Sedative & Analgesic Infusions in Horses

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Abstract: Sedation and analgesia provided by infusion rather than boluses provides flexibility in both duration and depth of sedation/analgesia. Traditional drugs like xylazine can be used but other alpha-2 agonists, opioids, ketamine, lidocaine and combinations of drugs are all options.
Key Words: equine, horse, sedation, analgesia, infusion

Analgesic infusions (Table 1)

Alpha-2 agonists

Alpha-2 agonists are commonly used to provide sedation in horses. The fact that the alpha-2 agonists also provide moderate analgesia makes them excellent drugs to incorporate into pain management protocols. The effects of alpha-2 agonists are reversible, although they are rarely reversed in horses. Detomidine is the alpha-2 agonist most commonly used for CRIs in horses. Adding butorphanol, either as a bolus or as an infusion, greatly augments the analgesia provided by the alpha-2 agonist. Because they have a higher alpha-2:alpha-1 receptor binding ratio, medetomidine and dexmedetomidine are more potent analgesic drugs than detomidine and have been used to provide analgesia and anesthetic stability in anesthetized horses (Bettschart-Wofensberger et al. Vet Rec 2001 and Ringer et al. Vet Anaesth Analg 2007; Marcilla et al. Vet Anaesth Analg 2010, respectively). In this situation, the dose is very low, thus offsetting the increased price of these drugs when compared to alpha-2 agonists traditionally used in horses. Romifidine, which may not be currently available, has been used as an analgesic CRI in anesthetized horses (Devisscher et al. Vet Anaesth Analg 2010).

Lidocaine

Lidocaine can be administered systemically to provide analgesia, although the mechanism of analgesia following systemic administration is not entirely clear. Proposed mechanisms include, but are not limited to, blockade of sodium channels or potassium currents in the dorsal horn of the spinal cord and direct inhibition of abnormal electrical charges from injured or inflamed peripheral nerves. In horses, lidocaine CRIs are commonly used to treat GI pain (Doherty Vet Clin NA Equine 2009), have been suggested for treatment of the pain of laminitis (Doherty &

Seddighi Vet Clin NA Equine 2010) and are effective against somatic pain (Robertson et al. Eq Vet J 2005). In addition to the analgesic effects, lidocaine ameliorates the inflammatory response in endotoxemic horses (Peiro et al. J Vet Intern Med 2010), the inflammatory response in horses with ischemic bowel (Cook et al. Am J Vet Res 2009) and improves GI motility following abdominal surgery (Doherty Vet Clin NA Equine 2009). IV lidocaine significantly decreased the amount of reflux and improved the clinical course in refluxing horses (Malone et al. Vet Surg 2006). IV lidocaine has been used to decrease the MAC in anesthetized horses (Doherty & Frazier Eq Vet J 1998). Mild ataxia in recovery has been reported in horses receiving lidocaine CRIs during general anesthesia but the problem is eliminated if the CRI is discontinued 20-30 minutes prior to the end of the procedure (Valverde et al. Eq Vet J 2005). Ataxia in conscious horses has not been reported at the clinically used rate of 50 microg/kg/min. A review article on the use of lidocaine CRIs in horses was published in 2010 by Doherty & Seddighi (Vet Clin NA Equine).

Opioids

The opioid class of drugs includes some of the most potent analgesic drugs available and opioids should be considered for any patient experiencing moderate to severe pain. Opioids can cause excitement in horses but this response is uncommon in painful horses and the low dose of opioids delivered in a CRI rarely results in agitation or excitement, even in non-painful horses. However, if excitement does occur, a light dose of a sedative (eg, detomidine) can be administered to the horse and the CRI rate maintained (if excitement is mild) or reduced (if excitement is moderate). If sedation occurs, the dose of the CRI can be decreased. Butorphanol, an opioid agonist-antagonist is the opioid most commonly used in horses. As an agonist-antagonist, butorphanol provides only moderate analgesia and has a ceiling effect for pain relief (ie, a point is reached where higher dosages result in more sedation but not more analgesia) but is also less likely than full agonist opioids to cause excitement in horses. Butorphanol CRIs have been used to control post-operative pain (Sellon et al. J Vet Intern Med 2004) and horses receiving butorphanol CRIs had less weight loss and lower pain scores and plasma cortisol concentrations than control horses. Also, non-painful horses receiving butorphanol CRIs had minimal to no behavior changes (eg, excitement or ataxia) whereas horses receiving a butorphanol bolus did exhibit some negative behavior (Sellon et al. Am J Vet Res 2001). Morphine and methadone are potent full agonist opioids that provide profound dose-related

analgesia. The full agonists are more likely to cause adverse effects than the partial agonists but the incidence of opioid-induced side effects, while present, has been overstated. Morphine CRIs are being used more commonly in horses (Clarke et al. Vet Anaesth & Analg 2005; Clarke et al. Vet Anaesth & Analg 2008). The potential for excitement in recovery is a concern of opponents of morphine CRIs, however, recoveries from anesthesia for elective surgical procedures was characterized by fewer attempts to attain sternal recumbency and standing, and a shorter time from the first recovery movement to the time of standing, in horses receiving an intra-operative CRI of morphine compared to horses not receiving a CRI (Clarke et al. Vet Anaesth & Analg 2008). The potent full agonist opioid fentanyl has also been safely and effectively used as a CRI in anesthetized horses (Ohta et al. J Vet Med Sci 2010). Methadone is commonly used in horses at the same dose that morphine is used, however, there are no publications on this technique.

Ketamine

Painful impulses cause N-methyl-D-aspartate (NMDA) receptors (among others) in the dorsal horn of the spinal cord to depolarize and prolonged depolarization of these receptors can lead to an amplification of the pain stimulus, resulting in what we commonly refer to as 'wind-up' or 'hypersensitization' or ‘central sensitization’. When this occurs, the patient may feel more pain than expected (hyperalgesia) or even feel pain in response to a non-painful stimulus (allodynia). By administering drugs that antagonize these receptors (like ketamine), we are able to alleviate this exaggerated response and make the pain easier to control. Ketamine is the NMDA-receptor antagonist most commonly used in veterinary medicine and NMDA receptor antagonist effects are achieved when ketamine is used as a low-dose CRI. A single low-dose bolus of ketamine or the high-dose bolus used for anesthetic induction can serve as a loading dose for a CRI but is unlikely to provide analgesia when used alone. Furthermore, the NMDA receptor antagonists strictly mediate sensitization and do not provide true analgesia, thus, these drugs must be administered in conjunction with true analgesic drugs (eg, opioids or NSAIDs). Ketamine has been used as a CRI to treat acute pain in anesthetized horses (Levionnois et al. Vet J 2010) and in conscious ponies (Peterbauer et al. Vet Anaesth Analg 2008). Ketamine administered at the most commonly reported dosages of 0.4-0.8 mg/kg/hr (6-12 microg/kg/min; Fielding et al. Am J Vet Res 2006) and even as high as 1.5 mg/kg/hr (25 microg/kg/min; Lankveld et al. J Vet Pharmacol Therap 2006) to horses does not result in sedation or excitement.

Combinations

CRIs that include multiple drugs are often more effective than CRIs of single drugs because the effects of analgesic agents from different drug classes are generally additive or synergistic. Any of the drugs listed above can be used in combination. Morphine-lidocaine-ketamine (MLK) is a popular combination used in small animals and MLK use has been used in anesthetized horses to decrease the inhalant gas requirement (Lerche & Muir ACVA Proceedings 2008). Morphine has been used in combination with medetomidine to provide 'reliable sedation and stable cardiorespiratory function in conscious, standing horses undergoing exploratory laparoscopy' (Solano et al. Eq Vet J 2009). Methadone can be used in place of morphine in all of these combinations. Lidocaine and ketamine have been used in combination to 'improve anesthetic and cardiovascular stability during isoflurane anesthesia' with no adverse effect on quality of recovery (Enderle Vet Anaesth Analg 2008). A combination of lidocaine, morphine, ketamine, detomidine and acepromazine ('pentafusion') appears to be a very potent analgesic (Abrahamsen ACVS Proceedings 2011). Many other combinations have been reported and/or used anecdotally.

Calculations of CRI dosages

Generally, dosing tables or individualized spread sheets (eg, there are very useful spreadsheets available at multiple websites, including one of my favorites at www. vasg.org) should be used for constant rate infusions. These sheets greatly improve the speed at which CRIs can be initiated and greatly decrease the chance of mathematical errors. However, CRI dosages can also be easily calculated using the formula:

- A = desired dose in microg/kg/min
- B = body wt in kg
- C = Diluent volume in mls
- D = Desired fluid rate in mls/hr
- E = Drug concentration in mg/ml

(A x B x C x 60)/(D x E x 1000) = mls of drug to add to diluent

Table 1: Analgesic infusions for horses. Some infusions can be administered either to the conscious or the anesthetized horse while some are better administered only under general anesthesia. The latter category is indicated in the comments column.

Drug(s)	Dosage	Comment or Tip
OPIOIDS		
Butorphanol	Loading dose: 18 mic/kg IV CRI: 23-25 mic/kg/hr	QUICK TIP: add 1 ml of 10 mg/ml butorphanol to 1-L LRS and administer at 1 L per hour per 450 kg. May need to administer an alpha-2 agonist to some horses. (Sellon et al. J Vet InternMed. 2004)
Morphine or methadone	Loading dose 0.15 mg/kg IV CRI: 0.1 mg/kg/hr	Improved recovery in horses anesthetized for elective surgical procedures. (Clarke et al. Vet Anaesth & Analg 2005 and 2008). No reference for methadone although clinical use is common.
ALPHA-2 AGONISTS: See tips for using alpha-2 infusions in STANDING horses in Table 2		
Dexmedetomidine	Loading dose 1-3.5 mic/kg IV CRI 0.5-1.5 (up to 3) mic/kg/hr	Analgesia + decreased inhalant dose = better blood pressure, usually contributes to better recoveries QUICK TIP: Mix 8 mls saline + 2 mls 0.5 mg/ml dexmedetomidine in 10 cc syringe. Final concentration is 100 mic/ml. Administer at 1 mic/kg/hr. Example: A 500 kg horse will get 5 mls/hr.
OTHER DRUGS		
Lidocaine	Loading dose: 1-1.5 mg/kg IV delivered over 10-20 mins CRI: 40-50 mic/kg/min	QUICK TIP: Add 150 mls 2% lidocaine per liter of fluids (generally 750 mls is added to a 5-L bag) and administer the fluids at 1 ml/kg/hr for a dose of 50 mic/kg/min.
Ketamine	Loading dose: 0.2-0.6 mg/kg 2-10 mic/kg/min (0.12-0.6 mg/kg/hr)	QUICK TIP: Add 3-6 mls to 1-L fluids, administer at 1 ml/kg/hr for 0.3-0.6ml/kg/hr. Intraop: 0.6mg/kg/hr x 450kg=0.27ml/hr dilute in 10 ml saline & use syringe pump 0.4-0.8 mg/kg/hr (6-13 mic/kg/min) has been used in either conscious or anesthetized horses (Fielding et al. AJVR 2006).
COMBINATIONS (Any of the drugs listed in this chart can be used in combination)		
Morphine (M), Lidocaine (L), Ketamine (K)	See next column	'Following a bolus of L 1.2mg/kg IV given over 20 minutes, an infusion of MLK was administered with the following rates: M at 0.1mg/kg/hour, L at 45µg/kg/minute and K at 17µg/kg/minute. (Lerche et

		al. ACVA 2008; ketamine was used as induction drug (2.2 mg/kg), which serves as bolus. This infusion is used most commonly during general anesthesia.
Medetomidine & morphine	See next column	Medetomidine (5 mic/kg IV) followed in 10 min by morphine (50 mic/kg IV) and 10 min later by a CRI of medetomidine and morphine (5 and 30 microg/kg/hr, respectively) (Solano et al. EVJ 2009). Most commonly for general anesthesia.
Lidocaine & ketamine	See next column	Lidocaine 1.5 mg/kg bolus over 10 minutes, followed by 40 mic/kg/min and ketamine 60 mic/kg/min, both reduced to 65% of the initial dose after 50 minutes, and stopped 15 minutes before the end of anesthesia. Either conscious or anesthetized horses. (Enderle VAA 2008)
Pentafusion	See next column & Table 3	Dosages: Lidocaine 3 mg/kg/hr; Ketamine 0.6 mg/kg/hr; Morphine 0.025 mg/kg/hr; Detomidine 0.0044 mg/kg/hr; Acepromazine 0.0022 mg/kg/hr (Abrahamsen ACVS Proc.2011). Most commonly used in conscious horses.

Table 2: Infusions for standing Sedation + Analgesia

Drug	**Dose**	**Tip**
Detomidine Used alone, the dose is usually higher than when used in combo. This 'sliding' dosing allows a quick onset of procedural sedation without continued deep sedation.	Loading dose: 8-10 mic/kg IV Start at 0.5-0.7 mic/kg/min and cut dose in ½ every 15 mins CRI: 0.5 mic/kg/min for 15 min, followed by 0.3 mic/kg/min for 15 min and finally 0.15 mic/kg/min until 5-15 mins prior to the end of the procedure. [0.5 mic/kg/min=30 mic/kg/hr]	QUICK TIP for 0.5 mic/kg/min starting dose: Remove 5 ml of fluid from a 500-ml bag of NaCl and add 5 ml of 10 mg/ml detomidine (for a final concentration of 100 microg/ml of detomidine). Following the loading dose, start the drip (using a 60 drop/ml set) at 0.005 drops/kg/sec (roughly 2 drops/sec/ 450 kg) for 15 mins; then 0.003 drops/kg/sec (roughly 1 drop/sec/450 kg) for 15 mins; and then 0.0015 drops/kg/sec (roughly 1 drop every other sec/450 kg) until 5-15 mins prior to the end of the procedure (the time between the discontinuance of the drip and the end of the procedure should be based on degree of sedation and invasiveness of the procedure). The drip rate should be adjusted to obtain the desired level of sedation. For smaller horses, 2.5 mls of detomidine

		can be added to the saline to improve accuracy of counting drops.
Detomidine + Butorphanol	Loading dose: 8-10 mic/kg detomidine + 20 mic/kg butorphanol IV CRI: 5-30 mic/kg/hr detomidine + 10-30 mic/kg/hr butorphanol	Can add butorphanol CRI. See tips on butorphanol in Table 1. When administered as a combination, the CRI rate is generally the same as the rate for either drug used alone but some clinicians advocate using only ½ of the butorphanol CRI rate.
Detomidine + Morphine	Loading dose: 8 mic/kg detomidine; WAIT 10 mins then 50 mic/kg morphine CRI: 5-30 mic/kg/hr detomidine + 30 mic/kg/hr morphine	More profound analgesia with addition of morphine. May cause more 'box walking' (pacing) after the CRI is discontinued but true excitement is highly unlikely. Can give additional dosages of alpha-2 agonists if pacing occurs.
Romifidine	Loading dose: 40-80 mic/kg CRI 18-30 mic/kg/hr	Can add butorphanol or morphine (see notes under detomidine)
Xylazine	Loading dose: 0.5-1.0 mg/kg CRI: 0.6-1.5 mg/kg/hr OR Loading dose: 1100 mic/kg CRI: 690 mic/kg/hr	TIP: Add 1000 mg (10cc) xylazine to 1-L saline and administer at 1 ml/kg/hr. Can add butorphanol or morphine (see notes under detomidine) (References for protocols at left: top protocol (Muller C. et al. Pferdeheilkunde 2012;28(6):668-674); bottom protocol (Ringer et al. Vet Anaesth Analg 2013;40(2):157-165 and Ringer et al. The Vet J 2013;195:228-234).
Medetomidine	Loading dose: 5 mic/kg CRI: 3.5 mic/kg/hr	Can add butorphanol or morphine (see notes under detomidine). More profound analgesia than other alpha-2s listed here. Also more expensive.

Table 3: Dr. Eric Abrahamsen's pentafusion protocol

Drug	Dose	Amount Required	Base Delivery Rate
Bag #1			68 ml/450 kg/h
Lidocaine	3 mg/kg/hr	1 liter	
Ketamine	0.6 mg/kg/hr	4000 mg	
Bag #2			68 ml/450 kg/hr

NaCl	NA	liter	
Morphine	0.025 mg/kg/hr	170 mg	
Detomidine	0.0044 mg/k/hr	30 mg	
Acepromazine	0.0022 mg/kg/hr	15 mg	

Dr. Abrahamsen likes 2 bags so that the rate of bag #2 can be decreased first and then, if the patient is comfortable, the rate of bag #1 can be decreased. The solution can also be made all in one bag and the rate decreased as pain is controlled. Primarily used for moderate to severe pain like pain of laminitis.

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