Equine Analgesics: What Do We Have and What Do We Need?

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Many drugs and administration techniques are now available to the DVM for the management of equine pain. However, there is still much information we need to manage pain effectively. An easy to use, validated pain scale would improve our ability to treat equine pain. More information about which drugs really work well, practical delivery techniques, and longer-lasting analgesics would also improve equine analgesia. Author’s address: Department of VSCS, Texas A&M University, College Station, Texas 77843-4474; e-mail: nmatthews@cvm.tamu.edu. © 2009 AAEP.

1. Introduction
In 2007, this author reviewed equine analgesics and pain management.1 Since that time, only one new equine analgesic has been approved. However, there have been some studies on evaluating pain and the effectiveness of previously mentioned treatments. There also has been a large increase in awareness of treating pain; many practitioners want to know how to do it better. This paper will try to summarize what is available and what is still needed to provide good analgesia.

2. What Do We Have?
The concept of balanced (or multimodal) analgesia is fundamental to formulating an analgesic plan. Balanced analgesia combines drugs with different modes of action or which act on different receptor types to provide good analgesia with lower dosages of each drug (thereby decreasing possible side effects). The simplest (yet widely used) combination of an α2-agonist (e.g., xylazine) for sedation and analgesia, local anesthetic block, and a non-steroidal anti-inflammatory drug (NSAID) provides balanced or “multi-modal” analgesia.

A multitude of such combinations may be formulated depending on patient need and the intended route of administration. Currently many drugs may be administered parenterally (e.g., IV, IM, SQ) and PO. Regional local anesthetic blocks (e.g., intra-articular [IA], epidural, four-point, etc.), transdermal (TD), and transmucosal (TM) are additional routes that may be used. Constant rate infusions (CRIs) of IV drugs allow a consistent blood concentration with overall lower doses being used and, therefore, fewer side effects.

3. Methods of Administration
Usual routes of administration (IV, IM, SQ, epidural injections, PO) are all very useful, but newer analgesics can be administered transdermally (by patch or topical application). CRIs allow the IV administration of lower doses (fewer side effects) to maintain consistent plasma concentrations, hence producing analgesia with fewer peaks and troughs. Many drugs may be administered by multiple methods depending on which method is most practical for the patient. An analgesic regimen might combine different drugs given by different routes, which could
help reduce injection pain or adverse gastrointestinal (GI) side effects and improve owner compliance.

4. Drugs

NSAIDs

Several different NSAIDs (phenylbutazone, flunixin, ketoprofen) have been widely and effectively used for pain management in horses. However, all have the potential to produce significant side effects, especially when used at high doses. Although not approved for use in horses in the United States, the newer NSAIDs, meloxicam (0.6 mg/kg, IV) and carprofen (0.7 mg/kg, IV), may have fewer side effects with good efficacy. The newest NSAID, firocoxib, is supposed to produce few side effects because of its great selectivity for cyclooxygenase 2 (COX-2) and sparing of cyclooxygenase 1 (COX-1) receptors. Transdermal 1% diclofenac may also have the advantage of decreased side effects, because it can be used on the specific site where analgesia is required with little systemic uptake. Because all are fairly similar, one’s choice of which NSAID to use is likely to depend on availability and cost. Although NSAIDs are very effective for pain reduction in horses, it is unlikely that they produce sufficient analgesia for severely painful conditions, but should be a basic “building block” of balanced analgesia. Veterinarians must remember also that severe or chronic pain is very difficult to treat; it may be “refractory” to analgesics that normally are quite effective. Chronic pain requires aggressive and multi-modal analgesia for successful treatment.

Opioid Analgesics

Opioids have been a mainstay of pain relief in both human and veterinary medicine. The usefulness of opioids as single agent analgesics in horses has been tempered by the propensity for opioids to produce excitement when administered alone in non-painful horses. Gastrointestinal stasis may also occur and is a significant concern in horses. Morphine (0.1 mg/kg, IV, IM), meperidine (4.4 mg/kg, IV, IM), methadone (0.22 mg/kg, IV), and oxymorphone (0.033 mg/kg, IV) have all been used alone for analgesia or with sedatives to facilitate standing surgery.

Butorphanol (0.01–0.1 mg/kg, IV, IM), an agonist-antagonist opioid, approved for use in the horse in the United States, has also been widely used for analgesia and sedation in conjunction with alpha-2 agonists. Although the degree of analgesia provided by butorphanol has been questioned, it has become widely used in equine medicine and may decrease the need for inhalants during general anesthesia. Nalbuphine is another agonist-antagonist opioid (much like butorphanol), which currently has the advantage of not being a scheduled drug. Nalbuphine (0.3 mg/kg, IV) has been evaluated with detomidine (0.01 mg/kg, IV) and acepromazine (0.05 mg/kg, IV) and produced good sedation with both; however, the analgesic effect was not evaluated. Analgesia (dental dolorimetry model) was evaluated with nalbuphine (0.75 mg/kg, IV) compared with morphine, butorphanol, and xylazine. No difference between groups was seen. Nalbuphine is less potent and efficacious than butorphanol but has been used for analgesia, especially in countries where other opioids are not available.

Buprenorphine (0.004–0.006 mg/kg, IV, IM, SQ) has the advantage of a long duration of action (6–8 h) but is not approved for equine use (or any veterinary use). Buprenorphine (SQ, q 8 h) has been used in multimodal analgesic management of laminitis and in conjunction with detomidine for standing procedures. However, a recent paper found that only higher doses of buprenorphine (10 µg/kg, IV) produced analgesia. The TM or PO absorption of buprenorphine has not been reported in horses; however, sublingual administration was used with clinical success, in a case report from 2007. In cats, TM buprenorphine is 100% bioavailable. A transdermal form of buprenorphine is available in the United Kingdom and Australia.

Fentanyl is a short-acting, mu-receptor opioid that produces increased locomotor activity in horses similar to the earlier opioid studies reported by Tobin et al. Transdermal fentanyl (fentanyl patches are now generic) is not approved for use in horses but has been used for analgesia. Uptake of transdermal fentanyl seems to be rapid in the horse but may also be very variable from horse to horse. Two 100-µg/h patches for a 450-kg horse are the typical dose. The two patches may be applied to a clipped area of the skin and bandaged in place to insure good skin contact. Because it is easy to place a bandage on the forearm or gaskin, these locations are easy sites to use, although a recent study showed better uptake when the patches were applied to skin from the thorax or groin. Although patches are supposed to provide analgesia for 72 h in people, reapplication at 48 h should be considered, depending on response and re-evaluation of pain. One study showed an improvement in analgesia for lameness when fentanyl patches were added to NSAID therapy.

Tramadol, a non-opiate mu-agonist for treatment of mild to moderate pain, has the advantage that it is not currently a scheduled drug. Tramadol has analgesic activity at the mu receptors but also seems to be a serotonin-uptake inhibitor and to lower the seizure threshold in people. Tramadol is not approved for veterinary use but is used extensively to treat mild to moderate pain in dogs and cats. The efficacy of tramadol has not been documented in horses; however, preliminary evidence points toward its effectiveness. Two reports on the pharmacokinetics of tramadol in horses provide conflicting information about its oral bioavailability. In humans, genetic variability affects tramadol concentrations and can be classified in four
categories ranging from “poor” to “ultra rapid metabolizer”; similar variability in horses might explain conflicts between reported kinetics. Further study is needed about effectiveness, dosing, and bioavailability.

\(\alpha_2\) Agonists

Xylazine, detomidine, romifidine, and medetomidine have all been used to produce sedation and analgesia by different routes (IV, IM, PO) and different injection techniques (periodic bolus versus CRI). These are versatile drugs and have been used by epidural injection to produce analgesia, as well as by intra-articular injection to provide analgesia.

Local Anesthetics

No discussion of analgesics would be complete without including local anesthetics, which can also be used in a variety of ways: local infiltration, anatomic nerve block, regional limb block or perfusion, epidurally, and by CRI. Although lidocaine and mepivicaine produce a short duration of action, bupivacaine offers the advantage of lasting for 6–8 h. Although more toxic (dose should be limited to 2 mg/kg), bupivacaine may be used as a regional block (e.g., perineal nerve) and will last into the post-operative period. Local anesthetic blocks (e.g., blocking the testicle during a castration or “splash blocking” ovarian pedicle during ovariohysterectomy) may be used in conjunction with injectable or inhalant anesthesia to provide analgesia while lowering needed inhalant anesthetic concentrations.

Epidural analgesia or anesthesia (e.g., morphine, bupivacaine, or combination), may be very useful. Caution must be used when administering an epidural in awake horses to protect against excessive ataxia produced by cranial migration of the local anesthetic. Ropivacaine is a newer, longer-acting local anesthetic, with a higher affinity for pain versus motor fibers (therefore, ataxia is less likely to occur). It has been used epidurally (0.08–0.1 mg/kg in a total volume of 8–9 ml) for standing surgery. CRIs of lidocaine have also been used for their prokinetic activity in post-operative colics and may provide analgesia for other procedures. An initial bolus of 1.3 mg/kg lidocaine, given over 15 min, is followed by 3 mg/kg/h.

Epidural Analgesia

Epidural analgesia may be achieved with maintenance of motor function by using morphine (0.1 mg/kg), ketamine (0.2–2 mg/kg), or tramadol (1 mg/kg). Xylazine (0.17 mg/kg) and detomidine (0.02–0.03 mg/kg) have been used alone or in combination with other drugs for epidural analgesia. Drugs may be administered as a single bolus or injection into an epidural catheter. An epidural catheter may be placed and maintained for long periods of time, which allows intermittent administration through the catheter.

Other Drugs

Gabapentin is an anticonvulsant that has been used for the treatment of neuropathic pain in humans, dogs, and horses. Although it is not clear exactly how it works, it may be useful in cases where nerve damage has occurred (e.g., surgical incision in the flank where nerves are severed) or in chronic pain conditions. The pharmacokinetics of orally administered gabapentin (5 mg/kg) have been described in the horse.

CRIs

Ketamine (0.4–0.8 mg/kg/h, IV) has been used for fairly prolonged administration with no appreciated side effects. Ketamine is very effective for patients with somatic pain (e.g., burns) and has been used for septic arthritis. The patients with grade 4–5 lameness did not miraculously become sound during the infusions, but appetite increased and the horses appeared more comfortable. Ketamine may be less likely to decrease GI motility than the opioids; however, specific information about affects on GI function are not available. Ketamine may also be used in conjunction with other drugs (e.g., lidocaine or butorphanol) because all work on different receptor sites.

Detomidine or medetomidine CRIs may be used to facilitate standing surgeries while keeping the sedation at a consistent level. Different publications have presented different “recipes” for detomidine. Detomidine has a relatively long half-life and will accumulate over time unless the dose is reduced. Accumulation of detomidine will lead to increasing depths of sedation and long recovery from sedation. Medetomidine has also been used by CRI for standing surgery; 5 µg/kg, IV, as an initial bolus, followed by 3.5 µg/kg/h, IV for 2 h. Medetomidine also has a fairly long duration of action, so reduction of the dose toward the end of the procedure is advised to prevent excessive sedation.

Butorphanol infusions (13 µg/kg/h, IV) provide analgesia for post-operative colics. Butorphanol-treated horses had shorter hospital stays, better appetites, and less weight loss than untreated horses.

Combinations of lidocaine with ketamine and an opioid (e.g., butorphanol) CRIs are being used to provide analgesia in horses; however, there are little data on their effectiveness. The combination called Pentafusion (lidocaine, 3 mg/kg/h; morphine, 0.025 mg/kg/h; ketamine, 0.6 mg/kg/h; detomidine, 0.04 mg/kg/h; and acepromazine, 0.002 mg/kg/h) has been promoted for equine analgesia.

5. What Do We Need?

First, in the author’s opinion, we need a validated pain scale for horses. Several investigators have worked to document the best way to score pain in
horses; current scales combine behavioral assessment of the horse (e.g., head position, activity) with physiologic data (e.g., heart rate and percent change from normal). These have been used for specific types of pain (e.g., orthopedic) but may need to be altered to provide good assessment for all types of pain. Various pain scales are widely used in humans, where pain is considered the fifth vital sign. The American Animal Hospital Association requires scoring, recording, and treating pain with every temperature, pulse, and respiration (TPR); perhaps AAEP should consider developing similar recommendations.

Second, we need practical delivery techniques. Intravenous CRIs are not always practical in facilities without 24-h monitoring. Newer delivery systems (e.g., disposable infusion discs and bulbs) may have promise for horses, but still require IV catheters.

More formulations of certain drugs might be helpful; oral formulations (which produce good blood levels) and long-lasting formulations for all of the commonly used analgesics (e.g., ketamine, butorphanol) would be enormously helpful for treating horses. In some instances, long-lasting formulations must be carefully used (to prevent masking a deterioration in condition), but for chronic pain, they are needed. More transdermal formulations might also be effective for targeting chronic pain.

There is also a great need for more research into equine pain, especially chronic pain (e.g., laminitis). We need better proof for what works as well as more information about adverse side effects. Are current equine pain models (e.g., thermal threshold and duodenal balloon models) really predictive for how analgesics work clinically? Do CRIs of lidocaine or butorphanol affect GI motility more or less than the commonly used analgesics (e.g., ketamine, butorphanol) would be enormously helpful for treating horses. In some instances, long-lasting formulations must be carefully used (to prevent masking a deterioration in condition), but for chronic pain, they are needed. More transdermal formulations might also be effective for targeting chronic pain.

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6. Summary

Effective treatment of equine pain is what every equine practitioner strives to achieve. However, the profession is still a long way from the ultimate goal, and much research and information are still needed. Newer drug formulations and delivery systems might be very useful in providing better equine analgesia.

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