Vol 19 No 2, p 197-200

CLINICAL EVALUATION OF KETAMINE WITH ROMIFIDINE AND DIAZEPAM, FOR TOTAL INTRAVENOUS ANAESTHESIA (TIVA) IN DROMEDARY CAMEL

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ABSTRACT

In this study a safe anaesthetic combination of ketamine-romifidine-diazepam required to efficiently maintain anaesthesia by constant rate infusion (CRI) in 8 camels undergoing various clinical surgery was evaluated. All patient were premedicated with romifidine at 60 µg kg^{-1} administered intravenously (IV). Anaesthesia was induced with IV ketamine 0.8 mg kg^{-1} and diazepam 0.1 mg kg^{-1}. Anaesthesia was maintained with CRI of ketamine 3.2 mg kg^{-1} $hour^{-1}$, diazepam 0.3 mg kg^{-1} $hour^{-1}$, and romifidine 180 µg kg^{-1} $hour^{-1}$. Mean anaesthetic time was 63.8 ± 19.2 minutes, and recovery time was 38.3 ± 6.1 minutes. Changes in heart rate, blood pressure and respiratory rate were evaluated. The quality of anaesthesia was regarded as good and adequate for the surgical procedures in all studied cases.

Key words: Anaesthesia, camel, diazepam, ketamine, romifidine, TIVA

Ketamine is a dissociative anaesthetic used widely for induction and maintenance of anaesthesia in a variety of species. It has sympathomimetic actions, resulting in an increased cardiac output, heart rate, mean arterial pressure and central venous pressure. Ketamine induces rigidity, hypertonicity, convulsions and spontaneous movements (Clarke *et al* 1982; Haskins *et al,* 1985; Kim *et al,* 2004). To eliminate these side effects a variety of other compounds such α_2 agonists and benzodiazepines are commonly given concurrently with ketamine (Hall *et al,* 2001). Romifidine is a potent, long acting and selective α_2-adrenoceptor agonist that produces effects characterised by sedation, muscle relaxation, decreased cardiac output and heart rate, and reduced respiratory rate. (England *et al,* 1996; Marzok and El-Khodery, 2009). Diazepam is a benzodiazepine derivative used mostly as a sedative, muscle relaxant, and to control convulsions of any origin (Averill, 1970; Hall *et al,* 2001). The purpose of this study was to determine, the safety of a surgically adequate ketamine-romifidine-diazepam dosage regimen required to induce and maintain anaesthesia by CRI, by evaluating anaesthetic depth, changes in heart rate, blood pressure and respiratory rate in dromedary camels.

Materials and Methods

Eight adult camels (5 males and 3 females) of different breeds (5 Majaheem, 2 Magateer and 1 Sheael) were scheduled to undergo general surgery (5 jaw fixation, 1 mastectomy, 1 abdominal hernia repair, and 1 ovarian cyst removal). These were aged 6.6 ± 2.8 years (range 4-13 years), and weighed 683.5 ± 127.6 kg (range 428-820 kg). Food but not water was with held for 48-72 hours before surgery. Camels were restrained in sternal recumbency. Approximately 50 minutes before anaesthesia, a 14 SWG catheter (1Braunüle MT Luer Lock, B. Braun Melsungen AG, Germany) was placed in a jugular vein. Romifidine (Sedivet, Boehringer Ingelheim, Germany) at 60 µg kg^{-1} was administered intra venously. Camels were then positioned as required for surgery, the hair over the area of surgery was shaved and the skin was prepared for aseptic surgery. Approximately 30 minutes after pre-anaesthetic medication, anaesthesia was induced with a combination of ketamine (Ketamil, Troy Laboratories, Australia) 0.8 mg kg^{-1} and diazepam (Farcozepam, Pharco Co., Egypt) 0.1 mg kg^{-1} administered IV. Four special syringes (60 mL; BD, NJ, USA) mounted on 3 syringe pumps, were used for continuous drug administration. These were connected to a catheter by a syringe pump connector

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in order to maintain anaesthesia. One infusion pump (AP 14, Ascor S.A, Poland) infused ketamine at a constant rate of 3.2 mg kg^{-1} $hour^{-1}$, and another 2 infusion pumps (Stoelting Syringe Pumps, Wood Dale, IL, USA) delivered diazepam at a constant rate of 0.3 mg kg^{-1} $hour^{-1}$ and romifidine at a constant rate of 180 µg kg^{-1} $hour^{-1}$. Once the surgery was completed, infusions were disconnected. Heart rate, respiratory rate, temperature and indirect blood pressure values determined with a cuff placed around the base of the tail connected to a patient monitor (Infinity Delta XL, Drager Medical, Germany) were measured and recorded before premedication, 10 minutes after premedication and then continuously until the end of surgery. Pulse oximetry connected to the monitor with the probe placed on tongue was placed on animal immediately after induction. Blood samples were collected from the jugular vein before pre-anaesthetic medication, 10, 30, 60 and 90 minutes after the induction. Quality of induction, presence or absence of spontaneous movement, and palpebral reflex were evaluated in each animal to determine the quality of anaesthesia. The time from disconnection of infusions to sternal posture with the ability to support and raise the head was recorded.

Results

Mean heart rate, respiratory rate and arterial blood pressure measurements are presented in table 1. Mean heart rate decreased after premedication with romifidine, but returned to baseline after induction and remained stable during anaesthesia. Mean respiratory rate decreased slightly after premedication, but returned to baseline after induction and tended to increase during anaesthesia. Mean arterial blood measurement decreased after romifidine premedication, but then elevated after induction and during the anaesthesia. Body temperature was within the normal physiological limit during the anaesthesia. The quality of induction was evaluated as good and rapid in all camels, as no signs of excitement were observed. Mean time scored from induction of anaesthesia to disconnection from anaesthetic infusion was 63.8 ± 19.2 minutes and the quality of anaesthesia was regarded as good and adequate for the surgical procedures in all camels. Neither movement nor heart rate response associated with surgical stimulation was observed. Eyes remain open with positive response to palpebral reflex throughout the anaesthesia in all cases. The quality of recovery was good and camels were able to support and raise their head in sternal posture in 38.3±6.1 minutes.

Discussion

In present study, CRI regimen of ketamine with romifidine and diazepam to induce safe and good plane of surgical anaesthesia, as assessed by good operating condition, good clinical parameters and good recovery, were determined successfully. The sedative effects of romifidine have been studied in camel (Marzok and El-Khodery, 2009) at 3 different doses (40,80, and 120 µg kg^{-1}), where profound sedation was achieved with 120 µg kg^{-1}, mild to moderate sedation with 80 µg kg^{-1} and no effect to mild sedation with 40 µg kg^{-1}. However, a dose 60 µg kg^{-1} of romifidine used in this study provided safe and effective sedation in all camels. A combination of inteavenous ketamine dose of 1-2 mg kg^{-1} and xylazine at dose of 1-2 mg kg^{-1} was sufficient to produce a 30 minutes period of recumbency and relaxation in camel (White, 1986). However, the ketamine infusion rate used in this study was based on previous experience (Almubarak *et al,* 2008) where

Table 1. Mean (± SD) values of respiratory rate (RR), heart rate (HR), mean arterial blood pressure (MAP), systolic arterial blood pressure (SAP), and diastolic arterial blood pressure (DAP) at the baseline (BL) and 10 minutes after premedication with romifidine (AR) and 5-100 minutes after the induction of anaesthesia. N; number of animals.

Time (min)	BL N 8	AR N 8	5 N 8	10 N 8	20 N 8	30 N 8	40 N 8	50 N 8	60 N 5	70 N 3	80 N 2	90 N 1	100 N 1
RR	14.3 ±3.8	12.3 ±2.8	17.1 ±5.5	16.9 ±5.71	12.9 ±1.6	15.3 ±2.7	16.5 ±4.1	19.0 ±6.7	17 ±3.2	18.3 ±3.8	20 ±8.5	26	24
HR	44.4 ±9.7	32.9 ±5.9	47.9 ±11.2	42.3 ±11.9	40.5 ±11.6	43.8 ±13.4	46.6 ±13.7	43.5 ±15.8	41 ±8.8	43.3 ±14.6	60.5 ±7.7	45	56
MAP	149.9 ±20.5	137 ±24.4	162.4 ±37.4	160.1 ±42.4	168.4 ±36.9	182.4 ±35.7	191 ±43.9	194.4 ±38.6	208.8 ±24.0	186.7 ±43.8	174.5 ±71.4	151	144
SAP	194 ±17.2	171.9 ±24.2	197.4 ±50.2	191.4 ±52.6	202.7 ±42.7	209.9 ±44.9	216.7 ±40.4	212.2 ±43.8	235.5 ±25.8	217.3 ±47.3	209.5 ±75.6	170	173
DAP	108.3 ±18.3	117 ±27.5	139 ±34.1	137.7 ±39.6	142 ±32.9	156.1 ±33.8	155.6 ±31.2	158 ±26.9	170.8 ±18.5	162.3 ±42.4	151.5 ±60.1	120	97

a premedication dose of xylazine (0.16 - 0.2 mg kg^{-1}) followed by induction and maintenance of anaesthesia by IV xylazine (0.16 - 0.2 mg kg^{-1}) and ketamine (0.8 mg kg^{-1}) was sufficient to achieve and maintain a satisfactory surgical anaesthesia in 55 camels. In foals, diazepam dose of 0.1- 0.2 mg kg^{-1} followed by ketamine 2.2mg kg^{-1} could be given safely to achieve very satisfactory anaesthesia (Hall *et al*, 2001). The dose of diazepam 0.1 mg kg^{-1} chosen in this study at induction and 0.3 mg kg^{-1} $hour^{-1}$ during maintenance appeared to be clinically safe when combined romifidine and ketamine. Moreover, the diazepam has very low toxicity and large doses given to dogs for prolonged periods do not produce any changes in liver or kidney function (Hall *et al* 2001). Heart rate increases after induction of ketamine in horses premidicated with α_2 agonists due to the sympathomimetic effect of ketamine (Clarke *et al*, 1986; Marntell and Nyman, 1996). However, the addition of benzodiazepine derivative, midazolam (Adams, 1997) or diazepam (Rossetti *et al*, 2008), can mitigate the sympathomimetic effect of ketamine and normalises the heart rate. Interstingly, the combination of ketamine and diazepam in sheep (Mouallem 1988) resulted in significant decrease in heart and respiratory rates. Mean Heart rate, respiratory rate, and arterial blood pressure measurement in this study fell under baseline values after premedication with romifidine as a typical effect of alpha-2 adrenergic agonists (Maze and Tranquilli, 1991; Wagner *et al*, 1991), but return or raised over "arterial blood pressure" baseline values after induction and during the maintenance of anaesthesia. This is in agreement with Marntell and Nyman (1996) who showed that the administration of ketamine after premedication with romifidine alone, or in combination with diazepam, returned the heart and respiratory rates to baseline levels, but with significant increase in the arterial blood pressure compared to baseline. The recovery time reported in this study was 38.3 ± 6.1 minutes. Fahmy *et al* (1995) reported recovery time of 22 ± 2.69 minutes in camels induced with IV dose of 1 mg kg^{-1} xylazine, 1 mg kg^{-1} diazepam and 2 mg kg^{-1} propofol, while Al-Mubarak *et al* (2008) reported recovery time of 10-13 minutes after 60 minutes of anaesthesia maintained by 1-3 mg kg^{-1} of propofol in camel. The rapidity of recovery in the previous two studies could be attributed to the propofol' pharmacokinetic (Mama *et al*, 1995; Hughes and Nolan, 1999). However, Al-Mubarak (2012) reported a recovery time of 37.6 minutes after continuous infusion rate of propofol 4 mg kg^{-1} $hour^{-1}$ and ketamine 3.3 mg kg^{-1} $hour^{-1}$ for period of 82.9 minutes in 7 camels. The adjunctive effect of ketamine to the propofol could explain the longer recovery time in this study and so their pharmacokinetics should be studied. The method of constant rate infusion used in this study was relatively easy, effective and safe, and neither difficulties nor complications attributable to the equipment used were observed in this study. In conclusion, the current study showed that CRI of ketamine-romifidine-diazepam provided good and safe anaesthesia in camels. However, further studies in larger case numbers are necessary to establish its safety.

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