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Evaluation of Intravenous Administration of Doxapram Prior to Xylazine Sedation in Camels (*Camelus dromedarius*)

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Abstract: The effects of doxapram on respiratory rate, heart rate, Arterial Blood Pressure (ABP) and some haematology and biochemistry parameters were carried out on six camels in two periods. In the first period, all camels received Intravenous (IV) 0.2 mg kg^{-1} xylazine while in the second period, same camels received IV 0.4 mg kg^{-1} doxapram, followed 10 min later by IV 0.2 mg kg^{-1} xylazine. Cardiopulmonary measurements were taken at baseline and were further recorded at 10, 20, 30, 40, 50 and 60 min after treatment in both periods. Mean respiratory rate, heart rate and ABP measurements decreased significantly after xylazine in the first period. Mean respiratory rate in the second period increased significantly at 10 min while systolic ABP increased significantly at 30 min when compared with first period. Mean heart rate decreased significantly at 20 min in the second period when compared with first period. There was a significant differences between the two periods in some measured haematological and biochemical parameters. Doxapram was useful to increase respiratory rate and ABP in xylazine sedated camels. Higher doses of doxapram needed further investigation in camels.

Key words: Camel, doxapram, xylazine, analeptic, sedation, haematology, biochemistry

INTRODUCTION

Doxapram is an analeptic used by veterinarians to reverse respiratory depression in animals (Meyer *et al*., 2010). Both receptor cites in central (brainstem) and peripheral (carotid artery and aorta) can be stimulated by doxapram (Yost, 2006; Bleul *et al*., 2010). It improves arousal and level of consciousness during general anaesthesia in human and animals (Winnie and Collins, 1966; Taylor, 1990) and also shortened recovery time after general anaesthesia in human (Riddell and Robertson, 1978).

It is commonly used to reverse opioid-induced respiratory depression (Bowdle, 1988; Meyer *et al*., 2010). Xylazine is an α2-adrenoceptor agonist used commonly as sedative in veterinary anaesthesia (England and Clarke, 1996). It produces respiratory depression, bradycardia, initial hypertension followed by a prolonged hypotension and decreased cardiac output, due to sympathetic blockade and vagal stimulation (Clarke and Hall, 1969; Maze and Tranquilli, 1991; Wagner *et al*., 1991). The effects of xylazine can be reversed by IV administration of doxapram in sheep and goats (Hall *et al*., 2001a). In camels, no studies have been reported on the combined use of doxapram with xylazine. Therefore, the objective of this study was to evaluate the efficacy of a single bolus dose of doxapram administered prior to xylazine and to observe effects on heart and respiratory rate, systemic ABP and some haematology and biochemistry parameters in healthy camels.

MATERIALS AND METHODS

Six healthy dromedary camels of two breeds, 4 Shoael and 2 Majaheem, 4 males and 2 females with mean age±SD 4.0±1.8 years and weight 393.7±136.8 kg were used in this two periods study. This study was performed with 5 days interval between the two periods. In the first period, all camel received xylazine (X-group) (Rompun, Bayer, Turkey) as a single IV dose of 0.2 mg kg^{-1} into the jugular vein. While, in the second period, all camels received doxapram (D-X-group) (Doxapram-V, Albrecht GmbH, Germany) as a single IV dose of 0.4 mg kg^{-1}, followed 10 min later by 0.2 mg kg^{-1} xylazine. Food but not water was withheld for 24 h before trials. Camels were restrained manually in sternal recumbency at least 3 h before start of trials. Baseline (before treatment) heart rate (manually by astethoscope), respiratory rate (counting thoracic movements) and rectal temperature (electronic thermometer) were assessed. Baseline indirect ABP 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 5AD, 10AD min after doxapram administration in the D-X group and at 10, 20, 30, 40, 50 and 60 min after xylazine administration in both groups.

Blood samples (14 mL) were taken at baseline, 10 and 60 min after xylazine administration in both groups. 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 analyzed within 2 h using an automated haematology analyzer (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 analyzed by automatic analyzer (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., CaryNC USA, 2002). Data presented as mean±SD unless otherwise stated. Data was calculated and tested for the significance using the t-test. Moreover, arc sine transformation was done to percentage data. The $p<0.05$ was considered significant.

RESULTS AND DISCUSSION

Table 1 shows that mean heart rate, respiratory rate and ABP measurements decreased significantly in X-group after treatment. After treatments in the D-X-group, mean heart rate decreased significantly between 10 and 60 min compared with baseline and decreased significantly at 20 min when compared with X-group. Mean respiratory rate in the D-X-group increased significantly at 10 min compared with X- group. There was significant decrease of mean ABP measurements after treatments in the D-X-group compared with baseline but SAP was significantly higher at 30 min when compared with X-group. There were significant differences between the two groups in the differential haematology at MO, MCV and PLT with significant decrease of RBC, HB and HCT in the X-group after treatment and significant decrease of HB in the D-X group after treatment (Table 2). There were also significant differences between the two group in the differential biochemistry at ALT, BUN, CA and GLU (Table 3).

Establishing and maintaining a secure airway is a major concern for care in patient during anaesthesia. The most frequent major complications in camels anaesthesia are regurgitation and aspiration pneumonia that interfere with ventilation. Endotracheal intubation is the most basic method to prevent airway obstruction and aspiration pneumonia but this could not be a possible routine due to difficulties in intubating this species because of narrow oropharynx space, elongated soft palate and very sharp teeth. Doxapram was described as a pharmacologic ventilator used in reviving patient following general anaesthesia (Winnie and Collins, 1966) and it has been used as well in treatment of drug-induced CNS depression (Rappolt *et al*., 1980). Xylazine is considered the most common premedication used in camels and was included in this study due to its cardiopulmonary depression characteristics that mimic clinical situation. This study demonstrates that heart rate, respiratory rate, ABP measurements decreased significantly in the X-group following IV 0.2 mg kg^{-1}

Table 1: Mean values±SD of Heart Rate (HR), respiratory rate (f_R) breaths/minute, beats/minute, Mean Arterial Blood Pressure (MAP), Systolic Arterial Blood Pressure (SAP) and Diastolic Arterial Blood Pressure (DAP) at the Baseline (BL), at 5 min after D Administration (5AD), at 10 min after D Administration (10AD) and 10-60 min after xylazine and doxapram-xylazine administration

	Time (min)								
Variables	BL	5AD	10AD	10	20	30	40	50	60
HR									
Xylazine	47.5±4.90^{a}	-	-	33.7±5.40^{b}	36.3±4.50^{bx}	34.2±8.70^{b}	31.8±5.90^{b}	31.3±5.40^{b}	33.2±9.20^{b}
Doxapram	42.3±4.30^{a}	38.7±3.70^{a}	36.8±5.20^{a}	29.5±4.10^{b}	29.0±5.00^{by}	29.7±4.30^{b}	28.7±5.50^{b}	27.5±2.90^{b}	27.7±3.50^{b}
f_R									
Xylazine	20.5±7.80^{a}	-	-	14.3±3.80^{bcx}	13.3±3.90^{bc}	15.7±4.10^{ac}	16.7±3.90^{ac}	15.0±2.10^{bc}	15.8±1.80^{ac}
Doxapram	18.3±4.00^{a}	15.7±4.00^{ab}	18.3±4.50^{a}	21.5±7.00^{acy}	16.7±3.90^{a}	16.7±5.00^{a}	14.0±4.20^{ab}	15.2±4.40^{ab}	14.3±4.50^{ab}
MAPmmHg									
Xylazine	129.3±19.8^{a}	-	-	119.5±10.8^{ac}	109.3±11.1^{bc}	108.3±10.1^{bc}	105.3±11.7^{bc}	111.3±18.3^{bc}	109.8±21.8^{bc}
Doxapram	140.8±11.6^{a}	132.2±25.5^{ac}	138.7±15.8^{a}	130.8±7.60^{ac}	116.0±9.70^{bc}	119.0±17.7^{bc}	117.0±12.0^{bc}	111.3±10.6^{b}	117.5±15.8^{bc}
SAP mmHg									
Xylazine	161.5±18.5^{a}	-	-	143.8±10.7^{ac}	139.0±11.9^{bc}	131.3±16.1^{bcx}	129.7±13.7^{bc}	131.2±20.9^{bc}	140.3±31.3^{bc}
Doxapram	175.5±13.5^{a}	168.3±24.6^{ac}	172.3±14.4^{acd}	155.8±8.70^{bc}	144.5±8.00^{b}	150.3±18.9^{bcey}	144.8±15.7^{b}	139.7±11.4^{b}	144.2±18.4^{b}
DAP mmHg									
Xylazine	96.0±22.2^{ax}	-	-	96.7±15.5^{a}	91.0±9.50^{a}	92.0±7.40^{a}	87.5±8.70^{a}	92.7±14.7^{a}	88.3±20.9^{a}
Doxapram	115.0±4.60^{ay}	105.3±26.0^{ac}	107.7±20.0^{ac}	112.5±7.60^{acd}	96.8±13.0^{bc}	100.7±15.5^{ac}	98.8±9.40^{ac}	93.0±10.0^{bce}	96.7±12.7^{bc}

$^{a-d}$Means within a row with different superscripts differ significantly ($p<0.05$). $^{x, y}$Means within a column with different superscripts differ significantly ($p<0.05$)

Table 2: Haematology (mean±SD) at baseline, 10 and 60 min after premedication with xylazine in the first period and after doxapram-xylazine administration in the second period

	Time (min)		
Variables	Baseline	10	60
RBC (cells µL^{-1})			
Xylazine	11.2±1.20^{ac}	10.7±1.60^{a}	9.8±1.60^{bc}
Doxapram	11.5±1.60	11.7±1.50	9.8±1.70
HB (g dL^{-1})			
Xylazine	13.9±1.90^{ac}	13.1±1.20^{a}	11.7±1.10^{ac}
Doxapram	14.0±1.90^{ac}	13.4±1.00^{a}	12.3±1.20^{ab}
HCT (%)			
Xylazine	32.5±3.30^{ac}	30.8±4.80^{a}	28.0±4.10^{bc}
Doxapram	32.1±4.20	33.4±4.10	27.9±4.80
WBC (g L^{-1})			
Xylazine	18.4±3.60	17.0±3.10	16.1±2.60
Doxapram	17.2±5.70	16.8±5.40	16.7±5.30
LY (%)			
Xylazine	36.9±8.70	35.9±9.30	34.2±8.70
Doxapram	37.9±9.40	34.1±8.70	33.0±7.70
MO (%)			
Xylazine	6.7±1.20^{x}	5.9±0.60^{x}	6.1±0.90^{x}
Doxapram	4.6±1.10^{y}	4.1±1.30^{y}	4.5±1.20^{y}
NE (%)			
Xylazine	56.5±8.30	58.2±9.40	59.7±8.90
Doxapram	57.6±9.70	61.9±9.60	61.7±10.1
MCV (fl)			
Xylazine	28.8±0.80^{x}	28.7±0.80	28.7±0.80
Doxapram	28.0±0.60^{y}	28.7±0.50	28.7±0.50
PLT (g dL^{-1})			
Xylazine	173.0±60.8	124.7±61.7^{x}	144.0±49.8
Doxapram	198.0±87.6	247.8±63.1^{y}	179.2±39.3

$^{a-d}$Means within a row with different superscripts differ significantly ($p<0.05$). $^{x, y}$Means within a column with different superscripts differ significantly ($p<0.05$)

Table 3: Serum chemistry (mean±SD) at baseline, 10 and 60 min after premedication with xylazine in first period and after doxapram-xylazine administration in the second period

	Time (min)		
Variables	Baseline	10	60
ALB (g dL^{-1})			
Xylazine	4.9±0.500	4.4±0.400	4.8±0.400
Doxapram	4.7±0.500	4.8±0.400	4.5±0.300
ALP (U L^{-1})			
Xylazine	91.2±39.80	72.1±32.60	81.2±31.30
Doxapram	74.0±31.40	75.2±41.10	79.0±40.20
ALT (U L^{-1})			
Xylazine	7.2±1.700^{x}	6.3±1.900^{x}	6.8±1.600^{x}
Doxapram	12.8±4.800^{y}	16.8±12.10^{y}	13.5±8.100^{y}
AMY (U L^{-1})			
Xylazine	629.5±237.5	621.8±241.5	616.7±238.7
Doxapram	723.3±194.2	737.0±180.7	717.0±154.5
BUN (mg dL^{-1})			
Xylazine	15.5±1.9.0^{x}	14.2±1.600^{x}	15.8±0.900^{x}
Doxapram	19.8±4.900^{y}	19.8±5.200^{y}	19.2±4.700^{y}
Ca (mg dL^{-1})			
Xylazine	4.1±0.800^{x}	3.4±1.700^{x}	4.5±0.700^{x}
Doxapram	5.6±1.700^{y}	5.3±2.100^{y}	6.9±1.200^{y}
PHOS (mg dL^{-1})			
Xylazine	14.0±2.100	11.9±1.800	13.4±1.700
Doxapram	13.5±1.900	14.2±1.600	14.4±1.600
CRE (mg dL^{-1})			
Xylazine	1.5±0.300	1.3±0.300	1.4±0.300
Doxapram	1.7±0.200	1.6±0.200	1.5±0.200
GLU (mg dL^{-1})			
Xylazine	7.5±1.900	6.5±0.600	7.3±1.000^{x}
Doxapram	6.7±1.600^{a}	8.5±4.700^{ac}	12.3±10.80^{bcy}
Na^+ (mmol L^{-1})			
Xylazine	152.5±8.200	142.3±9.800	146.3±6.900
Doxapram	153.3±2.400	151.2±3.300	148.8±3.300
K^+ (mmol L^{-1})			
Xylazine	6.3±2.500	7.1±2.200	7.4±1.600
Doxapram	6.5±3.200	6.6±3.000	7.6±2.300
TP (g dL^{-1})			
Xylazine	7.8±1.000	8.2±1.000	7.8±1.300
Doxapram	7.1±0.600	7.5±0.900	6.9±0.700
GLOB (g dL^{-1})			
Xylazine	2.1±0.500	2.2±0.500	2.2±0.500
Doxapram	2.4±0.500	2.6±0.600	2.4±0.500

$^{a-d}$Means within a row with different superscripts differ significantly ($p<0.05$). $^{x, y}$Means within a column with different superscripts differ significantly ($p<0.05$)

xylazine administration which is a typical effect of alpha-2 adrenergic agonists (Maze and Tranquilli, 1991; Wagner *et al*., 1991) due to sympathetic blockade and vagal stimulation. The cardiac effects of doxapram are usually mild in human and horses (Yost, 2006; Taylor, 1990) and there was a report of transient increase of heart rate within 30 sec after doxapram administration in calves (Bleul *et al*., 2010). Kim *et al*. (1971) demonstrated that in dogs, there was a marked cardiac effects after doxapram administration in hypovolemic dogs when compared with normovolemic dogs and referred that to release of catecholamines. However, this could explain the decrease of mean heart rate after doxapram administration in this study. Doxapram is an effective respiratory stimulant that transiently increases respiratory rate and tidal volume by increasing electrical activity in the inspiratory and expiratory centers of the medulla (Franz, 1985; Tobias *et al*., 2004). Administration of doxapram resulted in increased respiratory effort and depth in dogs (Tobias *et al*., 2004; Miller *et al*., 2002), increased respiratory rate and minute ventilation in horses (Giguere *et al*., 2007), increased minute ventilation in lambs (Bairam *et al*., 1990) and increased respiratory rate with decreased arterial pCO_2 in calves (Bleul *et al*., 2010). Mean respiratory rate in this study decreased after doxapram administration in the D-X-group at 5AD and then increased significantly at 10 min compared to X-group. This is in agreement with earlier results that showed maximum increases in respiratory rate after doxapram administration was reached within 10 min in calves (Bleul *et al*., 2010) and lasted after 20 min in lambs (Bairam *et al*., 1990). This short duration of clinical effect from doxapram may be attributed to its pharmacokinetics. Doxapram is metabolized very rapidly when given IV (Yost, 2006). Pharmacokinetic studies in humans (Robson and Prescott, 1979) and horses (Sams *et al*., 1992) revealed that blood levels decline rapidly after a single IV dose of doxapram due to redistribution of the drug from plasma and other well-perfused tissues such as

the brain, to less well-perfused tissues such as the skeletal muscles and adipose tissue. Doxapram administration generally increases ABP in horses (Taylor, 1990; Giguere *et al*., 2007), in calves (Bleul *et al*., 2010) and in lambs (Bairam *et al*., 1990). After doxapram administration in this study, mean ABP measurements were decreased at all measuring times compared with baseline but sSAP were significantly higher at 30 min compared with X-group. Whereas Bleul *et al*. (2010) noticed in calves that the effects of doxapram administration had a prolonged effect (120 min) on systemic ABP. These differences between results of this study and the other previous studies could be attributed to the low-dose (0.4 mg kg^{-1}) of doxapram used in this study. The recommended IV dose of doxapram ranges from 0.3-3 mg kg^{-1} in animals (Taylor, 1990; Bleul *et al*., 2010; Giguere *et al*., 2007; Tobias *et al*., 2004). However, there was no information regarding the dose rate of doxapram in camels, therefore, this loading dose of 0.4 mg kg^{-1} doxapram was chosen in this study to examine its efficacy and safety. It is also possible that immediate or transient increase in heart rate, respiratory rate, ABP measurements after doxapram administration in this study were not observe because measurement were made after 5 min and then at every 10 min intervals. Moreover, the use of indirect ABP monitoring have not allowed continuous monitoring of ABP. However, direct ABP measurement was not carried out in this study, as arterial catheterization is problematical in this species, due to their thick skin and muscle layers. Nevertheless, 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*., 2001b).

In this study, there was a significant decrease of RBC, HB, HCT and PLT after xylazine admintstration in the X-group and significant changes of MO, MCV and PLT between the two groups. Similar effects of xylazine on platelet number in camels have been reported elsewhere (Custer *et al*., 1977; Ahmed *et al*., 1996). Such effects may be due to haemodilution or increased spleen storage function (Ahmed *et al*., 1996). ALT, BUN and CA concetrations in the X-group were not significantly different when compared with baseline but were significantly lower compared with D-X-group. The decrease in ALT after xylazine administration was previously reported (Custer *et al*., 1977; Al-Busadah, 2002) and attributed to various factors such as changes in body temperature, haemodilution or more leakage of aspartate aminotransferase into plasma during xylazine sedation. GLU concentration was significantly increased following treatments in the D-X-group. This well known effect of xylazine is in accordance with other earlier studies in camels, cattle and dogs (Custer *et al*., 1977; Symonds and Mallinson, 1978; Goldfine and Arieff, 1979) and attributed to reduction in plasma insulin levels induced by binding of alpha-2 adrenoceptor on pancreatic β-cells (Hillaire-Buys *et al*., 1985). The most common side effects of doxapram are relatively minor (Yost, 2006) including hypoxia, hypertension, seizures and muscle rigidity (Yost, 2006; Tobias *et al*., 2004). However, no complication was noted during this study.

CONCLUSION

This study has shown that doxapram, at the dose given was safe and can be used to improve respiratory effort in camels with X-induced respiratory depression. Doxaprm partially resolve the respiratory depression and thus, further research needs to be done to determine the optimal dose, timing, frequency or continuous infusion, blood gas analysis and continuous capnography recording and direct BP measurement in order to establish its safety and use in camels.

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