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# EFFECTS OF TRAMADOL ON ANTINOCICEPTION, SEDATIVE AND SOME BIOCHEMICAL VARIABLES IN CAMELS (*Camelus dromedarius*)

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## ABSTRACT

This study was performed to evaluate the effects of intravenous (IV) 2.0 mg $kg^{-1}$ tramadol in five healthy camels. Antinociception (response to artery forceps), sedative, heart rate, respiratory rate, and temperature were recorded 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 minutes after treatment. There was significant effect on nociceptive threshold with peak effect at 20 minutes after treatment, and significant mild sedation was observed between 20-40 minutes after treatment. No significant difference could be detected in biochemical parameters, except significant decrease in alanine aminotransferase at 10 minutes after treatment. The results suggest that the tramadol at the dose given was safe, and useful for short time analgesia in camels.

**Key words:** Antinociception, camel, sedation, tramadol

Opioids are widely recognised as one of the most effective analgesics for moderate or severe pain (Webster, 2012). In recent years the discovery of specific receptor sites (μ, κ and δ) of action for the opioids and the identification in the central nervous system of endogenous ligands such as endorphins and encephalins that act at these receptors, has led to better understanding of the multiple actions of agonist and partial agonist opioid drugs, as well as providing the possibility of the development of more specific drugs with fewer side effects (Hall *et al,* 2001). Tramadol, a synthetic opioid, is an analgesic with mixed opioid and nonopioid activities (Garrido *et al,* 2000). The nonopioid activity is achieved through indirect activation of postsynaptic alpha-2-adrenoreceptor, blocking impulses reaching the brain (Duthie, 1998). Tramadol has been used as a pre-anaesthetic (Kongara *et al,* 2012), to improve the quality of anaesthetic induction, and to improve the characteristic of recovery (Ajadi *et al,* 2009). The pharmacokinetics of tramadol were studied in camels following a single injection at dose of 2.33 mg $kg^{-1}$, and characterised by a fast clearance, large volume of distribution and brief half-life (Elghazali *et al,* 2008). The analgesic and other clinical effects of both tramadol in camels is still unknown. Therefore, the aims of this study were to evaluate tramadol in terms of antinociceptive and sedative effects, with evaluating changes in heart rate, respiratory rate, temperature, and some biochemistry parameters in dromedary camels.

## Materials and Methods

Five healthy camels (three males and two females) of three breeds, two Magateer, two Sofor, and one 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. 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 tramadol (Tramal, Grünenthal GmbH, Aachen, Germany) as a single IV dose of 2.0 mg $kg^{-1}$. Sedation scores, nociceptive threshold, heart rate (manually by a stethoscope), respiratory rate (counting thoracic movements), and rectal temperature (electronic thermometer) were recorded before treatment (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

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**Table 1.** Mean values ± SD of respiratory rate ($f_R$), heart rate (HR), and temperature (Temp.) at the baseline (BL), and at 5-100 minutes after tramadol administration.

| Variables | Time (minutes) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | BL | 5 | 10 | 20 | 40 | 60 | 80 | 100 |
| $f_R$ | 23.6 ± 6.3 | 23.6 ± 6.1 | 26.6 ± 7.1 | 29.4 ± 4.3 | 28.2 ± 3.8 | 29.8 ± 5 | 28.8 ± 4.3 | 27.0 ± 5.1 |
| HR | 61.0 ± 16.8 | 62.0 ± 14.7 | 62.6 ± 9.2 | 59.2 ± 7.9 | 59.4 ± 14.6 | 49.4 ± 13.2 | 54.2 ± 9.3 | 53.6 ± 4.1 |
| Temp. °C | 38.1 ± 0.7 | 38.1 ± 0.7 | 38.2 ± 0.6 | 38.0 ± 0.1 | 38.0 ± 0.6 | 37.5 ± 0.6 | 38.1 ± 0.3 | 38.1 ± 0.4 |

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

| Variables | Time (minutes) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | BL | 5 | 10 | 20 | 40 | 60 | 80 | 100 |
| sedation score | 0 (0-0)$^{ab}$ | 0 (0-0)$^{ab}$ | 0 (0-1)$^{a}$ | 0.5 (0-1)$^{ac}$ | 1 (0-1)$^{ac}$ | 0 (0-1)$^{a}$ | 0 (0-1)$^{a}$ | 0 (0-0)$^{ab}$ |
| nociceptive threshold | 10 (10-10) $^{bcd}$ | 2 (0-10)$^{ace}$ | 1.5(0-6)$^{a}$ | 0.5 (0-4.5)$^{a}$ | 5 (1.5-6.5)$^{ace}$ | 6 (2-9)$^{bc}$ | 8 (3-10)$^{bc}$ | 9.5 (2-10)$^{bcd}$ |

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

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 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 tramadol 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

Table 1. showed no significant difference in mean respiratory rate, heart rate and temperature. Mean respiratory rate increased slightly after 20 minutes, while mean heart rate was slightly decreased after 60 minutes. Median (range) of sedation scores is presented in table 2. Significant mild sedation was observed between 20-40 minutes after treatment. Median (range) of nociceptive threshold is presented in table 3. The maximal effect was shown at 20 minutes after treatment. Table 3 Showed no significant difference in biochemical parameters, except significant decrease of ALT at 10 minutes after IV tramadol.

## Discussion

The tramadol dose of 2.0 mg $kg^{-1}$, used in this study, was based on pharmacokinetic parameters of intravenously administered tramadol in healthy camel (Elghazali *et al,* 2008), which is within recommended doses in other species, that ranges from 1.5 to 3 mg $kg^{-1}$ in dogs (Seddighi *et al,* 2009), 2.0 to 3.0 mg $kg^{-1}$ in horses (Dhanjal *et al,* 2009), and 2.0 to 4.0 mg $kg^{-1}$ in cats (Pypendop *et al,* 2009). Tramadol causes less respiratory depression compared with morphine in human (Vickers *et al,* 1992). However, mean respiratory rate in this study increased but not significatly after 10 minutes compared to baseline, similarly with results of previous studies in horses (Dhanjal *et al,* 2009; Seo *et al,* 2011), that suggested the cause may have been secondary to CNS stimulation. Tramadol is substantially haemodynamically stable (Duthie, 1998), although transient haemodynamic effects characterised by a moderate increase in blood pressure have been recorded after IV administration

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

| Parameter | Time | | |
|---|---|---|---|
| | Baseline | 10 | 60 |
| ALB (g/dL) | 4.1 ± 0.4 | 4.4 ± 0.3 | 4.3 ± 0.2 |
| ALP (U/L) | 243.4 ± 109.5 | 259.6 ± 115.1 | 249.0 ± 104.2 |
| ALT (U/L) | 17.2 ± 2.2 bc | 13.8 ± 2.3 a | 16.0 ± 2.5 ac |
| AMY (U/L) | 556.8 ± 33.56 | 585.8 ± 60.5 | 614.6 ± 38.5 |
| BUN (mg/dL) | 24.8 ± 8.5 | 25.0 ± 8.1 | 24.8 ± 8.7 |
| CA (mg/dL) | 10.0 ± 0.7 | 10.5 ± 0.6 | 10.8 ± 0.6 |
| PHOS (mg/dL) | 9.3 ± 0.9 | 9.6 ± 1.2 | 9.1 ± 0.1 |
| CRE (mg/dL) | 1.3 ± 0.2 | 1.3 ± 0.2 | 1.3 ± 0.2 |
| GLU (mg/dL) | 59.2 ± 27.1 | 52.0 ± 21.2 | 55.2 ± 24.3 |
| NA± (mmol/L) | 146.8 ± 7.1 | 148.6 ± 6.2 | 151.2 ± 2.8 |
| K± (mmol/L) | 8.0 ± 0.5 | 7.6 ± 1.2 | 8.2 ± 0.3 |
| TP (g/dL) | 5.7 ± 0.4 | 6.1 ± 0.4 | 6.1 ± 0.5 |
| GLOB (g/dL) | 1.5 ± 0.4 | 1.7 ± 0.5 | 1.7 ± 0.4 |

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

in human (Müller *et al,* 1982). Mean heart rate and temperature did not differ in this study from baseline, but there was transient decrease at 60 minutes. Tramadol provided efficient sedation in pediatric patients (Bedirli *et al,* 2012), and induced light sedation in horses in around 20 minutes (Seo *et al,* 2011). While data on sedative effects of tramadol in dogs are inconsistent (Seddighi *et al,* 2009). Tramadol did not provide sedation in dogs at two different studies (Natalini *et al,* 2007; Seddighi *et al,* 2009), while provided mild sedation in other study in dogs (Mastrocinque and Fantoni, 2003). Significant mild sedation was observed during this study between 20-40 minutes after treatment. Tramadol is both a weak opioid agonist with selectivity for the μ-receptor and a weak inhibitor of the reuptake of noradrenaline and serotonin. This dual mechanism of action may be attributed to the 2 enantiomers of racemic tramadol. The (+)-enantiomer has a higher affinity for the μ-receptor and is a more effective inhibitor of serotonin reuptake, whereas the (–)-enantiomer is a more effective inhibitor of noradrenaline reuptake and increases its release by autoreceptor activation. Tramadol is extensively metabolised in the liver, with the O-desmethyl (M1) metabolite of tramadol having a 200-fold higher affinity for opioid receptors than the parent drug (Scott and Perry, 2000). M1 is likely the principle reason for the analgesic effect produced by tramadol (Seo *et al,* 2011). In this study, the effect of IV tramadol on nociceptive thresholds was shown after 5 minutes, reaching peak at 20 minutes, then gradually decreased in next time points. In human, tramadol effectively relieved moderate to severe preoperative and postoperative pain associated with several types of surgery, and the overall analgesic efficacy with tramadol was comparable to that achieved using equianalgesic doses of parenteral morphine or alfentanil (Scott and Perry, 2000; Bedirli *et al,* 2012). Effects on nociceptive threshold after 3 mg $kg^{-1}$ tramadol administration were detected in dogs (Kongara *et al,* 2012), and were also detected in cat at 80 minutes and from 120 to 360 minutes after 2 mg $kg^{-1}$ of tramadol (Pypendop *et al,* 2009). In contrast, IV administration of tramadol (2 mg $kg^{-1}$) has no antinociceptive effect in horses (Dhanjal *et al,* 2009; Seo *et al,* 2011), and that was explained as M1, the main metabolite in humans, seemed to be only marginally produced in the horse (Giorgi *et al,* 2007). Conversely, in camels, the M1 was found to be the main metabolite following IV tramadol at 2.33 mg $kg^{-1}$ (Elghazali *et al,* 2008), which explained analgesic effectiveness monitored in this study. The peak analgesic effect occurred 1 to 4 hours after oral administration of tramadol in human, with analgesia persisting for 3 to 6 hours (Scott and Perry, 2000). The pharmacokinetic differences may explain the longer duration of tramadol effects reported in human compared to this study. It is documented that tramadol characterised by a fast clearance, large volume of distribution and brief half-life (Elghazali *et al,* 2008). Moreover, time of tramadol to reach maximum plasma concentration was reported 0.57 hour in camels (Elghazali *et al,* 2008), and1.6 hour in human (Scott and Perry, 2000). 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. In the current study, there were no significant differences in biochemical parameters after IV tramadol, except significant decrease of ALT at 10 minutes after IV tramadol. 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). However, most parameters obtained were clinically accepted in camels.

In conclusion, this study showed that IV tramadol, at 2 mg $kg^{-1}$, appears to be useful analgesic

agent in camels as determined by response to nociceptive stimulus, coupled with mild-transit sedation and minimal side effects.


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## 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.

Bedirli N, Egritas O, Cosarcan K and Bozkirli F (2012). A comparison of fentanyl with tramadol during propofol-based deep sedation for pediatric upper endoscopy. Pediatric Anesthesia 22:150-155.

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

Dhanjal JK, Wilson DV, Robinson E Tobin TT and Dirikolu L (2009). Intravenous tramadol: effects, nociceptive properties, and pharmacokinetics in horses. Veterinary Anaesthesia and Analgesia 36:581-590.

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):408-413.

Duthie DJR (1998). Remifentanil and tramadol. British Journal of Anaesthesia 81:51-57.

Elghazali MM, Barezaik IM, Abdel Hadi AA, Eltayeb FM, Al Masri J and Wasfi IA (2008). The pharmacokinetics, metabolism and urinary detection time of tramadol in camels. Veterinary Journal 178(2):272-277.

Garrido MJ, Valle M, Campanero MA, Calvo R and Trocóniz IF (2000). Modelling of the in vivo antinociceptive interaction between an opioid agonist, (+) O-desmethyltramadol, and a monoamine reuptake inhibitor, (−) O-desmethyltramadol in rats. Journal of Pharmacology and Experimental Therapeutics 295:352-359.

Giorgi M, Soldani G, Maera C, Ferrarini P, Sgorbini M and Saccomanni G (2007). Pharmacokinetics of tramadol and its metabolites M1,M2, and M5 in horses following intravenous, immediate release (fasted/fed) and sustained release single dose administration. Journal of Equine Veterinary Science 27:481-487.

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). W.B. Saunders, London, UK. pp 93-95.

Kongara K, Chambers JP and Johnson CB (2012). Effects of tramadol, morphine or their combination in dogs undergoing ovariohysterectomy on peri-operative electroencephalographic responses and post-operative pain. New Zealand Veterinary Journal 60(2):129-35.

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

Mastrocinque S and Fantoni DT (2003). A comparison of preoperative tramadol and morphine for the control of early postoperative pain in canine ovariohysterectomy. Veterinary Anaesthesia and Analgesia 30:220-228.

Mathews KA (1996). Nonsteroidal anti-inflammatory analgesics in pain management in dogs and cats. Canadian Veterinary Journal 37:539-545.

Müller H, Stoyanov M, Brähler A and Hempelmann G (1982). Haemodynamic and respiratory effects of tramadol during nitrous oxide-oxygen-artificial respiration and in the postoperative period. Anaesthesist 31(11):604-610.

Natalini CC, Polydoro AS and Crosignani N (2007). Effects of morphine or tramadol on thiopental anesthetic induction dosage and physiologic variables in halothane anesthetized dogs. Acta Scientiae Veterinariae 35:161-166.

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

Pypendop BH, Siao KT and Ilkiw JE (2009). Effects of tramadol hydrochloride on the thermal threshold in cats. American Journal of Veterinary Research 70(12):1465-70.

Scott LJ and Perry CM (2000). Tramadol: a review of its use in perioperative pain. Drugs 60(1):139-76.

Seddighi MR, Egger CM, Rohrbach BW, Cox SK and Doherty TJ (2009). Effects of tramadol on the minimum alveolar concentration of sevoflurane in dogs. Veterinary Anaesthesia and Analgesia 36:334-340.

Seo JP, Son WG , Gang S, Sujin Gang and Inhyung Lee (2011). Sedative and analgesic effects of intravenous xylazine and tramadol on horses. Journal of Veterinary Science 12(3):281-286.

Vickers MD, O'Flaherty D, Szekely SM, Read M and Yoshizumi J (1992). Tramadol: pain relief by an opioid without depression of respiration. Anaesthesia 47(4):291-6.

Webster L (2012). Efficacy and Safety of dual-opioid therapy in acute pain. Pain Medicine 13:S12-S20.