Errata

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Comparison of Xylazine/Tramadol and Xylazine/Pentazocine for Sedation and Analgesia in Dogs

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Running title- Sedation in dogs

Abstract

The effects of intramuscular administration of xylazine (1 mg/kg) -atropine (0.04 mg/kg) combined either with tramadol 4mg/kg or pentazocine 2 mg/kg were evaluated for quality of sedation and changes in physiological parameters over a 60 minute period in 5 intact Nigerian indigenous dogs of both sexes with mean body weight of 10.2 ± 1.5 kg (mean ± Standard deviation). Pentazocine demonstrated appreciable analgesia in combination with xylazine. Analgesia was produced in all the dogs with xylazine-pentazocine combination compared with only 2 dogs with xylazine- tramadol combination and one dog with xylazine alone. Onset and duration of analgesia with the xylazine-pentazocine group were 6.8 ± 3.3 and 31.2 ±7.1min respectively. Onset of sedation and time to sleep with xylazine-tramadol (12.2 ± 3.3 min and 16.8 min) were significantly longer ($p < 0.05$) than with xylazine alone (6.0 ± 3.4 min and 10.6±2.4 min) and with xylazine-pentazocine (5.8 ± 1.9 min and 8±2.3 min). There was no significant difference ($p>0.05$) in the sleep time of the dogs with the three treatments; xylazine (41.4±9.3min); xylazine-tramadol (39.8± 9.2 min) but xylazine-pentazocine (45.0± 3.3min) had the longest sleep time. The time to stand with both xylazine-tramadol and xylazine-pentazocine were significantly shorter ($p < 0.05$) than with xylazine alone. Peak sedation occurred by the 20th and 30th minute in all the dogs with the three treatments. Heart and respiratory rates, systolic, diastolic, mean arterial blood pressure and rectal temperature were within physiological range with the three treatment groups. It was concluded that xylazine-pentazocine produced preferred quality of sedation and therefore recommended for minor procedures associated with pain or premedication in dogs.

Keywords: Analgesia, dog, pentazocine, sedation, tramadol, xylazine

Introduction

Dogs are usually sedated to facilitate several clinical procedures including physical examination, grooming, diagnostic and minor surgical procedures (Murrell, 2016).

Common classes of drugs used to achieve sedation or tranquilization in dogs include the alpha2-agonists (xylazine, meditomidine, dexmedetomidine); the benzodiazepines (diazepam, midazolam), and the phenothiazines chiefly acepromazine (Clarke *et al*., 2014; Thomas and Lerche, 2017). Whereas diazepam produces no or mild sedation and phenothiazines produce mild to moderate sedation, the alpha 2 agonists are associated with deeper levels of sedation. Canine patients however, could be aroused from induced sleep with alpha 2 agonists when painful stimuli are applied which often result in veterinary staff being bitten by apparently sedated dogs (Thomas and Lerche, 2017). The sedation produced by alpha 2 agonists is dose dependent; thus, higher doses produce deeper levels of sedation that could be accompanied by severe and fatal cardiopulmonary depression (Clarke *et al*., 2014). The combinations of opioids with sedatives are sometimes used to make animals more manageable. Opioids have been combined with alpha 2 agonists to produce more reliable and predictive effects and to achieve dosage reduction effects of the individual drugs in the combination (Clarke *et al*, 2014).

Opioids are potent analgesics. Morphine, methadone, buprenorphine, butorphanol, hydromorphone, pentazocine and tramadol are some opioids currently in use in veterinary medicine for pain management (Kukanich and Wiese, 2015; Kerr, 2016). Apart from analgesia provision, opioids also typically produce dose- dependent central nervous system depression when administered alone. This effect can be profound when combined with other sedatives such as phenothiazines and α2-adrenergic receptor agonists. This combination results in synergism with the sedation and analgesia being greater than that capable of being achieved by either drug alone, and allow for dose reduction of both drugs (Clarke *et al*., 2014). Many opioids are highly controlled due to human abuse and are not readily available in developing countries. The unavailability of opioids has been recognized as one of the challenges with provision of analgesia for both veterinary and human patients in Nigeria and sub-Saharan Africa (Oguntoye and Eyarefe, 2017; Egede *et al*., 2017).

Tramadol is a synthetic racemic mixture of the 4-phenylpiperidine analogue of codeine (Vettorato, 2010) which is used widely in human medical practice (Wang *et al*., 2005). Tramadol in equipotent doses has the same analgesic effect as morphine in relieving mild-to-moderate pain (Tarradel *et al*., 1996; Mildh *et al.,* 1999). Apart from being a

weak mu agonist, tramadol is a serotonin and nor epinephrine re-uptake inhibitor; thus, providing analgesia by opioid and non- opioid mechanisms (Karrasch *et al*., 2015). Tramadol has recently received widespread acceptance in veterinary medicine (Thengchaisrl and Mahidol, 2019).

Pentazocine, (1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methylbut-2-enyl)-2,6-methano-3-benzazocin-8-ol) is a benzomorphan derivative (Harmer *et al*., 1983). It is the first opioid agonist-antagonist to be introduced into clinical practice as an analgesic and has been widely used in human clinical practice (Henderson, 2008). Pentazocine exerts its analgesic effect via agonism at the kappa receptor and is a weak antagonist at the μ receptor (Henderson, 2008). Although pentazocine is rarely used in veterinary medicine (Kukanich and Wiese, 2015), it has reportedly provided satisfactory post-operative analgesia following orthopaedic surgery in dogs when compared with buprenorphine and morphine (Taylor and Houlton, 1984); some recent publications have also emphasized its analgesic efficacy in dogs and buffalo (Udegbulam *et al*., 2021; Yadav *et al*., 2021). In man, when given intravenously, pentazocine produces 1/3rd to 1/4th the potency of morphine (Henderson, 2008). Pentazocine and tramadol are readily available in developing countries (Henderson, 2008; WHO, 2014).

Xylazine is the oldest alpha 2 agonist in Veterinary medicine and is widely used in several species including dog (Clarke *et al*., 2014).

This study therefore compared the quality of sedation and analgesia provided by combination of tramadol or pentazocine with xylazine in dogs as there is dearth of literature on the effects of these two opioids on xylazine sedation in dogs. The result of the study could also be a basis for rational choice of sedative-opioid combination in the absence of the more potent opioids, especially in developing countries.

Materials and Methods

Animals

The experimental animals consisted of 5 adult Nigerian indigenous dogs (2 intact males, 3 intact, non-pregnant, non-lactating females) and with mean body weight 10.2 ±1.5 kg (mean ±SD).

Housing

The dogs were housed in individual cages at the Kennel of the Department of Veterinary Surgery and Radiology, University of Ibadan.

Stabilization

Dogs were given a chemical bath with amitraz (Amitraz 20®, RoyRaphaels pharmaceuticals Co. Ltd, Nigeria).and dewormed with a triple wormer (worm-off® Hebei Kexing Pharmaceutical Co. Ltd, China) consisting of praziquantel 50mg; pyrantel pamoate 144mg;

febantel 150mg per tablet at a dosage of one tablet/10kg body weight. They were allowed an acclimatization period of two weeks to get them accustomed to their new environment, new feeding regime and handling. They were fed once daily with homemade food comprising of rice and fish. Water was provided free choice in all the cages.

Before commencement of the experiments, comprehensive physical examination was carried out on the dogs and they were adjudged to be healthy based on the result obtained therefrom and from results from haematology and serum chemistry evaluations.

Drugs

The drugs used for this study were:

(a) Xylazine (Xylased®Bioveta, Czech Republic) supplied as 20mg/ml solution for injection in 50ml vials
(b) Atropine(non-proprietary) supplied as 1mg/ml solution for injection in 1ml ampoule.
(c) Tramadol hydrochloride (Gland Pharma, India) supplied as 100mg/2ml solution for injection in 2ml ampoules.
(d) Pentazocine (Pentalab®, LABORATE pharmaceutical, India) available for parenteral injection supplied as 30mg/ml solution for injection in 1ml ampoules.

Study design

A simple randomized crossover design in which each dog underwent three series of experiments with a one-week interval between each experiment for drug wash-out was adopted for the study. In the first series (control , XYL), dogs were sedated with xylazine and atropine and normal saline. In the second series of experiments (XTR group), each dog was premedicated with xylazine and atropine followed by tramadol. In the third series (XPE), each dog was premedicated with xylazine and atropine followed by pentazocine.

Experimental Procedure

Food but not water was withdrawn from the dogs 12 hours prior to the commencement of the trials. In the control experiment, each dog was given intramuscular injections of xylazine at 1mg/kg with atropine at 0.04mg/kg and normal saline at the same volume as xylazine (XYL group). In the second experiment, each dog was given intramuscular injection of xylazine at 1mg/kg with atropine at 0.04mg/kg followed by intramuscular injection of tramadol at 4mg/kg (XTR group). For the third experiment each dog was given intramuscular injection of xylazine at 1mg/kg with atropine at 0.04mg/kg followed by intramuscular injection of pentazocine at 2mg/kg body weight (XPE group). For each experiment, calculated volumes of the xylazine and atropine were mixed together in one syringe for administration. Injections of saline, tramadol and pentazocine were

done immediately after xylazine-atropine injection. Physiological parameters (heart rate, respiratory rate, rectal temperature and blood pressure) were measured at onset of sedation and then subsequently at ten- minute intervals over a one-hour period. Analgesia was measured following onset of sedation using the paw pinch withdrawal method as previously described (Cruz *et al*., 1997). Selected indices for sedation were measured and calculated. Sedation quality was also assessed using a simple descriptive scale (Monteiro *et al*., 2016).

Calculated sedative indices

(a) Onset of sedation (OOS): time interval between drug administration to the time when dog became drowsy.
(b) Time to sleep (TTS): time interval between drug administration and when dog started to sleep
(c) Duration of sleep (DOS): time interval between when dog slept and when dog woke up.
(d) Onset of analgesia (OOA): time interval between drug administration to the time when pedal reflex was lost.
(e) Duration of analgesia (DOA): time interval between the loss and return of pedal reflex.
(f) Time to stand (TST): time interval between when dog woke up to when dog assumed a standing position.

Sedation scoring system:

0 – No sedation: dog still active and alert
1 – Mild sedation: less alert but still active
2 – Moderate sedation: drowsy, recumbent, relunctant to move and ataxic
3 – Profound sedation: very drowsy (sleeping) unable to walk

Measured physiological parameters**:** Heart rate in beats per minute was monitored with the aid of a precordial stethoscope, respiratory rate in breaths per minute by counting the number of complete movement of the rib cage in minutes, rectal temperature (in °C) and blood pressure (in mmHg) were measured with the aid of a portable multiparameter patient monitor (Berry® monitor Pm6 100b, Shangai Berry Electronic Tech Co Ltd, China).

Analysis of Data

All data were expressed as means ± standard deviation (SD) of five dogs. The means of the sedative indices (OOS, TTS, DOS, OOA, DOA and TTS) of the three treatment groups were compared with one way ANOVA and mean values of the measured physiological parameters were compared using ANOVA for repeated measures. Least significance difference was used as post-test where necessary and a value of $p < 0.05$ accepted as statistically significant.

Results

Sedation indices and sedation score

The mean values of sedation indices for the groups are shown on Table 1.

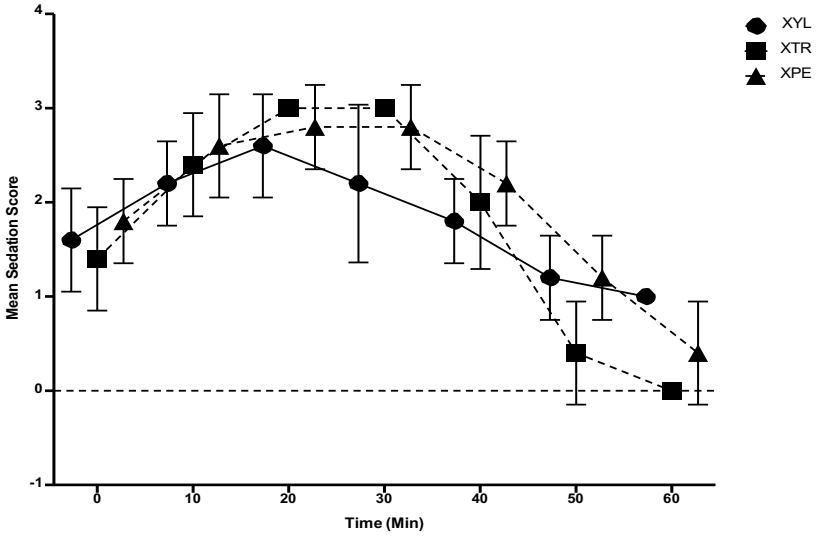
Table 1 shows the mean values (in minutes) of sedation and analgesic indices of the 5 dogs when given xylazinea alone or combined with either tramadolc or pentazocinec.

	Treatment groups		
Indices	XYL	XTR	XPE
OOS	6 ±3.4	12.2 ±3.3	5.8 ± 1.9
TTS	10.3 ± 1.7	15.8 ± 2.7*	8.2 ± 2.3
DOS	41.4 ± 9.3	39.8 ± 9.2	45.0 ±3.3
OOA	NEG	NEG	6.8 ± 3.3
DOA	NEG	NEG	31.2 ± 7.1
TST	15.4 ± 2.6	2.8 ± 0.8*	3.7 ± 0.6*

Data are expressed as means ± SD of 5 dogs
a, XYL- xylazine (control) xylazine 1mg/kg + atropine 0.04 mg/kg IM
b, XTR- xylazine 1mg/kg + atropine 0.04 mg/kg +tramadol 4mg/kg IM
c, XPE- xylazine 1mg/kg + atropine 0.04 mg/kg +pentazocine 2mg/kg IM
* $P<0.05$ versus control; NEG- negligible
TTS, time to sleep; DOS, duration of sleep
OOA, onset of analgesia; DOA, duration of analgesia; TST, time to stand

Whereas XTR had the longest onset of sedation (12.2 ± 3.3 min) and time to sleep (16.8 ±2.7min) which were significantly longer than the control (XYL group) ($p= 0.002$ and $p= 0.001$); XPE produced the longest duration of sedation (45.0 ± 3.3 min) but was not significantly longer than that of the control (XYL; $p= 0.43$) or XTR ($p = 0.13$) groups. All the five dogs demonstrated analgesia of mean duration of 31.2 ± 7.1 min and mean onset of 6.8 ± 3.3 with XPE while only one and two dogs showed analgesia with XYL and XTR respectively. All dogs had peak sedation by the 20th and 30th minutes post onset of sedation (Figure 1).

Figure 1: Mean sedation scores of the 5 dogs to the three treatments at various time points



Physiological parameters

Heart rate: The mean heart rate responses of the dogs ranged from 66.4 ± 17.8 to 141.6 ± 26.2 (beats/min) for XYL group, 115.2 ± 15.6 to 147.2 ± 24.8 (beats/min) for XTR and 116.8 ± 46.8 to 155.2±13.7 (beats/min) for XPE (Tabe 2). Mean heart rates were significantly higher than the control values in the XTR and XPE groups. They were also higher than the control at the 50th and 60th minutes but only in the XPE group.

Respiratory rate: The mean respiratory rate responses of the dogs are shown on Table 2. They ranged from 12.8 ± 3.3 to 20.8 ± 6.6 breaths/min (XYL), 16.0 ± 0.1 breaths/min (XTR) and 14.4 ± 4.6 breaths/min (XPE). There was no significant difference in respiratory rate responses of the dogs to the three treatments at all-time intervals although there was some fall in respiratory rates after the initial values taken at onset of sedation. However, no clinically significant respiratory depression was recorded as none went below 8 breaths/ minute acceptable for dogs under anaesthesia.

Rectal temperature: The mean rectal temperature responses of the dogs to the three treatments are shown on Table 2.

Table 2: Mean values of heart and respiratory rates and temperature responses of 5 dogs to sedation with xylazine alone (XYL[a]) and combined with tramadol (XTR[b]) or pentazocine (XPE[c])

Variable	Treatment	0[d]	10	20	30	40	50	60
Heart	XYL	66.4 ± 17.8	113.6 ± 52.2	143.2 ± 31.7	141.6 ± 26.2	136 ± 20.8	134.4 ± 12.8	121.6 ± 13.1
Rate	XTR	147.2 ± 24.84*	137.6 ± 20.1	141.6 ± 26.9	144.8 ± 5.9	138.4 ± 7.8	140.0 ± 10.6	115.2 ± 15.6
	XPE	116.8 ± 46.8*	143.2 ± 25	152.8 ± 11.8	151.2 ± 7.2	155.2 ± 13.7	151.2 ± 7.7*	144.0 ± 14.7*
Respiratory	XYL	20.4 ±6.1	20.8 ± 6.6	19.6 ± 9	14 ± 5.7	12.8 ± 3.3	17.6 ± 6.7	19.2 ± 4.4
Rate	XTR	19.2 ± 3.3	17.6 ± 2.2	16.8 ± 1.8	20 ± 2.8	16.8 ± 3.3	16.0 ± 0.1	16.8 ± 1.8
	XPE	20.8 ± 3.3	17.6 ± 5.4	15.2 ± 5.2	14.4 ± 4.6	15.2 ± 3.3	17.6 ± 4.6	18.4 ± 7.8
Rectal	XYL	39.1 ± 0.3	39 ± 0.4	38.9 ± 0.3	38.9 ± 0.3	38.7 ± 0.3	38.6 ± 0.2	38.4 ± 0.3
Temperature	XTR	38.2 ± 0.8*	38 ± 0.9*	37.9 ± 0.7*	37.8 ± 0.8*	37.6 ± 0.8*	37.5 ± 0.7*	37.4 ± 0.8*
	XPE	38.6 ± 0.4	38.6 ± 0.7	38.6 ± 0.5	38.4 ± 0.4	38.3 ± 0.3*	38.0 ± 0.5	37.7 ± 0.4
Systolic	XYL	162.4 ± 36.2	122.8 ± 23.1	135.8 ± 21	153.6 ± 38.2	167.6 ± 23.7	127.2 ± 36.7	132.4 ± 35
Blood	XTR	160.8 ± 28.6	141.2 ± 36.6	126.8 ± 37	145 ± 45.1	140 ± 35.2*	128.4 ± 36.1	140.2 ± 32.9
Pressure	XPE	122.6 ± 26.9	138.8 ± 41.9	139.8 ± 27.1	149 ± 39.7	157.2 ± 36.6	160 ± 27.2	166 ± 45.8
Mean	XYL	131.8 ± 40.1	88.8 ± 29	105.4 ± 20.6	121.6 ± 32.9	134.8 ± 10.7	95.6 ± 28.2	106.4 ± 36.5
Arterial	XTR	112 ± 64.8	118.8 ± 37.6	100.8 ± 38.2	109.4 ± 43.6	113 ± 37.1	102.4 ± 39.3	115.6 ± 33.8
Pressure	XPE	92.2 ± 15.1	108.6 ± 40.2	115.8 ± 26.4	113.8 ± 30.8	124.6 ± 34.3	127.6 ± 36	130.8 ± 41.6
Diastolic	XYL	117 ± 42.8	72.2 ± 32.7	91 ± 22.9	106.2 ± 31.4	118.8 ± 8.6	80.6 ± 29.7	93.8 ± 37.6
Blood	XTR	115.2 ± 34.3	108.4 ± 38.1	88.2 ± 40	92.2 ± 47	100.2 ± 38.5	90.2 ± 41.7	104 ± 35.6
Pressure	XPE	77.6 ± 14.2*	97.8 ± 41.6	104 ± 27.5	96.8 ± 30	108.8 ± 35.8	111.8 ± 43.2	113.8 ± 40.1

Data are expressed as means ± SD of 5 dogs
a, XYL- xylazine (control) xylazine 1mg/kg + atropine 0.04 mg/kg IM
b, XTR- xylazine 1mg/kg + atropine 0.04 mg/kg +tramadol 4mg/kg IM
c, XPE- xylazine 1mg/kg + atropine 0.04 mg/kg +pentazocine 2mg/kg IM
d, measurements made after the onset of sedation of the anaesthetized dogs
* $P<0.05$ versus control

Mean rectal temperatures ranged from 38.6 ± 0.2 to 39..1±0.3 º C with XYL; 37.4 ± 0.8 to 38.2 ± 0.8 º C with XTR and 37.7± 0.4 º C to 38.6 ± 0.4 º C with XPE. While temperature values were significantly lower in XTR than with XYL at all-time points temperature was lower with XPE than XYL only at the 40th minute.

Systolic Arterial Pressure

The systolic arterial blood pressure responses of the 5 dogs with the three treatments are shown in table 2. There was no significant ($p<0.05$) difference among the groups except at the 40th minute where SAP with the XTR group was significantly higher than with the control. While none of the SAP values was above the upper physiologic limit with all the treatments, the lower values were below the lower physiologic limits with xylazine and xylazine/pentazocine.

Mean arterial pressure

The mean arterial blood pressure responses of the dogs under sedation with the three treatments are shown in table 2. There was no significant difference between the mean arterial pressures with the three treatments. None of the MAP values recorded was below the acceptable limit of 60 mmHg acceptable for dogs under anaesthesia.

Diastolic arterial pressure

The mean diastolic pressure of the dogs following the three treatments are shown on Table 2.A significant difference in DAP values existed only in the XPE that had lower figures than the control immediately after administration of sedatives. There was fluctuation of DAP values in the three treatment groups with more increase from baseline values with XPE but decreases with XTR. However, DAP fell within physiologic limits in all the treatment groups.

Discussion

The result of this study showed that xylazine-pentazocine produced analgesia in all the dogs while analgesia was produced in only two dogs with xylazine-tramadol and only one dog with xylazine alone. It was surprising that tramadol did not produce analgesia in all the dogs since several clinical studies have shown its analgesic efficacy via various parenteral routes in dogs (Vettorato *et al*., 2010; Buhari *et al.* 2012; Mahidol *et al*., 2015; Ugwu *et al*., 2017, Giudice *et al*., 2017; Olivia *et al*., 2019). Preemptive administration of tramadol at 2 mg/kg in dog for ovariohysterectomy provided comparable analgesia to morphine at 0.2 mg/kg (Mastrocinque and Fantoni, 2003). However, similar to the result of our study some studies also did not demonstrate sufficient analgesia with tramadol (Donati *et al.,* 2021; Gültekin, 2021) while another study concluded that tramadol did not enhance acepromazine sedation in dogs (Monteiro *et al*, 2016). Tramadol did

not appear to influence the duration of sedation when added to xylazine in the current study as there was no significant difference ($p>0.05$) between duration of sedation when xylazine was used alone and in combination with tramadol in the dogs (Table 1). However, pentazocine prolonged the duration of sedation albeit not with statistically significant difference ($p= 0.43$) (Table 1). The reason for variation in analgesic efficacy with tramadol in xylazine- tramadol in our study and some other studies (Donati *et al.,* 2021; Gültekin, 2021) is not very clear. It may be that drug-drug interaction occurred at the receptor level especially as antagonism could occur with drugs with multiple receptors. The better analgesic efficacy with xylazine-pentazocine than xylazine-tramadol observed in this study is consistent with the result of another study in dogs that compared the analgesic effect of constant rate infusion of xylazine-pentazocine and xylazine-tramadol on pain in dogs that underwent digital amputation and concluded that pentazocine-xylazine CRI provided better analgesia when compared to tramadol-xylazine CRI (Udegbulam *et al*., 2021).

The times to stand with xylazine-tramadol and xylazine-pentazocine were significantly shorter than with xylazine alone (Table 1). This finding although unexpected, may be of advantage for quicker recovery for patients sedated with the sedative opiod combinations.

The physiological parameters of the 5 dogs when subjected to the three treatments are shown on Table 2. Heart rates of the dogs taken immediately after the onset of sedation (time 0) showed significant difference ($p<0.05$) with xylazine alone (66.4 ± 17.8 min) compared with xylazine-tramadol (147.2 ± 24.84) and xylazine-pentazocine (116.8 ± 46.8). Alpha 2-agonists are known to cause bradycardia (Clarke *et al*, 2014; Kerr *et al*; 2016) and this was why atropine, an anticholinergic was co administered. The low heart rate recorded with xylazine alone at this time despite atropine administration may be due to the paradoxical bradycardia sometimes observed following clinical doses of atropine (Dugdale, 2010). It has been suggested that this slowing of the heart is due to the stimulation of vagal centres in the brain before the peripheral anticholinergic effects of atropine occur (Dugdale, 2010). Overall, heart rates of dogs fell within the physiological range of 60-150 beats/min quoted for dogs under anaesthesia (Thomas and Lerche, 2017).

The blood pressure values of systolic arterial pressure, mean arterial pressure and diastolic arterial pressure of the dogs with the three sedative/ sedative combinations (Table 2) fell within the normal range of 110-190 mmHg (SAP) 55-110 mmHg (DAP) and 60-120 mmHg (MAP) quoted for dogs (Reuss-Lamky, 2010). This demonstrated safety of the dogs as none caused hypotension or hypertension

which might have been of some clinical concern.

The respiratory responses of the dogs (Table 2) under sedation with the three treatments also fell within acceptable limits of 10-30 breaths/minute in dogs (Thomas and Lerche, 2017).

None of the dogs was hypothermic although the dogs given xylazine-tramadol showed some significantly lower mean temperatures during the one hour period when compared with when given xylazine alone (Table2). Significant difference was observed only at the 40th minute with the xylazine-pentazocine dogs.

We therefore concluded that, xylazine-pentazocine appeared to be a better combination than xylazine-tramadol to achieve sedation or premedication in dogs when a painful procedure is anticipated in the absence of the commonly used opioids in dogs.

References

Buhari, S., Hashim, K., Yong Meng, G., Mustapha, N.M., Gan, S.H. Subcutaneous administration of tramadol after elective surgery is as effective as intravenous administration in relieving acute pain and inflammation in dogs. Sci. World J.1- 8 (2012). doi: 10.1100/2012/564939.

Clarke, K.W., Trim, C.M., Hall, L.W. Veterinary Anaesthesia (Saunders Elsevier, London 2014).

Cruz, M., Luna, S., P., L., Clark, R., M., O. Massone, F., Castro, G.B. Epidural anaesthesia using lignocaine, bupivacaine or a mixture of lignocaine and bupvacaine in dogs. J. Vet. Anaesth. 24(1): 30-32 (1997).

Donati, P.A., Tarragona, L., Franco. J.V., Kreil, V., Fravega, R., Diaz, A., Verdier, N., Otero, P.E. Efficacy of tramadol for postoperative pain management in dogs: systematic review and metaanalysis. Vet. Anaesth. Analg. 48 (3): 283-296 (2021). https://doi.org/10.1016/j.vaa.2021.01.003.

Dugdale A. Veterinary Anaesthesia Principles to Practice (Wiley-Blackwell, Oxford 2010).

Egede, J.F., Ajah, L.O., Umeora, O.U., Ozumba, B.C., Onoh, R.C., Obuna, J.A., Ekem, N.

Pentazocine alone versus pentazocine plus diclofenac for pain relief in the first 24 hours after caesarean section: a controlled randomized controlled study. J. Clin. Diagnostic. 11(4):1-5 (2017).

Giudice, E., Barillaro, G., Crinò, C., Alaimo, A., Macrì, F., Di Pietro, S. Postoperative pain in dogs undergoing hemilaminectomy:

comparison of the analgesic activity of buprenorphine and tramadol. J. Vet. Behav. 19 : 45-49 (2017).

Goudie-DeAngelis, E.M., Woodhouse, K.J. Evaluation of analgesic efficacy and associated plasma concentration of tramadol and O-desmethyltramadol following oral administration post ovariohysterectomy. Inter. J. Appl. Res. Vet. Med. 14(1):105-113 (2016).

Gültekin, Ç. Comparison of the analgesic effects of morphine and tramadol after tumor surgery in dogs. Open Vet. J. 11(4): 613–618 (2021).

Hall, L.W., Clarke, K.W., Trim, C.M. VeterinaryAnaesthesia (Saunders Elsevier, London 2001).

Harmer, M., Slattery, P.J., Rosen, M., Vickers, M.D. Comparison between buprenorphine and pentazocine given i.v. on demand in the control of postoperative pain. Br. J. Anaesth. 55:21 (1983).

Henderson, K. Pentazocine. Update Anaesth. 24 (1): 8-12 (2008).

Karrash, N.M., Lerche, P., Aarnes, T.K., Gardener, H.L., London, C.A. The effects of preoperative oral administration of carprofen or tramadol on postoperative analgesia in dogs undergoing cutaneous tumor removal. Can. Vet. J. 56: 81-822 (2015).

Kerr, C.L. Pain management: systemic analgesic. BSAVA Manual of Canine and Feline Anaesthesia and Analgesia (British Small Animal Veterinary Association, Gloucester 2016).

Kukanich, B., Wiese, A.J. Opioids. Veterinary Anesthesia and Analgesia (Blackwell, Iowa 2015).

Mahidol, C., Niyom, S., Thitiyanaporn, C., Supraset, A., Thengchaisri, N. Effects of continuous intravenous infusion of morphine and morphine-tramadol on the minimum alveolar concentration of sevoflurane and electroencephalographic entropy indices in dogs. Vet. Anaesth. Analg. 42:182-186 (2015). doi: 10.1111/ vaa.12185. Epub 2014 Jun 25.

Mastrocinque,S., https://pubmed.ncbi.nlm.nih.gov/12925179/ - affiliation-1 Fantoni, D.T. A comparison of preoperative tramadol and morphine for the control of early postoperative pain in canine ovariohysterectomy. 30 (4): 220-228 (2003). doi: 10.1046/j.1467-2995.2003.00090.x

Mildh, L.H., Leino, K.A., Kivera, O.A. Effects of tramadol and meperidine on

respiration, plasma catecholamine concentrations, and hemodynamics. J. Clin. Anesth. 11: 310-316 (1999).

Monteiro, E.R., Lobo, R.B., Nunes Jr., J.S., Rangel, J.P.P., Bitti, F.S. Tramadol does not enhance sedation induced by acepromazine in dogs Can. J. Vet. Res. 80:323–328 (2016).

Murrell, J.C. Pre-anaethetic medication and sedation. BSAVA Manual of Canine and Feline Anaesthesia and Analgesia. British Small Association (Gloucester, Kingdom 2016).

Oguntoye, C.O., Eyarefe, O.D. Nigerian veterinarians' attitude and response to small animal pain management. J.Vet. Med. Anim. Health 9 (12): 334-341. (2017).

Oliva, V.N.L.S., Albuquerque, V.B., Floriano, B.P., Meneghetti, T.M., Abimussi, C. J.X., Ferreira, J.Z., Wagatsuma, J.T., Laranjeira, G.M., Santos, P.S.P. Different rates of tramadol infusion for peri and postoperative analgesia in dogs undergoing orthopedic surgery Arq. Bras. Med. Vet. Zootec. 71 (1):127-136 (2019).

Reuss-Lamky, H.L. Blood pressure and end tidal CO2 in the anaesthetized patient. Anaesthesia for Veterinary Technicians. (Wiley Blackwell, Iowa 2010).

Tarradell, R., Pol, O., Farre, M. Respiratory and analgesic effects of meperidine and tramadol in patients undergoing orthopedic surgery. Meth. Find. Exp. Clin. Pharmacol. 18: 211-218 (1996).

Taylor, P.M., Houlton, J.E.F. Post-operative analgesia in the dog: a comparison of morphine, buprenorphine and pentazocine. J. Small Anim. Pract. 25: 437–451 (1984).

Thengchaisrl, N., Mahidol, C. (2019) Evaluating the effects of continuous intravenous infusions of tramadol and tramadol-lidocaine on sevoflurane minimum alveolar concentration (MAC) and entropy values in dogs. J. Vet. Med. Sci. 81 (5): 682-688 (2019). doi: 10.1292/jvms.18-0448

Thomas, J.A., Lerche., P. Anesthesia and Analgesia for Veterinary Technicians (Elsevier, Missouri 2017).

Udegbunam, R.I., Ogbodo, F.U., Onuba, C.A., Okereke, N.H., Ezeobialu, T.H., Udegbunam, S.O. Effect of constant rate infusion of tramadol-xylazine and pentazocine xylazine on acute pain response in xylazine-pentobarbitone anaesthetized dogs undergoing digital amputation. Alex. J. Vet. Sci. 70 (1): 140-150 (2021).

Ugwu N. Eze CA and Udegbunam R Assessment of the analgesic potency of constant rate infusion of tramadol hydrochloride and as an adjunct to ketoprofen in laparotomized bitches. Sokoto J. Vet. Sci. 15: 80 -87 (2017).

Vettorato, E., Zonca, A., Isola, M. Villa R, Gallo M, Ravasio G, Beccaglia M, Montesissa C, Cagnardi P. Pharmacokinetics and efficacy of intravenous and extradural tramadol in dogs. Vet. J. 183:310-315 (2010).

Wang G., Weng Y, Ishiguro Y, Sakamoto H and Morita S The effect of tramadol on serum cytokine response in patients undergoing pulmonary lobectomy. 17:444-450 J. Clin. Anesth. (2005)

WHO (2014) Tramadol Update Review Report Agenda item 6.1 Expert Committee on Drug Dependence Thirty-sixth Meeting Geneva, 16-20 June 2014 www.who.int › areas › quality_safety

Yadav P, Chaudhary R.N., Yadav R, Tiwari D.K, Dinesh, Kumar S, Kumar A, Tayal R (2021) Comparative Evaluation of the Isoflurane-sparing Effects of Butorphanol and Pentazocine in Buffaloes Undergoing Diaphragmatic Herniorrhaphy Indian J. Anim. Res. 55:6 pp 1-5.