Management of gastrointestinal pain

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Regular additions to the list of available analgesics have greatly eased the management of gastrointestinal dysfunction in the horse, and continuing research suggests that several more drugs are likely to be in use within the next decade. No drug comes without side effects, however. The increasing variety of products makes it more feasible to select the pharmaceutical agent providing the necessary analgesia with minimal complications. This review is designed to highlight the advantages and disadvantages of the drugs currently in use and as well as to provide information about some that may become more widely available in the near future.

Analgesic selection in horses with gastrointestinal dysfunction can be a critical point in case management. It is important to minimize perceived pain to the animal for its own sake as well as for that of the owner or caretaker. Additionally, a horse that is in pain is at risk of hurting itself and those around it. Providing at least short-term analgesia enables a better examination and more efficient treatment [127,167]. A poor or short duration of response to analgesics can also indicate a need for surgical exploration [38,61].

Pain can also have secondary effects on the animal. Continued pain leads to an increased metabolic rate and altered immune function, potentially leading to increased weight loss and delayed wound healing [115]. Pain may also lead to worsening of a primary gastrointestinal lesion by increasing reflexive adrenergic activity. Reduction of such pain-induced sympathetic tone may enable return to more normal motility and aid in the resolution of tympanic or impaction colic [172]. Control of pain may also minimize the incidence of impactions associated with rectovaginal lacerations and may be useful as a diagnostic tool, particularly when local analgesia is possible [113,171].

Many analgesics have anti-inflammatory properties as a primary or adjunctive mechanism of action. Release of inflammatory mediators is often

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a factor leading to a pain response in horses. Inflammation also increases the sensitivity of nerve fibers to continued release of such mediators [115]. In other species, it has been demonstrated that inflammation can activate additional afferent neurons, leading to a stronger pain response and, in some cases, a painful response to normal stimuli [24]. In other instances, inflammation has been shown to alter α -adrenoreceptor activity [24], which could alter afferent signaling (response to inflammation) and drug response. Inflammation and pain have been implicated in the development of postoperative ileus and human gastric dysfunction [24,75]; controlling one or both has been successful in several models at either preventing or treating the dysfunction [65,75].

Analgesic use before and during surgery may also lessen the need for postoperative analgesics and pain- or drug-associated complications [115,176]. Preemptive and intraoperative analgesia decreases the number and amount of anesthetic drugs required, helps to stabilize anesthesia, and may decrease postoperative analgesia requirements and postoperative morbidity, including gastrointestinal-related complications [115,176].

Analgesics can also hinder case management, however. By masking pain or fever or altering hemodynamic status, these drugs can impair monitoring and obscure a need for abdominal exploratory or allow a case to worsen unnoticed [61]. In many instances, these horses are receiving several different drugs that may have significant interactions. Finally, many of the available analgesics are known to affect the gastrointestinal tract, potentially worsening the original dysfunction. As a result, it is important to select a product that provides the necessary analgesia without being excessive and to carefully monitor for drug-related side effects. Client education is an important aspect of the process so as to ease concerns about appropriate pain relief as well as to watch for subtle indications of drug-related problems.

Abdominal pain arises most commonly from intestinal distention, intestinal muscle contraction (spasm), mesenteric tension, intestinal ischemia, intestinal inflammation, or peritonitis [61,114]. Afferent sensory fibers may extend to other regions of the intestinal tract, to local ganglia, or to the spinal cord. Many of the drugs in use today have well-understood mechanisms of action. Many have been tested on models of colic pain, often using a model of cecal distention [114]. In this model, a balloon is inserted into the cecum and gradually distended until the horse shows evidence of discomfort. Analgesics are compared based on their ability to alter the discomfort threshold. Having one model makes drug comparisons much easier, but this model is subject to variation within and between animals [93,127].

Nonsteroidal anti-inflammatory drugs

Drugs that inhibit the release of prostaglandins are among the most commonly used analgesics for equine visceral pain. Phenylbutazone, dipyrone,

ketoprofen, and flunixin meglumine are the most widely used nonsteroidal anti-inflammatory drugs (NSAIDs) [38,114]. These drugs are effective against inflammation-mediated pain sensation. They reduce the sensitivity of nerve endings to pain and likely have central effects as well (Table 1) [176].

Of this class, flunixin meglumine is believed to be among the most potent of visceral analgesics, and it is labeled for equine visceral pain [38,128]. In one study, 68% of 118 horses with medical colic showed a good to excellent response to the drug (1.1 mg/kg administered intravenously) within 1 hour, and 38% of the 118 horses improved within 15 minutes [167]. More severe cases (moribund or preoperative) also showed improvement after administration of flunixin meglumine. In cases of mild to moderate colic in another study, a good to excellent response was obtained in 98% of the cases using 1.1 mg/kg of flunixin meglumine administered intravenously [7]. Flunixin meglumine also relieved clinical signs of colic for 30 to 60 minutes in ponies subjected to an experimentally induced pelvic flexure impaction [95]. The drug was not effective at relieving pain in a cecal distention model, likely because of lack of inflammation-mediated pain [77]. Flunixin meglumine may be given at 1.1 mg/kg intravenously up to every 8 hours in horses with visceral pain; however, it may be effective at a reduced dose (0.25–0.5 mg/kg) and at longer intervals (up to 24–36 hours) [38,128]. Flunixin meglumine has the added advantage of having antiendotoxic properties at a low dose [149] as well as at 1.1 mg/kg [81,163], and it was better than either xylazine or butorphanol at maintaining bowel perfusion in anesthetized ponies [155,163]. Repeated high doses can potentially obscure a surgical lesion [38,61,128]. Besides altering signs of pain, flunixin alters mucous membrane color and relieves fever [128].

Ketoprofen is a newer NSAID that has been demonstrated to have analgesic effects similar to those of flunixin meglumine in cases of musculoskeletal and visceral pain when administered at 2.2 mg/kg intravenously or intramuscularly [7,52]. A higher dose (3.63 mg/kg) has been suggested for

Table 1
Equine analgesics commonly used for visceral pain

Drug	Recommended dose
Flunixin meglumine	0.25–1.1 mg/kg IV every 8–24 hours
Ketoprofen	2.2–3.63 mg/kg IV or IM every 24 hours
Phenylbutazone	≤4.4 mg/kg IV or PO every 12 hours
Xylazine	0.23–1.1 mg/kg IV 2.2 mg/kg IM
Xylazine plus butorphanol	1.1 mg/kg of xylazine IV plus 0.1 mg/kg of butorphanol IV
Detomidine	0.005–0.04 mg/kg IV
Detomidine plus butorphanol	0.01 mg/kg of detomidine IV plus 0.05 mg/kg of butorphanol IV
Butorphanol	0.1–0.4 mg/kg IV or IM
Lidocaine infusion	1.3 mg/kg by bolus IV plus 0.05 mg/kg/min by infusion IV

IV = intravenously, IM = intramuscularly, PO = orally.

laminitis cases but has not been evaluated for equine visceral pain [21]. Ketoprofen has been shown to have antiendotoxic activity similar to that of flunixin meglumine [111]. In the horse, ketoprofen seems to have a much wider therapeutic margin than most NSAIDs. No evidence of toxemia was seen after ketoprofen was given to horses at five times the recommended dose for 15 days [52], and it showed fewer side effects than either phenylbutazone or flunixin meglumine [97].

Phenylbutazone is considered less effective for equine visceral pain than flunixin meglumine [172]. It is more effective than flunixin meglumine at reversing endotoxin-mediated disruption of gastrointestinal motility, however [81]. Phenylbutazone is less effective at altering the cardiovascular effects of endotoxemia, and it has been suggested that use of phenylbutazone for treatment of colic would avoid the potential problems of masking such clinical signs of endotoxemia [81]. It should not be given above 4.4 mg/kg every 12 hours because of its higher toxicity risk [97]. When phenylbutazone and flunixin meglumine are combined, the pharmacologic effect of each may be prolonged. In one study, serum thromboxane B₂ production was suppressed for 8 hours after phenylbutazone, for 12 hours after flunixin meglumine, and for 24 hours after a combination of the two [148]. Combining NSAIDs may increase the potential for toxicity [128].

Dipyrone is no longer available but has been useful historically for horses with abdominal pain, particularly those with spasmodic colic [114]. Experimentally, it has been shown to antagonize bradykinin-induced intestinal spasm, but it did not alter normal activity or reverse spasm caused by nerve stimulation or cholinergic drugs [50]. It was not useful in cecal balloon distention models [93]. In general, dipyrone is considered a weak but safe analgesic in the horse [38,61,172].

Other NSAIDs have been evaluated for their analgesic properties in the horse, however, not in terms of visceral analgesia (Table 2). When evaluating new drugs, it is important to remember that most NSAIDs have been shown to concentrate at sites of inflammation; plasma levels and duration of persistence may not correlate with therapeutic effect [21]. Additionally, if a pain model does not involve an inflammatory process, the analgesic effects of these drugs may not be accurately reflected.

In terms of direct effects on equine intestinal function and viability, flunixin meglumine is the best studied of the NSAIDs. Particularly when compared with other analgesic classes, it has been regarded as having no significant effect on normal intestinal motility. Flunixin meglumine did not alter mechanical or myoelectric activity of the pony jejunum or pelvic flexure [68,95], had only minimal effect on the colon [90], and did not alter intraluminal pressure changes in the cecocolic area or in a pelvic flexure impaction model [95,140]. Neither flunixin meglumine nor ibuprofen altered the gastrocolonic reflex [136], and neither dipyrone nor flunixin meglumine altered intestinal transit time in normal horses [101]. Although flunixin meglumine (1.1 mg/kg administered intravenously) increased systemic vascular

Table 2
Selected equine analgesics with potential for use against visceral pain

Drug	Recommended dose	Current use	Comments	Reference
Ibuprofen	10–25 mg/kg IV or PO every 8–12 hours Adults: 20–25 mg/kg PO BID first day, then 10–15 mg/kg BID	Foals, chronic musculoskeletal pain	Minimal evidence of toxicity clinically, long-term effects unknown	[9]
Eltenac	0.5–1 mg/kg IV every 24 hours	Musculoskeletal pain	Equivalent to 1.1 mg/kg of flunixin meglumine, good antiedotoxic effects	[58,97,99,138]
Suxibuzone	7.5 mg/kg IV	Musculoskeletal pain	Converted to phenylbutazone	[70]
Naproxen	5 mg/kg IV or 4 g PO BID per horse	Myositis	More effective than phenylbutazone	[73,153]
Carprofen	0.7 mg/kg IV or PO every 12–24 hours	Musculoskeletal pain	Irritating if given intramuscularly, similar to phenylbutazone and flunixin meglumine in activity but longer acting	[72,88]
Romifidine	0.07 mg/kg IV	Foal sedation and analgesia	Similar to xylazine, significant hypotension associated	[57,120,162]
Transdermal fentanyl patches	2–3 100-µg/h patches for adult horses	Postoperative pain, musculoskeletal pain	May need additional analgesics for acute or severe pain	[106]
Intravenous butorphanol infusion	17.8 µg/kg IV, then 23.7 µg/kg/h infusion IV	Musculoskeletal pain (anecdotal)	No motor effects, tolerance can develop	[147]

IV = intravenously, PO = orally, BID = twice daily.

resistance, it did not alter jejunal blood flow in the same time frame and did not alter colic artery flow in a pelvic flexure impaction model [95,156]. It is subsequently believed not to compromise intestinal viability because of changes in vascular perfusion [156]. This may not be true of all NSAIDs [45]. More recent studies have raised additional concerns. Several NSAIDs did alter colonic contractility in vitro [166], and flunixin meglumine (but not etodolac) impaired mucosal healing because of inhibition of normal prostaglandin function [14].

Other reported gastrointestinal side effects of this class of drug include gastric ulceration, small intestinal edema, protein-losing enteropathy, and erosions and ulcers of the large intestine [15,97]. Foals seem to be particularly sensitive to development of diarrhea and phenylbutazone toxicosis [15,21]. At higher doses (8.8 mg/kg administered orally twice daily for 10 days), phenylbutazone has been associated with anorexia, weight loss, diarrhea, and oral ulcerations [23]. Phenylbutazone has also been implicated in the development of right dorsal colitis [12] and has been shown to alter colonic ion transport in vitro, potentially leading to pH changes in the horse [43]. In a study comparing phenylbutazone, flunixin meglumine, and ketoprofen, phenylbutazone had the greatest toxic potential and ketoprofen had the least [97].

As mentioned previously, monitoring of horses with abdominal pain is inhibited by these drugs through their ability to alter body temperature, mucous membrane color, and hemodynamic parameters [128]. These drugs do not result in ataxia or sedation, however, as do many of the other analgesics, making them useful for analgesia during surgical recovery and in similar situations [72]. These drugs are highly protein bound and can displace other protein-bound drugs, leading to an increase in activity of the displaced drugs [21]. This can be of particular concern during the anesthetic maintenance and recovery periods.

In summary, ketoprofen may replace flunixin meglumine as the primary NSAID used in the treatment of gastrointestinal pain in horses; dosage and frequency of administration remain to be optimized. Horses requiring repeated doses of either ketoprofen or flunixin meglumine may have more severe gastrointestinal dysfunction and should be considered potential candidates for surgical exploration. Supportive treatment to minimize gastric ulceration and renal dysfunction should be considered. Concern over the effects of current drugs on gastrointestinal function and healing persist and may lead to replacement of these drugs with newer NSAIDs. NSAIDs are the primary drugs available at this time for the management of chronic visceral pain in the horse.

Sedative analgesics

The combination of sedation with analgesia can be useful in the evaluation of horses with abdominal pain. The α_2 -adrenergic receptor agonists

such as xylazine and detomidine are potent as sedatives and as analgesics. They are faster acting but have a shorter duration of action than the NSAIDs [21,38]. In a pelvic flexure impaction model, xylazine (0.23 mg/kg administered intravenously) relieved clinical signs for 30 to 60 minutes [95]. In other experimental models using 1.1 mg/kg administered intravenously or 2.2 mg/kg administered intramuscularly, analgesia has been reported to last from 65 minutes to 4 hours [77,93,116]. Clinical use at 1.1 mg/kg administered intravenously suggests maximum effect at 3 minutes and a duration of 10 to 40 minutes depending on the severity of the pain [64]. Multiple studies using a cecal distention model of colic have shown that xylazine is better at relieving visceral pain than the tested opioids or NSAIDs, including flunixin meglumine, butorphanol, and morphine [77,93,116].

Combining xylazine with an opioid has been shown to give synergistic effects. When 1.1 mg/kg of xylazine was combined with 0.055 mg/kg of fentanyl, it provided more effective analgesia in a cecal distention model of visceral pain than did xylazine alone for up to 4 hours [127]. Xylazine (1.1 mg/kg administered intravenously) combined with butorphanol (0.1 mg/kg administered intravenously) better permitted flank laparotomy than did xylazine alone, with four of six horses comfortable for 30 minutes [134]. The analgesic effects of 0.1 mg/kg of butorphanol in a cecal balloon model were extended from 45 to 120 minutes when it was combined with 0.3 mg/kg of xylazine [117]. Acepromazine may also enhance the effects of xylazine, but because of its hypotensive effects, it is not recommended for use in most cases of gastrointestinal pain [61].

Detomidine is more potent and longer lasting than xylazine at doses greater than 0.005 mg/kg [21]. It has been shown to be effective in controlling visceral pain in horses [94]. Generally intravenous doses of 0.02 to 0.04 mg/kg are recommended, with the duration of activity being dependent on the dose [21,94]. In a cecal balloon distention model, the duration of action of detomidine was 13.5 minutes at 0.005 mg/kg, 45.5 minutes at 0.02 mg/kg, and 239 minutes at 0.16 mg/kg [94]. Increased sedation, decreased responsiveness, and increased ataxia were reported when detomidine (0.01 mg/kg) was combined with opioids [22]. If used in combination, butorphanol at 0.05 mg/kg was recommended [22].

Medetomidine, romifidine, dexmedetomidine, and radolmidine are newer drugs in this class. Romifidine (0.07 mg/kg administered intravenously) was more effective at allowing nasogastric tube passage in foals than was xylazine and provided a slightly longer period of analgesia [120]. In other studies, romifidine provided less analgesia and less sedation than xylazine or detomidine [57]. It has also been shown to have more significant hypotensive effects, making it riskier for use in many horses with colic [162]. At this time, medetomidine (0.004–0.01 mg/kg administered intravenously) does not seem to provide a significant sedative advantage compared with xylazine in the horse and has been associated with increased ataxia and prolonged blood pressure effects [13,61]. Dexmedetomidine has become increasingly popular

in human medicine because of simultaneous analgesia, sedation, and lack of respiratory depression [56]. When given intravenously (0.1–10 $\mu\text{g/kg}$) to goats, dexmedetomidine caused short-duration (<15 minutes) vasoconstriction, while maintaining balanced myocardial oxygen supply and demand [86]. This may allow dexmedetomidine to be a useful analgesic sedative for cardiovascularly compromised colic. Radolmidine seems to be most effective as an antinociceptive agent when given intrathecally as compared to epidurally or systemically in sheep [39]. When given intrathecally, this drug is not associated with significant sedation, motor effects, or hemodynamic depression in other species [39].

Most, if not all, α_2 -adrenergic receptor agonists can mask surgical pain. The effects of xylazine are generally short-lived, particularly in severe cases. Larger doses of detomidine (≥ 0.02 mg/kg) can suppress pain for several hours [61]. The use of detomidine in horses with abdominal pain may alter the decision for surgery, either by delaying it because of minimal pain signs [21,38,82] or by hastening the process because of the concern about missing a surgical lesion in a detomidine-treated horse.

Xylazine and detomidine have been found to have significant effects on the gastrointestinal tract directly and indirectly. Xylazine caused changes (primarily decreases) in the myoelectric activity of the stomach, small intestine, cecum, large colon, and small colon of normal ponies [20,68,69,90,135,140,142]. In the stomach, the alterations are reflected in decreased gastric emptying [36]. Xylazine was also found to reset the duodenal motility pattern and suppress intraduodenal pressure peaks [108,109]. Conversely, despite significant decreases in activity, cecal emptying was minimally affected at a dose of 0.5 mg/kg administered intravenously [90]. The duration of activity changes is dependent on the dose, with higher doses (1.1 mg/kg administered intravenously) lasting up to 120 minutes [20]. The effect on the cecum was prolonged (150 vs 120 minutes) when xylazine was combined with 0.1 mg/kg of butorphanol [142]. Similar prolonged effects were seen with morphine in the cecocolic region [140] and in the duodenum with a combination of 0.5 mg/kg of xylazine and 0.05 mg/kg of butorphanol [108]. In the duodenum, the inhibition of normal contractions increased from 30 minutes with xylazine alone to 60 minutes with both drugs and was more markedly changed with the latter. In a pelvic flexure impaction model, xylazine (0.23 mg/kg administered intravenously) stopped intraluminal pressure changes for 30 minutes [95]. Detomidine can also alter activity in the duodenum, large intestine, and cecum (only areas tested), with the duration of changes lasting up to 3 hours [108,135]. Clinically, decreased gastrointestinal sounds have been noted with both drugs [21], and xylazine and detomidine reversed diarrhea caused by administration of prostaglandin $F_{2\alpha}$ [135]. The newer drugs in this class have been shown to cause similar inhibition of gastrointestinal motility in other species [4,118]. In other species, α_2 -adrenergic receptor agonists also increase the absorption of fluid and electrolytes from the intestine [17]; this potential effect has not been

evaluated in the horse. Although these changes have the potential of slowing gastrointestinal motility and worsening impactions, they may also help to relieve intestinal spasm and pain [68,172]. Finally, the response to α_2 -adrenergic receptor agonists seems to be altered in some horses with naturally occurring colic and in bowel adjacent to areas of ischemia, making the effects of these drugs potentially different in these animals than in normal horses [103]. The gastrointestinal effects of the drugs can be reversed at least in part by tolazoline or yohimbine, but the analgesic activity is reversed as well [54,109,135]. Tolazoline and yohimbine have also been shown to alter normal intestinal activity [90,109].

The hemodynamic changes associated with α_2 -adrenergic receptor agonists are believed to significantly affect the gastrointestinal tract as well. Lateral cecal arterial blood flow was decreased to a greater extent than was cardiac output in normal ponies, and colic arterial blood flow was decreased rather than increased in a pelvic flexure impaction model [95,142]. The durations of cecal blood flow changes were dependent on dose and were not significantly different when butorphanol was added to the xylazine [20,142]. Local intra-arterial injection of xylazine into the jejunum of ponies resulted in a combination of vasoconstriction, increased activity, and increased oxygen use, which would suggest that it could have a negative effect on bowel viability [155]. The effects of repeated xylazine in this study were increased and prolonged; however, because most of the effects of xylazine are mediated centrally, the clinical contribution of local drug effects is unknown.

Care should be taken with these drugs in animals that are febrile (alteration in thermoregulatory mechanisms) or in shock because of the potential cardiovascular effects [128,172]. One nervous stallion with colic died after receiving xylazine (1.1 mg/kg), and acute collapse has been reported in other horses [44,51]. Horses under apparent heavy sedation can still be aroused and kick [64,128]. Detomidine or xylazine combined with an opioid such as butorphanol provides a better balanced stance (and is safer for procedures near the hindquarters) than does xylazine alone [46,105]. Behavior changes can occur with both drugs, including increased aggression (Internet communication, John Madigan, DVM, MS, 1996) [175]. Clinicians should be aware of potential interactions of α_2 -adrenergic receptor agonists with other drugs, particularly those undergoing hepatic metabolism. Clinical ileus was prolonged in a horse treated with xylazine and chloramphenicol, and the combination of intravenous potentiated sulfonamides and detomidine can result in fatal arrhythmias [54,128].

In summary, xylazine and detomidine are strong analgesics that can alleviate most equine visceral pain at least temporarily. Because of its shorter duration of action, xylazine is preferred in situations where assessment of the need for surgery is ongoing. Detomidine may be required to provide sufficient analgesia in some situations or if surgery is not an option. Careful communication with the owner and any referral institution is necessary to ensure appropriate case care and humane treatment. Repeated doses most likely

have significant clinical effects on gastrointestinal motility and blood flow. Decreasing doses of xylazine and detomidine with the addition of butorphanol may minimize effects on blood flow but may not diminish motility alterations.

Opioid analgesics

Several opioid analgesics have been evaluated in the horse. Most commonly, drugs from this group are combined with sedative analgesics to increase the analgesic effect and duration of action of those compounds as discussed previously. The opioids do have some analgesic effect when given alone, but because of excitatory effects, they need to be given at a low dose or combined with another drug [128]. In horses experiencing pain, the excitatory effects may be less evident, however [46].

In cecal balloon distention models, butorphanol was effective at relieving pain for 10 to 45 minutes at doses of 0.1 mg/kg and higher [117]. A dose of 0.2 mg/kg of butorphanol administered intravenously provided adequate pain relief for at least 60 minutes, and a dose of 0.4 mg/kg administered intravenously provided adequate pain relief for 90 minutes [76,77,116]. Experimentally, butorphanol has been found to be more effective than meperidine, morphine, methadone, levorphanol, and pentazocine at reducing equine visceral pain [76,77,93,116,117,127]. Clinically, butorphanol administered intravenously at a dose of 0.1 mg/kg provided good to excellent analgesia in 93% of colic cases [158]. Oxymorphone (10 mg for an adult horse) and morphine (0.66 mg/kg) have also been used successfully to manage colic pain in horses [30,124].

Recently, transdermal fentanyl patches and continuous intravenous butorphanol infusion have been investigated in the horse for general pain relief. A butorphanol infusion rate of 23.7 $\mu\text{g/kg/h}$ after a loading dose of 17.8 $\mu\text{g/kg}$ resulted in plasma concentrations that would be expected to give pain relief, and no behavioral side effects were observed [147]. The authors have successfully used a butorphanol infusion to provide relief from musculoskeletal pain but have observed the development of tolerance after approximately 48 hours. Transdermal fentanyl patches in the horse have been reported to result in rapid absorption of fentanyl, with plasma levels reaching levels greater than 2 ng/mL in only 4 hours [106]. Levels remained above 1 ng/mL for 54 hours and fell rapidly after patch removal. Although effective analgesic levels of fentanyl are not reported in the horse, effective analgesic levels for human beings are reported to be greater than 1 ng/mL. Based on the single reported study of fentanyl patch use in the horse, significant plasma levels were achieved in adult horses (mean body weight of 381 kg) with the application of two 100- $\mu\text{g/h}$ patches [106]. Larger horses may require the placement of three 100- $\mu\text{g/h}$ patches. Tolerance may be less of a problem than with other opioids [115]. Fentanyl patches are effective for

the relief of chronic pain, dull pain, and nonspecific widespread pain. Additional drugs may be required in animals with acute or severe pain. Butorphanol should not be used in combination with fentanyl because of its mixed agonist-antagonist effects, which could reverse the analgesic effects of the patch [115]. At the level of use reported, no adverse behavioral effects or changes in heart rate were attributed to the fentanyl [106]; however, delayed hair growth and changes in hair color have been anecdotally associated with fentanyl patch use.

Opioids are well known for their gastrointestinal side effects. Decreased gastrointestinal sounds, fecal passage, and constipation have been reported at a dose of 0.1 mg/kg of butorphanol administered intravenously [21,147]. Gastric emptying in normal ponies was delayed by 0.05 mg/kg of butorphanol administered intravenously, but the effect was short-lived [36], and minimal effect was detected on antroduodenal activity [110]. No overall decrease in transit time of a liquid marker was detected at a dose of 0.1 mg/kg administered intravenously [133]. This butorphanol dose did disrupt propulsive activity of the jejunum but did not affect the pelvic flexure [152]. Conversely, morphine significantly prolonged transit of a liquid marker in ponies at a dose of 0.4 mg/kg or higher administered intramuscularly [133]. In the same study, intestinal sounds were reduced, feces were drier, and abdominal discomfort occurred at higher doses of morphine. The combination of xylazine and morphine was reported to result in ileus and abdominal pain when used for standing analgesia [82]. Fentanyl (0.01–0.05 mg/kg administered intravenously) inhibited cecocolic propulsive activity in a dose-dependent manner and closed the cecocolic sphincter for 1 to 2 hours [137]. Combined with a potential for antisecretory activity as seen in other species, the motility effects of repeated dosing of these drugs could lead to an increased risk of impaction [11,172]. Recent work in mice suggests that inflammation leads to an upregulation of opioid receptors ($\delta > \mu > \kappa$) and increases the gastrointestinal effects of these drugs [165]. Butorphanol does not seem to impair oxygenation of bowel, however, and should not compromise intestinal viability [157]. The gastrointestinal side effects of these drugs can be reversed with naloxone (along with analgesic effects); however, naloxone can also cause abdominal distress in horses [79,133,172].

In summary, opioids are useful adjuncts for analgesia in the horse, particularly when combined with α_2 -adrenergic receptor agonists; however, their use may not alleviate changes in gastrointestinal function, and chronic use may lead to fecal drying and impactions. Additionally, newer methods of administration may enhance the use of these drugs. Transdermal fentanyl patches may offer a cost-effective method for relief of more chronic pain in the horse.

Local anesthetics

Intravenous lidocaine has been used as an analgesic in people for decades and is now being used in the horse to provide pain relief [34]. Low-dose

continuous lidocaine infusion was found to decrease postoperative pain scores and the amount of narcotics required after cholecystectomy and prostate surgery in people [53,130]. In ponies, intraoperative lidocaine decreased the halothane minimum alveolar concentration in a dose-dependent manner when given intravenously at 0.05 or 0.1 mg/kg/min after a loading dose of 2.5 or 5 mg/kg [34]. A related compound was reported to be effective in the treatment of colic over 30 years ago [100]. Intravenous lidocaine has been used anecdotally for the treatment of various impactions, including cecal impactions, in the horse [102,125]. Lidocaine enemas are used to prevent and treat rectal tears [144]. Lidocaine has also been used intragastrically in horses with gastrointestinal ulcers as a diagnostic tool to determine if colic pain was caused by the ulcers or another lesion (T. Ames, DVM, MS, personal communication, 2001).

In the human studies described previously, lidocaine infusion had the additional beneficial effects of decreasing the duration of postoperative paralytic ileus and shortening hospital stays [53,130]. This may occur directly or through interruptions of reflexive responses to pain, endotoxemia, or inflammation [53,98,146,170]. Lidocaine has been used to treat postoperative ileus and proximal duodenitis jejunitis in horses with moderate success at a dose of 0.05 mg/kg/h after a loading dose of 1.3 mg/kg [104]. At this dose rate, the analgesic effect is sufficient to mask signs of laminitis. The same dose rate has been used by the authors to treat severe cases of laminitis with good results and no evidence of tolerance.

At higher doses, lidocaine can cause central nervous system (CNS) excitement, including seizures [25]. In horses, muscle fasciculations and ataxia were detected at blood levels over 2.4 mg/L (E. Malone, DVM, PhD, unpublished observations), and seizures can occur at blood levels above 6 mg/L [34]. In a few cases, ataxia was associated with collapse. Lidocaine has a short half-life, however, and horses recover from side effects within minutes when the infusion is stopped or slowed. In a multicenter trial using lidocaine for reflux, major concerns related to the lidocaine included a potential increase in the incisional infection rate and masking of early signs of laminitis [104]. Direct effects of lidocaine on the equine pylorus [121] or jejunum have not been detected *in vitro* (E. Malone, DVM, PhD, unpublished observations); however, lidocaine was shown to increase contraction amplitude of the proximal duodenum of normal horses [121]. Lidocaine plasma levels can be increased by the concurrent administration of other drugs utilizing the hepatic cytochrome P450 system such as cimetidine and metronidazole.

In summary, intravenous lidocaine may be useful for the treatment of gastrointestinal pain in horses; however, close monitoring of the constant infusion rate is required to ensure efficacy and minimize toxicity. The ability of the drug to relieve severe pain likely masks the need for surgery, and horses being treated with this drug require close monitoring and occasional withdrawal of the drug to assess true pain status. It may be most useful in alleviating pain-induced sympathetic inhibitory tone and restoring normal

motility in cases of impactions or ileus. Local use may become more prevalent as we investigate its potential in the horse.

Epidural analgesia

Epidurals have long been used to alleviate abdominal pain in human beings, and epidural local anesthetic administration is associated with improved gastrointestinal function in people when compared with epidural or systemic opioids [1,154]. In horses, effective epidural analgesia has been obtained for hind limb but not forelimb pain [35,161]. Epidural morphine delivered at the lumbosacral space offered adequate postoperative analgesia for thoracotomies in dogs [126], implying that abdominal analgesia might also be achieved in veterinary patients. Although epidural morphine is thought to be helpful in alleviating abdominal pain in some species, the effects in horses remain unclear. Most likely, epidural catheters would be required to deliver the analgesic drugs in horses.

Local anesthetics have typically been used in horses for caudal epidural analgesia, and to achieve abdominal analgesia without significant hind limb motor blockade would be nearly impossible. Local anesthetics with fewer motor effects are now available for epidural administration in people. Ropivacaine, one of the new amide local anesthetics, seems to offer a lower risk of cardiovascular and CNS toxicity [143]. Although the analgesia is the same or slightly shorter with epidural ropivacaine, the motor blockade is less intense than with bupivacaine [10]. In a study comparing epidural ropivacaine and bupivacaine for abdominal surgery in human patients, no difference was seen in effects on gastrointestinal function after surgery [74]. Levobupivacaine, the *s*(–) enantiomer of bupivacaine, also offers a lower risk of cardiovascular and CNS toxicity [42]. The analgesia associated with epidural levobupivacaine is similar to or longer than that of bupivacaine, with less pronounced motor blockade. Epidural levobupivacaine offers good analgesia for human patients undergoing abdominal surgery [84], and the addition of morphine potentiates the efficacy of epidural levobupivacaine [26].

Broodmares and neonates

Most drugs given to broodmares can have potential adverse effects on the fetus and neonate. Opioids may cross the placenta readily and can lead to fetal cardiovascular and respiratory depression [46,128], primarily a concern if a cesarean section is required. In people, chronic opioid use is associated with low—birth weight infants, behavioral deficits, and increased neonatal mortality. Opioids also have the potential for altering milk letdown and maternal behavior, but clinically noticeable differences have not been detected in other species [37]. In cattle, xylazine increases intrauterine pressure and is believed to have abortigenic capabilities [87]. In horses, no specific effects of

the drug were detected in eight mares given 20 µg/kg/wk from day 14 to day 60 of gestation and then every 4 weeks until parturition [80]. Similarly, repeated detomidine doses caused temporary (90-minute duration) decreases in fetal heart rates but had no observed detrimental effects on the pregnancy [96]. Because of its high lipophilicity, dexmedetomidine leaves the maternal circulation quickly, and little drug is transported to the fetal circulation in people [2]. This characteristic may make dexmedetomidine a desirable drug for analgesia and sedation in pregnant mares. Only small amounts of phenylbutazone were detected in the milk of mares being treated, and no phenylbutazone was detected in the foals [27]. Phenylbutazone does cross the placenta, however, and the half-life of the drug is longer in neonatal foals [28]. Young foals may also be more sensitive to the toxic effects of phenylbutazone [21,27], and foals have been born with gastric ulceration and renal failure apparently related to in utero exposure. In other species, NSAIDs can lead to fetal malformations if used in early gestation, and in late gestation, they can lead to premature closure of the ductus arteriosus and delayed onset of labor [37]. Recent evidence that NSAIDs can alter bone and cartilage development could also be a concern in fetal development [123,138]. Conversely, flunixin meglumine helps to decrease endotoxin-induced luteolysis in early gestation [163]. In people, lidocaine does cross the placenta, but fetal levels are generally 50% to 70% of maternal levels, and although neonates seem to be more sensitive to the drug, no differences were detected if fetal blood levels were less than 2.5 µg/mL [145,150]. With the low doses used in horses for analgesia, fetal effects should be minimal.

Older horses

Drugs such as flunixin meglumine and phenylbutazone have been documented to have longer half-lives in older horses, perhaps because of changes in hepatic metabolism and protein binding [71,148]. The risk of toxicity may be lowered by increasing the interval between drug doses and by monitoring protein and renal parameters. Hepatic or renal dysfunction alters the metabolism of all major drugs discussed in this review and warrants additional monitoring and careful consideration of interval and dose.

Trauma, shock, and after exercise

No studies have been done on horses with gastrointestinal pain after strenuous exercise or significant trauma or other shock. Xylazine and detomidine were recently shown to provide safe and effective sedation after exercise when given at twice the normal dose to horses exercised on a treadmill; however, the drugs did lead to a prolonged increased body temperature [67]. Trauma to the abdomen can result in painful conditions that require analgesics to allow safe evaluation of the animal. These horses are at risk

of increased drug-related side effects because of poor organ perfusion and circulating blood volume. Analgesics with cardiopulmonary effects (e.g., xylazine, detomidine) or with lower toxicity thresholds (NSAIDs) should be used sparingly until vascular perfusion is improved. Combinations of drugs such as xylazine and butorphanol can provide analgesia with lower doses of agents that have nonadditive side effects. Opioids are generally safest to use in shocky animals but should be used judiciously in patients with suspected head trauma and respiratory depression [126].

Drug interactions

Many horses with gastrointestinal pain may be receiving other drugs besides analgesics, including antibiotics, antiulcer medications, antiendotoxic drugs, or motility modifiers. Horses undergoing anesthesia are subject to additional classes of drugs and additional adverse cardiovascular effects such as hypotension. Many of the drugs have overlapping toxicities or can affect the metabolism of other agents. Renal toxicity is of increased concern when NSAIDs are used in combination with each other or with antibiotics such as gentamicin, polymyxin B, or the cephalosporins [47,128]. Phenylbutazone may increase the plasma half-life of penicillin, and the combination of phenylbutazone and heparin may increase the risk of bleeding disorders [128]. Most NSAIDs are also highly protein bound and can displace other protein-bound drugs. This can alter anesthetic planes if NSAIDs are given during surgery or in recovery. The combination of an aminoglycoside, lidocaine, and polymyxin B could lead to enhanced neuromuscular blockade [59]. Fatal dysrhythmias may also occur when detomidine is used in combination with potentiated sulfonamides [128]. Drugs that alter hepatic microsomal enzymes can change the metabolism of other similar drugs, leading to potential toxicity when drugs such as phenylbutazone, lidocaine, diazepam, cimetidine, metronidazole, and omeprazole are used in combination [59,128]. If a potential for toxin ingestion exists, drugs that are known to slow intestinal transit time such as the opioids should be avoided until the toxin is eliminated from the gastrointestinal tract [128].

As mentioned previously, analgesic combinations may also be synergistic. Recent work suggests that not only are opioids synergistic with α_2 -adrenoceptor agonists but that they may also be synergistic with local anesthetics and with NSAIDs [19,83]. Conversely, combinations of opioids of different classes can hinder pain relief because of the reversal of agonists such as fentanyl by agonist-antagonists such as butorphanol [46].

Herbal therapy

A paucity of information exists regarding the use of herbs in horses, especially for the treatment of gastrointestinal disease. Nevertheless, certain

herbs are thought to have anti-inflammatory, antispasmodic, or analgesic effects in a variety of species. Ginger (*Zingiber officinale*) is an effective antiemetic [168] and possesses gastroprotective effects [179]. It is commonly used in the treatment of gastric ulceration and gastritis and could be useful in foals with gastric ulcers. Dai-Kenchu-To (containing xanthoxylum, ginseng, and ginger) inhibits distal colonic contractions in the rat and is commonly used to treat paralytic ileus in Japan [164]. Peppermint oil relaxes gastrointestinal smooth muscle via a reduction in calcium influx [63], and clinically effective enteric-coated and non-enteric-coated preparations of peppermint-caraway oil are commercially available [112]. Lavender (*Lavandula angustifolia*) oil and its primary ingredient (linalool) have postsynaptic nonatropine-like spasmolytic activity in the small intestine [91]. *Ocimum gratissimum* possesses spasmolytic actions similar to those of atropine [5]. Leaf extracts of *Salvia cinnabarina* have nonspecific spasmolytic effects in the small intestine [139]. Lamiaceae (*Satureja hortensis*) essential oil has in vitro antispasmodic effects and in vivo antidiarrhea effects [55]. *Boswellia serrata* has been shown to alleviate experimental ileitis and clinical colitis and to relieve the adverse gastrointestinal changes associated with NSAID administration [48,85]. Other plant extracts such as *Portulaca oleracea* [16], *Zataria multiflora boiss* [66], *Polypodium feei* [159], and *Marrubiin* [33] have known anti-inflammatory and analgesic properties mediated through opioid receptors, nonopioid receptors, and inhibition of prostaglandins. Many of these herbs and herbal extracts have the potential for use in horses with gastrointestinal disease, but studies need to be done on their efficacy and side effects in the horse before they can be recommended.

Acupuncture

Acupuncture has been shown to have an analgesic effect in acute intestinal colic [82], iatrogenic colic [18], cancerous abdominal pain [177], and enterospasm [62] in human beings. In one human study involving 14 patients with gastric ulcers, acupuncture treatment reduced gastric acid secretion and alleviated ulcer-related pain, with pain relief lasting for longer than 18 months in more than half of the patients [151]. Acupuncture may be less effective against pain because of ischemia [6]. Because acupuncture may also be useful in managing gastrointestinal dysfunction [32], it may become a useful adjunctive tool for treatment of horses with abdominal pain; however, much research has yet to be done in this field.

The future

New drugs, drug combinations, and routes of administration are rapidly changing the picture of pain management. In people, bupivacaine has been

used intraperitoneally to relieve postoperative ileus and pain [131], and intraperitoneal lidocaine plus an NSAID provided better analgesia and faster return of bowel function than intraperitoneal lidocaine plus the same NSAID given intravenously [40]. In a mouse peritonitis model, intraperitoneal morphine provided significant analgesia, although intravenous morphine did not, suggesting that peripheral receptors play an important role in inflammatory pain [129]. Ropivacaine gel has been applied rectally for the treatment of active distal ulcerative colitis in people [3], and a “GI cocktail,” a combination of oral lidocaine and antacids, is commonly used in the emergency room treatment of upper abdominal pain [171]. Clonidine, an α_2 -adrenergic agonist more commonly used for its antihypertensive effects, is showing promise as an effective analgesic agent for abdominal surgery in people [31,160]. Used intrathecally, clonidine provides analgesia without motor blockade [107]. More drastic measures such as neurolytic celiac plexus blocks have been used as adjunctive analgesia for upper abdominal pain in people [174].

An opioid antagonist in development seems to be capable of preventing morphine-related transit time delays without altering the analgesic effects of morphine [92]. Alternatively, peripherally acting kappa agonists such as fedotozine, which prevent visceral pain, are enhanced in inflammatory conditions and may actually stimulate gastrointestinal motility [8,60]. Research in horses suggests that such drugs should be effective and may be associated with minimal locomotor stimulation and gastrointestinal changes [78,137]. Tramadol is a synthetic, centrally acting, weak opioid agonist (one tenth the potency of morphine) commonly used in Europe for postoperative pain in people because of its lack of respiratory depression, decreased sedative effects, negligible abuse potential, and variety of formulations (oral, rectal, and parenteral forms administered intravenously or intramuscularly). Comparative studies have found tramadol to be more effective than NSAIDs for the control of postoperative pain in people [89]. Oral tramadol was compared with oral morphine in human patients with pancreatitis, and both were found to offer adequate analgesia; however, tramadol caused less disturbance in gastrointestinal function and was the preferred analgesic of a greater number of subjects [173]. Tramadol has been shown to be effective in horses when administered epidurally [119]. The effect of oral or parenteral tramadol on the equine gastrointestinal tract remains to be studied, but the results in human studies make tramadol a feasible possibility for the management of gastrointestinal pain in horses.

In addition to being used in the form of transdermal patches, opioids may be administered rectally, vaginally, or sublingually, opening up potential avenues for chronic pain relief [122,132]. A multivesicular, liposome-based, sustained-release preparation of morphine administered epidurally to dogs also resulted in extended duration of analgesia without an increase in side effects [178].

Research on the receptors involved in pain sensation has led to the development of new drugs and new applications [60]. Cannabinoids are effective analgesics and anti-inflammatory agents in other species, and some are available orally. These drugs offer similar potency to morphine but with longer duration and less significant gastrointestinal side effects [29]. NSAIDs combined with a nitric oxide donor may provide immediate gastric protection through the vasodilatory effects of the nitric oxide [169]. DL-phenylalanine seems to potentiate the effects of opioids through upregulation of the endogenous analgesia system and may be useful in the management of chronic gastrointestinal pain (e.g., gastric ulcers) [141]. Serotonin antagonists and octreotide have proven useful for the treatment of visceral pain in people [60]. Drugs belonging to the methyl-imidazolyl N-acylhydrazone class and leukotriene D₄ receptor antagonists are being evaluated in animals for their nociceptive abilities [41,49].

Summary

Choice of an analgesic for gastrointestinal pain requires consideration of the cause of the pain, desired duration of pain relief, need for sedation, and potential side effects and toxicity, particularly in light of other drugs being used and effects on the gastrointestinal tract. It is imperative that close monitoring be continued to ensure that surgical lesions or worsening conditions are detected. Recent research in the field may lead to new drugs, drug combinations, and avenues of treatment that minimize the side effects of these drugs while maximizing their efficacy.

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