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EFFECT OF MIDAZOLAM SEDATION IN DROMEDARY CAMELS (*Camelus dromedarius*)

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ABSTRACT

The study was designed to evaluate the suitability of midazolam as sedative in dromedary camels. Midazolam was administered at a dose 0.4 mg kg-1 body weight, intravenously as a bolus in 6 camels for induction of sedation and determination of sedative effects on the behaviour and various physiological, haematological and biochemical parameters of camels were evaluated. Midazolam produced sedation of short duration (5-7 min) with mild to moderate depression of palpebral and corneal reflexes, moderate salivation and lacrimation, mild to moderate relaxation of jaw, tail, limbs, abdomen and anus. Rectal temperature and pulse rate showed non-significant increasing trend whereas, significant increase in respiration rate was observed at 5 and 10 min 12.83±0.83 and 12.66±0.42, respectively while significant decrease in respiration rate at 40 min 10.0±0.5 were observed, compared with base line value of 11.0 ± 0.36. No appreciable changes in haematological parameters and the activity of ALP, ALT, AST and LDH enzymes were observed in the present study. Intravenous administration of midazolam proved safe sedative agent when used alone for chemical restraint for a variety of diagnostic and minor surgical procedures of short duration in camels.

Key words: Camel, dromedary, midazolam, sedation

Many diagnostic and therapeutic procedures in camels can be accomplished with physical and/or chemical restraint techniques (Abrahamsen, 2009). In practice, deep sedation is commonly used in camel practice in field situations (Ismail, 2016). Prolonged surgical procedure or inadequate effects of general anaesthetic agent often require supplementation with local analgesic or general anaesthesia (White *et al,* 1987; Fahmy *et al,* 1995). The risk involved with the potentially life threatening drugs acting on the nervous system is due to lack of understanding of various physiological and pharmacological aspects in camels. Despite the great advances in the use and understanding of sedative drugs in domestic animals, there have been few reports of their use in camels (Fouad, 2000). Chloropromazine hydrochloride, propoinyl promazine and acepromazine have been evaluated as sedatives in camels (Khamis *et al,* 1973; Ali *et al,* 1989). Alpha-2 agonists like xylazine, detomidine, medetomidine and romifidine has also been used for restraint, the calming of camels or stress reduction (Ali, 1988). The sedatives used alone or in combination with general anaesthetics minimise the undesirable effects on the physiological status of the camels.

Midazolam is a water soluble imidazole benzodiazepine derivative with sedative, hypnotic, anticonvulsant and muscle relaxant properties (Marjorie, 2001), 4 times more potent than diazepam (Stegmann, 1998) thus, preferred over diazepam (Reves *et al,* 1985). Midazolam has an early induction, short duration, rapid elimination and total body clearance (Court and Greenblatt, 1992; Thurmon *et al,* 1996), has minimal effects on cardiopulmonary system (Lemke, 2007; Butola and Singh, 2007) and thus may be preferred for combination anaesthesia in camels. In veterinary practice, midazolam has been used as sedative/preanaesthetic in cattle calves (Bishnoi and Saini, 2005), alpacas (Aarnes *et al,* 2013), Pigs (Smith *et al,* 1991), buffaloes (Cheema, 2002; Malik, 2008) and in goats (Stegmann, 1998), have less side effects than diazepam (Conklin *et al,* 1980; Pieri, 1983). However, perusal of literature reveals little information on the use of midazolam in dromedary camels. Considering the importance of this species and the scarcity of information, the study was designed to evaluate the suitability of midazolam as sedative.

Materials and Methods

The present study was conducted on randomly selected 6 adult healthy camels of either sex, aged 9 - 13 years and weighing 350 - 600 kg body weight. The optimal sedative dose of midazolam was standardised by conducting pilot trials in camels administered

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intravenously. Out of various dose trials, the midazolam (0.4 mg kg^{-1} body wt, intravenously) resulted in complete sedation. The animals were restrained in sitting position; food and water were withheld for 24hrs prior to the experimental trial.

Experimental Procedure

Midazolam was administered at a dose 0.4 mg kg^{-1} body weight, intravenously as a bolus in 6 camels for induction of sedation and determination of sedative effects on the behaviour and various physiological, haematological and biochemical parameters was done. The blood samples (10 ml) were collected from the jugular vein in EDTA containing and plain glass tubes for haematological and biochemical analysis, respectively. The blood sample was centrifuged and the serum separated and stored in refrigerator until use.

Recording of Observations

The parameters investigated during study were recorded at base line, 5, 10, 20, 40, 60 minutes and after 24 hrs of intravenous administration of midazolam.

Clinico-physiological Observations

Depth of sedation/anaesthesia was assessed by monitoring various reflexes like palpebral and corneal reflex, position of eye ball, salivation, lacrimation, relaxation of jaw, limbs, tail, abdomen and anus and response to pin-prick and bone-prick. These observations were graded as mild (+), moderate (++) and good (+++). Relaxation of jaw, tail, limbs, abdomen and anus were graded according to resistance observed. Response to pin-prick and bone-prick was graded mild when animal blinked the eyes at the time of prick, moderate when animal shooks its skin and moved the tail, eyelids or nostrils and good when animal moved its limbs tail or head at the time of prick. Rectal temperature, pulse rate and respiration rate were also recorded.

Haemato-biochemical Parameters

Haemoglobin, packed cell volume, total erythrocyte count, total leucocyte count and differential leucocyte count were estimated. Biochemical study was performed for quantitative estimation of alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactic dehydrogenase (LDH) enzymes on autoanalyser using standard kits.

The recorded data were subjected to the statistical analyses for interpretation of results to the methods suggested by Snedecor and Cochran (1967). The data were subjected to a two way analysis of variance (ANOVA) followed by a critical difference test for the comparison of mean values. A probability level of $P<0.05$ was considered as statistically significant. The mean values and standard error (SEM) were presented in tabular form.

Results and Discussion

Clinico-physiological Observations

Midazolam (0.4 mg kg^{-1}) administered intravenously as a sole agent produced change in normal behaviour of the camel (Table 1). Sanchez *et al* (1994) found midazolam (0.5 mg kg^{-1}) effective for restraint in cows. However, good sedation was observed in goats administered midazolam (0.4 mg kg^{-1}) intravenously (Stegmann, 1998). Midazolam (0.1–0.5 mg/kg) can cause paradoxic excitation, especially if administered rapidly intravenously to healthy adult ruminants (Seddighi and Doherty, 2016). The camels remained in sternal recumbency with the neck placed on the ground during onset of sedation however, lateral recumbency was observed in one camel at 10 min after intravenous administration of midazolam. It resulted in mild to moderate depression of palpebral and corneal reflexes, closure of eyelids with moderate salivation and lacrimation. The swallowing reflex decreased moderately during peak sedation. During sedation mild to moderate relaxation of jaw, tail, limbs, abdomen and anus was observed. Response to pin-prick was moderate at 5 min and mild to moderate at 10 min after administration. Response to bone - prick was found moderate at 5 and 10 min. The duration of sedation lasted for 5 - 7 min as shown by no response to pin-prick and bone-prick and absence of limb movements. Smith *et al* (1991) also observed a sedation of about 20 min. after single intramuscular injection or after incremental i.v. doses of midazolam in pigs. In another study, midazolam administered at a dose 0.5 mg kg^{-1} body wt. intravenously in buffalo calves induced sedation for 19.6 ± 2.61 min (Bishnoi, 2001). When used alone, midazolam could induce mild sedation for nonpainful procedures (e.g. radiography, ultrasonography) in tranquilised animals (Seddighi and Doherty, 2016). Midazolam causes muscle relaxation and mild tranquilisation, which when combined with anaesthetics like ketamine or propofol may improve the quality of induction or reduce the dose required to induce anesthesia (Pereira *et al*, 2006). Complete recovery from sedative effects occurred 35-40 min. after administration of midazolam evident as resumption of feed intake and walking without ataxia.

Table 1. Behavioural observations after intravenous administration of midazolam in camels (n = 6).

Observations	Time Interval (min)						
	Base Line	5	10	20	40	60	Hrs 24
Recumbency	**Sitting**	**Sitting**	**Lateral**	**Sitting/(Lateral)**	**Sitting**	**Sitting**	**-**
Palpebral Reflex	+++	++/(+++)	+/(++)	+++	+++	+++	+++
Corneal Reflex	+++	+++/(++)	++/(+++)	+++/(++)	+++	+++	+++
Eyeball Position	C	C	C/(D)	C/(D)	C	C	C
Salivation	-	+/(-)	++/(+)	+/++, (+/-)	-	-	-
Lacrimation	-	+/(++)	++/(+++)	+/++, (-)	-	-	-
Swallowing Reflex	+++	++	++	+++	+++	+++	+++
Jaw Relaxation	-	++	++	+	-	-	-
Tail Relaxation	-	++/ (+)	++	+	-	-	-
Limb Relaxation	-	+/(++)	++/(+)	-/(+)	-	-	-
Anus Relaxation	-	++	++/+++	+/(-)	-	-	-
Abdomen Relaxation	-	+/(-)	+/(-)	-	-	-	-
Pin Prick Response	+++	++	+/(++)	++/+++	+++	+++	+++
Bone Prick Response	+++	++/(+++)	++/(+)	+++	+++	+++	+++

- = Absent; + = Mild; ++ = Moderate; +++ = Good; C = Central; D = Downward rotation
Values in parentheses indicate variation from the response in one or two animals

The rectal temperature showed an increasing trend though statistically non-significant at different time intervals (Table 2). However, decreasing trend in rectal temperature was observed in buffalo calves till 45 minutes after administration of midazolam (Bishnoi, 2001) and at 60 minutes in pigs (Bustamante and Valverde, 1997) after administration of midazolam.

Pulse rate showed a non-significant increased value till 10 minutes while showed a regular decreasing trend at 20 min., till 24 hrs which are in accordance with the findings of Bishnoi (2001) in buffalo calves. However, significant increase in heart rate was observed in dogs (Jones *et al,* 1979). Non-significant change in cardio-pulmonary variables in goats was observed after administration of midazolam (Stegmann, 1998).

Significant increase in respiration rate was observed at 5 and 10 min 12.83 ± 0.83 and 12.66 ± 0.42, respectively, while significant decrease in respiration rate at 40 min.10.0 ± 0.5 were observed when compared with base line value of 11.0 ± 0.36. However, a significant decrease in respiration rate was seen in pigs (Smith *et al,* 1991) after midazolam administration. Bishnoi (2001) observed a non - significant decrease in the respiration rate in buffalo calves after administration of midazolam.

Haemato-biochemical Observations

No significant change was observed in the values of haemoglobin throughout experimental period. PCV value showed a non-significant increasing trend from 10 min. to 24 hrs while decreased at 5 min when compared to base line value. TEC, TLC and DLC did not show any appreciable change in their values in camels after administration of midazolam (Table 3). Bishnoi (2001) also reported non-significant change in haematological parameters in buffalo calves after administration of midazolam. Kashyap (1994) also reported non-significant change in hematological parameters in camels following administration of detomidine except for TLC values. However, a significant decrease in Hb and PCV along with decrease in TEC and TLC without any effect on DLC was observed in goats (Kumar and Thurmon, 1977) after intravenous administration of diazepam. The midazolam metabolites are conjugated and then excreted as glucuronides in the urine (Kronbach *et al,* 1989; Bauer *et al,* 1995). No appreciable changes in the activity of ALP, ALT, AST and LDH enzymes were observed in the present study (Table 4). Likewise, non-significant changes in activity of these enzymes had also been reported in buffalo calves after administration of midazolam (Bishnoi, 2001). In contrast to present study, an increase in activity of alkaline phosphatase after high doses of midazolam (45 mg kg^{-1}/day) was observed in dogs (Schlappi, 1983). Non-significant changes in the activity of ALP, ALT, AST and LDH enzymes were also observed in calves after diazepam sedation (Mirakhur *et al,* 1988). Kumar and Thurmon (1977) observed a mild increase in serum LDH and AST enzymes with no appreciable changes in ALP after diazepam administration in

Table 2. Physiological parameters after intravenous administration of midazolam in camels (n = 6).

Parameter	Time Interval (Min)						
	Base Line	5	10	20	40	60	24 Hrs
Rectal Temperature (° F)	97.51±0.35	97.69±0.31	98.08±0.31	98.19±0.27	98.43±0.23	98.71±0.21	97.90±0.26
Pulse Rate (Min^{-1})	43.16±0.56	46.33±0.95	48.16±0.57	47.00±2.95	45.83±2.89	44.83±2.37	–
Respiration Rate (Min^{-1})	11.00±0.36	12.83*±0.83	12.66*±0.42	11.00±0.73	10.00*±0. 51	10.86±0.80	10.66±0.73

* Significantly different from Base line value (P < 0.05).

Table 3. Haematological parameters after intravenous administration of midazolam in camels (n = 6).

Parameter	Time interval (min)						
	Base line	5	10	20	40	60	24 hrs
Hb (g/dl)	11.43±0.47	11.3±0.37	11.41±0.48	11.46±0.40	11.60±0.35	11.43±0.36	11.3±0.45
PCV (%)	27.16±0.87	26.16±0.94	27.33±1.02	27.66±0.84	27.33±0.95	28.5±0.99	27.6±0.98
TEC (x 10^6 μL^{-1})	9.33±0.49	9.16±0.40	9.66±0.33	10.16±0.16	10.00±0.00	9.33±0.33	9.33± 0.42
TLC (x 10^3 μL^{-1})	14.36±0.65	14.28±0.57	14.16±0.62	14.25±0.59	14.13±0.58	14.23± 0.66	14.26±0.66
DLC (%)							
Neutrophils	50.83±0.47	51.00± 0.68	51.16±0.47	51.33±0.33	50.83±0.60	50.66± 0.49	51.16± 0.40
Lymphocytes	41.00±1.06	40.83± 1.07	40.83±0.17	40.66±1.02	40.66±0.88	41.00± 1.06	41.0±0.93
Monocytes	2.0±0.25	2.0±0.25	2.00±0.25	1.83±0.30	1.5±0.22	1.50±0.22	2.0±0.25
Eosinophils	2.0±0.35	2.0±0.36	2.33±0.21	2.16±0.30	2.00±0.36	2.00±0.36	2.0±0.36

* Significantly different from Base line value (P < 0.05)

Table 4. Biochemical parameters after intravenous administration of midazolam in camels (n = 6).

Parameter	Time interval (min)						
	Base line	5	10	20	40	60	24 hrs
ALP (IU/L)	77.62±0.39	79.10±3.96	78.44±4.93	76.66±5.54	77.71±3.66	74.01±5.22	77.88±5.86
ALT (IU/L)	15.35±4.00	14.41±2.85	14.70±2.88	12.78±1.34	13.78 + 2.60	15.32 + 4.43	15.81±4.63
AST (IU/L)	118.11±21.18	125.25±22.76	124.29±22.05	123.12±21.06	118.31±5.87	112.98±6.08	120.53±21.14
LDH (IU/L)	555.81±46.34	567.40±50.02	564.59±48.02	560.75±53.65	542.01±49.11	596.56±44.31	571.59±50.44

* Significantly different from Base line value (P < 0.05)

goats. The non significant change in these enzymes favours its use in geriatric and compromised animals.

Thus intravenous administration of midazolam induces sedation for short duration at a dose (0.4 mg kg^{-1}). Midazolam could be used for chemical restraint for a variety of diagnostic and minor surgical procedures and declared safe sedative agent when used alone, or in combination with anaesthetic drugs to improve the quality of sedation in camels.

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