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An Assessment of Tramadol-Xylazine-Ketamine-Diazepam Combination in the Horse

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SUMMARY

Two sets of trials were carried out to evaluate the influence of tramadol premedication on xylazine-diazepam-ketamine anaesthesia in horses. Five horses comprising of both sexes (mean weight 276±39kg) were each anaesthetized twice. Treatment A (TXDK) consisted of intravenous injection of tramadol (2.5 mg kg^{-1}), followed five minutes later by xylazine (1.1 mg kg^{-1}), diazepam (0.11 mg kg^{-1}) and ketamine (2.2 mg kg^{-1}) while treatment B (SXDK) consisted of saline, xylazine, diazepam and ketamine of equal doses as treatment A. Post induction of anaesthesia, anaesthetic indices and physiological parameters were measured at 10 minutes interval for 60 minutes while blood were collected before and after each trial to evaluate haematological parameters.

The duration of lateral recumbency (DLR) was significantly ($p<0.05$) longer with TXDK (48.0±4.2 mins) when compared to that with SXDK (41.0±4.9 mins), while there were no significant difference in the duration of antinociception (DAN), number of attempts to stand (ATS), time to standing (TTS), and time to satisfactory limb co-ordination after standing (TSC). Similarly, there were no significant differences in the measured physiological and haematological parameters between and within the two groups. The quality of recovery from anaesthesia was adjudged good for both groups with no significant difference.

In conclusion, anaesthesia with xylazine-diazepam-ketamine following tramadol premedication at 2.5 mg kg^{-1} did not prolong the duration of antinociception but increased the duration of lateral recumbency. This showed that tramadol premedication prior to xylazine-diazepam-ketamine combination might not deepen analgesia produced by xylazine-diazepam-ketamine but might increase the duration of recumbency produced by the drug combination.

Key words: Anaesthesia, Analgesia , Horses, Ketamine, Premedication, Tramadol

INTRODUCTION

Currently, analgesics used for pain management in horses comprises mainly of three classes of drugs namely alpha$_2$ adrenergic agonist, non steroidal anti-inflammatory (NSAIDs) and opioids (Dhanjal et al., 2009). The alpha$_2$ adrenergic agonists such as xylazine, detomidine and medetomidine are used mostly for acute visceral pain but causes considerable sedation at doses used for analgesia; while NSAIDs such as phenybutazone, flunixin and ketoprofen are widely used especially for somatic and orthopeadic pain; they have side effects on the gastrointestinal, renal and coagulation systems (Dhanjal et al., 2009). On the other hand, apart from the regulatory control on opioids such as pethidine, butorphanol and pentazocine which make their practical use difficult, opioids also cause central nervous system (CNS) excitation,

sympathetic stimulation, increased locomotion and gastrointestinal stasis (Matthews, 2009). Despite these disadvantages, opioids are however widely used in combination with other sedatives such as alpha$_2$ agonists to achieve standing chemical restraint and field analgesia (Matthews *et al.*, 1991; Taylor, 2007). Butorphanol is a commonly used opioid as an adjunct for IV anaesthesia in horses and previous studies has suggested that butorphanol improved muscle relaxation, surgical conditions and prolong recumbency time (Matthews et al., 1991; Taylor, 2007). The routine use of butorphanol in field or ambulatory setting is however limited in most countries due to strict regulation and high cost.

Tramadol is an analgesic with mixed opioid and non-opioid activities whose non opioid activity is mediated through the alpha$_2$ agonist and serotonergic activities (Garrido *et al.*, 2000). Tramadol causes less respiratory depression compared with other opioids and it is not under strict regulatory control in many countries (Lewis and Han, 1996; Bhattacharya *et al.*, 2005; Natalini *et al.*, 2007; Ajadi *et al.*, 2009). Although tramadol is used extensively to treat mild to moderate pain in dogs and cats (Dhanjal *et al.*, 2009) and as a pre-anaesthetic in humans and dogs to facilitate tracheal intubation, reduce the dose of induction agents and improve recovery quality (Scott and Perry, 2000), its use either as analgesic or as a pre-anaesthetic in horses is still limited. By epidural injection, tramadol produced moderate analgesia at 1 mg^{-1} with no adverse effects on behavior (Natalini and Robinson, 2000) while by intravenous administration at 2 mg^{-1} it did not provide analgesia (Dhanjal *et al.*, 2009).
Since tramadol is an opioid analgesic with less strict regulation and cheaper cost, it may provide an alternative to the traditional opioids. This study was therefore designed to determine the benefit and safety of tramadol in xylazine-diazepam-ketamine anaesthesia in horses.

MATERIALS and METHODS

The protocol for this study was approved by the research and ethics committee of the College of Veterinary Medicine, University of Agriculture, Abeokuta, Nigeria. Five mixed breed horses comprising of both sexes (mean weight 276±39kg and mean age 7±0.2 years) were housed at the stables belonging to the Department of veterinary medicine and surgery. The animals were allowed to graze freely on paddock, supplemented with concentrates and vitamins. Water was provided ad libitum.

The study used a randomized cross-over design, the observers being unaware of the drug regimen that was employed. Horses were manually restrained for drug administration using a halter. All injections were administered intravenous (IV) following catheterization of the left jugular vein using a 14 gauge catheter. Each horse was anaesthesized twice with a period of at least two weeks between trials. In the first trial; treatment A (TXDK), the horses received 2.5 mg kg^{-1} of 5% tramadol (Plethico Pharmaceuticals Limited, India), followed five minutes later by 1.1 mg kg^{-1} of 2% xylazine hydrochloride (Xyl-M2, Arendonk, Belgium). And 3-5 minutes later, 0.11 mg kg^{-1} of 0.5% diazepam (Diazepam Injection BP, Calmpose, Ranbaxy laboratories limited, India) and 2.2 mg kg^{-1} of 5% ketamine (Ketamine Hydrochloride Injection USP, Rotex Medica. Bunsenstrasse, Trittau/Germany) were administered together. In the second trial; treatment B (SXDK), an equal volume of normal saline was administered in lieu of tramadol and five minutes later the other drugs were given as in treatment A. After induction of general anaesthesia, the horses were assisted by 6 handlers who gently positioned the animal on right lateral recumbency on a thick foamy mattress. The following assessments were then monitored:

Physiological parameters: These were monitored before and after induction and at ten minutes interval during each course of trial.

Rectal temperature was measured in centigrade using a clinical thermometer while the heart rate was counted in beats/minute with the aid of a precordial stethoscope. Respiratory rate was counted in breaths/minute by visual observation of chest excursion. Pulse rate, systolic, and diastolic blood pressures were all monitored with the aid of an automatic blood pressure monitor (Full automatic blood pressure monitor -model XJ 2002A, USA). The mean arterial pressure was calculated using the systolic and diastolic pressures according to McKelvey (2003).Anaesthetic indices: These were monitored as follows: (i) Onset of antinociception (OAN) Antinociception was determined by horses' reaction (leg withdrawal) to noxious stimuli produced by large Korcher forceps applied to the third ratchet at the pastern region. Time of loss of response to painful stimulus was recorded (ii) Duration of antinociception (DAN) was, defined as the time interval between loss and reappearance of response to noxious stimulus (iii) Duration of lateral recumbency (DLR) was defined as the time interval between assumption of lateral recumbency and repositioning to sternal recumbency; (iv) Time to standing (TTS) was defined as the time interval between assumption of sternal recumbency and first attempt to stand; (v) Numbers of attempts to stand (ATS) and (vi) Time to satisfactory co-ordination after standing (TSC) was defined as the time interval between standing and disappearance of ataxia. Recovery qualities (RQ) were assessed using a subjective ordinal rating scale of 1 (poor) to 3 (good). RQ was adjudged good if only one attempt was made to stand and TTS and TSC were less than 2 and 3 minutes respectively; it was considered fair if two attempts were made before standing and TTS and TSC were 2-4 minutes and 3-5 minutes respectively. RQ was adjudged poor if more than 2 attempts were made before standing and TTS and TSC were above 4 and 5 minutes respectively.

Haematology: Blood were collected through the jugular vein before and after each procedure for haematology. Heamatological parameters evaluated were packed cell volume (PCV), red blood cell (RBC), haemoglobin concentration (Hb) and white blood cell count (WBC).

Possible adverse events such as apnoea, ataxia, arrhythmia, cyanosis, sweating, diarrhea, urination, rigidity, excitability and death were recorded.

Data analysis: data were expressed as means (± SD). Duration of antinociception (DAN) and duration of lateral recumbency (DLR) were compared using student *t*-test. Haematological and physiological variables were compared using two-way analysis of variance (ANOVA). Duncan

Table 1: Anaesthetic indices for the tramadol (TXDK) and control (SXDK) groups

Group A (n=5)		Group B (n=5)	
Variables	Mean	Mean	Significant probability (P)
DAN	36.0±8.6	28.0±5.6	0.1160
DLR	48.0±4.2	41.0±4.9	0.0298*
ATS	1.0±0.0	1.0±0.0	0.1445
TTS	1.4±1.3	1.2±0.84	0.7845
TSC	2.8±2.2	1.4±1.3	0.2544
RQ	1.0±0.0	1.2±0.0	0.3739

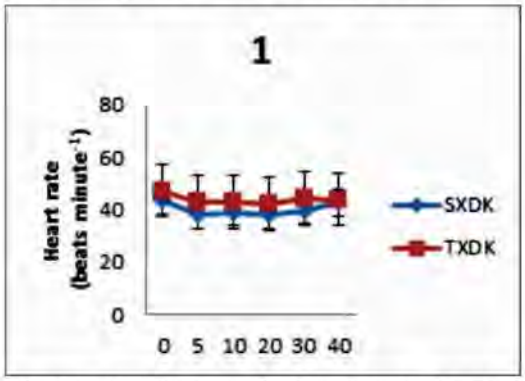

Figure 1: Changes in heart rate between the tramadol group (TXDK) and the control group (SXDK

New Multiple Range Test (DMRT) was used to separate variant means. A probability value less than 0.05 ($p < 0.05$) was considered significant in all cases

The mean duration of antinociception (DAN) obtained following treatment with TXDK (36.0±8.6 min) and SXDK (28.0±5.6 min)

were not significantly ($p>0.05$) different. There was however a significant ($p<0.05$) difference in the DLR (48.0±4.2 min) obtained in TXDK treated horses and DLR obtained in SXDK (41.0±4.9 min) treated horses. ATS, TTS, TSC and recovery qualities (RQ) were not significantly different (Table 1). All horses attempted to stand once and recovery was generally smooth for horses in both treatments. No adverse effects were observed in both treatments. Tramadol also had no significant effects on both the physiological (figures 1-4) and haematological parameters measured (Table 2).

Table 2: Haematological parameters for the tramadol (TXDK) and control (SXDK) groups

	Group A (N=5)				Group B (N=5)			
	Pre-induction		Post induction		Pre induction		Post induction	
Variable	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
PCV	35	5.8	33	3.6	36	2.2	33	2.1
Hb.	11	2.1	10	2.2	11	0.8	9.6	1.2
RBC	7.4	1.0	7.0	0.77	7.5	0.58	6.9	0.86
MCV	48	4.3	47	3.7	49	3.7	49	5.5
MCH	15	1.0	14	1.9	15	0.15	14	0.42
MCHC	31	4.1	30	4.7	30	2.4	29	4.5
WBC	10220	3061	8850	2782	9930	1954	9910	2325
Neut.	54	14	57	21	68	8.5	42	17
Lym.	43	16	42	22	30	7.5	56	18
Eos.	0.60	1.3	0.60	1.3	1.6	1.5	1.0	1.0
Mono.	0.20	0.45	0	0	0	0	0.6	0.89
Baso.	0	0	0	0	0	0	0	0

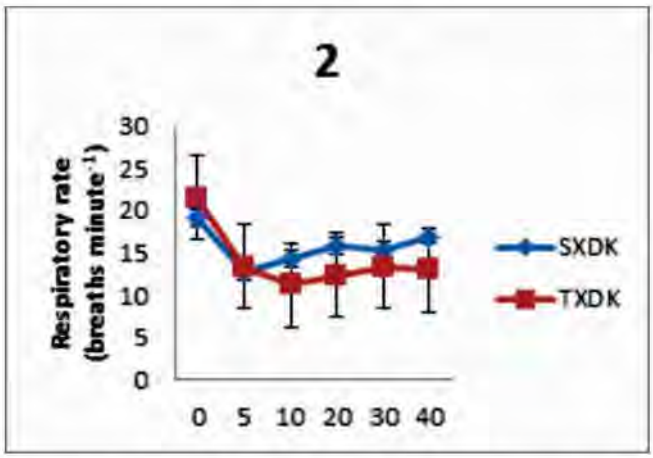

Figure 2: Changes in respiratory rate between the tramadol group (TXDK) and the control group (SXDK)

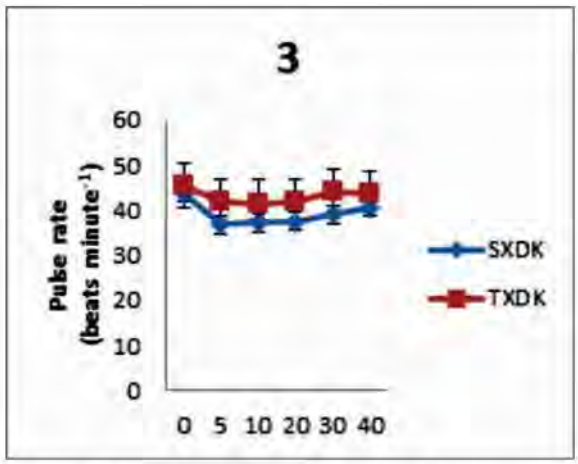

Figure 3: Changes in pulse rate between the tramadol group (TXDK) and the control group (SXDK)

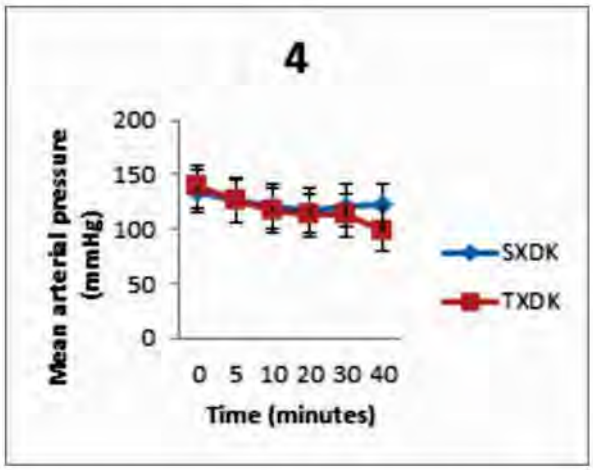

Figure 4: Changes in mean arterial pressure between the tramadol group (TXDK) and the control group (SXDK)

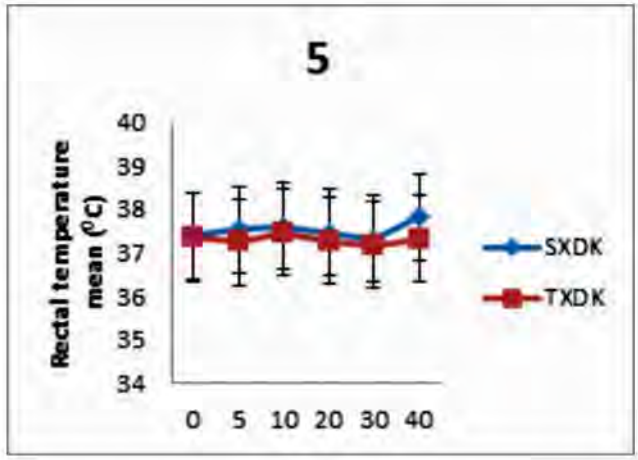

Figure 5: Changes in rectal temperature between the tramadol group (TXDK) and the control group (SXDK)

DISCUSSION

Tramadol at the dosage studied prolonged the duration of lateral recumbency but did not prolong the duration of antinociception of xylazine-diazepam-ketamine anaesthesia in horses. A similar study in horses showed that tramadol (2 mg kg^{-1}) when administered as single intravenous bolus did not prolong hoof withdrawal latencies to a thermal stimulus (Dhanjal *et al.*, 2009). This suggests that use of low doses of tramadol either as single bolus injection or as pre-anaesthetic seems to have no antinociceptive properties in horses. The increased lateral recumbency observed in this study might however be due to the additive effect of tramadol on the hypnosis of diazepam or on the general anaesthesia produced by xylazine-diazepam-ketamine combination.

Tramadol at the dose studied is safe for use in the horse, as there were no behavioral, haematological or cardiopulmonary adverse effects associated with its use. This finding further confirms earlier reports on the safety of tramadol usage in other species and in horses in particular (Natalini and Robinson, 2000; Natalini *et al.*, 2007; McMillan *et al.*, 2008; Ajadi *et al.*, 2009). The addition of tramadol did not significantly change any of the physiological parameters measured. The heart and pulse rates tended to decrease throughout the period of monitoring and these might be associated with effect of xylazine as similar results have been reported in pigs (Ajadi *et al.*, 2009). Rectal temperature also decreased in this study, though not significantly. A decrease in rectal temperature was recorded following systemic administration of alpha$_2$ adrenoceptor agonists in sheep (Nolan *et al.*, 1987). This finding was attributed to the depression of the hypothalamic thermoregulatory centre (Macdonald *et al*, 1988). The decrease in rectal temperature may also probably be as a result of reduced basal metabolic rate (BMR) and muscle activity (Ponder and Clarke, 1980). The decrease in respiratory rate observed during the period of monitoring might also be associated to the use of xylazine (Hall *et al.*, 2001) and not tramadol (Dhanjal *et al.*, 2009).

Previously, tramadol had been reported to have no effect on the heart and respiratory rates in horses (Dhanjal *et al.*, 2009), dog (Mastrocinque and Fantoni, 2003; McMillan *et al*, 2008), and humans (Turker *et al.*, 2005). The lack of respiratory-depressant effect of tramadol unlike other opioids is a major advantage for its use. Thus as earlier reported, animals premedicated with tramadol instead of the traditional opioids are likely to maintain better intra-operative respiratory function (Natalini *et al.*, 2007; Ajadi *et al.*, 2009).

In conclusion, although tramadol did not prolong the duration of analgesia it increased the duration of

lateral recumbency of XDK. The result of this study indicated that tramadol at the dose studied did not deepen analgesia produced with xylazine-diazepam-ketamine combination but deepened the anaesthetic effect of XDK. Further studies are needed to evaluate the effect of higher doses of tramadol on analgesic/antinociceptive effects of XDK in horses.

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