Treatment of Visceral Pain in Horses

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Visceral pain can be defined as pain originating in any internal organ and is often sub-divided to include the organs contained within each major body cavity, which are the thorax, abdomen, and pelvis (**Table 1**). Using this categorization, pain arising from the bladder would be a form of pelvic visceral pain. The term "colic" should be clearly defined because it is often misused. "Colic" is not a diagnosis; it is a clinical sign resulting from visceral pain within the abdomen. Mair and colleagues[1] state that there are approximately 100 conditions that result in abdominal pain in the horse, but the most common sources are the small and large intestine, hence the term "colic" most typically refers to gastrointestinal pain. Visceral pain may be acute, chronic, or recurrent in fashion, and some individuals may experience a combination of these manifestations. The cause of visceral pain may be organic (identifiable structural change in an organ) or dysfunctional (an abnormal change in organ function without identifiable pathologic changes).[2] Irritable bowel syndrome (IBS) in humans is an example of a dysfunctional disease that may affect up to 25% of the population[2]; whether similar syndromes exist in horses is less clear, but is considered plausible.[3,4] Ischemia, inflammation, muscle contraction (spasm) or distension may be the primary underlying cause of pain, and identifying which of these is responsible for the patient's discomfort is important for directing therapy. Considering the number of internal organs, it is not surprising that visceral pain is common in horses; however, it presents a challenge to the clinician because it can be difficult to make a definitive diagnosis. Ideally treatment is aimed at addressing the underlying pathology, but is often symp-tomatic with a primary focus on relieving pain; the latter is the focus of this article. Although treatment options for visceral pain have expanded in recent years, they remain suboptimal. In horses, the small and large intestines are the most prevalent

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Table 1 Origin and examples of visceral pain in the horse		
Origin	**Example: Acute**	**Example: Chronic**
Thorax • Lung • Pleura • Esophagus • Heart	• Pleuropneumonia • Choke • Trauma • Pericarditis	• Pleural abscessation • Neoplasia • Pericarditis
Abdomen • Stomach • Small intestine • Large intestine Cecum Large colon Small colon • Spleen • Liver • Pancreas • Kidneys • Ureters • Ovaries • Uterus	• Most causes of acute colic • Pancreatitis • Nephrolithiasis • Uterine artery hematoma, rupture • Metritis • Cholelithiasis • Uterine torsion	• Inflammatory bowel diseases • Enterolithiasis • Chronic diarrhea • Nephrolithiasis • Neoplasia • Cholelithiasis
Pelvis • Bladder • Testicles • Rectum • Anus • Vagina	• Cystitis • Urolithiasis • Testicular torsion • Rectal tear • Foaling trauma • Necrotic vaginitis	• Cystitis • Urolithiasis • Neoplasia

source of visceral pain, and this type of pain has received the most research and clinical attention. The pleura, kidneys, and stomach are, however, well recognized sources of pain and resultant suffering in equine patients. Horses of all ages, breeds, and sex may present with visceral pain, and examples are given in **Table 1**.

INCIDENCE AND IMPACT OF VISCERAL PAIN

Gastrointestinal and musculoskeletal diseases are two of the most clinically and economically important medical problems facing horses and their owners. In the National Animal Health Monitoring Systems (NAHMS) equine study conducted by the United States Department of Agriculture (USDA) in 2005, "colic" affected 2.4% of horses on a yearly basis (http://www.aphis.usda.gov/vs/ceah/ncahs/nahms/equine/equine98/economics.PDF). The economic impact of this was estimated to be $115 million per year in the equivalent study published in 1998 (http://www.aphis.usda.gov/vs/ceah/ncahs/nahms/equine/equine05/equine05reportpart1.pdf). These figures represent overall costs to the industry due to loss of use, hospitalization, veterinary care, and mortality.

VISCERAL PAIN ASSESSMENT

When assessing pain in animals and nonverbal human beings, one must remember that the assessment is always based on observations and interpretation of what is seen. Thus, when addressing an animal's status, one must be aware of inherent differences based on species, age, sex, genetics, environment, and source and duration of

the pain. Most published studies on visceral pain in horses, whether they are research or clinically based, are confined to abdominal causes and more specifically the intestinal tract.

Research Models

For research models of pain in animals, Gebhart and Ness[5] proposed the following necessary criteria: the subject must be conscious, the experimental stimulus mimics a natural stimulus, the stimulus is minimally invasive and ethically acceptable, the stimulus is controllable, reproducible, and quantifiable, and the responses are reliable and quantifiable. Most models of visceral pain in horses and other species involve acute distension of a portion of the gastrointestinal tract. Because many naturally occurring conditions causing abdominal visceral pain involve distension, such models have provided clinically meaningful information regarding analgesic medications for use in the horse. These models have involved cecal,[6,7] duodenal,[8–10] and colorectal[11,12] distension. The primary advantage of the cecal and duodenal distension models is that both the stimulus (distension) and associated behaviors (pawing, flank watching, and so forth) mimic the clinical syndrome of "colic." With colorectal distension, the associated response is not as clear and results may be more closely associated with the "urge to defecate" response in humans, and therefore not truly nociceptive in nature.[11] The major disadvantage of the cecal and duodenal models is the need for visceral cannulation, which is not necessary for colorectal distension; however, as is discussed later, the response to analgesic agents is not uniform throughout the intestinal tract.

Pain Assessment Tools

To claim that one has treated pain effectively implies that one can recognize it and measure or quantify it. Objective measures such as vital signs and plasma cortisol concentration circumvent the subjective nature of assessment; however, vital signs that might be predicted to be useful are affected not only by pain but a variety of other factors including hydration status, perfusion, sepsis and/or endotoxemia, fear, anxiety, and sedative or analgesic drugs. Pain-scoring tools must therefore be primarily based on behavioral indicators,[13] in combination with the judicious use of vital signs such as heart rate.[14]

To be useful, a pain-scoring system should meet the following criteria: it should include clearly defined assessment criteria, be suitable for all observers, be simple and quick to use, be sensitive, have identified strengths and weaknesses, and be validated. Possible deficiencies include bias and inter- and intraobserver variability. A lack of agreement between observers is one of the flaws of simple scoring systems such as the visual analog scale (VAS). When critically assessing scoring systems, the investigator should control for signalment (age, breed, sex), observer (veterinarian, student, owner/trainer), type and source of pain, and other effects (eg, food withdrawal and anesthesia). In a review of behavioral assessments of pain in equidae, Ashley and colleagues[13] point out that although some nonspecific "pain behaviors" are reported, specific behaviors can be identified and these differ depending on the cause of pain; for example, abdominal versus limb and hoof or dental pain. Vocalization (groaning), rolling, kicking at the abdomen, flank watching, and stretching are overt behaviors associated with abdominal pain[13]; however, other indicators can be easily overlooked. Pritchett and colleagues[14] recorded physiologic and behavioral variables in horses that underwent exploratory laparotomy for a variety of surgically correctable intestinal lesions, and compared these with control horses (no anesthesia, no surgery) and horses anesthetized for nonpainful procedures. Horses were videotaped and detailed

"time budgets" were calculated. Observers used a numerical rating scale (NRS) of behavior, which included head position, ear position, location in the stall, activity, lifting of the feet, and response to food. After surgery, horses spent significant periods of time doing nothing (resting) and had higher NRS scores compared with the other 2 groups, but displayed very few overt pain behaviors such as rolling, kicking, and pawing. In clinical practice these animals will often be overlooked and not given analgesics. Thus, this or similar scoring systems can be used to guide pain management in horses with abdominal pain, with the aim being to restore normal behaviors and activity levels (**Table 2**) and not simply to avoid overt pain behaviors.

TREATMENT OPTIONS
Approaches to Treatment of Visceral Pain

When identifiable, treatment is focused on correcting the underlying pathology; however, in many cases a definitive diagnosis may not be made or may take time to reach. It has been argued that pain management should be withheld until the cause of the pain has been identified because masking it will confound any ongoing diagnostic tests. However, this approach must be weighed against the dangers that painful horses pose to personnel working on them, the imposition of additional "procedural pain," for example, abdominocentesis and thoracocentesis, and, clearly, the welfare of the horse.

Table 2
Numerical rating scale for scoring abdominal pain in horses

Behavior Category	1	2	3	4
Overt pain behaviors[a,b]	None		Occasional	Continuous
Head position[b]	Above withers		At withers	Below withers
Ear position[b]	Forward, frequently moving		Slightly back, infrequent movement	
Location in stall[b]	At the exit, watching	In the center, watching exit	In the center, watching walls	At the middle or back, facing away from exit
Spontaneous locomotion[b]	Moving freely	Occasional steps		No movement
Response to door opening[c]	Moves toward door	Looks at door		No response
Response to approach[c]	Moves toward the person, with ears forward	Looks at person, with ears forward	Moves away from the person	Does not move, ears back
Foot lifting	Lifts feet easily if asked	Can lift feet if encouraged		Unwilling to lift feet
Response to offered food[c]	Reaches for food	Looks at food		No interest in food

[a] Overt pain behaviors include pawing, sweating, flank watching, flehmen, rolling, lying down and standing up repeatedly, groaning.
[b] Combine all these scores to obtain a posture score.
[c] Combine these scores to obtain a socialization score.
Data from Pritchett LC, Ulibarri C, Robertson MC, et al. Identification of potential physiologic and behavioral indicators of post-operative pain in horses after exploratory celiotomy for colic. Appl Anim Behav Sci 2003;80:31–43.

Pain itself can result in ileus, which has many negative consequences (reflux, fluid and electrolyte losses) and adds to the overall pain burden of the patient. In addition, it is now well understood that the longer pain goes untreated, the greater the risk of long-term sensitization and hyperalgesia that result from an unmitigated afferent barrage of noxious stimuli into the central nervous system.[15] Thus, pain control emerges as the single most important therapeutic factor when treating visceral pain in horses.

Surgery

Whereas many painful visceral conditions can be treated medically, conditions such as strangulating and nonstrangulating bowel obstructions and removal of renal, cystic, or ureteral calculi require surgical intervention, and pleuritis typically requires thoraco-centesis at a minimum, possibly with thoracoscopy or rib resection. If surgical therapy is not a practical or financial option for a given individual with such a condition, eutha-nasia may represent the most practical and humane method of analgesia. If surgical therapy is elected, analgesia is an important component of perioperative management.

SYSTEMIC PHARMACOLOGIC THERAPY

There are a limited number of analgesics available to treat severe pain in horses. At present, the most commonly used analgesic medications include the α_2-adrenergic agonists, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. Because many of these do not always produce the desired results or are associated with adverse effects, other more novel analgesic drugs are currently under investigation for use in the horse, and are also discussed here. In the horse, most available information pertaining to visceral pain is restricted to the gastrointestinal tract. However, the drugs discussed in this article are likely to have similar effects on visceral pain arising from other organs. The commonly used drugs and their suggested doses are outlined in **Table 3**.

α_2-Adrenergic Drugs

Major disadvantages of all the α_2-adrenergic agonists for prolonged analgesic therapy include the immediate and profound decrease in gastrointestinal motility that occurs after their administration and the relatively short duration of analgesia provided.[16–19] Fewer undesirable side effects are seen when butorphanol is administered as a constant rate infusion instead of boluses; whether this approach would be beneficial when using α_2-adrenergic drugs to treat horses with abdominal pain has not been thoroughly explored.

Specific α_2-adrenergic drugs

Xylazine Xylazine is very commonly used to provide sedation and analgesia for both diagnostic procedures and treatment of visceral pain in horses. Xylazine provides excellent visceral analgesia of short duration; up to 90 minutes in some models.[7,20,21] Adverse effects associated with its administration include the aforementioned nega-tive effects on motility combined with hypertension and bradycardia followed by hypo-tension.[17,22–24] Due to the relatively short duration of its effects, xylazine, either alone or in conjunction with butorphanol, is an excellent choice for sedation and analgesia during the initial evaluation of horses presenting for colic. Dosages from 150 to 250 mg for an average 450 to 550 kg adult horse typically facilitate passage of a nasogastric tube and rectal palpation.

Detomidine Detomidine is commonly used in horses to provide sedation for diag-nostic procedures and to alleviate abdominal pain.[25] Its use results in a characteristic

Table 3
Commonly used visceral analgesic medications

Class of Drug	Drug	Dosage (mg/kg)	Route	Dosing Interval (h)	Comments
NSAIDs	Flunixin	0.25–1.1	IV, PO	8–24	Avoid max. dose >2×/d
	Ketoprofen	2.2	IV	24	
	Phenylbutazone	2.2–4.4	IV, PO	12–24	Avoid extravascular injection
α_2-Agonists	Xylazine	0.2–1.1	IV, IM	prn	Sedation typically outlasts analgesia
	Detomidine	0.005–0.04	IV, IM	prn	Sedation typically outlasts analgesia
	Medetomidine	0.004–0.01	IV	prn	
Opioids	Butorphanol bolus	0.02–0.1	IV, IM	3–4	Can increase locomotion if used as sole agent in adults
	Butorphanol infusion	18 μg/kg bolus over 15 min then 13–23 μg/kg/h	IV	CRI	Typically not used longer than 12–24 h
	Morphine	0.12–0.66	IV		Combine with α_2-agonist
Other	Lidocaine (2%, 20 mg/mL)	1.3 mg/kg bolus over 10–15 min then 3 mg/kg/h (75 mL/h for 500 kg)	IV	CRI	Main adverse effects are neurologic and associated with rapid administration or accumulation
	N-Butylscopolammonium bromide	0.3 mg/kg	Slow IV	Once	Causes transient tachycardia
	Ketamine	0.4–1.2 mg/kg/h	IV	CRI	Hyperexcitability possible at higher dosages

Please note that these are suggested dosages and routes only. The dose, route, and frequency of administration should be considered individually for each case. Special consideration should be given to the current medical status, organ function, and concurrently administered medications.

Abbreviations: CRI, continuous rate infusion; IM, intramuscular; IV, intravenous; PO, by mouth; prn, "as needed."

dose-dependent head drop, ataxia, and decrease in heart rate, respiratory rate, and gastrointestinal motility.[26,27] In an experimental model of cecal distension, detomidine was effective in alleviating the associated pain.[28] In a duodenal distension model, a marked and immediate decrease in duodenal contractions occurred after 10 and 20 μg/kg (intravenously), but analgesia was both dose and location dependent; 10 μg/kg provided no visceral antinociception whereas 20 μg/kg provided 15 minutes of antinociception. The effects on colorectal distension were different, with 10 μg/kg and 20 μg/kg increasing colorectal distension threshold for 15 and 165 minutes, respectively.[16] Elfenbein and colleagues[16] measured the plasma concentration that correlated with visceral analgesia, which provides the pharmacokinetic data necessary to design infusion rates for future study. These investigators also demonstrated that the plasma concentration required for analgesia was in the order of 10 times that required for sedation, which emphasizes that sedation does not equal analgesia, especially with the α_2-agonists.

Medetomidine/dexmedetomidine Medetomidine and dexmedetomidine are not licensed for use in the horse and are considerably more expensive than xylazine, detomidine, and romifidine. Medetomidine infusions have been used successfully as part of a balanced anesthetic protocol.[29] Medetomidine combined with morphine (both given as infusions) provided suitable conditions for standing laparoscopy in horses[30] and is discussed later in the section Multimodal Approaches to Therapy. Commercially, medetomidine has now been replaced by dexmedetomidine, and to the authors' knowledge this drug has not been evaluated in horses for its visceral analgesic properties in a research or clinical setting.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs have well-documented visceral analgesic and anti-inflammatory properties, but adverse effects including gastric and colonic ulceration, impairment of jejuna, epithelial restitution following ischemic injury, and renal tubular necrosis are reported.[21,31–33] Despite this fact, flunixin meglumine remains likely the most important and commonly used medication available for the treatment of visceral pain in horses. As such, many horses with abdominal pain will recover completely with one administration of 1 mg/kg flunixin via the intravenous, intramuscular, or oral route. The positive and negative effects of this class of drugs are discussed in detail elsewhere in this issue and thus are not further discussed here.

Opioids

Opioids have not been widely used to treat clinical pain in horses in comparison with other species including humans. Reasons for this include the apparent narrow margin between analgesia and excitation or arousal, and difficulty in demonstrating a consistent and quantifiable analgesic action.[34] In pain-free horses, opioid administration has resulted in adverse effects, predominantly excitement, whereas clinical reports of opioid use in painful animals are more encouraging. Opioid receptor–binding studies demonstrate distinct differences in the distribution and density of opioid receptors within the central nervous system between horses and other species, but the clinical significance of these data is still unclear.[35,36]

Specific opioids
Butorphanol Butorphanol is a κ (OP2) agonist and competitive μ (OP3) antagonist, which is labeled for use in horses. When administered by bolus injection, butorphanol provides a moderate degree of somatic and a slightly greater degree of visceral analgesia in the horse; however, it also causes decreased gastrointestinal

motility.[17,21,37,38] Adverse effects such as ataxia, decreased defecation, and borborygmi after a single intravenous injection are less apparent when it is given as a continuous infusion.[39] No antinociceptive properties were measurable when an infusion was used in a research model of visceral distension.[10] The effect of butorphanol on gastrointestinal motility appears to vary with the segment of the gastrointestinal tract, dosage, and method of administration. Bolus administration of butorphanol did not significantly alter antroduodenal motility in one study[40] but resulted in delayed gastric emptying in another.[18] When administered as a constant rate infusion, butorphanol did not significantly alter duodenal motility.[10] In clinical patients undergoing exploratory laparotomy for colic, butorphanol infusion (13 μg/kg/h for 24 hours) did delay passage of feces following surgery. However, overall there were clear advantages to its use in this manner[39]: pain scores were significantly decreased in the immediate postoperative period; horses lost significantly less weight, had improved recovery characteristics, and on average were discharged 3 days earlier than control horses (flunixin meglumine only).[39] These benefits translated to an overall cost savings of approximately $1000.

Morphine The use of morphine in horses is controversial. When used at doses of 0.1 to 0.2 mg/kg intravenously or as an infusion (0.1 mg/kg/h) in horses undergoing surgery, no undesirable effects were reported and it significantly improved the quality of recovery, presumably because of its analgesic effects or perhaps its sedative effects in a clinical setting.[41–43] Morphine provided pain relief in a cecal distension model but inhibited colonic motility.[6] The role of systemically administered morphine for the alleviation of abdominal pain is currently unclear; as with the α_2-agonists, short-term use may be effective and beneficial, but long-term use (several days) may result in ileus. As with butorphanol, infusions may reduce the unwanted side effects, and deserve further study.

The biggest concerns regarding the use of morphine are its effects on gastrointestinal motility and therefore the potential increased risk of colic. A dose of 0.5 mg/kg intravenously every 12 hours for 6 days to normal horses resulted in decreased defecation frequency, fecal moisture content, and gastrointestinal sounds.[44] Those effects were mostly mitigated by the concurrent administration of N-methylnaltrexone, an opioid antagonist that does not cross the blood-brain barrier.[45]

In a study of 496 horses that underwent orthopedic surgery, 14 developed colic; the use of morphine was associated with a fourfold increased risk of colic compared with the use of no opioids or butorphanol.[46] In another study of 533 horses that underwent anesthesia but not surgery or nonabdominal surgery, 3.6% of horses developed colic within 7 days of anesthesia; significantly more horses were in the surgery group, but the use of morphine was not associated with an increased risk.[47]

Fentanyl In conscious research horses, fentanyl failed to produce significant visceral or somatic antinociception at serum concentrations above the nociceptive threshold in other species.[9] At high plasma concentrations (>5 ng/mL), some but not all horses became agitated. Also, very high (13.31 ng/mL) serum concentrations of fentanyl are necessary to achieve minimal (18%) isoflurane minimum alveolar concentration reduction in horses.[48] The use of transdermal fentanyl patches was initially met with enthusiasm, but uptake of fentanyl from a transdermal patch is highly variable in horses.[49,50] This information, combined with the disappointing results of intravenous infusions and cost, limit the utility of fentanyl for treatment of visceral pain in horses.

Tramadol Tramadol is an analogue of codeine and although not a controlled substance, some of its analgesic properties are related to its opioid properties.

Tramadol has a short half-life, low oral bioavailability (~3%), and the active metabolite M1 is a minor metabolite that may limit its usefulness in horses relative to other species.[51] No opioid-related excitement was reported but somatic analgesia could not be demonstrated with tramadol administration at doses ranging from 0.1 to 1.6 mg/kg intravenously.[52] Epidural administration of tramadol (1.0 mg/kg) resulted in significant antinociception at lumbar and thoracic dermatomes within 3 hours of administration, which lasted for 5 hours,[53] but it is currently unknown whether this would translate to visceral analgesia. Thus, the role of tramadol for the alleviation of pain in horses remains to be determined.

Sodium Channel Blockers

Lidocaine is an aminoamide local anesthetic that prevents propagation of action potentials by binding to voltage-gated sodium channels. Lidocaine, administered as an intravenous infusion, is commonly used in horses for its potential analgesic, prokinetic, and anti-inflammatory properties.[8,54–58] Variable doses of intravenous lidocaine are reported; loading doses vary from 1.3 to 5.0 mg/kg and infusion rates vary from 25 to 100 µg/kg/min. Clinical signs of toxicity in conscious horses include skeletal muscle tremors, altered visual function, anxiety, ataxia, collapse, and electrocardiographic changes, which can occur at serum concentrations between 1.65 and 4.53 µg/mL (mean 3.24 ± 0.74 [SD] µg/mL).[59] It is noteworthy that the neurologic manifestations of toxicosis may be masked by general anesthesia.

Using electroencephalographic changes as an objective measure of nociception in anesthetized ponies, intravenous lidocaine infusion (5 mg/kg loading dose, 100 µg/kg/min infusion) obtunded the response to castration, lending support to the role of lidocaine as a visceral analgesic.[60]

Lidocaine administration following exploratory laparotomy has been associated with reduced small intestinal size and peritoneal fluid accumulation,[57] and improved survival.[61] In one hospital setting, the intraoperative use of lidocaine was thought to reduce the incidence of postoperative ileus by approximately 50%[62] and in a multi-center study of horses with enteritis or postoperative ileus, lidocaine infusion decreased the volume and duration of reflux compared with saline-treated controls.[56] Following experimentally induced small intestinal ischemia, lidocaine improved mucosal healing by an unknown mechanism that may be related to the decreased production of inflammatory cytokines.[63]

Because treatment of horses with gastrointestinal disease may need to be prolonged, it is important to understand how the duration of infusion affects the disposition of lidocaine and also how the pharmacokinetics might be altered by disease or general anesthesia, so that appropriate changes in the infusion rate can be made to avoid toxicosis. The target steady-state concentration of lidocaine for the treatment of ileus is thought to be between 1.0 and 2.0 µg/mL (mean 0.98 µg/mL).[64] In healthy horses, steady-state serum concentrations slightly below this suggested that targets were reached 3 hours after starting a continuous rate infusion at 50 µg/kg/min (no bolus), and did not accumulate over a 96-hour study period.[65] However, in a clinical setting accumulation can be demonstrated.[66] Cetiofur sodium and flunixin meglumine decrease the protein binding of lidocaine, therefore lower infusion rates of lidocaine should be used in horses receiving highly protein bound drugs.[66] Plasma concentrations may also be affected by liver disease or by changes in liver blood flow that occur under general anesthesia. A bolus dose of 1.3 mg/kg followed by an infusion of 50 µg/kg/min results in higher serum concentrations in anesthetized as compared with awake horses,[67] and in the former these were within the range reported to be toxic in conscious horses.[59]

Lidocaine: other applications

Many horses that present with abdominal pain will undergo a rectal palpation. Intra-rectal lidocaine (15 mL, 2% solution) increases rectal wall compliance and facilitates rectal palpation, and likely decreases the risk of rectal tears.[11] The pain associated with other diagnostic procedures such as thoracocentesis and abdominocentesis can be decreased by local infiltration with lidocaine or another local anesthetic.

In mares undergoing laparoscopic ovariectomy, the addition of 10 mL of 2% lidocaine injected into the mesovarium to a protocol of intravenous xylazine and butor-phanol and epidural detomidine resulted in fewer pain responses compared with intra-ovarian injection of saline.[68]

N-*Methyl-D-Aspartate Antagonists*

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist commonly used for dissociative anesthesia, may have a very important role to play in the prevention of central hypersensitivity,[15] and has somatic antinociceptive properties when administered as a constant rate infusion at subanesthetic doses in both anesthetized and conscious horses.[69,70] Subanesthetic doses of ketamine decreased overall gastrointestinal transit time in comparison with saline control,[71] in contrast to studies in dogs.[72] The ability for ketamine to produce visceral analgesia in horses is currently unknown. Ketamine also has well-documented anti-inflammatory properties in several species; it reduced the production of tumor necrosis factor α, interleukin (IL)-6, and IL-8 in human blood and in dogs in response to endotoxin stimulation.[73,74]

Antispasmodic Medications

N-Butylscopolammonium bromide (NBB) has both anticholinergic and antispasmodic properties, and is labeled for the treatment of spasmodic colic. In an experimental model of cecal balloon distension, NBB had an analgesic effect in 6 of 8 ponies.[75] In another similar trial, NBB had a brief analgesic effect as well as a transient negative effect on cecal contractions.[76] In horses, administration of NBB produced visceral antinociception, as indicated by a significantly increased colorectal distension threshold and a small but nonsignificant increase in duodenal distension threshold.[10] The administration of NBB also decreases rectal tone for facilitation of a rectal examination.[77] In all reports the duration of effect is of short duration (15–20 minutes).

NONPHARMACOLOGIC THERAPY

Despite anecdotal reports in individual horses, the benefits of acupuncture for the relief of abdominal pain in horses have not been substantiated by large clinical trials or in a research model of duodenal distension.[78] This is clearly an area in need of further research.

MULTIMODAL APPROACH TO THERAPY

Severe pain may be refractory to single analgesic therapy and may require a multi-modal approach to pain management, employing drugs with different mechanisms of action. Despite the potential for improved analgesia, for example in a small clinical study of horses with pain that was refractory to NSAID therapy alone, the addition of the fentanyl transdermal therapeutic system appeared to be effective based on subjective evaluation.[79] However, others have warned that the use of such combinations may also increase the potential for adverse effects, especially alterations in gastrointestinal motility or behavior.[17]

As previously discussed, infusions of drugs often result in fewer adverse effects. An infusion of medetomidine (5 μg/kg/h) combined with morphine (30 μg/kg/h) provided

reliable sedation and stable cardiorespiratory function during standing laparoscopy surgery.[30] Only a few drug combinations and doses have been studied to date, but this concept should be further explored to find the most effective protocols to treat severe, especially chronic, visceral pain in horses.

FUTURE DIRECTIONS
New Approaches to Treatment

There is much work to be done to develop effective treatment protocols that do not have significant adverse effects for horses with visceral pain. The rigorous use of pain-scoring systems will produce more reliable information from clinical studies. The role of infusions and combinations of drugs looks promising. Because of the high prevalence of visceral pain in humans and the need for more effective treatments, this is an area of intense research. New targets include transient receptor channels, and purinergic and adenosine receptors,[80–82] which may also apply to horses.

SUMMARY

Overall, although much work has focused on the evaluation and treatment of visceral pain in horses, the basic tenets of treatment involve identification of the source and cause of pain and alleviation of that cause, if possible. Pharmacologic therapy typically involves unimodal therapy with an NSAID (phenylbutazone, firocoxib, or most commonly, flunixin meglumine) as a starting point for mild cases. For more severe or prolonged causes of pain, a combination of an α_2-adrenergic agonist (xylazine, detomidine) with an opioid (typically butorphanol) as single or repeated bolus injection allows for facilitation of diagnostic procedures or short-term (<24 hours) therapy. For protracted cases, constant rate infusion of lidocaine, with or without addition of butorphanol or ketamine, can provide visceral analgesia with the potential for a decreased incidence of adverse effects.

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