Pathology of the Small Intestine: Motility Dysfunction (Ileus) (16-Dec-2003)

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Introduction
Pathology of the small intestine includes topics such as response to obstruction, ischemia/reperfusion injury, adhesions, and motility disorders. Most of these topics, except motility disorders, have been covered in the Pathology of the Small and Large Intestine section. This lecture will consequently selectively cover motility dysfunction.

Definition and Incidence
Motility dysfunction is often termed ileus which is defined as the impairment of aboral transit of gastrointestinal (GI) contents. The term has been used in several different ways in the equine literature. It has sometimes been used very broadly and included both functional and mechanical obstructions whereas in other reports it’s use has been limited to functional impairment of GI transit. The author will restrict his use of the term to the more specific definition of the term, a functional obstruction (adynamic ileus) of aboral GI transit.

Ileus is one of the most commonly encountered complications of equine gastrointestinal surgery. In horses, postoperative ileus (POI) occurs predominantly after correction of lesions involving the small intestine. POI may also be seen after correction of ascending colon lesions, primarily large colon volvulus. Traumatic handling of the intestine, intestinal distention, resection and anastomosis, and intestinal ischemia may contribute to ileus in these cases. Other conditions that have been associated with ileus are anterior enteritis, peritonitis, electrolyte imbalances, endotoxemia, and anesthesia. In a recent report, POI developed in 21% of horses undergoing surgical treatment of colic, and 13% of these cases died [1]. Although our management of these cases has improved, postoperative ileus is still associated with 40% of all postoperative deaths in horses with colic [1].

Physiology of Normal Motility
Interstitial cells of Cajal (ICCs) are nonneural cells of mesenchymal origin. ICCs are responsible for generating electrical activity. ICCs demonstrate cyclic changes in membrane electrical potential which are called "slow waves" or "pacesetter potentials". The ICCs form networks located surrounding small intestinal circular muscle at both the longitudinal muscle (myenteric border) and the submucosal border. The ICCs and smooth muscle cells are connected to each other by gap junctions which enable the electrical activity of one cell to affect the activity of an adjacent cell (electrical coupling) through the movement of ions. Slow waves generated by th ICCs spread passively into both longitudinal and circular smooth muscle. Since the frequency of the membrane oscillations is highest in proximally located cells in the small intestine, these slow waves are initiated orally and propagated aborally. The depolarizations are subthreshold in that they do not depolarize the cell sufficiently to reach the threshold to generate an action potential. These subthreshold fluctuations are controlled primarily by intrinsic properties of the smooth muscle cells. Additional depolarizing (excitatory) input from the enteric (intrinsic) or autonomic (extrinsic) nervous system allows the membrane to reach the threshold potential necessary to generate an action potential. "Spike potentials" or spiking activity refer to membrane fluctuations which exceed the depolarization threshold for an action potential and so are associated with muscle contraction. Spiking potentials usually are superimposed on slow waves since at the peak of slow wave depolarization the cell is closest to it’s threshold for generating an action potential. This is why slow waves are also called pacesetter potentials.

The activity level of the intestine is not constant but goes through periods of quiescence alternating with periods spiking activity. The pattern of these different activity periods in the stomach and small intestine is called the migrating myoelectric complex (MMC) [2,3]. There are 4 phases of the MMC. Phase 1 describes a period in which there are no spike potentials and so no contractions occur. Phase 2 is a period of intermittent spike potentials. Phase 3 is associated with regular spiking...
activity. Phase 4 is associated with rapidly diminishing contractile activity. Each phase migrates down the stomach and small intestine. Phase 3 is generally associated with propulsion of ingesta. In the horse, phase 2 has also been associated with propagation of ingesta [4]. In the cecum and large intestine, slow waves and spiking activity also occur. However MMCs are not evident. Instead, short spike bursts (SSB) occur during mixing and long spike bursts (LSB) occur during propulsion of ingesta [2].

Pathophysiology and Therapeutic Modification

It should be evident from the above description of the physiology of normal motility that many different factors must be precisely coordinated in order to produce productive motility patterns. The intestine must contract in coordinated manner but the aboral section must simultaneously be inhibited and so relax if progressive transit is to occur. An imbalance in the factors controlling excitation and inhibition of gastrointestinal tract smooth muscle may predispose a horse to ileus. Consequently, an attempt has been made to identify prokinetic agents that potentially would restore the balance between excitatory and inhibitory control of contractility. Pharmacological modulation aimed at increasing excitatory activity has principally involved the administration of para-sympathomimetic agents which increase cholinergic transmission, such as bethanechol or neostigmine [4]. Similarly, cisapride works as an indirect parasympathomimetic by stimulating serotonin receptors and so enhancing acetylcholine release [5,6]. Attempts to block inhibitory components of contractility have focused on the sympathetic system. Sympathetic hyperactivity should respond to alpha-adrenergic blockers such as yohimbine and acepromazine, while administration of alpha-adrenergic drugs such as xylazine and detomidine should decrease motility [5]. Metaclopramide, which among other activities has antidopaminergic properties, and nonsteroidals have also been used to intervene in ileus cases [5].

Diagnosis

Disruption of propulsive motility results in the sequestration of fluid, gas, and ingesta in the segment of the GI tract which is dysfunctional and in the intestine proximal to the abnormal area. This distension occurs primarily in the stomach and small intestine, but can occur in the large intestine, especially with colitis, endotoxemia, or ischemia following an large colon volvulus. The first signs associated with ileus are depression and anorexia. As the intestine distends, the horse demonstrates increasing signs of abdominal distress, such as pawing, flank watching, lying down and rolling. Borborygmi is usually decreased or absent. The heart rate is elevated at first due to the pain associated with the distention. The mucous membranes become discolored and capillary refill time is prolonged. Hemoconcentration is reflected by increases in the packed cell volume and total protein. Decreases in plasma chloride and potassium are the most common electrolyte abnormalities seen, although sodium and chloride may also be low. As the severity of the intestinal distension increases, abdominal distension may become grossly visible. Rectal examination will aid in determining if the small or large intestine is involved. In foals, both abdominal radiography and ultrasonography can be quite helpful in assessing distension. Nasogastric decompression often retrieves from 3 to 10 liters of fluid. The response to nasogastric decompression provides an important clue that the problem is a functional problem. After decompression, the horse should show some improvement, such as decreased pain, and decreased heart rate. If no alleviation of signs are observed, careful thought should be given as to the likelihood that the problem may be a mechanical lesion and not a functional ileus.

Supportive Therapy

Although a variety of prokinetic agents have been administered to horses in an attempt to improve GI motility in ileus cases, the lack of consensus as to which one if any are effective attests to their therapeutic limitations. Consequently, the hallmark of treatment remains supportive therapy. Included in this supportive therapy are fluid, acid-base, and electrolyte therapy important in any horse with colic. Antibiotics are also indicated if there is compromise intestine or the possibility of bacterial contamination. Caution should be exercised when treating these horses with the common analgesics such as the alpha agonist xylazine and detomidine, and the narcotic agonist/antagonist butorphanol (Torbugesic) as these medications have the potential to depress GI motility with repeated use.

Nasogastric decompression -

Repeated attempts to relieve of gastric distention is imperative in treating a horse suspected of suffering from ileus. In certain cases reflux may not be obtained during the first attempt. In horses where nasogastric reflux is obtained, the tube can be left in place or removed and intermittently replaced to check for reflux. The frequency that attempts are made to decompress a horse with reflux is dependent both on the clinical signs and the amount of reflux retrieved at each session. An increasing heart rate is probably one of the most sensitive clinical indications to attempt to retrieve reflux. Signs of increasing abdominal pain is another indication. As the volume of reflux begins to decline and reaches less than 1 to 2 liters/hour, the interval between reflux attempts can be increased. It is not unusual to obtain a liter or more per hour of reflux from horses, especially those who have a nasogastric tube left in place. This should not be mistaken as a condition that necessarily requires continued
treatment. If there is any doubt, the tube should be withdrawn and the horse’s heart rate and level of pain monitored closely.

**Anti-inflammatory and "anti"-endotoxin drugs**

Intestinal distention, ischemia, and trauma occurring during decompression and/or resection and anastomosis all induce inflammation of the bowel wall with an increase in the production of inflammatory mediators such as prostaglandin I2 and E2 and tumor necrosis. Endotoxin can also stimulate production of these mediators. Each of these inflammatory mediators has been shown to depress motility when infused experimentally into horses [7]. Consequently nonsteroidal Anti-inflammatory drugs are recommended for horses with GI inflammation who have ileus or are at risk for developing ileus. The most commonly used SAID is flunixin meglumine (Banamine). It alleviates some of the systemic effects of endotoxin and also provides some analgesic relief. The recommended dose is 0.25 mg/kg TID, IV or 1.1 mg/kg BID, IV. The other commonly used SAID is phenylbutazone. Although this drug is not as potent as flunixin in blocking the cardiovascular effects of endotoxin, it does appear effective in reducing the motility disturbances associated with experimental endotoxin infusion [7]. The dose is 2 - 4.4 mg/kg BID, PO or IV. Ketoprofen (2.2 mg/kg BID, IV) has not been evaluated in ileus models, however due to it’s anti-prostaglandin and anti-leukotriene actions, may also be effective in promoting motility. In addition to blocking endotoxin effects, the analgesic properties of these drugs may attenuate potential inhibitory sympathetic reflexes.

Another drug that we use at our hospital to treat horses with ileus is polymyxin B, a cationic antibiotic that binds lipid A and neutralizes endotoxin. The recommended dose is 6000 IU/kg SID, IV. Dimethyl sulfoxide (DMSO) is a hydroxyl radical scavenger commonly used to treat endotoxemia and other inflammatory processes in horses. Although it has not been evaluated relative to promoting GI motility, it’s anti-inflammatory actions may be beneficial in preventing or decreasing the severity of ileus. The dose used varies from 0.5 mg/kg to 1.0 g/kg (10% solution in 5% dextrose). Commercially available hyperimmune serum contains anti-LPS antibodies to *Escherichia coli* (Polyimmune-J) or *Salmonella typhimurium* (Endoserum). These anti-LPS antibodies theoretically cross react with endotoxins from all gram negative bacteria. The evidence for their efficacy has not been very conclusive.

There has been some evidence in laboratory animals that blocking the influx of inflammatory cells with anti-adhesion antibodies blocks POI. Using selective COX-2 inhibitors has also been effective in blocking POI. This author has found that in an in vitro model, selective COX-2 inhibition does not improve smooth muscle contractile activity after small intestine distention. However, the non-selective COX inhibitor indomethacin was effective in blocking contractile inhibition. (Unpublished data). This would support the use of a nonselective COX inhibitor such as flunixin meglumine for the prevention and treatment of POI.

**Prokinetics**

**Bethanecol**

Bethanecol chloride (Urocholine) is a muscarinic cholinergic agonist which stimulates acetylcholine receptors on gastrointestinal smooth muscle, causing them to contract. Support for the use of bethanecol in the treatment of motility disorders in the horse is predicated on observations in normal horses that it increases the rate of gastric and cecal emptying as measured by radiolabeled isotopes and it induces premature MMC phase 3 like activity in the ileum [8]. Although it’s efficacy in the treatment experimentally induced motility dysfunction has been questioned in the horse [4] and other species [5], it’s prokinetic effects in normal horses and the clinical impression of it’s benefit in treating horses with ileus supports it’s use in the treatment of certain GI motility dysfunctions such as POI and cecal impacting. The recommended dose is 0.025 mg/kg IV or SO, q 4-6hrs. The most common side effect of the drug is salivation with abdominal cramping and diarrhea occurring less frequently.

**Neostigmine**

Neostigmine methylsulfate is a cholinesterase inhibitor which increases the level of acetylcholine at the synaptic junction. In studies on normal horses the effects of neostigmine (0.022 mg/kg IV) varied depending on the location of the gastrointestinal tract examined [8,9]. It was shown to delay gastric emptying and decrease propulsive motility in the jejunum but increase propulsive motility at the pelvic flexure [9]. In another study neostigmine increased the amplitude of rhythmic contractions in both resting and distended jejunum in anesthetized ponies [10]. More recently, neostigmine (0.025 mg/kg SO) was shown to induce premature phase 3 like activity in the ileum and increase the rate of cecal emptying. There has been no consensus as to the recommended use of this drug. It appears to be an effective drug for large colon motility problems, but these occur infrequently. Some evidence suggests it may also be useful for POI with small intestinal motility dysfunction. However, it’s use for impacting or in cases with excess GI distention has not been recommended due to the apparent force of drug induced
contractions [8]. The most common side effect is abdominal pain.

**Acepromazine and Yohimbine**
Both of these drugs are alpha-adrenergic antagonists. Elevated serum catecholamines have been associated with increased synthesis of norepinephrine in the bowel wall in humans after laparotomy. Norepinephrine is an inhibitory neurotransmitter released by postsynaptic sympathetic neurons at the enteric ganglia. It inhibits the release of the excitatory neurotransmitter acetylcholine by stimulating alpha-2 receptors located on cholinergic neurons. Acetylpromazine maleate (Acepromazine) facilitates small intestinal transit in normal ponies [11]. Based on clinical impression, acepromazine administered at 0.01 mg/kg IM q 4hrs is thought to reduce the severity of POI in horses with small intestinal lesions. Care should be taken to make sure the horse is well hydrated as the drug can produce hypotension. Yohimbine (Yobine) administered at 75 µg/kg was demonstrated to attenuate some of the negative effects endotoxin has on propulsive motility [12]. Since this drug is a selective α-2 antagonist, it does not produce the hypotensive response seen with acepromazine.

**Erythromycin**
Erythromycin is a macrolide antibiotic that enhances GI motility by acting on a motilin receptors on smooth muscle and acting on enteric neurons through motilin and/or 5-HT3 receptors to stimulate the release of acetylcholine. It is a commonly used drug to treat gastroparesis in humans. At 0.5 - 1.0 mg/kg in 1 liter of saline infused over 60 minutes QID, the drug induces small intestinal phase 3 like activity and increases the rate of gastric and cecal emptying in normal horses [13]. Side effects are infrequent but some clinicians have reported observing abdominal pain. More recently erythromycin has been associated with predisposing the horse to significant diarrhea.

**Metaclopramide**
Metaclopramide (Reglan) is thought to exert it’s prokinetic actions primarily though dopamine receptor antagonism [4,5]. It may also indirectly stimulate acetylcholine release and block adrenergic activity. In a POI model, metaclopramide was more effective in restoring gastrointestinal coordination, a measurement of motility strongly correlated to return of normal transit, than adrenergic antagonists or cholinergic agonists [4]. In horses the drug is commonly administered at a dosage of 0.25 mg/kg, diluted in 500 ml of saline, infused over 30 - 60 minutes. Some evidence suggests that a continuous infusion (0.04 mg/kg/h) may be more effective [14]. Metaclopramide (especially at the 0.25 mg/kg dose) may cause extrapyramidal side effects such as excitement, restlessness, and sweating. It may also produce abdominal cramping.

**Cisapride**
Cisapride (Propulsid) is probably the most commonly used prokinetic in human medicine [5]. It appears to function as an indirect cholinergic stimulant by selectively enhancing the release of acetylcholine from postganglionic neurons in the myenteric plexus. In numerous trials in other species cisparide appeared more effective than metaclopramide in stimulating progressive small and large intestinal motility in experimental ileus models. It has also been shown to be effective in preventing POI in horses [15]. Unfortunately, it is only available as an oral preparation which is unsuitable for horses with reflux. Recently it was found that the drug is not absorbed in a consistent manner rectally in horses and so this route of administration should not be relied on. Use of the oral preparation in horses with large colon motility dysfunction may be efficacious. The bioavailability of the oral praparation in the horse is not as good as in humans and so the recommended dose is 0.3 - 0.4 mg/kg.

**Lidocaine**
Lidocaine hydrochloride has four proposed mechanisms of action. It may 1) reduce the concentration of circulating catecholamines by suppressing the sympathoadrenal response; 2) suppress activity of the primary afferent neurons involved in reflex inhibition of gut motility; 3) stimulate smooth muscle directly; and 4) decrease the inflammatory response. The dose used to treat horses is an initial bolus of 1.3 mg/kg IV administered over 5 minutes followed by 0.05 mg/kg/min in saline over 24 hours [16]. Side effects include muscle fasiculations, trembling, and ataxia.

**Prognosis**
It is the author’s impression that the incidence of POI is decreasing. This may be due to more timely referrals and improved anesthetic, surgical, and medical management of the high risk cases. When ileus does occur, the horse is often treated with different prokinetics dependent on which clinician happens to take care of the horse. This author prefers to use lidocaine on cases with significant small intestinal inflammation as the first prokinetic. However, I have seen other clinicians use all of the above listed prokinetics. It is likely that each of them will promote motility to a limited extent in certain cases, but none of them will dramatically increase progressive motility in the horse with ileus. However, it is also the authors impression that
with appropriate supportive therapy the ileus most likely will be transitory and resolve in 2 to 6 days. In cases which don’t respond, a second laparotomy may be indicated.

References