic importance (El-Ashker et al. 2010). However, other reports established other clinical (Sutton et al. 2009; Smith et al. 2010) and biochemical (Hassel et al. 2009; Niinist et al. 2010) variables to predict the outcomes of equine colic caused by various disease conditions rather than PBZ toxicity.

The biochemical and haematological findings support the clinical suggestion

Hypoproteinemia and hypoalbuminemia were probably attributed to gastrointestinal losses resulting from ulceration and haemorrhages. This finding agree with that previously described by Galvin et al. (2004); Davis (2005); Reed et al. (2006); McConnico et al. (2008) who mentioned that hypoproteinemia and hypoalbuminemia were considered as sensitive biochemical indicators of PBZ toxicity in horses. Moreover, the significant increase of liver enzymes could be attributed to hepatic injury and would suggest hepatic damage caused by PBZ toxicity (Ellison and Jacobs, 1990) where as the changes of leucogram profile in non-survived horses might suggest presence of severe endotoxemia. Similarly, McConnico et al. (2008) mentioned that neutropenia was a constant characteristic hematologic findings in horses treated with PBZ. On the contrary, MacAllister et al. (1993) stated that the mean values of leucogram profile of horses experimentally treated with PBZ at 4.4 mg kg^{-1} for 13 days remained within normal limits.

The effect of treatments upon the survival of horses presented with PBZ toxicity was difficult to assess. Clearly, the treatment was often ineffective in part since so many horses were severely ill at the time of presentation. Based on our findings in this study, discontinuation of PBZ administration, early and aggressive treatments to promote healing of ulcerated mucosa as well as efforts to maintain acid-base and fluid balance were the most rational approaches to the treatment of PBZ toxicity.

Post-mortem findings of non-survived cases supported the clinical and biochemical results and confirmed our suspicious. Hemorrhagic and ulcerative inflammation of the entire right dorsal colon and cecum as well as non hemorrhagic ulcerative lesions in the glandular portion of the stomach were found. This finding confirms that gastrointestinal ulcerations are constant side effects of PBZ administration in horses. Similar findings were previously reported by MacAllister (1983); Collins and Tyler (1984); Meschter et al. (1990); Karcher et al. (1990); Reed et al. (2006).

It could be concluded that clinical examination provides valuable diagnostic information about the adverse effects of PBZ in horses. Additionally, owners need to be aware of the possibility of complications to their horses even when they administer PBZ with the therapeutic dose. It is suggest that estimation of the selected biochemical variables might help predict the clinical outcome of PBZ toxicity in draft horses.

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تقييم المتغيرات الإكلينيكية و المعملية كمؤشرات تشخيصية وتنبؤية للتسمم بالفينايل بيوتازون في خيول الجر

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اجريت هذه الدراسة لتقييم المتغيرات الإكلينيكية و المعملية كمؤشرات تشخيصية وتنبؤية للتسمم بالفينايل بيوتازون في خيول الجر. لهذا الغرض تم استعراض السجلات الطبية لعدد ثمانية وثلاثون من خيول الجر المصابة بالتسمم بالفينايل بيوتازون. تم التشخيص المبدئي على أساس تاريخ الحالة والفحص البدني ، وتتبع تشريح الجثة في الحالات التي لم تستجب للعلاج الطبي. وفقا للنتائج الإكلينيكية ، تم تصنيف الخيول المصابة إلى مجموعتين: شملت الأولى عدد ٢١ حصانا استجابوا للعلاج الطبي بينما شملت المجموعة الثانية عدد ١٧ حصانا لم تستجيب للعلاج . أظهرت نتائج الفحص المعملي أن للمالونيالدهايد ، وأكسيد النيتريك ، اسبارتات أمينيو ترانسفيراز ، جاما جلوتاميل ترانسفيريز، السوربيتول ديهيدوجينيز، البيليروبين ، اليوريا ، والكريتينين زيادة كبيرة في الخيول التي لم تستجب للعلاج مقارنة بالخيول التي استجابت للعلاج ، وفي الوقت نفسه ، اظهر نشاطا سوبر اكسيد ديسموتاز ، بروتين البلازما ومستويات الزلال انخفاضا ملحوظا.

ويمكن أن نخلص إلى أن الفحص الإكلينيكي و المعملي يمكن أن يوفرا معلومات قيمة حول التشخيص والتنبؤ بالآثار السلبية للفينايل بيوتا زون في خيول الجر كما تشير النتائج أيضا إلى أن تقدير هذه المتغيرات البيوكيميائية قد يساعد على التنبؤ بنتائج التسمم بالفينايل بيوتازون في خيول الجر.