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ANTINOCICEPTIVE, SEDATIVE, AND CARDIOPULMONARY EFFECTS OF INTRAVENOUS LIDOCAINE IN ONE-HUMPED CAMELS (*Camelus dromedarius*)

A.I. Almubarak
College of Veterinary Medicine and Animal Resources, Camel Research Centre
King Faisal University, Al-Hassa, Saudi Arabia

ABSTRACT

Intravenous (IV) 3 mg kg-1 lidocaine was evaluated in 7 healthy camels. Baseline nociceptive threshold, sedation score, respiratory rate, heart rate, arterial blood pressure (ABP) and rectal temperature were determined, and further recorded at 5, 10, 20, 40, 60 minutes after treatment. Some haematology and biochemistry parameters were assessed at baseline, and at 10, 60 minutes after treatment. There was significant effect on nociceptive threshold at all time points compared to baseline, and significant increase in sedation score between 5 and 40 minutes. Respiratory rate, heart rate, and rectal temperature did not differ significantly, while diastolic ABP increased significantly at 10 minutes after treatment. There was no significant difference in all haematological and biochemical measured parameters. These results showed that IV lidocaine was safe, useful in providing antinociception and sedation, and coupled with minimal cardiovascular effects in camels.

Key words: Antinociception, camel, lidocaine, sedation

Lidocaine, which is commonly used as a local anaesthetic, has also been used IV as part of combination anaesthetic techniques to complement general anaesthesia in domestic animals (Vesal *et al,* 2011). It has been used intravenously (IV) to reduce the requirement for injectable and inhalant anaesthetics in horses, calves, goats, and dogs (Muir *et al,* 2003; Doherty *et al,* 2007; Vesal *et al,* 2011; Mannarino *et al,* 2012), and to provide post operative analgesia in conscious horses and dogs (Smith *et al,* 2002; Torfs *et al,* 2009). The antinociceptive or sedative effects of IV lidocaine alone have not been examined thoroughly when administered preoperatively or in conscious healthy animals. When the IV lidocaine was administered in healthy conscious cats, it provided no effect on thermal antinociception (Pypendop *et al,* 2006). Similar results were found in dogs (MacDougall *et al,* 2009) but were associated with mild to moderate sedation, and some signs of toxicity. The objective of this study was to evaluate the antinociceptive and sedative effects of single bolus of IV lidocaine, and to observe the effects on heart rate, respiratory rate, systemic arterial blood pressure, and some haematology and biochemistry parameters in camels.

Materials and Methods

Seven healthy dromedary camels of two breeds, 5 Shoael and 2 Majaheem, 5 males and 2 females, with mean age ± SD 4.8 ± 1.8 years, and weight 455 ± 72.9 kg were used for this study. Food, but not water, was withheld for 24 hours before trials. Camels were restrained manually in sternal recumbency at least three hours before start of trials. Baseline sedation score, nociceptive threshold, heart rate (manually by a stethoscope), respiratory rate (counting thoracic movements), and rectal temperature (electronic thermometer) were assessed. Baseline indirect blood pressure values were assessed by oscillography using a cuff placed around the base of the tail and connected to a patient monitor (Infinity Delta XL, Drager Medical, Germany). These parameter values were further recorded at 5, 10, 20, 40, 60 minutes after treatment. After baseline data were obtained, all camels received IV lidocaine (Lidocaine Hydrochloride USP, Pharmaceutical Solution Industry, Saudi Arabia) at 3 mg kg^{-1} through jugular vein over one minute. Sedation was scored using a 4-point scale (0 = no sedation with normal movement; 1 = mild sedation: slightly decreased movement and reduced eye alertness; 2 = moderate

SEND REPRINT REQUEST TO A.I. ALMUBARAK email: aimubarak@kfu.edu.sa

sedation: moderately decreased movement and resistance to handling; 3 = deep sedation: markedly decreased movement and no resistance to handling) based on a previously published scoring system in camel (Marzok and El-Khodery, 2009). Nociceptive threshold was obtained using a visual analogue scale (VAS) with 0 representing no pain and 10 representing the worst pain possible (Mathews, 1996). Nociceptive threshold was tested by application of Kocher "1:2 teeth" artery forcep (Albert Waeschle Ltd. Dorset, UK) to skin areas of perineal, tarsus, thigh, and abdomen. Positive nociceptive responses to the stimuli were defined as purposeful avoidance movements of head, neck, trunk, limbs, tail; contracture of the anus and turning of the head towards the stimulation site (Dehkordi *et al,* 2012). Two blinded assessors, who were familiar with the camel's normal behaviour, were responsible for assessing sedation and response to the nociceptive stimulus throughout the study.

Blood samples (14 ml) were taken at baseline, 10 and 60 minutes after lidocaine administration. They were collected from the jugular vein via disposable syringes and divided into EDTA tubes for haematologic evaluation, and to plain tubes without anticoagulant for the biochemical analysis. For haematological evaluation, each tube was inverted 2-3 times to ensure thorough mixing, and analysed within 2 hours using an automated haematology analyser (VetScan HM2, Abaxis Veterinary Diagnostics, USA) for total erythrocyte count (RBC), haemoglobin (HB), haematocrit (HCT), white blood cell count (WBC), lymphocytes (LY), monocytes (MO), neutrophil (NE), mean cell volume (MCV), and platelet count (PLT). For biochemical analysis, serum was harvested by centrifugation and stored at -80 °C until analysed by automatic analyser (VetScan VS2, Abaxis Veterinary Diagnostics, USA) for albumen (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), amylase (AMY), urea nitrogen (BUN), calcium (CA), phosphorus (PHOS), creatinine (CRE), glucose (GLU), sodium (NA+), potassium (K+), total protein (TP), and globulin (GLOB).

Statistical analysis was performed using the General Linear Model (GLM) procedure (SAS Institute Inc, Cary NC USA, 2002). Data presented as mean ± SD unless otherwise stated. Data was calculated and tested for the significance using 't' test. Moreover, arc sine transformation was done to percentage data. P value of less than 0.05 was considered significant.

Results

Table 1. Shows that mean respiratory rate, heart rate and rectal temperature did not differ significantly as compared to baseline. Mean arterial blood pressure measurements did not differ significantly as compared to baseline, except significant increase of diastolic arterial pressure (DAP) at 10 minutes after lidocaine administration. Median (range) of sedation scores and nociceptive threshold are presented in table 2. There was significant increase in sedation score between 5 and 40 minutes compared with baseline, and there was significant effect on

Table 1. Mean values ± SD of respiratory rate (fR) breaths minute -1, heart rate (HR), beats minute -1, mean arterial blood pressure (MAP), systolic arterial blood pressure (SAP), and diastolic arterial blood pressure (DAP) at the baseline (BL), and at 5-60 minutes after lidocaine administration.

Variables	BL	5	10	20	40	60
fR	22 ± 4.2	19.7 ± 4.3	18 ± 4.9	20.7 ± 2.1	19.3 ± 3	9.1 ± 3.7
HR	52.6 ± 9.9	53.7 ± 12.5	52.6 ± 9.4	51.1 ± 8.6	50.6 ± 10.9	49.4 ± 9.1
Temp. °C	37.3 ± 0.5	37.3 ± 0.4	37.6 ± 1.1	37.3 ± 0.3	37.2 ± 0.4	37.1 ± 0.4
MAP mmHg	130.9 ± 11.6	147 ± 30.3	143.4 ± 15.3	144.9 ± 16.9	128.6 ± 16.3	140.7 ± 27.5
SAP mmHg	171 ± 20.1[a]	170.7 ± 30[a]	176.6 ± 24.8[a]	189.6 ± 28.6[ab]	161.1 ± 21.2[ac]	173.3 ± 30.8[a]
DAP mmHg	101.6 ± 16.9[ac]	114.1 ± 16.4[a]	120.1 ± 16.3[ab]	116.1 ± 16.5[a]	105.7 ± 16[a]	117.6 ± 23.4[a]

[abc] Means within a row with different superscripts differ significantly ($p<0.05$).

Table 2. Median (range) of sedation scores and nociceptive threshold at the BL, and at 5-60 minutes after lidocaine administration.

Variable	Time					
	BL	5	10	20	40	60
sedation score	0(0-0)[a]	3 (2-3)[b]	2 (1.5-3)[c]	2 (0-2)[d]	1 (0-1.5)[e]	0 (0-1.5)[a]
nociceptive threshold	10(10-10)[a]	2.5 (1-4.5)[b]	3.5(0-4.5)[b]	3.4 (0-6)[c]	4.5 (3-6)[d]	6.7 (4-7.5)[d]

[abcd] Medians in row with different superscripts differ significantly ($p<0.05$).

nociceptive threshold at all time points compared to baseline. Table 3 shows the haematological parameters, while table 4 shows serum biochemistry parameters, with no significant difference could be detected in all measured parameters as compared to baseline.

Table 3. Haematological parameters (mean ± SD) at baseline, 10 and 60 minutes after lidocaine administration.

Parameters	Time		
	Baseline	10	60
RBC (cells/µl)	11.2 ± 1.4	10.7 ± 0.7	11.5 ± 1.1
HB (g/dL)	14.4 ± 1.1	14.3 ± 0.6	13.6 ± 0.7
HCT (%)	30.3 ± 3.0	28.9 ± 2.1	31.7 ± 4.4
WBC (g/L)	17.1 ± 3.9	16.7 ± 3.8	17.7 ± 3.6
LY (%)	33.9 ± 6.3	33.4 ± 6.2	31.9 ± 5.8
MO (%)	4.5 ± 0.9	3.8 ± 1.1	3.8 ± 1.1
NE (%)	61.7 ± 6.8	62.7 ± 7.1	64.2 ± 6.4
MCV (fl)	27.4 ± 1.3	27.0 ± 1.0	27.9 ± 1.6
PLT (g/dL)	137.1 ± 42.9	176.7 ± 75.5	137.9 ± 53.7

[abcd] Means within a row with different superscripts differ significantly ($p<0.05$).

Table 4. Serum biochemistry (mean ± SD) at baseline, 10 and 60 minutes after lidocaine administration.

Parameters	Time		
	Baseline	10	60
ALB (g/dL)	4.2 ± 0.4	4.5 ± 0.5	4.5 ± 0.2
ALP (U/L)	129.9 ± 22.3	131.3 ± 37.3	125.1 ± 52.1
ALT (U/L)	17.6 ± 2.1	19.0 ± 3.1	17.7 ± 2.8
AMY (U/L)	565.9 ± 82.1	595.1 ± 68.0	587.7 ± 63.6
BUN (mg/dL)	15.9 ± 3.2	16.6 ± 4.8	16.4 ± 2.9
CA (mg/dL)	9.7 ± 0.6	9.9 ± 0.9	9.9 ± 0.8
PHOS (mg/dL)	9.5 ± 1.5	9.9 ± 1.8	10.2 ± 2.2
CRE (mg/dL)	1.4 ± 0.3	1.5 ± 0.3	1.3 ± 0.2
GLU (mg/dL)	88.6 ± 28.1	97.4 ± 39.7	83.2 ± 49.2
NA+ (mmol/L)	140.6 ± 13.3	148.3 ± 16.1	148.7 ± 7.0
K+ (mmol/L)	7.9 ± 1.0	7.9 ± 0.9	8.1 ± 0.7
TP (g/dL)	6.5 ± 0.7	6.8 ± 0.7	6.8 ± 0.3
GLOB (g/dL)	2.2 ± 0.4	2.3 ± 0.3	2.4 ± 0.3

[abcd] Means within a row with different superscripts differ significantly ($p<0.05$).

Discussion

The mechanism of action for lidocaine's analgesic and sedative effects is poorly understood (Smith *et al,* 2004; Vesal *et al,* 2011). It has been documented that the final analgesic action of IV lidocaine is a reflection of its multifactorial action, and it has been suggested that its central sensitisation is secondary to a peripheral anti-hyperalgic action on somatic pain and central on neuropathic pain, which result on the blockade of central hyperexcitability (Lauretti, 2008). Whatever the mechanism, there is considerable evidence for the efficacy of lidocaine infusion in providing analgesia in a number of species and situations (Vesal *et al,* 2011).

The pharmacokinetics of IV lidocaine in camels have not been investigated, therefore, and based on other studies (Doherty and Frazier, 1998; Dzikiti *et al,* 2003; MacDougall *et al,* 2009), a loading dose of 3 mg kg^{-1} was used in this study.

Sedation was detected after IV lidocaine in dogs and human (Shim *et al,* 2002; Szmuk *et al,* 2007; MacDougall *et al,* 2009), and ataxia was also detected in horses (Solìs and McKenzie, 2007). In this study, deep to moderate sedation was shown after lidocaine administration in 5 and 10 minutes, followed by mild sedation towards 40 minutes. Moreover, and by 30 seconds to 1 minutes after lidocaine administration, three camels went immediately to lateral recumbency, and remained recumbent laterally for the next 7-9 minutes.

Pain is a multifactorial entity, and cannot be studied by a single method, therefore, studies using more than one type of nociceptive stimulus present more information relevant to clinical pain and analgesia (Steagall *et al,* 2007; Millette *et al,* 2008).

Mechanical, thermal, and electrical stimuli are the most commonly used methods in preclinical experimental assessment of nociception (Love *et al,* 2011). Antinociception was assessed in this study by application of artery forceps, a method used frequently to assess absence of response to a noxious stimulus (Docquier *et al,* 2004; Prado *et al,* 2008; Ajadi *et al,* 2009). Although this method is subjective, error was reduced by the two blinded assessors, who were familiar with the camel's normal behaviour, and responsible for assessing response to the nociceptive stimulus throughout the study.

The analgesic effect of IV lidocaine in conscious animals is controversial (Vesal *et al,* 2011). IV lidocaine had no effect on nociceptive thresholds in dogs or cats (Pypendop *et al,* 2006; MacDougall *et al,* 2009), but provided antinociception in horses (Murrell *et al,* 2005). Several studies have shown that lidocaine administration significantly decreases inhalant requirements (Muir *et al,* 2003; Doherty *et al,* 2007; Vesal *et al,* 2011; Mannarino *et al,* 2012), and decreased post-operative analgesic requirements (Torfs *et al,* 2009) with benefits similar to morphine

(Smith *et al,* 2002). During this study, the peak effect of nociceptive thresholds was reported at 5 minutes after IV lidocaine administration, then gradually decreased in next time points, but still significantly observed at 60 minutes when compared to baseline. The nociceptive thresholds recorded in this study is higher than thresholds reported in previous studies (Murrell *et al,* 2005; MacDougall *et al,* 2009).

Mean heart rate, respiratory rate, and temperature after IV lidocaine in this study were not different from baseline, which is in agreement with previous studies in dogs (Kapur *et al,* 1988; Leone *et al,* 1988; Chandler *et al,* 2006) and horses (Dzikiti *et al,* 2003; Murrell *et al,* 2005; Malone *et al,* 2006). However, an increase in heart rate was reported after lidocaine administration in horses (Torfs *et al,* 2009), and dogs (Nunes *et al,* 1998), but remained within a clinically acceptable range, and that was referred to a very high concentrations of lidocaine used at their study. In contrast, Pypendop and Ilkiw (2005) found, in anaesthetised cat, that heart rate was lower after lidocaine administration. Mean ABP measurement in this study increased but not significantly after lidocaine administration at 5,10 and 20 minutes. This is similar with other results reported in dogs (Hashimoto *et al,* 1985; Nunes *et al,* 1998; MacDougall *et al,* 2009) that showed marginal but not significant increase in blood pressure measurements during IV lidocaine administration. However, the increase of mean ABP measurement in this study remained within clinically acceptable limits. Arterial catheterisation is problematical in this species, due to their thick skin and muscle layers, and so monitoring direct arterial blood pressure measurement and arterial blood gases has not been done in this study. The method of indirect oscillometry for blood pressure measurement used in this study provides useful information in most horses, but may produce erroneous values in a small number (Hall *et al,* 2001). In the current study, there was no significant difference in haematological or biochemical parameters after lidocaine administration. However, most parameters obtained were within the normal range of camels (Mohri *et al,* 2008; Hussein *et al,* 2012).

In conclusion, this study demonstrated that IV lidocaine provided antinociception and sedation, coupled with minimal cardiovascular effects in camels. However, further work needs to be done with evaluation of other cardiorespiratory parameters, including invasive blood pressure measurements, blood gas analysis and continuous capnography recording. Moreover, investigating pharmacokinetics of lidocaine with different IV loading doses and continuous rate infusions used for prolonged duration, with identifying blood serum concentrations which resulted in clinical sign of intoxication, is necessary to establish its use and safety in camels.

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