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SHORT COMMUNICATION

Preliminary investigation comparing a detomidine continuous rate infusion (CRI) combined with either morphine or buprenorphine for standing sedation in horses

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Abstract

Objective To compare sedative and analgesic properties of buprenorphine or morphine for standing procedures combined with a detomidine continuous rate infusion (CRI).

Study design Blinded, prospective, randomized clinical pilot study.

Animals Ten horses presented for dental or sinus procedures.

Methods Horses received 0.02 mg kg^{-1} acepromazine intravenously (IV), followed 30 minutes later by detomidine 10 μg kg^{-1} IV. Five minutes later, buprenorphine 0.01 mg kg^{-1} ($n = 6$) or morphine 0.1 mg kg^{-1} ($n = 4$) was administered IV. Detomidine was administered by CRI (0.2 μg kg^{-1} min^{-1}) and adjusted to maintain appropriate sedation. Heart rate, respiratory frequency, gastrointestinal motility and rectal temperature were measured; pain, ataxia and sedation were scored. Sedation, pain scores and ataxia scores were analysed using a mixed linear model. Detomidine dose and procedure success scores were compared using Wilcoxon's rank sum test. Complications between groups were analysed using Fisher's exact test.

Results Two horses had incomplete data. Weights and ages were not different between groups ($p = 0.15$ and $p = 0.42$, respectively). The dose rate for detomidine was not different between groups (0.33 ± 0.02 μg kg^{-1} min^{-1} in the buprenorphine group and 0.33 ± 0.05 μg kg^{-1} min^{-1}, in the morphine group $p = 0.89$). Intraoperative visual analogue scale scores were greater after buprenorphine than morphine (mean ± SD, buprenorphine 48 ± 4, morphine 40 ± 5, $p = 0.0497$). Procedure duration was not different between groups (buprenorphine 142 ± 33, morphine 140 ± 12 minutes). All horses treated with buprenorphine experienced complications compared with none in the morphine group ($p = 0.0286$).

Conclusions and clinical relevance At the doses used, buprenorphine produced greater sedation but more post-operative complications than morphine. However,

Type I or Type II errors cannot be excluded and larger studies are required to confirm these findings.

Keywords buprenorphine, horse, morphine, pain, sedation

Introduction

Standing sedation in horses using α_2-adrenoceptor agonist infusions have gained popularity as an alternative to general anaesthesia for many procedures. A detomidine infusion often requires additional doses of sedatives or analgesics for surgical procedures (Love et al. 2013). Buprenorphine and morphine have been described for use in combination with α-2 agonists for standing procedures in clinical practice (Van Dijk et al. 2003).

Buprenorphine is licensed for analgesia in horses and is effective experimentally and clinically (Van Dijk et al. 2003; Carregaro et al. 2007; Love et al. 2013). However, buprenorphine, in common with other opioids, may have undesirable side effects in horses including increased spontaneous locomotor activity and central excitation, although these are ameliorated by the use of α-2 agonists (Carregaro et al. 2007). Despite the provision of analgesia when using morphine (Solano et al. 2009), it may also have undesirable effects, including reduced gastrointestinal motility and increased central nervous system excitation at higher doses (Boscan et al. 2006). Morphine has been used in equine practice since the 1920s. However, it is not licensed for horses in the United Kingdom.

The objective of this pilot study was to determine whether there was a difference in analgesic efficacy, sedation quality and the side-effect profile between these two

agents when used with a detomidine continuous rate infusion (CRI) in horses undergoing dental and sinus procedures. We hypothesized that there would be no difference.

Materials and Methods

Animals

Ten horses presented for surgical dental and sinus procedures were enrolled in this prospective, clinical pilot study that had institutional ethical approval (VIN/13/012). Owner consent was obtained. Horses less than 1 year of age, stallions, horses with co-morbidities, or those with aggressive behaviour were excluded.

Randomization and blinding

Horses received either buprenorphine 0.01 mg kg^{-1} intravenously (IV) or morphine 0.1 mg kg^{-1} IV (http://www.randomization.com). The investigator was unaware of the treatment group.

Baseline measurements

Physiological data, head height (from the ground) and sedation, ataxia and pain scores were recorded before drug administration.

Procedure

Horses received acepromazine maleate (Calmivet 5 mg mL^{-1}; Vetoquinol UK Ltd, UK) 0.02 mg kg^{-1} and flunixin meglumine (Meflosyl 5%; Zoetis UK Ltd, UK) 1.1 mg kg^{-1} IV, 30 minutes prior to surgery. Immediately before surgery, the horses were placed in stocks and detomidine 10 µg kg^{-1} (Domosedan 10 mg mL^{-1}, Orion

Corporation, Finland) was administered IV, followed after 5 minutes by either buprenorphine 0.01 mg kg^{-1} IV (Vetergesic, 0.3 mg mL^{-1}; Sogeval UK Ltd, UK) or morphine 0.1 mg kg^{-1} IV (Morphine sulphate 30 mg mL^{-1}; Martindale Pharmaceuticals, UK). A detomidine infusion was started immediately at 0.6 µg kg^{-1} min^{-1} IV using a syringe driver (Graseby 3300; Williams Medical Supplies Ltd, UK). Five minutes later, the head height was measured and the head raised for surgery. All horses received a maxillary or mandibular nerve block appropriate for the procedure using 50:50 mepivacaine hydrochloride (Intra-epicaine 2%; Dechra Veterinary Products Ltd, UK) and bupivacaine hydrochloride (Marcain 0.5%; Astrazeneca, UK). Throughout the procedure, the detomidine infusion rate was adjusted up or down by 0.5 mL $hour^{-1}$ based on ataxia scores being greater or less than two (assessed by the single investigator). Only one surgeon was involved in the study. Where rapid increases in sedation were required, detomidine (5 µg kg^{-1} IV) was administered. The total dose of detomidine administered per kilo per minute was recorded.

Intraoperative measurements

The heart rate and respiratory frequency (f_R) were recorded every 5 minutes during surgery. Sedation and ataxia were recorded every 15 minutes.

Assessments of sedation, ataxia and pain

Sedation was scored using a visual analogue scale (VAS) on a 100-mm line where 0 was no sedation, and 100 was maximum sedation. Ataxia was scored using a simple descriptive scale (SDS) adapted from England et al. (1992). Pain was scored using a

dynamic, interactive visual analogue scale (DIVAS) where 0 mm was no pain and 100 mm was maximum possible pain (Love et al. 2013).

Postoperative measurements

Physiological data and sedation, ataxia and pain scores were recorded at 2, 3, 4 and 24 hours after test-drug administration. If additional post-operative analgesia was deemed necessary (by the surgeon or the investigator), flunixin meglumine (1.1 mg kg^{-1} IV) was administered. A pain-scoring tool was not used to determine if extra analgesia was required. At the end of the procedure, the surgeon assessed the adequacy of sedation and gave a score out of 4 (1 being ideal and 4 being highly inadequate sedation leading to premature termination of the procedure).

Statistical analyses

All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., NC, USA). Student's t-test was used to compare weight and age between the groups. Baseline data for HR, f_R, temperature, DIVAS (pain), SDS (ataxia) and VAS (sedation) were compared using Wilcoxon's rank sum tests. A change in head height, total detomidine dose, the number of top up doses of detomidine, the duration of the procedure and overall adequacy of sedation for the procedure were compared using Wilcoxon's rank sum tests. The total number of complications between groups was compared using Fisher's exact test.

Intra- and post-operative data were analysed separately. Normality was assessed using a Kolmogrov–Smirnov test or a Mauchly test for sphericity. All repeated measures data (VAS scores, DIVAS scores, rectal temperature, heart rate and respiratory rates)

were assessed using a mixed linear model (Proc mixed). $P < 0.05$ was considered statistically significant.

Results

Data were collected from 10 horses and preliminary analyses conducted. In the morphine group, there was an Irish sports horse, pony, thoroughbred and a cob. In the buprenorphine group, there were two ponies, one cob, one Hanoverian, one Connemara and one thoroughbred. In the morphine group, there were two geldings and two mares. In the buprenorphine group, there were three geldings and three mares. Two horses were excluded for protocol violations leaving four horses per group. One horse was excluded because it was discharged too early, and a complete data set was not obtained. The second horse's procedure only lasted 45 minutes and was excluded owing to the small number of intraoperative measurements obtained. There were no statistical differences between the groups for weight, age, baseline values for sedation, ataxia and pain, head height before drug administration and baseline physiological variables (Table 1).

Intraoperative data

There were no differences between the groups in duration of surgery, the total dose of detomidine administered or percentage change in head height (Table 1). Horses treated with buprenorphine had higher intraoperative sedation scores than those treated with morphine ($p = 0.0497$). There were no differences in ataxia scores between the groups ($p = 0.7811$) nor HR ($p = 0.63$), f_R ($p = 0.94$) and overall adequacy of sedation ($p = 0.4286$), (Table 1).

Postoperative data

There were no statistical differences between the groups for post-operative sedation ($p = 0.6$), ataxia ($p = 0.49$) or pain scores ($p = 0.85$) (Table 1). One horse in the buprenorphine group required treatment for abdominal pain 24 hours after surgery. Pain scores (DIVAS) at the 24-hour time point were used to perform a sample size estimation for future studies. Using the mean and standard deviation from the population at that time point, for an effect size of 6 (on the DIVAS scale), a power of 0.85 (β-value), and an α-value of 0.05, the sample size required to demonstrate a statistically significant difference between the treatment groups would be 97 subjects per group using a two-tailed test.

All measured physiological variables remained within clinically acceptable limits, with no statistically significant differences between groups (Table 1). The mean temperature of the horses that received buprenorphine tended to be lower at 3 and 4 hours post-operatively than those that received morphine ($p = 0.34$) (Table 1).

Complications

All horses in the buprenorphine group exhibited at least one post-operative complication compared to none in the morphine group ($p = 0.0286$). The complications observed were box-walking (4/4), abdominal pain requiring medication (1/4), tremors/shivering (4/4) and head bobbing with hypersensitivity to noise (2/4). The head-bobbing was severe enough to limit clinical examination. The head movement was constant and continued in the stable even when the horse was only being observed. Box walking in two of the buprenorphine-treated horses was mild, the other two constantly walked around the stable. When restrained for clinical

examination using a head collar and lead rope, they weight-shifted between legs, tossed their heads and resisted examination. The horse that required additional analgesia was exhibiting signs of abdominal pain only at the 24-hour assessment time. Flunixin had no impact on the data collection for this horse, as it was administered after the last assessment.

Discussion

Our hypothesis was not supported. Both protocols provided adequate sedation and analgesia for the procedures, but side effects of clinical concern were observed in horses receiving buprenorphine. Hence, we believe these data should be published at this stage of the pilot study despite the small numbers of horses.

Complications in the buprenorphine group included central nervous system excitation with head-bobbing and box-walking, which were inconvenient and potentially dangerous, rendering examination of the horses difficult, although none were injured as a result of the behaviour. These signs have all been previously reported in pain-free horses receiving buprenorphine alone (Carregaro et al. 2007; Davis et al. 2011). It is possible the use of a nerve block in these horses ameliorated much of the clinical pain and, therefore, the side effects may have been more pronounced. However, this premise should also apply to the morphine group, suggesting that the negative side effects of morphine were less pronounced compared to buprenorphine. The potential for developing signs of abdominal pain after opioid or detomidine administration to horses is well recognized (Boscan et al. 2006), although various management factors may also be implicated.

Another possible explanation for the opioid-mediated side effects seen in these buprenorphine-treated horses is the administration of detomidine. Pakkanen et al. (2015) reported that horses treated with detomidine and MK-467 (a peripheral α-2 receptor antagonist) had lower plasma concentrations of butorphanol than those treated with detomidine alone suggesting that detomidine slows the excretion of concurrently administered drugs. It is possible that the detomidine infusion used in our study resulted in higher plasma concentrations of buprenorphine and morphine than are normally achieved after administration of these agents alone. Buprenorphine and morphine have similar half-lives in experimental studies on horses (Knych et al. 2014; Love et al. 2015). However, the pharmacodynamics of morphine in horses have not been evaluated. Therefore, the clinical duration of action of morphine is yet to be determined, and this may account for different responses to the agents seen in our study. It may be appropriate to administer a lower dose of buprenorphine with α-2 agonist infusions to reduce the occurrence of opioid-mediated side effects. Studies measuring plasma concentrations of buprenorphine in combination with detomidine CRI are required to confirm or refute this.

An unexpected finding of this study was the similarity in detomidine doses between groups, despite greater sedation in the buprenorphine group. This may be attributed to the protocol that dictated small changes in the infusion rate in response to perceived inadequate or over-sedation. Future studies allowing a greater variation in rate, or starting with a lower initial infusion rate might detect differences in detomidine requirement.

Limitations that may have affected the results of this study include possible variation in the degree of analgesia provided by the local nerve blocks used in each case. However, given the similarity of the total detomidine dose administered between groups, it is likely that the analgesia provided by nerve blockade was similar between groups. The variability in the site of the surgical procedure may also have caused differences in pain, sedation and ataxia assessments between horses. There is also the possibility that the duration of action of agents used for the nerve blocks resulted in the majority of post-operative assessments being carried out while the nerve block was still effective. Future studies may address this by having later data collection points.

One of the objectives of this study was to assess the analgesia provided post-operatively by the two agents. There are no data comparing buprenorphine and morphine for analgesic purposes in horses on clinical patients. Therefore, an *a priori* power calculation was not performed. The retrospective power calculation determined that 97 horses per group would be needed to identify a difference in analgesia scores at the 24-hour time point. This number of horses makes continuing the study impractical, especially given the complications identified. Future studies may wish to use a lower dose of buprenorphine and to collect additional data between 4 and 24-hours post drug administration to remove the confounding effect of residual analgesia provided by nerve blocks.

Conclusion

This study indicated that while buprenorphine combined with a detomidine infusion provided a greater depth of sedation for standing procedures around the head in horses, it was associated with a higher incidence of complications than morphine.

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Table 1 Results of baseline variables obtained and of the variables obtained during the intra- and post-operative periods for assessment of horses treated with either morphine or buprenorphine in combination with a detomidine infusion for standing dental and sinus procedures. Data are presented as the mean and standard deviation or median and range where applicable.

Variable	Baseline		Intraoperative		3 hours post-operative		4 hours post-operative		24 hours post-operat	
	M	B	M	B	M	B	M	B	M	B
Weight (kg)	498 (363 – 540)	562 (487 – 692)	-	-	-	-	-	-	-	-
Age (years)	12.0 (8.5 – 15.0)	9.5 (6.0 – 14.0)	-	-	-	-	-	-	-	-
VAS (mm) for sedation	0	0	**40 (5)****	**48 (4)****	21 (0-48)	33.5 (0.0-60.0)	14 (0-21)	3.5 (0.0-30.0)	0 (0-0)	0 (0-0)
DIVAS (mm) for pain	0 (0 – 27)	12 (0 – 33)	-	-	0 (0-0)	0 (0-28)	0 (0-30)	13 (0-34)	34 (0-51)	17 (0-48
SDS (0–3) for ataxia	0	0	2 (1 - 3)	2 (2-3)	1 (0-1)	1 (0-2)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)

Heart rate (bpm)	40 (36 – 40)	39 (36 – 44)	32 (22 - 40)	32 (20 - 40)	42 (28 – 44)	36 (28 – 44)	40 (32 – 48)	38 (28 – 44)	42 (30 – 48)	44 (40 –
Respiratory rate (bpm)	8 (8 – 12)	8 (8 – 12)	8 (4 - 16)	8 (4 - 16)	7 (6 – 8)	10 (4 – 12)	7 (6 – 10)	10 (8 – 12)	7 (6 – 16)	10 (8 – 1
Temperature (degrees C)	37.3 (37.0 – 37.5)	37.6 (36.6 – 37.7)	-	-	36.9 (36.6 – 37.6)	36.5 (36.4 – 36.5)	37.1 (36.6 – 37.3)	36.0 (35.3 – 36.4)	37.3 (37.1 – 37.6)	37.6 (37. 37.7)
Change in head height (% change from baseline)	-	-	63 (34 – 71)	71 (57 – 74)	-	-	-	-	-	-
Duration of procedure (minutes)	-	-	142.5 (100.0 – 173.0)	140 (129 – 157)	-	-	-	-	-	-
Complications	-	-	-	-	-	-	-	-	0 of 4	4 of 4*

(no. of horses)									**	
Detomidine (mcg kg^{-1} min^{-1})	-	-	0.35 (0.26 – 0.38)	0.32 (0.30 – 0.37)	-	-	-	-	-	-
SDS (1–4)										
Adequacy of sedation	-	-	1 (1-1)	1 (1-2)	-	-	-	-	-	-

M, morphine; B, buprenorphine; VAS, visual analogue scale; SDS, simple descriptive scale; DIVAS, dynamic interactive visual analogue scale; bpm, beats per minute or breaths per minute, degrees C, degrees Celsius.

Bold text = normal distribution, mean (SD)

Un-bold text = data presented as median (range)

***P*-value < 0.05, a significant difference was found between the treatment groups.

Intra-operative values = average of all data at all intra-operative time points.