

GASTROINTESTINAL PHARMACOLOGY



BASICS

OVERVIEW

- Gastrointestinal (GI) motility modifiers in ruminants can be used to treat a variety of GI dysmotility disorders, malfunction of the esophageal groove reflex or to aid placement of reticulum magnets.
- GI disorders of ruminants that could potentially benefit from motility modification include paralytic ileus, cecal dilatation and abomasal displacements.
- Data regarding GI motility modifiers in ruminants are sparse due to the complex nature of the control systems responsible for GI motility in the bovine.

SYSTEMS AFFECTED

- Digestive

PATHOPHYSIOLOGY

- GI motility is regulated by myogenic, neural and chemical systems, with a fourth regulatory system involving the interstitial cells of Cajal, believed to have a function in establishing the pacemaker activity of the GI cells.
- It is important to recognize that the neural control of GI motility refers to the extrinsic system that includes the vagus nerve and the sympathetic pelvic, lumbar colonic and hypogastric nerves, and the intrinsic system. This system consists of ganglia with efferent axons to the smooth muscle cells, afferent sensory axons, and the interconnective nerve strands located in the myenteric and submucosal plexuses.
- Chemical control of GI motility is performed by various hormones and neurotransmitters. These compounds are released from nerve endings of both the extrinsic and intrinsic nervous systems that supply the GI tract.

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- Pharmacologic compounds capable of influencing GI motility either imitate or antagonize the effects of endogenous transmitters.
- Motility modifiers are categorized as cholinergics, adrenergics, anti-dopaminergics, serotonergics, motilin agonists, opioid receptor-blockers or lidocaine based upon their mechanism of action and their main target receptor. A key factor in the cascade of smooth muscle contractions is the serum calcium concentration of the affected animal.
- Correction of pre-existing hypocalcemia and other electrolyte imbalances and rehydration are crucial to every protocol dealing with the treatment of GI motility disorders. Most of these disorders are multifactorial, therefore treatment protocols should not be restricted to the administration of motility modifiers and should always include treatment of concurrent metabolic disorders, infectious diseases and evaluation of management practices.
- Many of the compounds described in this chapter do not have approved versions available for use in cattle in the USA
- Appropriate milk and meat withdrawal times must be followed for all compounds administered to food producing animals.

CHOLINERGIC AGENTS

- Acetylcholine (ACh) is the natural cholinergic neurotransmitter released from cholinergic axonic terminals.
- In the GI tract, ACh released from nerve terminals binds to muscarinic receptors in the intrinsic nervous system of the gut. Cholinergic compounds have an effect on either the release or breakdown of ACh and have some ability to affect GI motility.

Bethanechol

- Bethanechol mimics the effect of ACh and is classified as a directly acting parasympathetic agonist. This compound has high affinity for muscarinic receptors of the GI tract with a much lower affinity for smooth muscle cells of the vascular system.
- When dosed at 0.07 mg/kg subcutaneously (SC), this compound was found to increase overall myoelectric spiking activity in cows.

Neostigmine

- Neostigmine is classified as an indirectly acting parasympathetic agonist due to its ability to inhibit acetylcholinesterase, which hydrolyzes ACh. The effect of neostigmine is less restricted to the GI tract than that of bethanechol.
- This compound dosed at 0.02 mg/kg SC increased myoelectric activity but the effect was most pronounced upon uncoordinated spikes.

Metoclopramide

- Metoclopramide represents a first generation prokinetic compound. Prokinetics have the ability to stimulate, coordinate and restore gastric, pyloric and small intestinal motility. Metoclopramide works by enhancing the release of ACh from postganglionic cholinergic nerve terminals, sensitizing muscarinic receptors and reducing hydrolysis of ACh by inhibiting acetylcholinesterase.
- Numerous studies at varied dosages have discovered that this compound alone does not affect GI motility and that it can cross the blood brain barrier causing restlessness and excitement. However, when metoclopramide (0.1 mg/kg SC) was used in combination with bethanechol (0.07 mg/kg SC) increased spike rates were reported.

Atropine and scopolamine

- Atropine and scopolamine are naturally occurring alkaloids. They bind competitively to muscarinic receptors and are classified as parasympathetic antagonists.
- Atropine (0.04 mg/kg IV) completely eradicates abomasal myoelectric activity for up to three hours. Adverse effects are ruminal bloat and tachycardia.

ADRENERGIC AGENTS

- Norepinephrine is the naturally occurring neurotransmitter of most sympathetic postganglionic nerve terminals, binding to both alpha and beta adrenergic receptors. These terminals are located postsynaptically on intestinal smooth muscle cells.
- Presynaptic stimulation by inhibition of ACh release is more important than postsynaptic stimulation because smooth muscle cells receive little postganglionic sympathetic innervation.

Xylazine and detomidine

- Xylazine and detomidine have potent alpha-2 agonistic properties; yohimbine is an alpha-2 receptor blocker; tolazoline is an alpha-1 & 2 receptor blocker and D1-propanolol is a beta-receptor blocker. Stimulation of adrenergic receptors results in inhibition of GI motility.

- The stimulating effect of adrenoceptor blockers is restricted to disease processes accompanied by a hyperactive state of the sympathetic nervous system.
- D1-propranolol has been shown to have no significant effect on contractility in vitro on bovine colonic tissue or in vivo on the ileoceccocolic area of healthy cows when dosed at 0.2 mg/kg IM.
- Xylazine induces widespread reduction in GI motility when dosed at 0.2 mg/kg IM, and adverse effects have included salivation, ruminal bloat, hypothermia and bradycardia.
- Yohimbine (0.125 mg/kg IV) or tolazoline (0.25-0.5 mg/kg IV) may be used for xylazine reversal. Tolazoline should not be used in camelids due to the potential for severe adverse reactions.

ANTIDOPAMINERGIC AGENTS

- Dopamine is the precursor of norepinephrine and epinephrine. Dopaminergic receptors have been demonstrated in the GI tract of laboratory animals and sheep but not cattle.

Domperidone

- Domperidone is a potent and specific dopamine-receptor antagonist that binds to dopaminergic receptors and does not cross the blood-brain barrier. This compound can block the stimulatory effects of dopamine on the rumen and forestomachs of goats.

SEROTONINERGIC AGENTS

- Serotonin is stored in the GI tract mainly in the enterochromaffin cells and is involved in regulation of GI motility by either enhancing or inhibiting it by binding to the receptors.

Cisapride

- Cisapride represents a prokinetic drug that has been studied as a potential excitatory agent that would exert its effects by increasing the release of Ach at postganglionic nerve terminals. However, cisapride did not affect myoelectric activity at the ileoceccocolic area of healthy cows in vivo or increase contractility of smooth muscle preparations in vitro at a dose of 0.08 mg/kg IV.

OTHER COMPOUNDS

Motilin

- Motilin is a hormone that initiates contractile activity by binding to specific receptors situated on smooth muscle cells.

Erythromycin lactobionate

- Erythromycin lactobionate has been demonstrated to bind to motilin receptors situated on smooth muscle cells. This compound increases myoelectric activity in the abomasum and duodenum for up to eight hours following either IV or IM injection in healthy cattle.

- Opioid peptides in the gut are represented by met-enkephalin and leu-enkephalin. Receptors for these peptides are present in the myenteric plexus and activation causes inhibitory effects by hyperpolarization of neurons, preventing neuronal excitation.

- **Naloxone** did not affect myoelectric activity of the ileoceccocolic area of experimental cows when administered at 0.05 mg/kg IV.

- **Lidocaine** blocks voltage-gated channels and this blockade is thought to contribute to a motility promoting effect in postoperative ileus in other species. However, lidocaine does not have significant effects on in-vitro abomasal or duodenal tissues of healthy cows.



MISCELLANEOUS

SEE ALSO

- Camelid: Gastrointestinal Disease
- Fluid Therapy: Oral
- Food Animal Residue Avoidance Databank (FARAD) (www.fiveminutevet.com/ruminant)

ABBREVIATIONS

- Ach= acetylcholine
- FARAD= Food Animal Residue Avoidance Databank
- GI= gastrointestinal

Suggested Reading

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