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Clinical Evaluation of Acepromazine, Xylazine and Butorphanol in Different Combinations for Standing Sedation in Horses: A Hemato-Biochemical Study

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Abstract The objective of this study was to compare four intravenous sedative combinations in adult horses for heamatological and biochemical changes. Twenty four adult, mixed-breed horses of either sex weighing 200 ± 400 kg were used for the purpose. The intravenous sedative combinations used were: acepromazine (0.04 mg/kg) + butorphanol (0.02 mg/kg) in group A, xylazine (0.5 mg/kg) + butophanol (0.02 mg/kg) in group B, acepromazine (0.04 mg/kg) + xylazine (0.5 mg/kg) in group C and acepromazine (0.03 mg/kg) xylazine (0.5 mg/kg) and butorphanol (0.02 mg/kg) in group D. All four combinations induced non-significant decrease in Hemoglobin (Hb), packed cell volume (PCV) and total leukocyte count (TLC). However, these parameters fluctuated within normal range. Biochemical attributes were within physiological limits, however a nonsignificant increase in blood glucose, ALT and ASTvalues were observed. The values returned to normal during recovery ruling out any renal or hepatic toxicity. The study indicates that none of the sedative combination used in the present study produced any serious deleterious effect on various hemato-biochemical parameters indicating their safety on various vital organ functions; hence all of these sedative drug regimens can safely be used in routine clinical cases of surgery of short duration under field conditions.

Keywords Acepromazine, Butorphanol, Horses, Standing sedation, Xylazine.

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Introduction

Numerous agents have been used to produce standing chemical restraint in horses. Currently, three groups of drugs are commonly used viz. phenothiazines, alpha-2 agonists, and opioids [1]. Acepromazine and the alpha-2 adrenoeceptor agonists are the most commom individual agents used for chemical restraint, but it is well recognized that addition of an opioid enhances their sedative effects without seriously

compromising vital function [2]. Alpha-2 adrenoreceptor agonists are undoubtedly the main-stem component of any standing sedation protocol in horses. It is realistically impossible to provide a reliable, stable, and profound degree of sedation without using alpha-2 adrenoreceptor agonist. Xylazine, romifidine, detomidine, and dexmedetomidine are available for use in horses [3]. Their peak effect is achieved within approximately 2 to 5 and 15 to 30 minutes after intravenous and intramuscular administration, respectively [4]. All alpha-2 agonists produce reliable, sedative, visceral, and somatic analgesic, and muscle-relaxant effects [5]. Common side effects of all alpha-2 agonists include bradycardis, second-degree atrioventricular block, biphasic hypertension followed by hypotension, increased urine production, moderate hyperglycemia, sweating, and decreased gastrointestinal motility [3]. Acepromazine maleate, a phenothiazine derivative, is one of the most common drug used for tranquilization and preanaesthetic medication in equines [6]. In this species, ACP decreases blood presure, as a result from peripheral alpha-adrenergic blockade resulting in vasodilation [7]. Acepromazine is a potent neuroleptic agent with relatively low toxicity. It induces mild to moderate tranquilization, muscle relaxation and a decrease in spontaneous activity. Butorphanol tartrate is a synthetic opioid with agonist-antagonist properties. It is convenient to use, as in most countries it is not subject to such stringent controls as are some other opioids. The combination of xylazine and butorphanol at the doses generally used in clinical practice produces minimal and transient haemodynamic effects and no significant respiratory depression [8]. Butorphanol is used alone and in combination with xylazine and acepromazine to provide safe, reliable and potent sedative and analgesic effect in equines [9].

Materials and Methods

Study was conducted on twenty four adult horses of either sex weighing 200 to 400 kg presented for various surgical procedures. The animals were weighed before administration of any drug using a large animal weighing machine. Rectal temperature, heart rate and respiratory rate were measured, heart and lungs were auscultated, and mucous membranes and skin turgor were evaluated before study. The skin at the site of intravenous injection i.e. left side of jugular vein was shaved and aseptically prepared for injection before 20 min of the start of administration of drugs. Subsequantly, an 18 gauge intravenous catheter was inserted percutaneously into the jugular vein and fixed with an adhesive. Administration of normal saline solution was started @ 20 drops per minute just to maintain the patency of catheter and the animal was left undisturbed for a period of 20 minutes. All the procedures were conducted in a separate and quite operation theatre.

These animals were divided into four groups viz. A, B, C and D comprising six animals in each group. The animals of group a received an intravenous bolus of mixture of acepromazine [Ilium acepril-10 injection (10 mg/ml), Troy laboratories PTY. Limited, 35 Glendenning RD Glendenning new 2761 Australia (@ 0.04 mg/kg)] + butorphanol [Butrum (1 mg/ml), Astro Pharmaceutical Pvt Ltd Mandideep dist. Raisen (M.P.) (@ 0.02 mg/kg)]. Animals of group B received a mixture of xylazine [Xylazin (20 mg/ml), Indian Immunologicals Limited, Stanex drugs and chemicals Pvt. Ltd. Hyderabad (@ 0.5 mg/kg)] + butorphanol (@ 0.02 mg/kg) as an intravenous bolus. Animals of group C received an intravenous bolus of a mixture of acepromazine (@ 0.04 mg/kg) + xylazine (@ 0.05 mg/kg). Animals of group D were administered with a cocktail of acepromazine (@ 0.03 mg/kg) + xylazine (@ 0.5 mg/kg) and butorphanol (@ 0.02 mg/kg), intravenously. All these drugs were mixed in the same syringe and administered slowly through the intravenous catheter placed in jugular vein.

The animals were evaluated for the changes in different hematological and biochemical parameters at different time intervals viz before administration of any drug (baseline) and at 15, 30 45, 60 and 90 minutes after administration of drug. Blood samples (5 ml) were collected from jugular vein was collected in clean, dry vials containing EDTA at different time intervals as mentioned above for estimation of hemoglobin (Hb), packed cell volume (PCV), differential leukocytes counts (DLC) and total leukocyte count (TLC) using hematology autoanalyzer (Hematology analyzer (abacus), manufactured by Diatron Gmbh,

Table 1. Observation on hematological and biochemical parameters before and after sedation.

Group	Time intervals (min) 0	15	30	45	60	90
Mean ± SE of hemoglobin (g/l) in different groups of animals at different time intervals						
A	13.62 ± 0.625	12.25^{ab} ± 0.322	11.87 ± 0.657	12.37 ± 0.898	12.50 ± 0.540	12.12^{a} ±0.554
B	13.37 ± 0.625	11.62^{a} ± 0.746	11.50 ± 0.735	12.00 ± 0.645	12.37 ± 0.625	12.75^{ab} ± 0.520
C	12.97 ± 0.201	12.15•^{ab} ± 0.253	12.25 ± 0.201	12.10• ± 0.248	12.42 ± 0.193	12.47^{ab} ± 0.221
D	14.25 ± 0.155	14,12^{b} ± 0.110	14.12 ± 0.193	13.75 ± 0.248	13.82 ± 0.217	13.90^{b} ± 0.204
Mean ± SE of packed cell volume (%) in different groups of animals at different time intervals						
A	39.00^{b} ± 0.816	37.50 ± 0.577	37.50 ± 1.290	37.75 ± 0.707	37.50^{b} ± 1.290	37.25 ± 0.957
B	34.50^{a} ± 1.936	35.00 ± 2.483	33.25 ± 2.39	33.25 ± 1.887	34.25^{a} ± 1.750	34.25 ± 2.015
C	37.75^{ab} ± 1.314	34.75 ± 1.493	35.25 ± 1.181	35.50 ± 1.190	35.75^{ab} ± 1.314	35.50 ± 0.866
D	38.50^{b} ± 0.645	37.25 ± 0.750	36.50 ±0.645	36.50 ± 0.866	36.75^{ab} ± 0.750	37.00 ± 0.577
Mean ± SE of total leukocyte count (× 10^9/L) in different groups of animals at different time intervals						
A	8.37^{b} ± 0.455	8.05^{b} ± 0.468	7.89^{bc} ± 0.489	7.98^{b} ± 0.410	7.64^{ab} ± 0.518	7.68^{ab} ± 0.566
B	7.20^{a} ± 0.353	6.63^{a} ± 0.440	6.47^{a} ± 0.374	6.56^{a} ± 0.403	6.48^{a} ± 0.371	6.46^{ab} ± 0.488
C	7.06^{a} ± 0.407	6.78^{a} ± 0.404	6.81^{ab} ± 0.396	6.62^{a} ± 0.412	6.48^{a} ± 0.447	5.26^{a} ±1.433
D	9.11^{b} ± 0.199	9.052^{b} ± 0.180	8.48•^{c} ± 0.132	8.27•^{b} ± 0.082	8.26•^{b} ± 0.139	8.47•^{b} ± 0.205
Mean ± SE of neutophils (%) in different groups of animals at different time intervals						
A	57.25^{b} ± 0.853	57.50^{b} ± 0.957	59.00^{bc} ± 0.816	59.75•^{b} ± 1.108	57.75^{ab} ± 0.478	56.50^{a} ± 0.866
B	55.25^{b} ± 0.750	56.75^{ab} ± 0.853	56.50^{ab} ± 1.190	58.00•^{ab} ± 1.080	57.50^{ab} ± 0.912	57.00^{a} ± 0.707
C	52.50^{a} ± 1.040	53.75^{a} ± 1.376	54.75^{a} ± 1.250	55.00^{a} ± 1.471	55.75^{a} ± 1.108	54.50^{ab} ± 0.645
D	60.75^{c} ± 0.853	61.25^{c} ± 0.853	61.00^{c} ± 0.816	60.75^{b} ± 0.853	61.50^{b} ± 1.931	61.50^{b} ± 1.931
Mean ± SE of lymphocytes (%) in different groups of animals at different time intervals						
A	37.25^{a} ± 0.250	36.75^{a} ± 0.250	36.00^{a} ± 0.707	34.75*^{a} ± 0.750	36.50^{a} ± 0.288	36.75^{a} ± 0.250
B	39.00^{ab} ± 1.290	36.50^{a} ± 1.040	36.00*^{ab} ± 0.912	36.75^{a} ± 1.181	37.26^{b} ± 1.030	37.50^{b} ± 1.040
C	41.25^{b} ± 1.250	40.25^{b} ± 1.108	39.25^{b} ± 1.493	38.25^{b} ± 1.250	37.25^{b} ± 1.314	38.00^{b} ± 1.354
D	39.00^{ab} ± 1.290	36.75^{a} ± 1.250	35.25^{a} ± 1.493	35.50^{ab} ± 1.040	34.75^{ab} ± 1.030	35.25^{ab} ± 1.493
Mean ± SE of Seum glucose (mg/dL) in different groups of animals at different time intervals						
A	94.50^{ab} ± 0.645	94.75 ± 0.478	96.50 ± 0.500	96.50 ± 0.645	97.00* ± 1.290	96.25 ± 0.478
B	85.50^{a} ± 5.074	90.25 ± 5.039	91.25 ± 5.039	91.00 ± 5.400^{a}	90.25 ± 5.764^{a}	91.50 ± 5.377
C	99.25^{b} ± 1.108	101.75 ± 1.376	102.25 ± 1.436	102.75 ± 1.436	104.00* ± 1.224	103.25 ± 1.250
D	96.00^{b} ± 2.943	98.00 ± 2.677	99.50 ± 2.466	100.25 ± 2.250	101.00 ± 2.857	101.25 ± 2.868
Mean ± SE of serum creatinine (mg/dL) in different groups of animals at different time intervals						
A	0.87 ± 0.004	1.16^{b} ± 0.004	1.16 ± 0.012	1.17^{b} ± 0.008	1.17^{b} ± 0.004	1.15 ± 0.012
B	1.15 ± 0.012	1.16^{b} ± 0.004	1.16 ± 0.012	1.17^{b} ± 0.008	1.17^{b} ± 0.004	1.15 ± 0.012
C	1.26 ± 0.020	1.25^{c} ± 0.016	1.27 ± 0.020	1.28^{b} ± 0.032	1.26^{c} ± 0.008	1.24 ± 0.014
D	1.33 ± 0.014	1.33^{d} ± 0.018	1.34 ± 0.012	1.33^{c} ± 0.020	1.33^{d} ± 0.007	1.32 ± 0.022
Mean ± SE of ALT (IU/L) in different groups of animals at different time interval						
A	10.25^{ab} ± 0.250	10.75^{ab} ± 0.408	11.25 ± 0.250	12.75* ± 0.250	12.25 ± 0.288	12.25^{b} ± 0.250
B	11.25^{b} ± 1.108	12.25^{b} ± .853	12.25 ± 0.853	12.75 ± 1.108	13.00 ± 0.912	13.75^{b} ± 0.853
C	11.75^{b} ± 1.030	12.75^{b} ± 1.030	13.75 ± 1.030	13.50 ± 0.866	13.75 ± 0.853	14.00^{b} ± 0.707
D	8.00^{a} ± 0.408	8.75^{a} ± 0.478	9.00 ± 0.408	9.25 ± 0.629	9.50 ± 0.645	9.00^{a} ± 0.408
Mean ± SE of AST (IU/L) in different groups of animals at different time interval						
A	197.82 ± 1.613	198.55 ± 1.676	198.42^{b} ± 1.214	198.05^{b} ± 0.457	199.35^{b} ± 1.205	197.52^{b} ± 0.841
B	205.37 ± 1.319	206.37 ± 0.855	206.45^{c} ± 1.309	207.52^{d} ± 0.887	205.35^{c} ± 0.877	205.55^{c} ± 1.697
C	192.42 ± 4.705	193.20 ± 2.449	192.72^{a} ± 0.841	194.40^{a} ± 2.004	193.35^{a} ± 0.388	192.62^{a} ± 1.797
D	201.62 ± 1.766	201.40 ± 1.533	202.42^{bc} ± 2.005	203.50^{c} ± 0.371	203.42^{c} ± 1.495	202.00^{c} ± 0.129

Wien Australia). The blood samples (3 ml) were also collected in clean, dry vials at the same time intervals for separation of serum to estimate, blood glucose, aspartate aminotransferase, alanine aminotransferase and creatinine using commercialy available kits (Span Diagnostics Ltd), on semiautomatic chemistry analyzer (Semi Auto Chemistry Analyzer, Model–CHEM-400, Version V5.1 P EI. Product Parwanoo).

One way ANOVA (analysis of variance) and Duncan's multiple range test (DMRT) were used to compare the means at different time intervals among different groups. One way ANOVA (analysis of variance) was also used to compare the mean values at different intervals with their base values in each group.

Results and Discussion

Hemoglobin decreased non significantly in the animals of all groups during observation period. A non significant decreased in Packed cell volume (PCV) and Total leukocytes count (TLC) was also recorded in all groups after administration of different sedatives. Pooling of circulatory blood cells in the spleen or other reservoirs secondary to decreased sympathetic activity may explain the decrease in Hb, PCV and TLC recorded in the present study [10]. The decrease in PCV and Hb during the period of sedation might be due to shifting of fluid from extravascular compartment to intravascular compartment in order to maintain normal cardiae output in animals [10]. The reduction in TLC correlate with the vasodilation and emigration of leukocytes into spleen and lungs thus producing leucopenia probably due to redistribution of leukocytes in to the body rather than acute reduction in their number [11]. Similar findings have also been reported after xylazine administration in goats [12] and in xylazine and butorphanolpremedicated horses during xylazine-ketamine anaesthesia by [13]. The decrease in hemoglobin and packed cells volume can be explained by the alpha-adrenergic blocking effect of acepromazine which might cause relaxation of the spleen and consequently led to splenic sequestration of erythrocytes [14]. Differential leukocyte count (DLC), in the present study, fluctuated within normal physiological limit in the animals of all the groups. Slight neutrophilia and decrease in lymphocytes were observed in all groups which might be due to stimulation of adrenal gland and restoration of ACTH level. Similar observations have also been reported after xylazine, guaifenesin, thiamylal sodium, and halothane administration in horses [15]. In contrary to our finding, neutropenia, lymphocytosis and eosinopenia in horses induced with xylazine-ketamine combination and premedicated with xylazine and butorphanol have been also reported [13].

An increase in serum glucose level was observed in all the groups of animals, however, the values returned around the baseline but remained higher than the baseline for rest of the observation period. Hyperglycemia observed in the present study might be attributed to alpha-2 adrenergic inhibition of insulin released from beta pancreatic cells and to an increased glucose production in the liver [5]. Moreover, stimulation of alpha-2 adrenorceptors leads to inhibition of beat cellselectrical activity and suppreses insulin secretion [16], as well as administration of sedative caused protracted decrease in basal, local cerebral metabolic rate for glucose utilization [17]. Similar observations were reported in buffaloes and goats [18]. A significant hyperglycemia was also reported in horses induced and maintained with ketamine or propofol and premediated with acepromazine-xylazine [19].

A non significant increase in serum creatinine level was observed in all the groups of animals, however, the values returned around the baseline but remained higher than the baseline for rest of the observation period. The increase in serum creatinine levels might be attributed to the temporary inhibitory effects of anaestheti/sedative drugs on the renal blood flow, which in turn might have caused a rise in serum creatinine level [20]. A significant increase in serum creatinine levels after butorphanol-xylazine-ketamine-midazolam and butorphanol-xylazine-ketamine administration has been reported in horses [13].

An increase in Serum ALT and AST levels were observed in all the groups of animals, however, the values returned around the baseline but remained higher than the baseline for rest of the observation period. The elevation in the levels of transaminases indicates an altered permeability of plasma membrane

and/or cellular damage but they are not organ specific [21]. The elevation in serum transaminases have been reported during anaesthesia in response to surgery [22]. Similar to our findings, a non significant increase in ALT and AST levels after butorphanol-xylazine-ketamine midazolam and butorphanol-xylazine-ketamine administration in horses have been also repoted [13].

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