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Standardization of dose of acepromazine as a sedative in buffalo calves

Vijay Nain, Sonu Devi, Umed Singh Mehra and Amit Kumar

Abstract
In the present investigation, six experimental trials were undertaken on clinically healthy male buffalo calves (*Bubalus bubalis*), 5 to 10 months of age, and weighing 60 to 140 kg. Effect of acepromazine (0.05 mg/kg, i.m.), was evaluated in twelve animals. The calves were ataxic after 6.16±1.07 minutes and went into sternal recumbency in 74.16±22.28 minutes of drug administration. There was good sedation without analgesia. The animals were standing with ataxia after 131.5±17.80 minutes and complete recovery took 211.83±6.94 minutes of its administration. Significant hypotension (15%) and tachycardia were observed. In conclusion, acepromazine (0.05 mg/kg, I.M.) can be safely used for chemical restraint of normovolemic buffaloes.

Keywords: acepromazine, buffalo calves, dose, sedative

Introduction
Sedatives, tranquilizers and related drugs are frequently used to calm animals for a variety of hospital procedures ranging from as an aid in handling for routine work and minor surgical procedures as well as to lessen the amount of anaesthetic agents needed to induce anaesthesia *i.e.* as premedicants. It is not easy to select a drug/a combination of drugs for preanaesthetic medication especially in ruminants. The basic problem lies in the fact that there are large species variations in response to a drug. Variation are also observed even amongst the breeds within a species. Therefore, it may be dangerous to extrapolate data from one species to another for clinical application. Due to this reason it becomes imperative to evaluate each sedative or preanaesthetic drug in each of the individual species before it can be recommended for clinical use. Acepromazine is routinely used in equidae, however, there is limited information regarding the effects of this drug on buffaloes. Acepromazine is a neuroleptic drug of phenothiazine class. Phenothiazine blocks the actions of variety of chemical mediators including acetylcholine, 5-Hydroxytryptamine (5-HT), catecholamines and histamine. In addition to tranquilisation, acepromazine decreases the arterial pressure (Kerr *et al.*, 1972; Bogan *et al.* 1978) [7, 1], central venous pressure (Klen and Sherman 1977; Muir *et al.*, 1979b) [8, 13], packed cell volume (Mackenize and Snow 1977) [11] in horses. Stepien *et al.* (1995) [20] reported that the combination of acepromazine-buprenorphine was well tolerated haemodynamically in dogs. Its antiemetic properties make acepromazine a useful drug to be used for the prevention of motion sickness in dogs and its antispasmodic property has led to its use in colic in horses (Hall *et al.*, 2001) [5]. This study was done to standardize the dose of acepromazine and study its sedative effects and hematobiochemical changes after administration.

Materials and Methods
In the present investigation, six experimental trials were undertaken on clinically healthy male buffalo calves (*Bubalus bubalis*), 5 to 10 months of age, and weighing 60 to 140 kg. Before carrying out the actual experiments, all the buffalo calves were dewormed with fenbendazole (FentasTM - Fenbendazole BP (Vet) 1.5 g, Intas Pharmaceuticals Ltd. Matoda-382210, Ahemdabad) and kept under similar managemental schedule. Pilot trials were done to standardize the dose rate and route of administration of acepromazine (Ilium Acepril -10 (acepromazine maleate, 10 mg/ml) TROY Laboratories PTV. Limited. 98 Long street Smithfield. NSW 2164 Australia). For detailed studies, based on the results of pilot trials, dose rate of acepromazine was finalized 0.05 mg/kg via intramuscular route. Various parameters were investigated before administration of the drug, at peak effect of the drugs, after recovery from the effect of drugs, and at 24 hours after administration of drugs.

Each animal was weighed a day before the experiment and had free access to feed and water. Following protocol of experiment was followed:

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Drugs administered	Parameters investigated
Acepromazine (n=no. of animals, n=6)	Behavioural changes, rectal temperature, heart rate, respiration rate, haemoglobin(Hb), packed cell volume(PCV), erythrocyte sedimentation rate(ESR), blood/plasma glucose, cholesterol, urea nitrogen, creatinine, total proteins, albumin, calcium, inorganic phosphorus, magnesium, sodium, potassium, chloride, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALKP) and bilirubin Systolic pressure, diastolic pressure, mean arterial pressure (MAP), pulse pressure, central venous pressure (CVP) and electrocardiogram (ECG)

Experimental Protocol

Sedative studies were conducted in confined area. The animals were kept free and allowed to take feed. Rectal temperature and respiration rate were recorded just before administration of acepromazine, along with the ambient temperature, to form the base values. The blood samples were collected in two sets of heparinized (10 units/ml) test tubes, one out of which was for harvesting plasma for biochemical parameters and the other to determine haematological parameters and one set of sodium fluoride (3.8%) test tubes, for determining glucose (1:10). After collection of blood samples, drugs were administered in accordance with *vide ante* protocol.

Hematological Analysis

Blood samples collected from jugular venipuncture at various time intervals were used for haematological and blood or plasma biochemical studies. Haematology included estimation of haemoglobin, erythrocyte sedimentation rate and packed cell volume by standard methods. For biochemical studies plasma was harvested from the heparinized blood taken in second tube by centrifugation at 3000 rpm for 30 minutes. Plasma was stored at -20ºC and utilized for analysis of various biochemical parameters. Blood containing sodium fluoride (3.8%) was centrifuged at 3000 rpm for 30 minutes. Plasma was stored at 4ºC and utilized for analysis of glucose.

Behavoural Changes

The method used to determine the action of central nervous system depressant in the present study was based on similar studies by Peshin et al. (1980, 1993) [7, 18] and from local standards of our laboratory. Local variables and their possible effects have also been considered in standardization of these procedures. The animals were then observed to record the behavioural changes, namely: Spontaneous motor activity, Lowering of head Onset of salivation, urination, defaecation and lacrimation, Vocalization (if any), Dropping of lower lip, Weak time (time elapsed from administration of drug to onset of ataxia), Down time (time elapsed from administration of drug to onset of sternal or lateral recumbency), Relaxation of muscles. Qualitative and subjective analgesic effect of drugs were judged by observing physical response of the medicated animal to cutaneous hypodermic needle pricks or scratching of rib periosteum with needle after its subcutaneous insertion. Recovery from effect of drugs was taken to have occurred by: Sternal recumbency and head righting reflex, Standing time, with ataxia, Browsing time: time elapsed from administration of drug to occasional nibbling of grass and Complete recovery, without ataxia.

Haemodynamic Studies

The calves were comfortably secured on experimental table in right lateral recumbency. By taking all aseptic precautions, the carotid artery and jugular vein were exteriorized under local infilteration analgesia using 2% lignocaine hydrochloride. The blood pressure was recorded using mercury manometer. The mean arterial pressure (MAP) and pulse pressure were calculated as under:

$$MAP = \frac{\text{Systolic Pressure} + 2\ \text{Diastolic Pressure}}{3}$$

Pulse Pressure = Systolic Pressure — Diastolic Pressure

Electrocardiographic Studies (ECG)

The ECG was recorded using base-apex lead. For this purpose, the positive electrode was placed subcutaneously at the sternum and the negative electrode at the caudal border of scapula on the left side of the animal. Heart rate was recorded from ECG tracings. The CVP was recorded against a vertical water column with zero point taken at the sternum manubrium. All parameters were recorded before administration of drug to act as base values and at 5, 10, 15, 30, 45, 60, 75 and 90 minutes of drug administration.

Statistical Analysis

The statistical analysis of data was done by one-way-analysis of variance and Duncan's multiple range test (Duncan, 1955).

Results

Behavioural Parameters

After administration of acepromazine animals showed decreased spontaneous activity with ataxia (6.16±1.07) till they assumed sternal recumbency at 74.16±22.28 minutes. There was no cutaneous analgesia. Other signs included mild salivation, urination, defaecation and lacrimation. Animals appeared sleepy with head down but aroused on approach. Relaxation of muscles was manifested by milk fever posture; relaxation of tail, anus and prepuce at 26.16±2.92 minute of acepromazine administration. Recovery from the effects of acepromazine was marked by nibbling of straw and grass feed (109.5±13.25). Animals stood up by 131.5±17.80 minute but were ataxic. Animals recovered from the effects of acepromazine after 211.83±6.94 minutes of its administration.

Physiological and Hematlogical Parameters

Rectal temperature and respiration rate remained within the normal range (Table 1). The effects of acepromazine on various haematological and blood-biochemical parameters are shown in tables 2 and table 3, respectively.

Table 1: Effects of intramuscular administration of acepromazine (0.05 mg/kg) on rectal temperature and respiratory rate in six buffalo calves.

Parameters (units)	Before administration of drug	At peak effect of drug	At recovery from effect of drug	24 hours after administration of drug
Ambient Temperature (ºC)	$34.33^a \pm 0.210$	$34.33^a \pm 0.210$	$34.00^a \pm 0.000$	$34.33^a \pm 0.210$
Rectal Temperature (ºC)	$38.26^a \pm 0.327$	$38.16^a \pm 0.187$	$37.82^a \pm 0.202$	$38.03^a \pm 0.215$
Respiration rate (per minute)	$29^a \pm 5$	$30^a \pm 5$	$24^a \pm 3$	$23^a \pm 2$

Mean values are presented here with (±) their respective standard errors (n = 6). Means with same superscripts vary non- significantly (P> 0.05)

There was no significant variation in any of the investigated parameters at varying time intervals after acepromazine administration. However, the values of packed cell volume were lower than the base values up to recovery stage.Its effect on rectal temperature and respiratory rate are shown below in table 1. There were no significant variations in these parameters.

Table 2: Effects of intramuscular administration of acepromazine (0.05 mg/kg) on haematological parameters in six buffalo calves.

Parameters (units)	Before administration of drug	At peak effect of drug	At recovery from effect of drug	24 hours after administration of drug
Haemoglobin (g/dl)	$9.33^a \pm 0.927$	$7.75^a \pm 0.919$	$8.00^a \pm 0.774$	$9.20^a \pm 0.937$
Erythrocyte Sedimentation Rate (mm first hour)	$52^a \pm 11.221$	$53^a \pm 11.979$	$60^a \pm 8.902$	$51^a \pm 11.454$
Packed Cell Volume (%)	$27^a \pm 2.836$	$24^a \pm 2.928$	$24^a \pm 2.629$	$27^a \pm 2.577$

Mean values are presented here with (±) their respective standard errors (n=6). Means with same superscripts vary non- significantly (P>0.05)

Electrocardiographic Changes

There were no major changes in the ECG in the present study on buffalo calves at any stage of the experiment. All parameters were recorded before administration of drug and at 5, 10, 15, 30, 45, 60, 75 and 90 minutes of drug administration shown in graphs 1-9 respectively (Fig. 1).

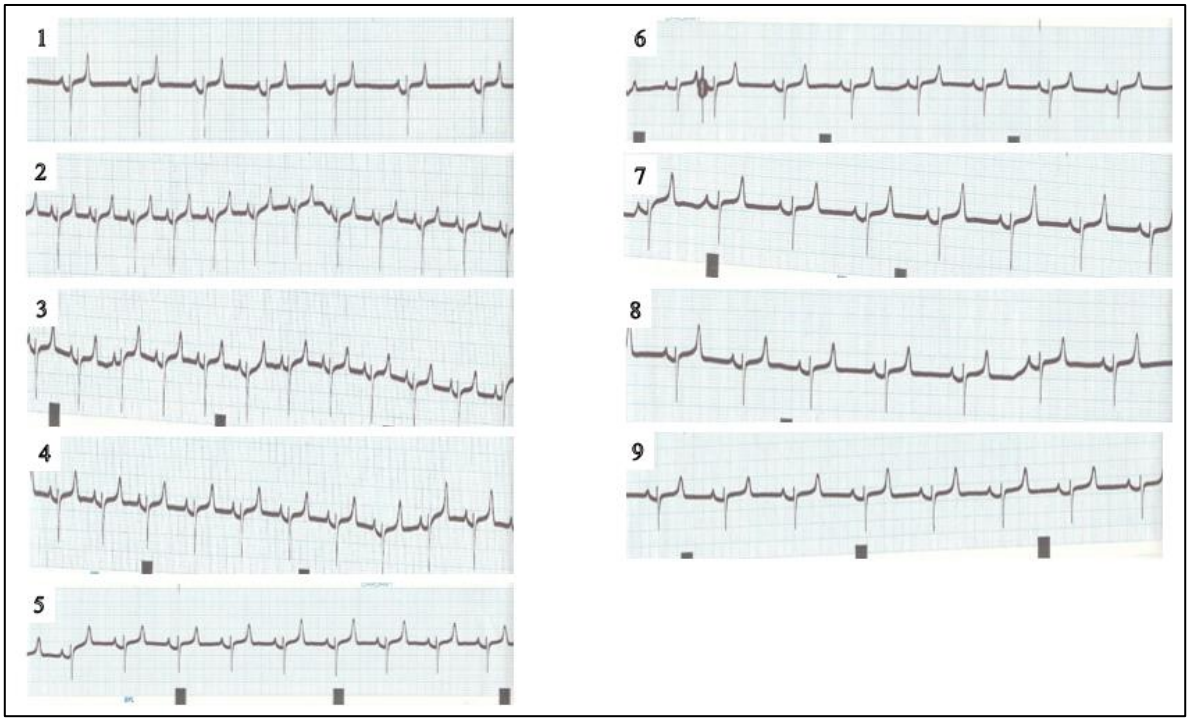

Fig 1: Electrocardiographs before administration of drug and at 5, 10, 15, 30, 45, 60, 75 and 90 minutes of administration of acepromazine.

Table 3: Effects of intramuscular administration of acepromazine (0.05 mg/kg) on blood-biochemical parameters in buffalo calves.

Parameters (Units)	Before administration of drug	At peak effect of drug	At recovery from effect of drug	24 hours after administration of drug
Blood glucose (mg/dl)	$64.98^a \pm 5.435$	$74.93^a \pm 5.838$	$70.96^a \pm 4.760$	$57.45^a \pm 8.229$
Cholesterol (mg/dl)	$41.60^a \pm 2.332$	$40.13^a \pm 2.368$	$39.35^a \pm 1.385$	$42.18^a \pm 2.559$
BUN (mg/dl)	$20.70^a \pm 0.138$	$20.73^a \pm 0.291$	$20.65^a \pm 0.153$	$20.87^a \pm 0.158$
Creatinine (mg/dl)	$1.54^a \pm 0.177$	$1.63^a \pm 0.291$	$1.59^a \pm 0.268$	$1.85^a \pm 0.200$
Total proteins g/dl)	$3.78^a \pm 0.274$	$3.51^a \pm 0.503$	$3.50^a \pm 0.240$	$3.64^a \pm 0.243$
Albumin (g/dl)	$2.93^a \pm 0.088$	$2.98^a \pm 0.065$	$2.98^a \pm 0.082$	$2.92^a \pm 0.115$
Calcium (mg/dl)	$6.35^a \pm 0.323$	$7.33^a \pm 0.986$	$6.97^a \pm 1.444$	$6.62^a \pm 0.497$
Phosphorus (mg/dl)	$6.52^a \pm 0.517$	$6.18^a \pm 0.636$	$6.43^a \pm 0.316$	$6.42^a \pm 0.382$
Magnesium (mg/dl)	$2.39^a \pm 0.047$	$2.39^a \pm 0.044$	$2.40^a \pm 0.043$	$2.39^a \pm 0.038$
Sodium (mmol/l)	$108.76^a \pm 8.245$	$107.45^a \pm 6.076$	$99.56^a \pm 9.636$	$106.56^a \pm 7.594$
Potassium (mmol/l)	$4.25^a \pm 0.176$	$4.40^a \pm 0.211$	$3.90^a \pm 0.370$	$4.50^a \pm 0.217$

Chloride (mmol/l)	103.56^{a} ± 7.633	94.34^{a} ± 4.758	92.56^{a} ± 3.919	97.18^{a} ± 2.483
Bilirubin (mg/dl)	0.10^{a} ± 0.047	0.09^{a} ± 0.027	0.12^{a} ± 0.036	0.11^{a} ± 0.0455
SGOT (U/l)	16.23^{a} ± 1.365	17.02^{a} ± 1.540	17.31^{a} ± 0. 819	16.09^{a} ± 0.992
SGPT (U/l)	20.39^{a} ± 1.382	22.97^{a} ± 2.927	22.36^{a} ± 1.671	23.42^{a} ± 2.113
ALKP (U/l)	96.60^{a} ± 5.863	99.00^{a} ± 5.825	97.10^{a} ± 5.700	97.10^{a} ± 5.594

Mean values are presented here with (±) their respective standard errors (n=6).Means with same superscripts vary non-significantly (*P*>0.05)

Hemodynacic parameters

The effects of acepromazine on heart rate, systolic pressure, diastolic pressure, pulse pressure, mean arterial pressure and central venous pressure are shown in tables 4 and figure. Heart rate increased significantly at 5 minutes of acepromazine administration (58 ± 4 beats per minute) and remained significantly higher up to 15 minutes of drug administration as compared to base value (38 ± 1 beats per minutes). Mean arterial pressure fell significantly at 5 minutes of drug administration (140.33 ± 3.887 mm Hg) from base value of 148.67 ± 1.856 mm Hg), it further fell significantly to 126.00 ± 2.539 mm Hg at 30 minutes of drug administration. There was a significant reduction in pulse pressure throughout the period of observation from the base value of 17.50 ± 1.204 mm Hg. No significant variation was observed in central venous pressure throughout the period of observation.

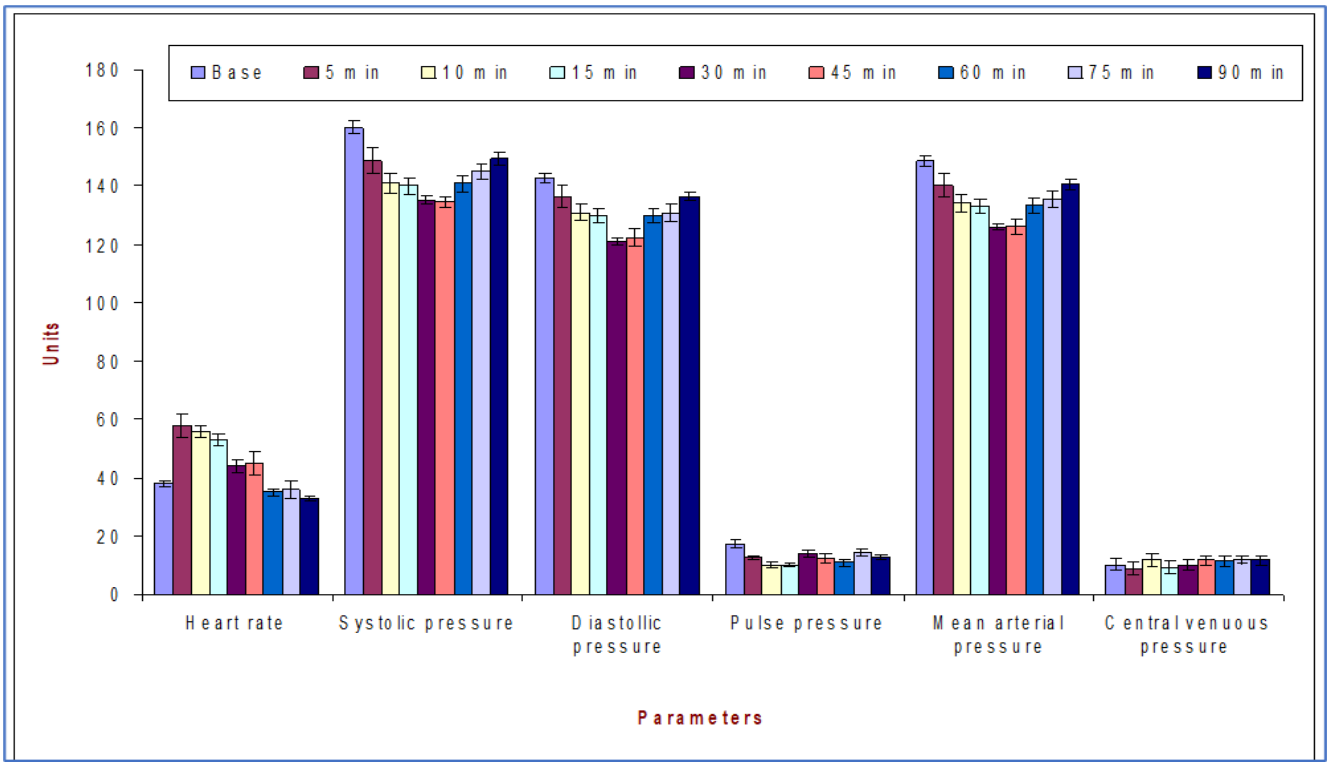

Fig 2: Effect of acepromazine on heart rate, systolic pressure, diastolic pressure, pulse pressure, mean arterial pressure and central venous pressure

Table 4: The effect of intramuscular administration of acepromazine (0.05 mg/kg) on heart rate, systolic pressure, diastolic pressure, pulse pressure, mean arterial pressure and central venous pressure.

Parameters (units)	Base	Acepromazine							
		5 min	10 min	15 min	30 min	45 min	60min	75 min.	90 min.
Heart rate (beats per minute)	38^{cd} ± 1	58^{a} ± 4	56^{a} ± 2	53^{a} ± 2	44^{bc} ± 2	45^{b} ± 4	35^{d} ± 1	36^{d} ± 3	33^{d} ± 1
Systolic pressure (mm Hg)	160.17^{a} ± 2.28	148.83^{b} ± 4.277	141.17^{bcd} ± 3.370	140.00^{cd} ± 2.683	135.17^{d} ± 1.492	134.50^{d} ± 1.821	140.83^{bcd} ± 2.663	145.17^{bc} ± 2.701	149.33^{b} ± 2.092
Diastolic pressure (mm Hg)	142.67^{a} ± 1.687	136.33^{ab} ± 3.739	131.00^{b} ± 2.633	129.83^{b} ± 2.372	121.17^{c} ± 1.108	122.33^{c} ± 2.859	130.00^{b} ± 2.324	130.83^{b} ± 2.903	136.50^{ab} ± 1.544
Pulse pressure (mm Hg)	17.50^{a} ± 1.204	12.50^{bc} ± 0.619	10.17^{c} ± 1.046	10.17^{c} ± 0.543	14.00^{b} ± 1.342	12.17^{bc} ± 1.720	10.83^{bc} ± 0.945	14.33^{ab} ± 1.382	12.83^{bc} ± 0.792
Mean arterial pressure (mm Hg)	148.67^{a} ± 1.856	140.33^{b} ± 3.887	134.33^{b} ± 2.848	133.17^{bc} ± 2.372	126.00^{c} ± 1.065	126.33^{c} ± 2.539	133.50^{bc} ± 2.487	135.50^{b} ± 2.861	140.67^{b} ± 1.745
Central venous pressure (cm water)	10.287^{a} ± 1.869	8.82^{a} ± 2.020	11.85^{a} ± 2.177	9.33^{a} ± 2.035	10.19^{a} ± 1.775	11.69^{a} ± 1.321	11.78^{a} ± 1.676	11.91^{a} ± 1.369	11.72^{a} ± 1.418

Table showing arithmetic mean of values obtained before and at various intervals after its administration. Mean values are presented here with (±) their representative standard errors (n=6). Means with different superscripts vary significantly (*P*<0.05)

Discussion

The pre-anaesthetic medication plays an important role in safe anaesthetic management of clinical patients. In veterinary practice especially while handling large animals, one of the advantages of using tranquilisers is better and safe restraint of the animal. This in turn minimizes stress and associated side effects. Several of these agents are either used alone or in combination to achieve the desired effects. Although most of the agents have been extensively studied in horses and dogs, several gaps exist as far as knowledge on the effects of several of these agents in bovines is concerned. In the present study main objective was to evaluate acepromazine. The acepromazine is a phenothiazine derivative and is extensively used in dogs and horses (Popovic *et al*., 1972; Muir *et al*. 1979a; Parry *et al*., 1982; Kojima *et al*., 1999 and Hall *et al*., 2001) [19, 15, 16, 9, 5]. It is more potent than chlorpromazine and promazine, and has relatively low toxicity. In the present investigation, sedative studies showed that the drug had good tranquilisation effect on calves. However, the dose of 0.05 mg/kg I.M. showed marked individual variations in respect of time function i.e. down time ranged from 10 to 124 minutes. Similarly standing time ranged from 69 to 192 minutes, In contrast, complete recovery was in a comparatively narrow range of 179 to 226 minutes. All phenothiazine derivatives have been stated to cause a fall in body temperature partly due to increased heat loss because of the resetting of the central thermoregulatory mechanisms (Hall and Clarke, 1991) [6]. Hypothermic effect has also been linked with the depletion of catecholamine substances within the hypothalamus (Gross, 1995) [4]. In the present study, there were no significant variations in the rectal temperature of the buffalo calves after administration of acepromazine. There was only reduction of 0.44ºC in the rectal temperature at recovery but at the same time the ambient temperature at this stage was higher about 0.33ºC. As far as haemodynamic effects of acepromazine are concerned, wide variations have been reported in the dogs and horses. In general, reduction in the blood pressure and a compensatory tachycardia are observed. A dose related fall in blood pressure after intravenous administration of acepromazine in the dogs has been reported, with the lowest dose of 0.11 mg/kg producing the same hypotensive effect as that with 1.1 mg/kg (Coulter *et al*., 1981) [2]. On the contrary, studies of Muir and Hamlin (1975) [14] in dogs showed that significant changes in the arterial pressure of dog do not occur when intravenous dose is less than 0.04 mg/kg. Ludders *et al*. (1983) [10] recorded wide variations in the reduction in blood pressure in the dogs which ranged from 2.3 ± 6.0 to 16.8 ± 14.2% with an intravenous dose of 0.05 mg/kg to 0.2 mg/kg. In the present study, the mean arterial pressure reduced significantly after 5 minutes of administration of acepromazine. The maximum mean hypotensive effect was 15% when compared with base values. However, by 90 minute of drug administration, the effect was only 5%. Although the hypotension was significant, it can not be said to be critical from clinical point of view in normovolaemic animals. Compensatory tachycardia developed within 5 minute of the intramuscular administration of acepromazine and remained upto 45 minutes. In the horse, arterial pressure has been reported to remain significantly below the control values for more than six hours after intravenous administration of 0.025 mg/kg of acepromazine (Parry *et al*., 1982) [16]. However, according to Muir *et al*. (1979b) [13] intravenous administration of acepromazine in the horses (0.09 mg/kg) produces non-significant decrease in heart rate and cardiac output but the mean arterial pressure and CVP decrease 15 minutes following the injection. As per Kerr *et al*. (1972) [7] phenothiazine derivatives block $\propto_1$-adrenergic receptors which lead to hypotension primarily due to peripheral vasodilation. However, similar mechanism cannot be said to operate in the present buffalo calves as there were no variations in CVP. In the horse, indirect effect through central nervous system and autonomic reflexes have also been stated to be the cause of hypotension produced by acepromazine (Marroum *et al*., 1994) [12]. It may be mentioned that the animals of the present study were apparently healthy and appeared to be normovolemic based on the base line values of haemodynamic values. The result shows that acepromazine can be safely used as far as chemical restraint of normovolemic calves is concerned. Accroding to Hall *et al*. (2001) [5], in healthy and normovolemic dogs and horses, the cardiovascular effects of acepromazine are well tolerated, however, fainting and cardiovascular collapse have been observed to occur occasionally in animals with shock or hypovolemia. The administration of acepromazine to the buffalo calves of present study produced sustained hypotension (15% fall in MAP). Therefore, administration of acepromazine in buffaloes with significant hypovolaemia can not be recommended till further studies prove otherwise.

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