Vol 20 No 1, p 23-27

SEDATIVE, ANALGESIC AND BIOCHEMICAL EFFECTS OF BUTORPHANOL IN CAMELS (*Camelus dromedarius*)

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ABSTRACT

Intravenous (IV) 0.2 mg kg^{-1} butorphanol was evaluated in five healthy camels. Sedation score, nociceptive threshold (using artery forceps), heart rate (HR), respiratory rate (fg), and rectal temperature (Temp.) were determined at baseline, and further recorded at 5, 10, 20, 40, 60, 80, 100 minutes after treatment. Some biochemical parameters were assessed at baseline, and at 10, 100 minute after treatment. Significant mild sedation and significant effect on nociceptive threshold was observed between 5 and 60 minutes. Mean (fg) and Temp. did not differ significantly, while HR increased significantly at 10 minutes after treatment. No significant difference could be detected in all biochemical measured parameters, except significant decrease in alanine aminotransferase at 10 minutes after treatment. This study showed that IV butorphanol produced short-term satisfactory analgesia, coupled with mild sedation and minimal side effects in camels.

Key words: Antinociception, camel, lidocaine, sedation

Butorphanol is a synthetic opioid with agonist–antagonist properties (Monteiro *et al,* 2009). It is commonly used as a preoperative sedative and analgesic, a supplement to balanced anaesthesia, and for suppression of post anaesthesia shaking (Vogelsang and Hayes, 1991). It has been used widely in several veterinary species (Kalpravidh *et al,* 1984a; Court *et al,* 1992) and in llama for its analgesic effects with minimal side effects (Barrington *et al,* 1993; Carroll *et al,* 2001a). It was reported to be superior with visceral analgesia rather than somatic pain (Hall *et al,* 2001). In camels, no studies have been reported on the use of butorphanol. Therefore, the objective of this study was to evaluate the antinociceptive and sedative effects of single bolus of IV butorphanol, and to observe the effects on heart and respiratory rate, and some biochemistry parameters in camels.

Materials and Methods

Five healthy camels (three males and two females) of three breeds, 2 Magateer, 2 Sofor, and 1 Shoael, with a mean body weight of 190 ± 56.1 kg, and aged 1.6 ± 1.9 years old (ranged between 8 months to 6 years), were used in this study. All camels were considered to be healthy, based on the results of a physical examination. 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. All camels received butorophanol (Alvegesic, Cp-pharma, Burgdorf, Germany) as a single IV dose of 0.2 mg kg^{-1}. Sedation scores, nociceptive threshold, heart rate (HR) (manually by a stethoscope), respiratory rate (fg) (counting thoracic movements), and rectal temperature (Temp) (electronic thermometer) were recorded at baseline, and at 5, 10, 20, 40, 60, 80, 100 minutes after administration of the treatments. 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 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,

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Table 1. Mean values ± SD of respiratory rate (f_R) breaths minute $^{-1}$, heart rate (HR), beats minute^{-1} and temperature (Temp.) at the baseline (BL), and at 5-100 minutes after butorphanol administration.

Variables	Time (minutes)							
	BL	5	10	20	40	60	80	100
f_R	23.6 + 6.1	27.8 + 3.8	27.4 + 7.3	26.6 + 4.5	28.2 + 3.8	25.2 + 2.6	25.4 + 7.0	27.2 + 7.2
HR	59.2 + 7.3^{bc}	69.6 + 8.9^{ac}	76.8 + 15.5^{a}	67.8 + 8.0^{ac}	71.0 + 15.9^{ac}	66.6 + 8.0^{ac}	72.4 + 18.1^{ac}	61.6 + 4.3^{bc}
Temp. °C	38 + 0.5	37.9 + 0.6	38.0 + 0.5	38.3 + 0.6	38.3 + 0.6	38.1 + 0.5	38.2 + 0.7	38.1 + 0.5

^{abc} Medians in row with different superscripts differ significantly ($p<0.05$).

Table 2. Median (range) of sedation scores and nociceptive threshold at the BL, and at 5-100 minutes after butorphanol administration.

Variables	Time (minutes)							
	BL	5	10	20	40	60	80	100
Sedation score	0 (0-0)^{bc}	1 (0-1)^{a}	1 (0-1)^{a}	1 (0-1)^{a}	0.5(0-1)^{a}	0.5 (0-1)^{a}	0 (0-1)^{ac}	0 (0-0)^{bc}
Nociceptive threshold	10 (10-10)^{b}	3.5 (0.5-5)^{ade}	1.5 (0-9)^{a}	2.5 (0-5)^{ad}	3.5 (0.5-8.5)^{ade}	5 (0.5-5.5)^{ade}	6 (1.5-7.5)^{ace}	7.5 (5-10)^{bc}

^{abcd} Medians in row with different superscripts differ significantly ($p<0.05$).

trunk, limbs, tail; contracture of the anus and turning of the head toward 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 (10 ml) were taken at baseline, 10, and 100 minutes after butorphanol administration from the jugular vein via disposable syringes and transferred into plain tubes without anticoagulant for the 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 the 't' test. Moreover, arc sine transformation was done to percentage data. P value of less than 0.05 was considered significant.

Results

Mean respiratory rate, heart rate, and temperature are presented in table 1 (mean ± SD). Mean respiratory rate and rectal temperature did not differ from baseline after treatment. Mean heart rate increased significantly at 10 minutes after treatment. Median (range) of Sedation scores is presented in table 2, with significant increase in sedation score between 5 and 60 minutes compared to baseline. Median (range) of nociceptive thresholds (table 2) were significantly different between 5 and 80 minutes compared to baseline. Table 3 shows serum biochemistry parameters with no significant difference in all measured parameters as compared to baseline, except significant decrease of ALT at 10 minutes after butorphanol administration.

Table 3. Serum biochemistry parameters (mean ± SD) at baseline, 10 and 100 minutes after tramadol administration.

Variable	Time		
	BL	10	100
ALB (g/dL)	4.2 ± 0.3	4.2 ± 0.6	4.2 ± 0.3
ALP (U/L)	281.8 ± 198.9	277.4 ± 199.6	284.6 ± 209.2
ALT (U/L)	26.2 ± 13.7^{bc}	24.4 ± 16.4^{a}	22.0 ± 14.3^{ac}
AMY (U/L)	602.6 ± 57.4	611.2 ± 94.0	606.8 ± 46.3
BUN (mg/dL)	24.8 ± 9.7	23.4 ± 8.8	23.8 ± 9.2
CA (mg/dL)	10.5 ± 0.5	10.4 ± 0.6	10.3 ± 0.7
PHOS (mg/dL)	9.4 ± 0.9	9.7 ± 1.3	8.8 ± 1.1
CRE (mg/dL)	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.4
GLU (mg/dL)	61.2 ± 19.4	67.2 ± 17.8	80.6 ± 7.0
NA+ (mmol/L)	150.0 ± 3.0	149.4 ± 9.3	150.8 ± 4.5
K+ (mmol/L)	7.9 ± 1.0	7.8 ± 0.9	7.5 ± 1.1
TP (g/dL)	5.9 ± 0.8	5.9 ± 1.0	5.9 ± 0.7
GLOB (g/dL)	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.5

^{abc} Means in row with different superscripts differ significantly ($p<0.05$).

Discussion

The pharmacokinetics of butorphanol have not been studied in camel. However, Butorphanol has been studied in several veterinary species with

recommended doses range from 0.05-0.2 mg kg^{-1} in horses, alpacas, llamas, and sheep (Stick *et al,* 1989; Waterman *et al,* 1991; Barrington *et al,* 1993; Carroll *et al,* 2001a; Garcia-pereira *et al,* 2007; Hofmeister *et al,* 2008), and 0.2 and 0.8 mg kg^{-1} in dogs (Sawyer *et al,* 1991). A butorphanol dose of 0.2 mg kg^{-1} IV appears optimal in horses (Kalpravidh *et al,* 1984a), and behavioural changes were severe if a dose rate of 0.2 mg kg^{-1} was exceeded in sheep (Waterman *et al,* 1991). Moreover, lower doses were found to be superior to higher doses, indicating that the dose-response curve is bell shaped (Hall *et al,* 2001). Therefore, a dose rate of 0.2 mg kg^{-1} was chosen in this study to examine its efficacy and safety in camels. Butorphanol is a high-affinity κ-opiate receptor agonist. At the μ-opiate receptor, butorphanol is a weak antagonist, or only a partial agonist. Most of the drug's analgesic effects have been attributed to the κ -receptor effects (Sellon *et al,* 2004). Various studies demonstrated the analgesic efficacy of butorphanol on both superficial and visceral pain, and showed the importance of using more than one method for the assessment of antinociception but in this study application of artery forceps was used, 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. In horses, the analgesic effect of butorphanol on visceral pain was dose-dependent with short to intermediate duration 'approximately 90 minutes' (Kalpravidh *et al,* 1984a; Muir and Robertson, 1985), but it was ineffective on superficial pain (Kalpravidh *et al,* 1984a; Brunson and Majors, 1987; Spadavecchia *et al,* 2007). Similar results were found in dogs, where butorphanol provided visceral antinociception (Houghton *et al,* 1991), but did not provide adequate post operative analgesia (Inoue *et al,* 2006; Camargo *et al,* 2011). In this study, antinociception occurred within minutes after IV butorphanol, with maximum effect at 10 minutes, then gradually decreased in next time points, which is in agreement with other finding in llamas and sheep (Waterman *et al,* 1991; Carroll *et al,* 2001a) where butorphanol provided superficial analgesia for a period of 90-120 minutes. The sedative effect of opioids results from their interaction with μ and κ receptors, and in addition, other factors may influence that as type of receptor activated, the dose, differences in pharmacokinetics, the number of observers assessing sedation, and individual variation (Muir, 2002; Monteiro *et al,* 2009). It has been hypothesised that the sedative effect of butorphanol is mainly because of binding at the κ receptors (Kamerling *et al,* 1989; Lamont and Mathews, 2007). Butorphanol was reported to produce marked sedation in human (Dershwitz *et al,* 1991), and mild sedation in dogs, cats, and neonatal foals (Ansah *et al,* 2002; Arguedas *et al,* 2008; Girard *et al,* 2010), while generally produced adverse behavioural changes associated with central nervous system excitement in horses (Kalpravidh *et al,* 1984a; Sellon *et al,* 2001), sheep (Waterman *et al,* 1991), and goats (Carroll *et al,* 2001b). That was explained by the mixed activity of butorphanol at μ receptors. In llamas, butorphanol caused transient sedation in two cases (out of six cases), and transient excitation in another two cases (Carroll *et al,* 2001a). In this current study, mild sedation was shown after butorphanol administration between 5 and 20 minutes in all camels, except in one camel that showed no sign of sedation at any time. Adverse behavioural change was not observed during this study, perhaps as all camels were restrained manually in sternal recumbency during whole study. Although cardiovascular stability provided by butorphanol is desirable (Carroll *et al,* 2001b), the results are variable between different studies. There was no change in heart rate after butorphanol administration in a number of studies in horses (Robertson *et al,* 1981; Sellon *et al,* 2001; Hofmeister *et al,* 2008), but an increase in heart rate was observed in another study in ponies (Kalpravidh *et al,* 1984b). Reduction in heart rate after butorphanol adminisrtaion was observed in other studies in dogs (Greene *et al,* 1990; Girard *et al,* 2010; dos Santos *et al,* 2011), and in llamas (Carroll *et al,* 2001a), and that was attributed to an increase in vagal tone (Greene *et al,* 1990). This study showed similar results to previous report in ponies (Kalpravidh *et al,* 1984b), where a significant increase in heart rate was only shown at 10 minutes after butorphanol administration, and this could be as a result of CNS stimulation.

In the current study, there were no significant differences in biochemical parameters, except decrease in ALT concentration detected at 10 minutes after butorphanol administration. This decrease could be attributed to various factors such as changes in body temperature, haemodilution or more leakage of aspartate aminotransferase into plasma (Custer *et al,* 1977). There was an increase but with no significance detected in GLU concentration at 100 minutes after butorphanol administration. This increase could be

related with a generalised stress response (Rand *et al,* 2002; Harms *et al,* 2005).

In conclusion, this study showed that single injection of 0.2 mg kg^{-1} butorphanol produced short-term satisfactory analgesia as determined by response to nociceptive stimulus, coupled with mild-transit sedation and minimal side effects. However, further work needs to be done with evaluation of other cardiorespiratory parameters, including arterial blood pressure measurements, blood gas analysis and continuous capnography recording. furthermore, investigating pharmacokinetics of butorphanol with different IV and IM loading doses and continuous rate infusions used for prolonged duration, with clinical evaluation is required to establish its use in camels.

Acknowledgement

The author gratefully acknowledges Dr. M Alkhalifah, and Dr. K Abursais for the blind assessment and assistance in data collection. Prof. M Mandoor for the statistical analysis. Deanship of Scientific Research in King Faisal University for the financial support.

References

Ajadi AR, Olusa TA, Smith OF, Ajibola ES, Adeleye OE, Adenubi OT and Makinde FA (2009). Tramadol improved the efficacy of ketamine–xylazine anaesthesia in young pigs. Veterinary Anaesthesia and Analgesia 36:562-566.

Ansah OB, Vainio O, Hellsten C and Raekallio M (2002). Postoperative pain control in cats: clinical trials with medetomodine and butorphanol. Veterinary Surgery 31:99-103.

Arguedas MG, Hines MT, Papich MG, Farnsworth KD and Sellon DC (2008). Pharmacokinetics of butorphanol and evaluation of physiologic and behavioural effects after intravenous and intramuscular administration to neonatal foals. Journal of Veterinary Internal Medicine 22:1417-1426.

Barrington GM, Meyer TF and Parish SM (1993). Standing castration of the llama using butorphanol tartrate and local anaesthesia. Equine Practice 15:35-39.

Brunson DB and Majors LJ (1987) Comparative analgesia of xylazine, xylazine/morphine, xylazine/butorphanol, and xylazine/nalbuphine in the horse, using dental dolorimetry. American Journal of Veterinary Research 48:1087-1091.

Camargo JB, Steagall PV, Minto BW, Lorena SE, Mori ES and Luna SP (2011). Post-operative analgesic effects of butorphanol or firocoxib administered to dogs undergoing elective ovariohysterectomy. Veterinary Anaesthesia and Analgesia 38:252-259.

Carroll GL, Boothe DM, Hartsfield SM, Martinez EA, Spann AC and Hernandez A (2001a). Pharmacokinetics and pharmacodynamics of butorphanol in llamas after intravenous and intramuscular administration. Journal of the American Veterinary Medical Association 219:1263-1267.

Carroll GL, Boothe DM, Hartsfield SM, Waller MK and Geller SC (2001b). Pharmacokinetics and selected behavioural responses to butorphanol and its metabolites in goats following intravenous and intramuscular administration. Veterinary Anaesthesia and Analgesia 28:188-195.

Court MH, Dodman NH, Levine HD, Richey MT, Lee JW and Hustead DR (1992). Pharmacokinetics and milk residues of butorphanol in dairy cows after single intravenous administration. Journal of Veterinary Pharmacology and Therapeutics 15:28-35.

Custer R, Krammer L, Kennedy S and Mitechell Bush (1977). Haematologic effects of xylazine when used for restraint of bactrian camels. Journal of the American Veterinary Medical Association 171:899-901.

Dehkordi SH, Bigham-Sadegh A and Gerami R (2012). Evaluation of anti-nociceptive effect of epidural tramadol, tramadol-lidocaine and lidocaine in goats. Veterinary Anaesthesia and Analgesia 39:106-110.

Dershwitz M, Rosow CE, DiBiase PM and Zaslavsky A (1991). Comparison of the sedative effects of butorphanol and midazolam. Anaesthesiology 74(4):717-724.

Docquier MA, Lavand'homme P, Boulanger V, Collet V and De Kock M (2004). Questioning the cardiocirculatory excitatory effects of opioids under volatile anaesthesia. British Journal of Anaesthesia 93(3):408-13.

dos Santos PSP, Nunes N, de Souza AP, Márlis L De Rezende, Celina Td Nishimori, Danielli P De Paula and Patrícia C Ferro Lopes (2011). Haemodynamic effects of butorphanol in desflurane-anesthetised dogs. Veterinary Anaesthesia and Analgesia 38:467-474.

Garcia-Pereira FL, Greene SA, Keegan RD, Garcia-Pereira FL, Greene SA, Keegan RD, McEwen MM and Tibary A (2007). Effects of intravenous butorphanol on cardiopulmonary function in isoflurane-anaesthetised alpacas. Veterinary Anaesthesia and Analgesia 34:269-274.

Girard NM, Leece EA, Cardwell J, Adams VJ and Brearley JC (2010). The sedative effects of low-dose medetomidine and butorphanol alone and in combination intravenously in dogs. Veterinary Anaesthesia and Analgesia 37(1):1-6.

Greene SA, Hartsfield SM and Tyner CL (1990). Cardiovascular effects of butorphanol in halothane-anaesthetised dogs. American Journal of Veterinary Research 51:1276-1279.

Hall LW, Clarke KW and Trim CM (2001). Principles of sedation, analgesia and premedication. In: Veterinary Anaesthesia. (10th edn) Hall LW, Clarke KW, Trim CM (eds) WB Saunders, London, UK. pp 100.

Harms CA, Lewbart GA, Swanson CR, Kishimori JM and Boylan SM (2005). Behavioural and clinical pathology changes in koi carp (*Cyprinus carpio*) subjected to anaesthesia and surgery with and without intra-operative analgesics. Comparative Medicine 55(3):221-226.

Hofmeister EH, Mackey EB, and Trim CM (2008). Effect of butorphanol administration on cardiovascular parameters in isoflurane-anaesthetised horses – a retrospective clinical evaluation. Veterinary Anaesthesia and Analgesia 35:38-44.

Houghton KJ, Rech RH, Sawyer DC, Durham RA, Adams T, Langham MA and Striler EL (1991). Dose-response of intravenous butorphanol to increase visceral nociceptive threshold in dogs. Proceedings of the Society for Experimental Biology and Medicine 197:290-296.

Inoue T, Ko JC, Mandsager RE, Payton ME, Galloway DS and Lange DN (2006). Efficacy and safety of preoperative etodolac and butorphanol administration in dogs undergoing ovariohysterectomy. Journal of the American Animal Hospital Association 42:178-188.

Kalpravidh M, Lumb WV, Wright M and Heath RB (1984a). Analgesic effects of butorphanol in horses: dose–response studies. American Journal of Veterinary Research 45:211-216.

Kalpravidh M, Lumb WV, Wright M and Heath RB (1984b). Effects of butorphanol, flunixin, levorphanol, morphine and xylazine in ponies. American Journal of Veterinary Research 45:217-223.

Kamerling S, Wood T, DeQuick D, Weckman TJ, Tai C, Blake JW and Tobin T (1989). Narcotic analgesics, their detection and pain measurement in the horse: a review. Equine Veterinary Journal 21:4-12.

Lamont LA and Mathews KA (2007). Opioids, nonsteroidal anti-inflammatories, and analgesic adjuvants. In: Lumb and Jones' Veterinary Anaesthesia and Analgesia. Tranquilli WJ, Thurmon JC, Grimm KA (eds). Blackwell Publishing, Oxford. pp 241-271.

Marzok M and El-Khodery S (2009). Sedative and analgesic effects of romifidine in camels (*Camelus dromedarius*). Veterinary Anaesthesia and Analgesia 36:352-360.

Monteiro ER, Junior AR, Assis HM, Campagnol D and Quitzan JG (2009). Comparative study on the sedative effects of morphine, methadone, butorphanol or tramadol, in combination with acepromazine, in dogs. Veterinary Anaesthesia and Analgesia 36:25-33.

Muir WW (2002). Drugs used to treat pain. In: Handbook Veterinary Pain Management. Gaynor JS, Muir WW(eds). Mosby, St Louis, USA. pp 142-163.

Muir WW and Robertson JT (1985). Visceral analgesia: effects of xylazine, butorphanol, meperidine, and pentazocine in horses. American Journal of Veterinary Research 46:2081-2084.

Prado TM, Doherty TJ, Boggan EB, Airasmaa HM, Martin-Jimenez T and Rohrbach BW (2008). Effects of acepromazine and butorphanol on tiletamine-zolazepam anaesthesia in llamas. American Journal of Veterinary Research 69(2):182-188.

Rand JS, Kinnaird E, Baglioni A, Blackshaw J and Priest J (2002). Acute stress hyperglycaemia in cats is associated with struggling and increased concentrations of lactate and norepinephrine. Journal of Veterinary Internal Medicine 16(2):123-132

Robertson JT, Muir WW and Sams R (1981). Cardiopulmonary effects of butorphanol tartrate in horses. American Journal of Veterinary Research 42:41-44.

Sawyer DC, Rech RH, Durham RA, Adams T, Richter MA and Striler EL (1991). Dose response to butorphanol administered subcutaneously to increase visceral nociceptive threshold in dogs. American Journal of Veterinary Research 52:1826-1830

Sellon DC, Monroe VL, Roberts MC and Papich MG (2001). Pharmacokinetics and adverse effects of butorphanol administered by single intravenous injection or continuous intravenous infusion in horses. American Journal of Veterinary Research 62:183-189.

Sellon DC, Roberts MC, Blikslager AT, Ulibarri C and Papich MG (2004). Effects of continuous rate intravenous infusion of butorphanol on physiologic and outcome variables in horses after celiotomy. Journal of Veterinary Internal Medicine 18(4):555-563.

Spadavecchia C, Arendt-Nielsen L, Spadavecchia L, Mosing M, Auer U and van den Hoven R (2007). Effects of butorphanol on the withdrawal reflex using threshold, suprathreshold and repeated subthreshold electrical stimuli in conscious horses. Veterinary Anaesthesia and Analgesia 34:48-58.

Stick JA, Loeffler BS, Arden WA and Chou CC (1989). Effects of butorphanol tartrate on arterial pressure, jejunal blood flow, vascular resistance, O2 extraction, and O2 uptake in halothane-anaesthetised ponies. American Journal of Veterinary Research 50: 1202-1206.

Vogelsang J and Hayes SR (1991). Butorphanol tartrate (stadol): a review. Journal of Post Anesthesia Nursing 6(2):129-135.

Waterman AE, Livingston A and Amin A (1991). Analgesic activity and respiratory effects of butorphanol in sheep. Research in Veterinary Science 51:19-33.