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Vijay Nain
Veterinary Surgeon, Department of Animal Husbandry & Dairying, Government of Haryana, Haryana, India

Sonu Devi
Ph.D., Scholar, Department of Veterinary Pharmacology and Toxicology, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, Haryana, India

Umed Singh Mehra
Ph.D., Scholar, Division of Animal Reproduction, Indian Veterinary Research Institute, Uttar Pradesh, India

Amit Kumar
Ph.D., Scholar, Division of Animal Reproduction, Indian Veterinary Research Institute, Uttar Pradesh, India

Corresponding Author
Vijay Nain
Veterinary Surgeon, Department of Animal Husbandry & Dairying, Government of Haryana, Haryana, India

Haemodynamic effects of midazolam 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 to study the sedative action of of midazolam (0.2 mg/kg, i.m.). All the animals became ataxic within 3.33±0.76 minutes and went into lateral recumbency in 34±15.85 minutes after the administration of midazolam. There was a good muscle relaxation but no analgesia. The animals were standing with ataxia by 112.0±17.79 minutes and recovered after 183.5±17.79 minutes. The haemodyanamic changes showed that although there was about 15% reduction in MAP at 30 minute after administration of midazolam along with compensatory tachycardia and unaffected CVP, yet mean MAP value was never less than 120 mmHg. Slight increase in the amplitude of primary T-wave was observed in the electrocardiograms after midazolam administration. In conclusion, Midazolam (0.2 mg/kg, I.M.) can not be used for standing restraining of buffaloes because of severe ataxia caused by these drugs. However, good muscle relaxation achieved along with minimal cardiopulmanory effects should make use of this drug as a good preanaesthetic.

Keywords: Buffalo calves, dose, midazoalm, 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. Midazolam is a water soluble imidazole benzodiazepine with sedative, hypnotic, anticonvulsant and muscle relaxant properties (Gross, 2001) [9]. It has short duration of action with rapid elimination half-life in humans (Reves *et al.*, 1978) [15]. It has a rapid onset of action after intravenous administration (Crevoisier *et al.*, 1981) [6]. In veterinary medicine, midazolam is not used as widely as other agents such as diazepam. It has been reported to produce profound central nervous system depression in dogs when administered in combination with xylazine and butorphanol (Tranquilli *et al.*, 1991) [20] and with ketamine in cats (Chamber and Dobson, 1989) [4]. Midazolam has minimal effect on cardiopulmonary system in pigs and dogs (Smith *et al.*, 1991; Butola and Singh, 2007) [18, 2].

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 midazolam (Mezolam™, midazolam injection B.P., 5 mg/ml, Neon Laboratories Ltd. 28 Mahal Ind. Est. M. Caves Road, Andheri (East) Mumbai-400093, India). For detailed studies, based on the results of pilot trials, dose rate of midazolam was finalized 0.2 mg/kg via intramuscular route. Various hemodynamic and behivoural 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:

Drugs administered	Parameters investigated
Midazoalm(n=no. of animals, n=6)	Behavioural changes, 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.

Behavioral 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) [13, 14] 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, defecation 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:

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

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
1. Behavioural parameters
The spontaneous activity of animals decreased after the administration of midazolam. Within 3.33±0.76 minute of intramuscular administration of midazolam, calves became ataxic with lowering of head by 7.76±0.95 minute. All the animals went into sternal recumbency (34.0±15.85 minute). The animals appeared sleepy. There was moderate to complete relaxation of muscles of tail, prepuce and anus but jaw muscles were not relaxed and swallowing reflex was not abolished. Two animals urinated and defaecated. All the animals showed watery salivation. There was no cutaneous analgesia and animals attempted to get up or raised the head on pinpricks. The animals showed swaying of hind quarter while standing and milk fever posture with chin placed on ground. Animals were browsing after 104±16.27 minute of drug administration and stood up after 112.0±17.79 minute. They remained standing with ataxia, limbs wide apart. Complete recovery took 183.5±10.92 minutes (156 to 233 minute)

2. Electrocardiographic changes
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). Slight increase in the amplitude of primary T-wave was observed in the electrocardiograms after midazolam administration. There were no other major variation.

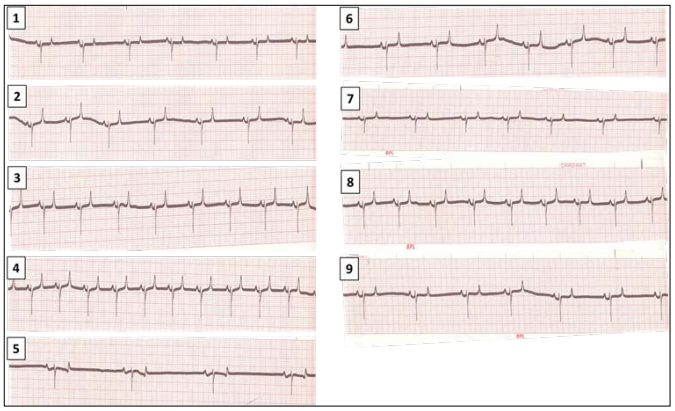

Fig 1: Electrocardiographs before administration of drug and at 5, 10, 15, 30, 45, 60, 75 and 90 minutes of administration of midazolam

3. Hemodynamic parameters
The effects of midazolam on heart rate, systolic pressure, diastolic pressure, pulse pressure, mean arterial pressure and central venous pressure are shown in table 1 and figure 2. There was some increase in heart rate after midazolam administration but the change was not significant (P>0.05). The pulse pressure did not show any significant changes at any period of observation. The value decreased to 9.67 ± 1.054 mm Hg at 45 minutes from base value of 11.84 ± 0.794 mm Hg as compared to the base value (11.83 ± +0.749 mm Hg). Mean arterial pressure reduced significantly to 123.17 ± 3.710 mm Hg at 30 minutes of drug administration from base value of 145.17 ± 2.182 mm Hg. No significant change was seen in central venous pressure at any period of observation.

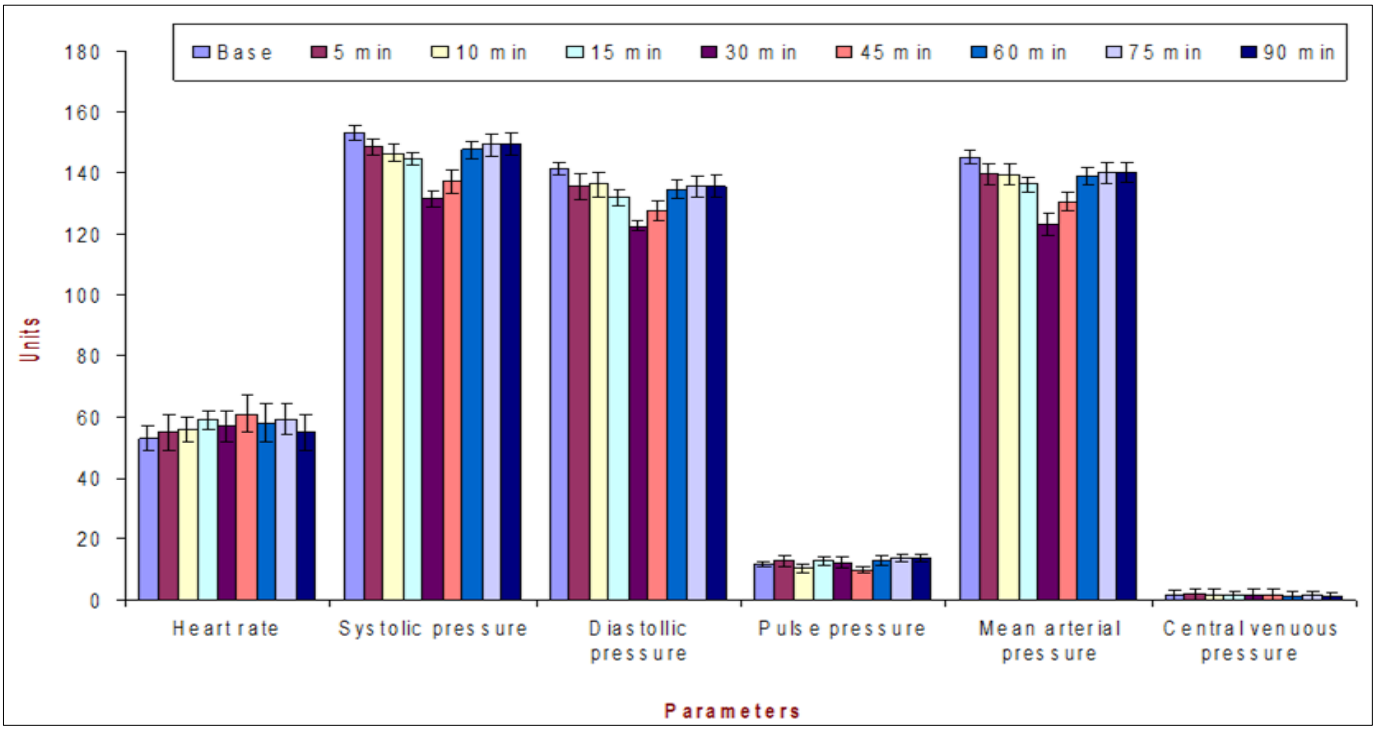

Fig 2: Effect of midazolam on heart rate (beats/min), systolic pressure (mm Hg), diastolic pressure (mm Hg), pulse pressure (mm Hg), mean arterial pressure (mm Hg), and central venous pressure (cm water)

Discussion

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. In the present study main objective was to evaluate efficacy of midazolam as a sedative in buffalo calves. Midazolam maleate is a relatively new drug of benzodiazepine group and approved by the FDA in 1986 for use in humans. Unlike diazepam, midazolam is water soluble. The drug has been evaluated in cow calves @ 0.3 mg/kg and 0.5 mg/kg and was considered to be safe agent on the basis of cardiovascular studies (Bishnoi, 2001 and Chander, 2004) [1, 5]. In the present study there was rapid onset of sedation. Animals became ataxic within 3.33 ± 0.76 minutes after I.M administration of midazolam. All the animals went into sternal recumbancy (34 ± 15.83). Midazolam rapidly enters the C.S.F. and its lypophilicity coupled with its high metabolic clearance and rapid elimination produce a short duration of action.

Table 1: The effect of intramuscular administration of midazolam (0.2 mg/kg) on heart rate, systolic pressure, diastolic pressure, pulse pressure, mean arterial pressure and central venous pressure

Parameters (Units)	Base	Midazolam							
		5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
Heart rate *(beats per minute)*	$53^{a} \pm 4$	$55^{a} \pm 6$	$56^{a} \pm 4$	$59^{a} \pm 3$	$57^{a} \pm 5$	$61^{a} \pm 6$	$58^{a} \pm 6$	$59^{a} \pm 5$	$55^{a} \pm 6$
Systolic pressure *(mm Hg)*	$153.17^{a} \pm 2.372$	$148.50^{a} \pm 2.446$	$146.50^{a} \pm 2.705$	$144.83^{ab} \pm 2.039$	$131.67^{c} \pm 2.741$	$137.17^{bc} \pm 3.609$	$147.50^{a} \pm 2.849$	$149.33^{a} \pm 3.547$	$149.50^{a} \pm 3.519$
Diastolic pressure *(mm Hg)*	$141.33^{a} \pm 2.044$	$135.67^{ab} \pm 4.137$	$136.17^{ab} \pm 3.885$	$132.00^{abc} \pm 2.769$	$122.67^{c} \pm 1.606$	$127.50^{bc} \pm 3.243$	$134.67^{ab} \pm 3.084$	$135.50^{ab} \pm 3.354$	$135.67^{ab} \pm 3.480$
Pulse pressure *(mm Hg)*	$11.83^{a} \pm 0.749$	$12.83^{a} \pm 1.740$	$10.33^{a} \pm 1.476$	$12.83^{a} \pm 1.302$	$12.33^{a} \pm 1.764$	$9.67^{a} \pm 1.054$	$12.83^{a} \pm 1.905$	$13.83^{a} \pm 1.078$	$13.83^{a} \pm 1.078$
Mean arterial pressure *(mm Hg)*	$145.17^{a} \pm 2.182$	$139.67^{ab} \pm 3.575$	$139.50^{ab} \pm 3.566$	$136.17^{ab} \pm 2.469$	$123.17^{c} \pm 3.710$	$130.67^{bc} \pm 3.263$	$138.83^{ab} \pm 2.857$	$140.00^{ab} \pm 3.567$	$140.17^{ab} \pm 3.535$
Central venous pressure *(cm water)*	$12.39^{a} \pm 1.679$	$13.84^{a} \pm 1.894$	$13.53^{a} \pm 1.836$	$11.19^{a} \pm 1.482$	$13.68^{a} \pm 1.839$	$15.00^{a} \pm 1.833$	$13.49^{a} \pm 1.450$	$12.05^{a} \pm 1.51$	$11.62^{a} \pm 1.166$

Means with different superscripts vary significantly ($P< 0.05$) (n=6). Means with different superscripts vary significantly ($P< 0.05$)

Its distribution half-life is one and half of prototype drug of its own group i.e. diazepam. The drug in small dosages gives excellent basal sedation and is most acceptable for short procedures (Gross, 1995) [10]. The animals completely recovered without ataxia after 183 ± 10 minutes. Smith *et al.* (1991) [18] also observed a sedation of about 20 mintue after single intramuscular injection or after incremental i.v. dosages of midazolam in pigs. Castro *et al.* (1988) found slightly diminished palpebral reflex and centrally positioned eyeball in dogs. Forster *et al.* (1980) [8] observed drowsiness and loss of eyelash reflex more often in male than female after midazolam (0.15 mg/kg) i.v. in human patients while Stegmann (1999) [19] found ataxia and sternal recumbancy after 0.4 mg/kg midazolam i.v. in goats. In the present experiment, all the animals responded to pinpricks at tail, indicating that the nociceptive threshold did not appear to be affected by midazolam. The effect of benzodiazepines on response to painfull stimuli are not well defined. Some studies

report that parenterally administered benzodiazepines have some analgesic activity, other findings do not support analgesic activity (Rosland *et al.*, 1987) [17]. The haemodyamic changes after administration of midazolm showed that, although there was about 15% reduction in MAP at 30 minute after midazolam administration along with compensatory tachycardia and unaffected CVP, yet mean MAP value was never less than 120 mm Hg. Therefore, these cardiovascular changes can not be said to be of major consequences as for as healthy animals are concerned, unless fluid volume of the patients is critically compromised. Midazolam @ 0.2 mg/kg used in the present study is not expected to seriously compromised the cardiovascular system of buffaloes. These changes are in contrast to those observed after midazolam administration in goats @ 0.4 mg/kg where the drug not only blunted the hypertensive effect of ketamine but also cause greater fall in MAP and along with a decreases in heart rate (Stegmann, 1999) [19]. According to Reves *et al.* (1985) [16] in humans midazolam @ 0.15 mg/kg i.v. produces significant reduction in systolic and diastolic pressure along with significant tachycardia. These changes in humans have been related to decrease in systemic vascular resistance and reduction in myocardial contractility by a direct action. The effect of midazolam in different species are highly variable. Stegmann (1999) [19] did not observe any significant cardiopulmonary change in goats. While Jones *et al.* (1979) [12] reported a significant increase in heart rate in dogs; reverse was true in pigs (Smith *et al.* 1991) [18]. Jangra (2004) [11] observed considerable reduction in heart rate at 10 minutes after administration of midazolam in goats. There was also arterial hypoxemia along with desaturation of Haemoglobin. In conclusion, Midazolam (0.2 mg/kg, I.M.) can not be used for standing restraining of buffaloes because of severe ataxia caused by these drugs. However, good muscle relaxation achieved along with minimal cardiopulmanory effects should make use of this drug as a good preanaesthetic.

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