Update on equine analgesia

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Categories : Equine, Vets

Date : February 15, 2016

ABSTRACT

Equine practitioners may not be good at recognising pain in horses, although we use pain as a key diagnostic indicator in colic and it is an important consideration in perioperative patients. NSAIDs are widely used – particularly in lame horses where phenylbutazone and its prodrug suxibuzone stand up well in trials against the modern cyclooxygenase-2 (COX-2)-selective products. Gastric and renal side effects must be considered and occasional reports exist of pancytopenia and ulcerative cystitis with phenylbutazone.

Although the COX-2-selective drugs have the theoretical advantage of less potential to disrupt normal homeostasis, in reality, clinically important side effects with NSAIDs are rare when used at therapeutic doses. Evidence shows buprenorphine has potential in the perioperative patient and, although optimal protocols remain to be defined, tramadol, an opiate that can be given orally, can be useful
in challenging cases such as laminitis.

Alleviating pain in patients is a goal we can all agree is important, but we may not be as good as we'd hope at recognising pain in horses.

Figure 1. Rolling is a classic sign of colic. Image: Wikimedia Commons/ John Harwood.

In a survey of Dutch and Flemish practitioners asked to attribute pain scores to specific clinical conditions, considerable variation appeared in the scores vets assigned (Dujardin and van Loon, 2011). In the same survey, a substantial proportion of the respondents considered their knowledge of pain recognition and analgesic therapy to be insufficient or moderate.

Acute, severe pain is perhaps most easily recognised. In a survey of 228 UK equine practitioners looking at the frequency of use of diagnostic criteria in colic, 87% identified response to analgesia followed by rectal examination (76%) and nasogastric intubation (44%; Curtis et al, 2015).

Signs of severe colic, such as rolling, are usually obvious (**Figure 1**). Low-grade pain and pain not associated with abdominal disease can be hard to detect and go unrecognised. In particular, intrathoracic pain and pain associated with injuries to the thoracic cage, withers and spine can be hard to pinpoint. When assessing pain scores for horses, Taffarel et al (2015) found heart rate was the most consistent and objective tool and, looking specifically at postoperative cases, they highlighted numerous other behaviours indicative of acute pain.

Figure 2. Reluctance to move is a classic sign of pain in horses, which can even extend to reluctance to stand. Image: Alice Hieghton-Jackson. (This foal was not in pain; the image was used to illustrate reluctance to stand.)

Comfortable horses interact with their environment, look out over their stable door and eat. Reluctance to move (**Figure 2**) and restlessness indicate pain, while pain on palpation, looking at the flank (**Figure 3**) and kicking at the abdomen suggest localised pain. Behaviours such as lifting hindlimbs, extending the head, lateral and/or vertical head movements and pawing are also observed in uncomfortable horses.

Analgesic use

Analgesics are used more in horses than other large animals – more than 90% of Canadian vets use analgesics for equine surgeries (Hewson et al, 2007). Common indications for analgesic use are colic, musculoskeletal pain and perioperative use. An increasingly large number of analgesics are either licensed for use in horses or supported by research evidence, but it is likely most equine vets use a relatively small range.

American Association of Equine Practitioners member vets primarily use phenylbutazone and flunixin as anti-inflammatory drugs (Hubbell et al, 2010). Similar work has not been performed in the UK, but no reason exists to suspect the situation would be different.

Analgesics desirable characteristics

The ideal analgesic has predictable effect and duration, minimal side effects and is easy to prescribe, purchase and administer – lacking any impact on the horse's future status for human consumption. Of course, the ideal analgesic does not exist – to a large extent, the most appropriate analgesic will be dictated by the specific clinical indication.

Figure 3. Looking at the flank suggests colic. Image: fotolia/callipso88.

With colic, predictable level of analgesia and duration of action are key characteristics. Effective analgesia is desirable, but potent drugs are usually avoided for fear of masking declining clinical status in a horse that would be best served by surgical exploration, rather than controlled with extremely potent analgesics.

Safety is important, but analgesia for colic is generally delivered over a short time frame, therefore potential side effects associated with long-term use are irrelevant. Potential damage to the gastrointestinal tract and effects on gastrointestinal motility are critical, and the impact of concurrent shock and volume depletion must be considered.

Similar considerations come into play with perioperative pain, but the level of analgesia required may be modified by the exact surgical indication and specific procedure. With some procedures, it will be appropriate to provide potent analgesia – for example, with surgical repair of fractures or other painful orthopaedic surgeries. In these cases, multimodal analgesia may be indicated.

Most practitioners are perhaps most familiar with analgesia for chronic musculoskeletal disease. Here, side effects associated with chronic use in otherwise fairly healthy animals are important and issues such as palatability and ease of administration may influence specific choices. Again, a range of potency is needed and, in some horses with particularly painful musculoskeletal conditions, such as laminitis, a multimodal approach may be useful.

NSAIDs

NSAIDs have analgesic, antipyretic and anti-inflammatory properties, and are a cornerstone of

equine practice. All NSAIDs inhibit some component of the enzyme system that converts arachidonic acid into the prostaglandins and thromboxane, and all cells possess arachidonic acid, which is oxidised to COX or 5-lipoxygenase. With the exception of ketoprofen that inhibits both pathways, the NSAIDs used in equine practice exert their effects primarily by inhibiting COX.

COX has two forms – COX-1, the constitutive form, and
COX-2, the inducible form. COX-1 is responsible for producing prostaglandins involved in regulating normal cellular processes such as vascular homeostasis, gastric and renal function and coordinating circulating hormones. COX-2 is primarily responsible for inflammatory responses.

NSAIDs inhibit COX-1 and COX-2 to variable degrees and it is this mechanism that underpins differences in their harmful effects (Goodrich and Nixon, 2006). There is no benefit in combining NSAIDs; indeed, this seems to magnify their toxic effects (Kivett et al, 2014; Reed et al, 2006).

NSAIDs for musculoskeletal pain

Randomised controlled trials (RCTs) are few, but those that have been performed show little difference in efficacy between NSAIDs for treatment of musculoskeletal pain.

In an RCT involving 253 horses with osteoarthritis, firocoxib and phenylbutazone had comparable efficacy, with clinical improvement after 14 days of treatment being 85% with firocoxib and 87% with phenylbutazone, although firocoxib was associated with improved scores for pain on manipulation, joint circumference and range of motion, but not lameness or joint swelling (Doucet et al, 2008). Similarly, in an RCT comparing suxibuzone and phenylbutazone in lame horses, no significant differences were found between the drugs' ability to alleviate lameness (Sabate et al, 2009).

Carprofen has a potentially beneficial effect on proteoglycan, which may provide a specific indication for use of this drug in horses with osteoarthritis (Goodrich and Nixon, 2006), but this benefit has yet to be confirmed, with large-scale trials in naturally occurring clinical disease.

In the absence of clear differences in efficacy, selection of specific NSAIDs for chronic use in musculoskeletal disease is generally driven by other factors. Horses treated with phenylbutazone are excluded from the human food chain, although a study of equine tissue destined for human consumption demonstrated the illegal and erratic presence of trace amounts of phenylbutazone in horse meat is not a public health issue (Lees and Toutain, 2013).

Suxibuzone may be more readily accepted by horses than phenylbutazone (Sabate et al, 2009) and palatability studies have shown differences between phenylbutazone products. Perhaps most importantly, the potential for harmful side effects drives decision-making, but when NSAIDs are used at therapeutic levels, toxic effects are relatively uncommon in horses (Goodrich and Nixon, 2006).

Clinically relevant side effects can include gastrointestinal and renal damage, and disruption of proteoglycan synthesis. Phenylbutazone has been linked to pancytopenia and bone marrow suppression, together with various other drugs (Lavoie et al, 1987) and to ulcerative cystitis (Aleman et al, 2011).

Meloxicam is less harmful to gastric mucosal permeability measured by sucrose permeability than phenylbutazone in an in vivo experiment, but no differences were found in squamous or glandular ulceration between treatment groups (D'Arcy-Moskwa et al, 2012). The clinical relevance of this difference is questionable, given the large price difference between the licensed products. In foals or smaller ponies, the meloxicam preparation can be more easily titrated for bodyweight. This is a practical advantage – particularly since foals are prone to gastric ulceration.

Early studies comparing suxibuzone with phenylbutazone suggested suxibuzone might be less ulcerogenic than phenylbutazone (Monreal et al, 2004) – a surprising observation, given suxibuzone is a prodrug rapidly converted to phenylbutazone by a first-pass mechanism in the liver (Delbeke et al, 1993).

Subsequent studies have not confirmed this observation (Andrews et al, 2009) and it is likely little difference exists in the two drugs with respect to gastrointestinal side effects. Together, they probably are the most commonly used products for management of chronic lameness in horses.

NSAIDs for colic

Renal and gastrointestinal effects become a little more prominent when the case in question is presenting for colic. These horses may have volume depletion and cardiovascular compromise, which may, in turn, potentiate harmful effects of NSAIDs.

Phenylbutazone and meloxicam attenuated diuresis and natriuresis, and reduced glomerular filtration rate, compared with results for the control solution, when horses were treated with furosemide as a model for volume depletion (Raidal et al, 2014). Firocoxib, a COX-2 inhibitor, did not retard mucosal recovery in ischaemia injured intestine, whereas flunixin did (Cook et al, 2009) – an effect most relevant in horses undergoing intestinal surgery.

Novel NSAIDs, such as ketorolac, are on the horizon (Bianco et al, 2015) and may prove useful in equine colic, but, for most clinicians, selection of NSAID in colic is largely driven by predictable level of potency, so repeated use allows individual practitioners to feel comfortable they can recognise horses not responding as well as others.

Opiates

Morphine and methadone are used commonly in equine hospitals, but are not used widely in practice. For most equine clinicians, the most accessible are butorphanol, buprenorphine and

tramadol.

Buprenorphine has been extensively researched and evidence is accumulating from RCTs supporting its use in horses – particularly in perioperative patients. It is administered with sedation and provides analgesia over a longer period than butorphanol, with peak antinociceptive effects occurring between three-quarters of an hour and six hours after administration.

A placebo-controlled trial confirmed buprenorphine provided effective analgesia after castration (Love et al, 2013) and buprenorphine provided better anaesthetic conditions than butorphanol for field castration in a RCT involving 47 ponies, in which the butorphanol group required more intraoperative ketamine and rescue drugs (Rigotti et al, 2014). Another RCT showed postoperative pain scores were lower with buprenorphine than butorphanol in 98 undergoing elective surgeries (Taylor et al, 2015).

Tramadol is not specifically licensed for use in horses, but shows clinical potential – particularly where an oral preparation is required for multimodal analgesia or where side effects are limiting the use of NSAIDs. A fairly high dose is required in horses, but a study has shown tramadol given orally at 10mg/kg twice a day reduced signs of forelimb discomfort, whereas 5mg/kg did not (Guedes et al, 2015).

New directions

The search for new approaches to analgesia continues – particularly for managing acute, severe pain where continuous rate infusions of combinations of opiates and other agents show promise. Some evidence suggests neuropathic pain may be important in horses, particularly in laminitis (Jones et al, 2007), and this opens new avenues for therapy, although, to date, gabapentin – the main agent that has been applied – has proved disappointing, despite individual case reports supporting its use (Davis et al, 2007).

Gabapentin has poor bioavailability (Terry et al, 2010) and the optimal dose remains to be defined. It seems likely while, in many situations, the drugs will continue to hold a central place in our therapeutic arsenal, multimodal protocols offer future solutions.

- Some drugs in this article are used under the cascade.

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