Proceedings of the 11th Annual Resort Symposium of the American Association of Equine Practitioners (AAEP)

January 25 - 28, 2009 - Gold Coast, Australia

ACKNOWLEDGMENTS
Dr. Stephen M. Reed, Educational Programs Committee Chair
Carey M. Ross, Scientific Publications Coordinator

Published by the American Association of Equine Practitioners
www.aaep.org
Treatment of Ileus and SIRS in Horses with Colic

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CASE PRESENTATION: Broodmare with colic

Signalment: 12 year old, Thoroughbred mare.
History: Mare is 9 months pregnant, no previous health problems.
Colic History:
- Mare was normal the previous evening.
- Found with colic in the morning.
- 3 gallons of gastric reflux.

Examination:
- Condition: Normal
- Duration: 4-5 hours since mare found with colic.
- Pain: None at admission
- Signs:
  - Temp = 98.7°F; HR = 52 bpm; RR = 12 rpm.
  - MM color = red; MM refill = 4 sec.
  - Gastric reflux = 2 liters
  - Intestinal motility = no borborygmi
  - Rectal examination = Slightly distended small intestine; 2-4 loops.
  - Peritoneal fluid analysis: Color = orange; TP = 3.6 g/dl; WBC 25410/µl (99% pmn’s)
  - Ultrasound = slight distention of the small intestine.

Clinical laboratory evaluation:
- PCV = 55%; TP = 5.5 g/dl
- WBC = 7400/µl; neutrophils
- Na = 148 meq/l; K = 4.9 meq/l; Ca (total) = 7/9 mg/dl;
- Creatinine = 3.8 mg/dl; SDH = 91 IU/l; CK = 2530 UI/l

Questions:
1. Does the mare need surgery?
2. Is the mare in shock?
3. What is the best way to treat ileus?
4. What is the risk to the pregnancy?
5. What is the prognosis?
Intestinal motility is inherent in the intestinal muscle. The myocyte exhibits an innate rhythm with altered flux of the membrane potential known as slow waves. Depolarization of the cell membrane needs to reach the threshold potential to start contraction by allowing release of sufficient calcium to activate the contractile proteins in the muscle cell. The alteration in the myocyte membrane to allow the cyclic depolarization to reach the action potential threshold is altered by the myenteric nervous system or by mechanical or chemical events within the intestine. Because myocytes are connected at gap junctions which allow exchange of molecules, the electrical activity is passed from one cell to the next propagating a coordinated contraction which along the intestine.

Pacemaker activity is believed to originate in the interstitial cells of Cajal. Interposed between neurons and myocytes, these cells appear to stimulate slow wave production. Though slow waves by themselves do not induce contractions, they are essential for initiation of spiking activity which generate contractions during the phases of intestine activity. Phase-I is the resting phase or the phase with no spiking activity. Phase-II has intermittent spiking activity; slow waves do not always generate a contraction. Phase-III has regular spiking activity with nearly all slow waves. Cycling through the phases creates rhythmic contractions called “migrating myoelectrical complexes”. During phase-IV the action potentials cease returning the intestine to phase-I and the beginning of another cycle.

The cecum and large colon also have pacemakers at specific anatomical sites; cecal base and body and the pelvic flexure and right dorsal colon respectively. Activity is measured as short spiking bursts which create mixing activity or long spiking bursts that are associated with progressive motility. Motility can be directed orally or aborally from these pacemakers, which appear to coordinate both retention for digestion as well as transit aborally.

Reflex peristalsis can occur without any external neural control. Boluses of food, mucosal stretch and chemical interaction can created a reflex signal which relaxes the circular muscle aborally and constricts the muscle oral as the peristalsis moves aborally along the intestine. The primary neurotransmitters are acetylcholine, substance P, calcitonin gene-related peptide. Serotonin (5-hydroxytryptamine) can also activate serotonin type-4 receptors on the intrinsic afferent neurons. Vasoactive intestinal peptide, nitric oxide, somatostatin and serotonin are also released by interneurons to facilitate signal transmission. Other neurotransmitters from inhibitory neurons include neuropeptide Y, gamma aminobutyric acid, gastrin releasing peptide and pituitary cyclase activating peptide. Most of these neurotransmitters such as nitric oxide are non-adrenergic-noncholinergic, referred to as NANC neurotransmitters.

Extrinsic control of intestinal motility is through the autonomic nervous system. Efferent neurons are either sympathetic or parasympathetic. The sympathetic system works via postganglionic neurons which release norepinephrine which acts on alpha2 adrenoreceptors to inhibit the release of acetylcholine, thus decreasing motility. Parasympathetic stimulations come via preganglionic fibers to the intestinal ganglia where postganglionic fibers are stimulated and cause cholinergic stimulation or release of NANC neurotransmitters (Fig. 1). Extrinsic afferent fibers in the intestine also help control motility. By sensing tension, nutrients, osmolarity, pH, temperature, pain, prostaglandins and chemokines afferents created reflexes excite or inhibit intestine through out the GI tract.
Figure 1: The sympathetic and parasympathetic neurons affect motility via post ganglionic neurons. Norepinephrine and acetylcholine are the primary neurotransmitters which subsequently stimulate inhibitory receptors or other neuropeptides which inhibit or excite smooth muscle.

Other endogenous mediators such as prostaglandins and opioids can also affect motility. The type of prostaglandin determines the response. PGE₂ increases longitudinal muscle contractions but inhibits circular muscle contractions. Prostacyclin inhibits circular muscle contraction but is variable in longitudinal muscle, whereas PGF₂ increases contractions in both layers. It appears the predominate effect of prostaglandins is to inhibit motility as demonstrated by the increase in intestinal activity when cyclooxygenase is blocked with non-steroidal anti-inflammatory drugs.

Endogenous or exogenous opioids also decrease intestinal motility. This is most evident in humans were treatment with an opioid antagonist for constipation due to narcotic administration for pain.

Causes of Ileus

Ileus is usually caused by nervous stimulation through the sympathetic nervous system or due to inflammation, which can affect the intrinsic or extrinsic system of motility control. Pain or mechanical irritation stimulates afferent neurons, which either by reflex or by central inhibition create ileus. Calcitonin gene related peptide can mediate this response. Though this response can be centrally mediated due to environmental stimulation, the most likely cause is from the gut itself. Nonadrenergic noncholinergic neurotransmitters are also likely associated with ileus and specifically postoperative ileus. Nitric oxide and vasoactive intestinal peptide have both been implicated in creating ileus. This is true after surgical manipulation where blocking these neurotransmitters decreases ileus.
Intestinal inflammation can cause ileus. This seems contradictory as horses with colitis appear to have decreased transit time. When the mucosa is inflamed and secretion is increased, the bowel response to the increased volume and increases motility albeit abnormally. Alternatively bowel distention, endotoxemia, and bowel wall inflammation due to ischemia inhibit intestinal motility. Damage to ganglia, muscle, serosa and mucosa can create change in the intrinsic regulation of motility. Reflexes can either stimulate inhibitory receptors or with severe damage all reflexes may be impaired. The nerves and ganglia can also be responsible for activating inflammation or enhancing it via neuropeptides, which act on receptors to stimulate release of proinflammatory mediators and stimulate the vasculature and subsequent neutrophil infiltration. Production of excess prostaglandins during an inflammatory insult can contribute to altered motility. These effects have not been studied in the horse, but the effect of nonsteroidal anti-inflammatory drugs and compounds which decrease reperfusion injury suggest that these mechanisms are important in creating ileus and specifically postoperative ileus.

**Treating Ileus**

Approximately 20% of horses undergoing colic surgery develop ileus. This is almost always related to small intestine disease. Treatment is aimed at decreasing intestinal inflammation, providing analgesia and stimulating progressive contractions with prokinetics.

Numerous drugs affecting motility have been evaluated in normal horses. Though not considered prokinetics, flunixin meglumine and phenylbutazone decrease intestinal inflammation and the systemic response to endotoxin by decreasing prostaglandin production. In addition to this direct anti-inflammatory effect, which fosters normal motility these compounds, decrease pain may help decrease a sympathetic response.

Alpha<sub>2</sub> agonists, which can decrease pain, also have a direct inhibitory effect on motility. Though both xylazine and detomidine are commonly used for colic they do not appear to have a detrimental effect on motility after the initial effect wears off. Butorphanol also inhibits myoelectric activity in the equine jejunum but does not appear to cause ileus once its analgesic effects have worn off.

Some prokinetic drugs have been used clinically for more than half a century (Table 1). Most prokinetic drugs have been tested in normal horses rather than in experimental or clinical case of ileus. Classic pharmacologic descriptions of cholinergic activity of neostigmine and bethanechol and have not been supported by clinical efficacy. Similarly alpha-adrenergic blockers have had limited success in stimulating normal motility in horses with post operative ileus though yohimbine decreased the severity of experimentally induced ileus. Ileus created experimentally responded to cisapride, which increases acetylcholine release.

Few clinical trials have examined the efficacy of prokinetic drugs for treatment of equine postoperative ileus and those reporting success are limited to cisapride, metoclopramide, erythromycin, and lidocaine. Recent research has questioned usefulness of these compounds in horses with injured or inflamed intestine. A model utilizing an in vitro intestinal distention decreased the contractile response to cisapride, erythromycin, and metoclopramide. In a recent studies in normal horses after anesthesia lidocaine did not increase motility in the small intestine.
but did decrease transit time. It is possible that lidocaine’s main mechanism of action is analgesia or decreasing inflammation.

New compounds that have yet to have reported use in clinical cases include tegaserod a selective serotonin subtype 4 receptor agonists and methylnaltrexone an opioid antagonist. Both stimulate pelvic flexure and jejunal motility in vitro. Mosapride which is also a serotonin subtype 4 receptor agonist has not been tested clinically. Though the use of prokinetics is logical to help stimulate motility as soon as possible, use of anti-inflammatory agents is just as important to help reduce the inflammatory response known to occur in previously distended or ischemic intestine.

Because inflammation from intestinal distention or ischemia can cause inflammation of the enteric nervous system and muscle, it is logical that prokinetics will not be able to simulate motility via the nervous system or direct action on myocytes. The lack of response to prokinetic drugs in horses suffering from moderate to severe intestinal injury and the lack of need for prokinetic administration with minimal intestinal injury suggests that prokinetic drug effectiveness is limited in horses with injured intestine. Only lidocaine appears to be of some value for treatment of postoperative ileus in horses with injured intestine, possibly due to its anti-inflammatory or analgesic effects rather than from direct stimulation of intestinal motility.

Table 1: Prokinetic drugs listed with mechanism of action, dosage and potential effectiveness.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neostigmine</td>
<td>Inhibits cholinesterase</td>
<td>0.022 mg/kg IV or 0.044 mg/kg SQ or IM</td>
<td>No value for small intestine</td>
</tr>
<tr>
<td>Bethanecol</td>
<td>Stimulates acetylcholine receptors</td>
<td>0.025 mg/kg SQ</td>
<td>Improves gastric emptying</td>
</tr>
<tr>
<td>Metaclopramide</td>
<td>Dopamine antagonism and stimulates 5-HT receptors</td>
<td>0.01-0.05 mg/kg</td>
<td>Improves motility but can cause excitement and restlessness</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Enhances the release of acetylcholine mediated through 5-HT₄ receptors</td>
<td></td>
<td>Not longer available</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Stimulates motilin release.</td>
<td>0.5-1.0 mg/kg IV over 60 minutes</td>
<td>Effective for cecal impaction but can cause enteritis.</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Decreases catecholamines; decreases afferent neuron activity; direct smooth muscle stimulation; decrease intestinal inflammation.</td>
<td>1.3 mg/kg bolus over 5 minutes followed by 0.05 mg/kg/mg continuous rate infusion.</td>
<td>No apparent direct stimulation of motility after anesthesia.</td>
</tr>
<tr>
<td>Mosapride</td>
<td>5-HT₄ receptor agonist</td>
<td>0.5-2.0 mg/kg IV</td>
<td>Increased small intestine and cecal motility. Not tested in clinical cases</td>
</tr>
<tr>
<td>Methylnaltrexone</td>
<td>Opioid receptor antagonist</td>
<td>1.0 mg/kg IV</td>
<td>Decreased effects of morphine on motility.</td>
</tr>
<tr>
<td>Tegaserod</td>
<td>5-HT₄ receptor agonist</td>
<td>0.27 mg/kg orally</td>
<td>Accelerated transit. Not tested in clinical cases</td>
</tr>
</tbody>
</table>
Systemic Inflammatory Response Syndrome

The horse with compromised intestine is at risk for absorbing endotoxin into the blood stream. Experimental endotoxemia from .001 to .01 µg/kg causes colic, diarrhea, poor peripheral perfusion, lactic acidosis, leucopenia, and venous pooling. Higher doses cause death as a result of circulatory shock. Recently the response to endotoxemia has been recognized as a systemic response to overwhelming production of proinflammatory mediators, which create a systemic inflammatory response syndrome (SIRS) and shock.

Pathogenesis

Endotoxin, a lipopolysaccharide, is a toxin, which must interact with the immune system to cause shock. Key to endotoxin activity is the macrophage. Both fixed and circulating macrophages have receptors which respond to endotoxin and bacterial proteins by producing numerous cytokines (tumor necrosis factor, platelet activating factor, and interleukins) in response to endotoxin. The cytokines in turn cause other cells to release mediators including prostacyclin, thromboxane, reactive oxygen species, proteases, histamine serotonin, and leukotrienes. Receptors also exist for gram-positive bacteria and their proteins.

Clinical Signs

Signs of endotoxemia or SIRS include depression, colic, initial periods of loose stool, cyanosis, increased heart and respiratory rates, and fever. As shock progresses and hypotension is evident by the poor pulse quality, cyanosis (with cyanotic line around the gingiva), sweating, and cold extremities. Intestinal borborygmi cease during endotoxemia. Laboratory values which help identify shock and specifically endotoxic shock include increase in PCV, neutropenia in the first 3-4 hours followed by a toxic left shift, lactic acidosis, and reduced platelet numbers, and prolongation of prothrombin or activated partial thromboplastin times.

Treatment

The basis of treating endotoxic shock is restoration of circulatory volume. Normally rapid infusion of a balance electrolyte solution such as lactated Ringer's or acetated Ringer's will improve perfusion. In cases where perfusion is so poor that normal solutions may take too long to provide adequate perfusion, use of hypertonic saline solution may help in immediate resuscitation. When 7 or 8% saline solutions (1-3 liters) are rapidly infused, water drawn into the circulation increases blood pressure and cardiac output helping to sustain the animal until adequate balanced electrolyte solutions can be administered.

Anti-endotoxin antiserum has recently been advocated as a therapy for endotoxemia. However, there are still mixed reports about the success of antiserum or endotoxin vaccine in protecting against endotoxemia. Horses vaccinated with an antigen from the core portion of the lipopolysaccharide of the J-5 mutant E coli were not protected against sublethal endotoxemia in one study, but clinical reports indicate some benefit. The use of a methylated Salmonella endotoxin with adjuvant has been found to be valuable when used as a vaccine. The hyperimmune serum from horses vaccinated with this salmonella endotoxin horses has also been
shown to prevent the development of laminitis after experimental carbohydrate overload and protect against a sublethal intravenous endotoxin challenge. This therapy has also been tested in horses with colic and suspected endotoxemia, and though hyperimmune serum appears to be beneficial, the clear proof of efficacy is not available.

In clinical cases the anti-serum produced from horses vaccinated with the J-5 E. coli or methylated salmonella may be helpful in preventing the ongoing effects of endotoxemia which occur from continued bowel injury. Horses having endotoxic reactions with cyanotic mucous membranes, dehydration, increased heart rates and ileus will often respond rapidly after anti-serum administration. Horses have occasionally had physical reactions to rapid administration of the methylated salmonella antiserum or plasma. These problems may be avoided by either reducing the administration rate, diluting the antiserum or by heating the antiserum to at least room temperature prior to administration. Administration of antiserum is recommended in any horse where damaged intestine could produce endotoxemia. The earlier treatment is started the better chance of reducing the effects of endotoxin.

Plasma without antibodies to endotoxin is useful in several medical colic diseases including enteritis and peritonitis or in any disease where loss of protein can be massive. Fresh plasma can also provide coagulation factors, fibronectin and immunoglobulins felt to be important in the defense against endotoxemia or septicemia. Plasma administration is indicated when the total plasma protein is below 4.0 g/dl. Ten liters is usually required to elevate the plasma protein level adequately in the adult horse, particularly when protein loss may be continuing.

Non-steroidal anti-inflammatory drugs inhibit cyclo-oxygenase activity and thereby help reduce the production of prostaglandins during endotoxemia. The use of flunixin meglumine helps to reduce the horse’s response to endotoxin by completely blocking the production of thromboxane and prostacyclin. Colic, diarrhea, fever and pulmonary hypertension are all prevented when flunixin was administered during a sublethal challenge of endotoxin. Unfortunately, flunixin can mask the signs of impending shock, without preventing fatal irreversible shock. Combined with fluid therapy the use of flunixin is one of the most helpful treatments available for endotoxemia, and its use is associated with an increased survival rate. Alternative NSAIDs ketoprofen (0.5 mg/kg IV) and eltenac (0.5 mg/kg IV) have also been shown to block prostaglandin production and clinical signs of endotoxemia. Ketoprofen has also been shown to block the leukotriene production though its effectiveness in clinical cases has not been reported.

Before information about the equine systemic response to endotoxemia became available, corticosteroids were considered to be the treatment of choice for shock associated with colic. Even though the inhibitory effect of corticosteroids on phospholipase activity and tumor necrosis factor should prevent the initiation of the arachidonic acid transformation to prostaglandins, the protective effects in the horse with endotoxemia are not as pronounced as with NSAID’s. To have a beneficial effect corticosteroids must be given prior to endotoxin entering the system making it almost impossible to use in a clinical situation. The possible potentiation of laminitis or a detrimental effect on healing after surgery is also a concern. Therefore, corticosteroids are not advocated in the treatment of endotoxemia.
Treatment of endotoxemia with heparin is controversial. It is useful in preventing microthrombi and promoting anticoagulant activity of antithrombin III. Low dose heparin (40 units/kg subcutaneously TID) has been used to help prevent signs of endotoxemia and as a preventative for laminitis. RBC aggregates have been found during treatment with heparin increasing concern about plugging of capillaries. Use of low molecular weight heparin (molecular weight 4000-5000) at 150 units/kg SQ followed 12 hours later by 125 units/KG SQ is currently recommended as it does not cause RBC agglutination. In cases of impending DIC 100 units/kg, TID, IV are needed to provide anticoagulation.

Polymixin B (6000 units per Kg every 8-12 hours) lessens clinical signs of experimental endotoxemia. This is attributed to its ability to decrease tumor necrosis factor in experimental endotoxemia. Like most treatments the optimal affect with Polymixin B will be when it is administered at or just prior to endotoxin release. Pentoxyfylline has also been shown to decrease cytokine production during endotoxemia. Treatments of 8 mg/kg two to three times daily have decreased the effects of experimental endotoxemia. Its use clinically for endotoxemia is similar to other treatments; it effect is optimal when administered at the time of endotoxin release.

One of the complicating factors associated with bowel ischemia is the "reperfusion injury". This phenomenon can cause damage to the intestinal mucosa and serosa once reperfusion of an affected segment has occurred or as the result of increased perfusion of organs after low flow or poor perfusion during shock. Reperfusion injury is caused by the release of toxic oxygen and hydroxyl radicals in the tissue and by white blood cells, which have been attracted to injured tissue. The damage induced by these substances can cause continued endotoxin absorption due to the damaged intestinal mucosal barrier. Dimethyl sulfoxide (DMSO), a hydroxyl radical scavenger, has been used to reduce the injury normally observed during reperfusion. There are still questions about how effective DMSO is in sparing the mucosa from reperfusion injury in the horse, and there is no proof that this is clinically beneficial to the horse during endotoxemia. Recently intestinal permeability increases due to reperfusion were partially controlled with DMSO administration at a dose of 20 mg/kg. There have not been any apparent detrimental effects associated with its use clinically. DMSO also should be given as early as possible when shock is anticipated or as soon as it is detected and the possibility for reperfusion exists. Clinical use is directed at preventing continuing intestinal injury, intestinal adhesions or laminar injury in the foot.

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