GASTRO-INTESTINAL MOTILITY IN HORSES: A PRACTICAL OVERVIEW OF THE THERAPEUTIC USE OF PROKINETIC AGENTS

Gastro-intestinale motiliteit bij het paard:
een praktisch overzicht van het therapeutisch gebruik van prokinetica

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ABSTRACT

Equine practitioners often need to address problems associated with decreased gastro-intestinal motility in colic horses. Likewise, ileus is a notorious complication in horses that is predominantly seen after surgical intervention for small intestinal colic. Understanding the physiological mechanisms that are responsible for normal GI motility in horses and knowing which factors predispose horses to ileus, will help clinicians to better understand the clinical picture of a colic horse and to determine when and which prokinetic treatment should be chosen in any specific case.

However, due to the lack of fundamental research, the knowledge of pharmacological activity pathways and therapeutic efficacy of prokinetic medication in colic horses is very fragmented. Often research results in other species are extrapolated to the horse, without any pharmacological evidence that enteral receptor populations that serve as pharmacological target to induce intestinal propulsion in these species are equally important in horses. A possible discrepancy in these receptor populations between humans and horses could partially explain the inconsistent clinical efficacy of human prokinetic agents such as cisapride, metoclopramide and domperidone in equine colic cases. Furthermore, due to the lack of large, double-blind multi-center clinical studies, the evaluation of the therapeutic efficacy of many prokinetic agents that are used in colic horses is very subjective. The lack of non-invasive techniques to evaluate gastro-intestinal motility in healthy and colic horses contributes to this subjectivity.

As rule of thumb, it can be stated that for the treatment of stasis of the cranial part of the GI tract of horses, mainly lidocaine, metoclopramide and erythromycin should be used. In cases of colonic hypomotility, naloxone, neostigmine, erythromycin and lidocaine are the drugs of choice. With regard to sedation of colic patients, it should be mentioned that acepromazine and xylazine both will negatively influence GI motility to a lesser extent than the alpha 2 agonists detomidine and romifidine. However, in colic cases expressing shock and endotoxemia, the use of acepromazine is hampered by its pronounced hypotensive effects.

SAMENVATTING

Koliek is bij het paard vaak geassocieerd met een afgenomen gastro-intestinale motiliteit. Ook de post-operatieve motiliteitsproblemen na abdominale koliekchirurgie zijn alom bekend.

Voor de clinicus is het belangrijk een duidelijk inzicht te hebben in de processen die een rol spelen in de normale gastro-intestinale motiliteit bij het paard. Weten welke factoren het ontstaan van ileus bij het paard in de hand werken kan een grote hulp zijn bij het klinisch inschatten van de koliekpatiënt en kan helpen bij de beslissing wanneer en welke prokinetische therapie er het best wordt opgestart.

Omwille van een totaal gebrek aan fundamenteel koliekonderzoek is de kennis van de farmacologische werking van motiliteitsstimulerende middelen bij het paard erg gefragmenteerd en soms zelfs totaal afwezig. Vaak worden onderzoeksresultaten van studies bij andere diersoorten of bij de mens zomaar geëxtrapoleerd naar het

paard. Toch is dit niet zo evident omdat men uit onderzoek weet dat er vaak grote interspeciesverschillen bestaan in de motiliteitsverantwoordelijke receptorpopulaties in de darm. Kortom, wat belangrijk is als farmacologisch werkingspunt voor een prokineticum in de darm van de mens is niet noodzakelijk aanwezig bij het paard en vice versa.

Door een gebrek aan uitgebreide dubbelblind, multi-center studies wordt de klinische efficiëntie van humane prokinetische middelen bij koliekpaarden vaak erg subjectief geëvalueerd. Het feit dat er tot op de dag van vandaag geen degelijke niet-invasieve meettechnieken bestaan om de gastro-intestinale motiliteit bij het paard te evalueren, werkt die subjectiviteit nog meer in de hand.

Gebaseerd op de huidige kennis kan men stellen als vuistregel dat voor de behandeling van stase van het craniale maag-darmstelsel van het paard vooral lidocaïne, metoclopramide en erythromycine in aanmerking komen. Een afgenomen motiliteit van het colon wordt het best behandeld met naloxone, neostigmine, erythromycine of lidocaïne. Acepromazine en xylazine hebben als sedativa een minder uitgesproken negatief effect op de gastro-intestinale motiliteit dan de alfa 2-agonisten detomidine en romifidine. Hiermee kan rekening gehouden worden als de sedatie van een koliekpatiënt noodzakelijk blijkt. Het gebruik van acepromazine dient echter wel vermeden te worden in geval van shock of endotoxemie, dit omwille van de uitgesproken hypotensieve neveneffecten.

INTRODUCTION

Gastro-intestinal hypomotility or ileus in horses can manifest itself in many degrees of severity and in association with a multitude of pathologic conditions. However, the condition is mainly encountered in association with abdominal colic, both intra-and extra-abdominal surgery, after extensive or repetitive use of sedatives for the purpose of orthopedic interventions, in conjunction with the use of opioid analgetics and, last but not least, as part of the clinical picture of specific intoxications. Therefore, equine practitioners tend to be confronted with the problem quite often, both under hospital and field conditions. Systemic shock, endotoxemia, ionary imbalances, intestinal dilation, ischemia, inflammation, pain, peritonitis and anesthesia are all ileus-triggering factors (French *et al.*, 2002). Which events exactly take place during the pathogenesis of ileus in horses still remains to be elucidated. Proposed viewpoints on the subject are mainly extrapolated from human medicine, due to the lack of fundamental research in horses. Afferent nociceptive input like pain and inflammatory responses to intestinal surgical manipulation can cause adrenergic hyperactivity and concomitant ileus. Also parasympathetic hypoactivity, dopaminergic hyperactivity and local entero-enteric reflexes have all been proposed as possible ileus triggering mechanisms in horses (Gering and Hunt, 1986). Many prokinetic drugs have been used in equine colic patients, each with its own specific modulation of one of the aforementioned proposed mechanisms. Up until now, however, no overall successful treatment protocol has been proposed to the equine practitioner. Depending on where in the GI tract the problem is localized, different prokinetic agents should be used, and it has to be mentioned that the main point of action of these drugs does not always correspond in horses and humans. Furthermore, the predominant point of view currently is that the prokinetic treatment has to be part of a total therapeutic plan in which the correction of blood parameters such as ionary imbalances and the provision of anti-endotoxemia treatment are equally important (Delesalle *et al.*, 2005c; Moore and Barton, 2003). The purpose of this paper is to provide the equine practitioner with an up-to-date overview of what can be concluded about the use of prokinetic treatment in horses based on the numerous in vivo and ample in vitro studies that have been performed. A practical table with dosing regimens and indication of site of action should help optimize future decision making concerning prokinetic treatment.

THE MOTOR UNIT OF THE EQUINE GI TRACT

From mouth to anus, the wall of the GI tract consists of 4 layers (Figure 1). The inner layer is the tunica mucosa. The submucosa, which lies underneath, facilitates mobility between the elastic mucosa and the more rigid tunica muscularis, which is the third layer of the intestinal wall. Finally, the tunica serosa embraces the three aforementioned layers, creating the outer jacket of the intestine. Peroperative manual manipulation of the intestine can cause mechanical irritation and inflammation of this layer, leading to localized peritonitis and adhesions.

At the level of the tunica mucosa, numerous finger-like protrusions, called the intestinal villi, create a significant increase in the resorption capacity of the in-

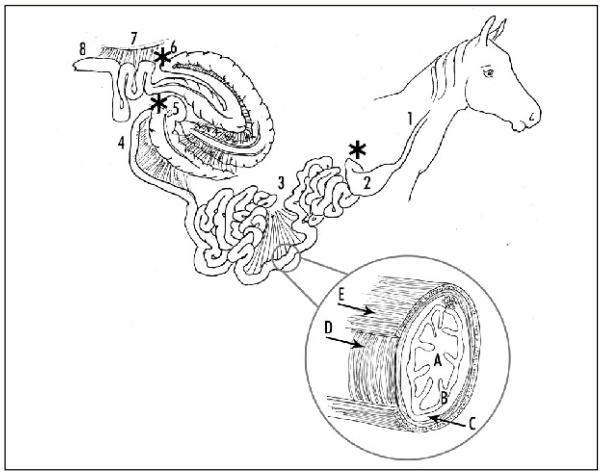

Figure 1. Anatomy of the equine GI tract. Zoom view: detail of the different layers of the intestinal wall. (1)esophagus; (2) stomach; (3) jejunum; (4) ileum; (5) cecum; (6) pelvic flexure; (7) small colon; (8) rectum; (A) intestinal lumen; (B) mucosal layer with muscularis mucosae; (C) submucosal layer with Meissner's nerval plexus; (D) inner circular muscle layer; (E) outer longitudinal muscle layer (in between D and E: Auerbach's nerval plexus); (*) enteric pacemaker nodes responsible for myoelectrical coupling between neighboring parts of the GI tract.

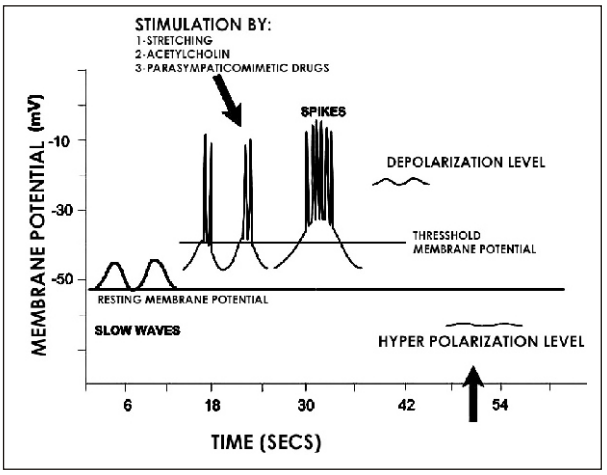

Figure 2. Slow waves and spikes: the necessary ingredients for normal enteric myoelectrical activity.

ner surface of the intestine. The tunica mucosa is provided with its own muscular tissue, which extends into each of these protrusions. However, the important outermost muscle layers of the intestine are localized in the tunica muscularis. Here, an inner circular muscle layer embracing the tunica mucosa and an outer longitudinal muscle layer, oriented in the longitudinal direction of the intestine, can be distinguished. In each muscle layer, neighboring smooth muscle cells are connected by means of "gap junctions". The throughput of electrical currents from one smooth muscle cell to the next is facilitated by means of these specialized contact points, which enable the muscle-layer to react as one large syncitium.

The Interstitial Cells of Cajal (ICC) have to be viewed as an intermediate neuro-muscular form. Like the pacemaker cells of the cardiac sinus node, they show a rhythmic electrical depolarization (Figure 2). These electrical depolarizations spread like waves in the muscular layers via the aforementioned gap junctions. As in humans, ICC cells are encountered in the horse along the full length of the GI tract. However, several specialized regions, such as the gastro-duodenal junction, the caeco-colonic junction and the pelvic flexure, are encountered with pronounced ICC densities. These regions can be viewed as "intestinal pacemaker nodes", which create myo-electrical coupling between different parts of the GI tract (Hudson *et al.*, 1999) (Figure 1).

NEURONAL INPUT OF THE EQUINE GI TRACT

One typical feature of the GI tract is the extensive autonomy with which it regulates its own functions. For this purpose, the intestine is provided with its own enteric nervous system, the so-called "gut brain", which makes contractile activity possible, even without external input. This intrinsic enteric nervous system contains two major components: Meissner's neuronal plexus, which is embedded in the tunica submucosa, and Auerbach's plexus, which is localized between the longitudinal and the circular muscle layers of the tunica muscularis (Figure 1, 3B).

However, too much functional autonomy would hamper the integration of the intestinal functions into the bigger picture of the body physiology. Here, the extrinsic or vegetative nervous system, represented by the sympathetic and parasympathetic nervous system, plays a modulating role. Just like the principles of Ying and Yang, the two nervous systems are each other's counterpart. By means of a complex network of interneurons, localized at the level of the neuronal plexi of the enteric nervous system, they process all incoming information, thus making it possible for the intestine to formulate a suitable and integrated motor response (Figure 3).

Finally, there is the brain, which has an undeniable influence on GI functionality. The detrimental effects of psychological factors such as stress on the GI motility of humans are channeled by this "gut-brain axis".

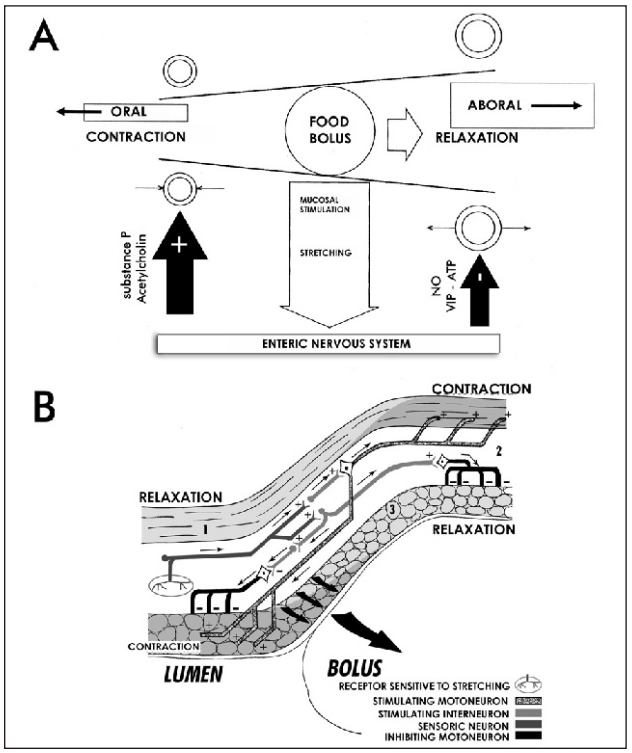

Figure 3. The peristaltic reflex: (1) outer longitudinal muscle layer; (2) Auerbach's nerval plexus; (3) inner circular muscle layer; (+) stimulation; (-) inhibition.

Likewise, in horses several stressful factors such as sudden changes in management or environment have been implicated in the pathogenesis of colic (Goncalves *et al.*, 2002).

It is clear that any damage to the enteric nervous system has significant implications for GI motility. For example, decreased neuronal density at the level of the myenteric plexus can be found in some horses with acute or chronic impaction of the cecum and/or colon (Schusser and White, 1997; Schusser *et al.*, 2000). Spastic contractions at the level of these impactions can partially block vascular supply to the intestinal wall, leading to neuronal degeneration. Therefore, although they sometimes seem not to be alarming, swift and proper treatment of cecal and colonic impactions is important in order to prevent long-term damage and problems.

TRANSDUCTION OF MESSAGES AT THE ULTRASTRUCTURAL LEVEL

Both messengers (neurotransmitters, hormones) and receivers (different types of receptors) are equally important for orchestrating the communication that is needed to realize motor activity at the level of the intestine.

Upon electrical activation, neurons will release different kinds of neurotransmitters at their terminal endings. These released neurotransmitters can either facilitate or inhibit motor activity. Acetylcholine is an important excitatory neurotransmitter, which modulates its activity through the activation of cholinergic neurones or through direct activation of smooth muscle cells. Many prokinetic agents directly or indirectly stimulate the release of acetylcholine.

On the other hand, when noradrenalin, as a neurotransmitter, activates adrenergic receptors localized on cholinergic neurons, acetylcholine release will be suppressed, thus leading to decreased motor activity.

There is also the "NANC" or "non-adrenergic, non-cholinergic" system, which involves several non-cholinergic, non-adrenergic inhibitory and excitatory neurotransmitters. For example, the release of NO (nitric oxide), VIP (vaso-active intestinal peptide) or ATP will cause relaxation of enteric smooth muscle cells, whereas Substance P will facilitate contraction (Figure 3A).

NO is generated not only by neuronal NO synthase, but also by inducible NO synthase produced by inflammatory cells. Indeed, histological examination of dilated and/or vascularly compromised small intestinal segments of colic horses often reveals the presence of extensive damage not visible ton the naked eye, which leads to a massive influx of inflammatory cells into the mucosa, the muscularis externa and the serosa (Dabareiner *et al.*, 1993 a,b). After being activated, the attracted macrophages produce NO synthase. This leads to the production of quantities of NO which are far more significant than the quantities that are produced in response to nerval stimulation. It has been proposed that this could lead to decreased motor activity, which in turn could trigger the condition of ileus. Furthermore, the binding of NO with superoxide anions can generate the formation of peroxynitrite, which in turn enhances tissue damage.

As mentioned previously, the neurotransmitters rely on a multitude of receptor types to transmit their messages to the target tissues. These receptors can be localized both on neurons and directly on the smooth muscle cells. Up until now, several receptor types have been shown to be involved in the regulation of intestinal motility. It is well known that the cholinergic receptors – which are activated by acetylcholine and the adrenergic receptors, which in turn are activated by noradrenalin – are capable of modulating intestinal motility. Tachykinine receptors are activated by

the aforementioned NANC system and motilin receptors by the peptide motilin. Most of the receptors are located on the outer cell membrane. However, NO receptors are localized intracellulary (Domeneghine *et al.*, 2004).

In conclusion, it can be stated that pharmacological modulation of GI motility can be accomplished by stimulation or inhibition of the release of specific neurotransmitters, or by direct action on enteric receptor populations.

BASAL MOTOR ACTIVITY OF THE GI TRACT

The mixing and propulsion of food in the GI tract is realized by the perfect cooperation between tonic activity, phasic activity and the peristaltic reflex.

Tonic activity

Even under resting conditions, the GI tract is always contracted to a certain degree, which is known as the so-called "basal tonus". Any rhythmic activity that occurs is always superposed upon this basal tonus. The overall narrowing of the inner intestinal lumen that is realized by the basal tonus enhances the efficiency of the intestinal propulsive and mixing contractions that occur. Indeed, the generally weak phasic contractions, which do not always succeed in occluding the intestinal lumen, will do so at times when the basal tonus is sufficiently pronounced. Many neurotransmitters and hormones exert a direct or indirect (via neurons) effect on the smooth muscle layers of the GI tract and thus help to determine the degree of basal tonus (basal degree of contraction) of the intestine.

Phasic activity

Both neuronal and non-neuronal components, such as ICC cells, cooperate to realize the regular phasic motor activity, which can be seen at the level of the stomach and the small and large intestines (Hirst and Edwards, 2004). The spontaneous fluctuations of the resting membrane potential, which are a typical feature of the ICC cells, are transmitted to the neighboring smooth muscle cells via the aforementioned gap junctions. Like the ripples that are generated by throwing a stone into a pond, these so-called "slow waves" spread themselves over the intestine. Although far from strong enough to generate actual contraction of smooth muscle cells, these slow waves change the membrane potential of the intestinal smooth muscle cells to such an extent that they become sensitive to stimulation by neurotransmitters such as acetylcholine. When the released acetylcholine stimulates smooth muscle muscarinic receptors during the upward positive deflection of the resting membrane potential triggered by the passing slow wave, the threshold potential for contraction will be crossed, and this will trigger the opening of ion channels and a concomitant depolarization, which is better known as "action potential" or "spike". Finally, a contraction will take place. Therefore the slow waves determine not only the timing and the direction, but also the speed with which smooth muscle contractions spread out over the intestine.

In conclusion, it can be stated that the prerequisite for the occurrence of phasic contractions is the presence of normal slow wave activity. Moreover, the release of excitatory neurotransmitters during the plateau phase of the slow waves is necessary for generating spike activity and concomitant contraction (Figure 2). In cases where both excitatory and inhibitory neurotransmitters are released at the same time, the resulting activity will be the summation of the opposing effects triggered by the two neurotransmitter types. In humans, the spontaneous electrical and motor activity that is seen at the level of the stomach and small intestine some time after the ingestion of a meal shows a typical cyclic pattern better known as the "migrating myoelectrical complex" or "MMC" or "inter-digestive enteral housekeeper" (see below). As soon as a meal is consumed, this cyclic pattern is replaced by an active enteric digestion pattern.

In horses suffering from grass disease the ICC cell density is clearly diminished (Hudson *et al.*, 2001). A comparable evolution of the ICC cell density can be observed in full-thickness biopsy specimens of the pelvic flexure of colic horses presented with acute large colon impaction or displacement. Conversely, no changes in ICC cell density could be observed in jejunal segments of horses suffering from small intestinal volvulus (Fintl *et al.*, 2004). In those acute colic cases where a decreased amount of ICC cells is encountered, this decrease should probably be viewed merely as a cause rather than as a consequence of the colic episode.

The peristaltic reflex

The peristaltic reflex (Figures 3, A and B), is the result of a perfect coordination between the neuronal and muscular components of the intestine. The occurrence of the reflex is based on (1) the perception of the presence of a food bolus (sensor neurons/cells), (2)

the transmission of this message to a neuronal network specially designed for information integration and determination of a suitable response (interneurons), and (3) the execution of the imposed tasks (motor neurons), which implies a normal functionality of both the inner circular and outer longitudinal muscle layers of the tunica muscularis. Propulsion of food is accomplished by contractions of the circular muscle layer at the oral pole of the food bolus and a simultaneously occurring relaxation of that same muscle layer at the aboral pole. At the same time, the longitudinal muscle layer contracts at the aboral pole and relaxes at the oral pole. This results in the active movement of the food bolus in the aboral direction, which is called propulsion. It is important to realize that the induction of true propulsive activity is a prerequisite for an effective prokinetic agent. Some of these formulations will only create spastic contractions of the intestine, sometimes accompanied by the expression of abdominal pain by the treated horse. These signs of abdominal discomfort can sometimes by misinterpreted by the clinician as a sign of true and pronounced effectiveness of the administered pharmacon. However, it should always be kept in mind that the coordination with which the intestinal contractions take place is of outmost importance.

ENTERIC MOTILITY PATTERNS

The Migrating Myoelectrical Complex (MMC) of stomach and small intestine

As mentioned previously, the Migrating Myoelectrical Complex or MMC or "enteral housekeeper" is a typical electrical and motility activity pattern with a cyclic character that can be seen at the level of the stomach and small intestine some time after the ingestion of a meal. The colon can express a similar interdigestive electrical pattern, better known as the "Colonic Migrating Myoelectrical Complex" or "CMMC". However, here the electrical activity is not always accompanied by motor activity (see below).

The MMC represents a series of strong and pronounced contractile activity fronts that propagate over the stomach and small intestine in the aboral direction. It is generally accepted that these waves serve to evacuate meal residues and cellular debris that are not propulsed by the normal digestive peristaltism. Disruption of the normal MMC pattern can predispose the small intestine to bacterial overgrowth, hence the designation "enteral house-keeper" (Nieuwenhuys *et al.*, 2000).

In humans the MMC motor pattern starts a few hours after the ingestion of a meal. However, it is immediately interrupted by the active ingestion of food, to be replaced by a typical slow propulsive motor pattern, which optimizes complete digestion of the ingested food. In horses, however, the MMC pattern is continuously expressed, despite ad libitum ingestion of food (Baker and Gerring, 1994). Therefore the equine MMC has to be viewed as an active part of the digestive motor activity and, in contrast to humans and dogs, it realizes active transportation of chyme. Researchers presume that the MMC in herbivorous animals predominantly serves to prevent the backflow of chyme, rather than functioning as an enteral house-keeper (Hunt, 1985; Baker and Gerring, 1994). Therefore, disturbing the MMC cycle in horses can have significant implications for the active transportation of ingested food.

The motility pattern of the MMC typically consists of 4 phases, each with its own specific duration. During phase 1 – "the silent phase" –, there is no motor activity. Phase 2 is characterized by a series of irregular contractions, directly followed by phase 3, which is represented by numerous clearly defined propulsive rhythmic contractions with maximal frequency and amplitude. The MMC will first appear in the antrum of the stomach, after which it will be propagated with decreasing velocity over duodenum and jejunum. Phase 4 represents the transition phase from phase 3 to phase 1 (Ruckebusch *et al.*, 1971).

In horses, there is always a transient episode of mechanical inactivity of the stomach, during the manifestation of phase 2 and 3 in the jejunum. Similar findings have been reported in ruminants and pigs (Ruckebusch and Bueno, 1975, 1976; Ruckebusch and Merritt, 1985).

An average of 20 MMC cycles a day can be recorded in horses. Almost all phase 3 activity will propagate all the way from the proximal jejunum, up to the terminal ileum. The long duration of phase 3 and the fact that this duration even increases going down the jejunum to the ileum, is a typical feature of the horse, which has never been found in other species (Sasaki and Yoshihara, 1999). Probably, this is associated with the fact that the MMC in horses fulfils an important role in the fast and efficient transportation of chyme to the cecum and colon. Indeed, the high mean velocity of 32 cm/min with which the MMC is propagated across the equine stomach and small intestine is unique in hor-

Table 1. Specific features of the equine "migrating myoelectrical complex" or MMC (duration (min), propagation speed (cm/min)).

	Proximal jejunum	Distal jejunum	Ileum
phase 1	-	31,6 17,0	22,3 14,4
phase 2	122,2 26,3 (1+2)	110,8 67,0	95,3 63,5
phase 3-4	7,9 1,7	29,0 6,1	44,6 9,0
Duration MMC cycle (min)	130,1 26,0	183,9 72,2	**160,8 56,3**
Propagation (cm/min)		± 32	**12,5 à 7,3**

ses. Apparently, nature provides all the tools needed to transport the vegetarian diet as fast as possible across the lengthy small intestinal tract, to be accommodated in the large intestine, where the digestion of fibers can start (Ruckebusch, 1981; Davies and Gerring, 1983a) (Table 1).

The "Colonic Migrating Myoelectrical Complex" (CMMC)

In accordance with the small intestine, the colon disposes over its own typical digestive and inter-digestive myoelectrical pattern of motion, during which the activity in the ileum, cecum and colon are clearly coupled (Ross *et al.*, 1989; Ross *et al.*, 1990; Roger *et al.*, 1985; Rutkowski *et al.*, 1989; Lester *et al.*, 1998a,b). The coordination of this myoelectrical coupling between different regions of the large intestine, is probably orchestrated in pacemaker nodes, which are localized in the intestinal wall of the cecum and in the tenial bands of the colon (Burns *et al.*, 1992) (Figure 1). However, in contrast with the MMC of the small intestine, the electrical activity of the CMMC is not always accompanied by mechanical activity.

The myoelectrical activity that can be registered at the level of the pelvic flexure consists of (a) isolated "long spike bursts (LSB)" that are propagated both in the oral and the aboral directions and help with the mixing of the chyme; (b) a slowly (0.5-1.0 cm/min) aborally migrating cluster of "short spike bursts (SBB)" and "long spike bursts (LSB)" occurring every 10 to 15 minutes, and (c) a series of pronounced and repetitive "long spike bursts (LSB)" that occurs sporadically and lasts for 3 to 6 minutes. These electrical waves, which propagate themselves with high velocity (3 cm/sec) in the aboral direction, are better known as the "Colonic Migrating Myoelectrical Complex" or "CMMC". There is a clear increase in LSB activity in horses when food is ingested.

It is now known that these coordinated contractile colonic waves cause a pronounced back and forward movement of the pelvic flexure between the diaphragm and the pelvis. Hence the importance of free mobility of the colon and the detrimental effects of adhesions on normal colonic digestion. It is possible that colonic displacements, like nephro-splenic entrapment, are preceded by the excessive expression of such back and forward movements (Roberts and Seawright, 1983; Sellers *et al.*, 1982a).

Little is known about the possible occurrence of defective intestinal motility patterns during gastrointestinal colic in horses. Up until now, no non-invasive registration techniques that are applicable in true clinical cases have been available. Therefore, all information has to be extrapolated from experimental colic models in which colic is artificially mimicked in healthy horses (Sellers *et al.*, 1982b). For example, colic can be experimentally induced by the creation of an intra-or extra-luminal obstruction at the level of the small or large intestine or by occluding the mesenterial arteries (Phaneuf *et al.*, 1972; Lowe *et al.*, 1980; MacHarg *et al.*, 1986; King and Gerring, 1989; Davies and Gerring, 1985). Trauma-induced post-operative ileus is mimicked by manual mechanical irritation and serosal dehydration of parts of the small intestine (Gerring and Hunt, 1986). Endotoxemia is artificially mimicked by the IV administration of E. coli lipopolysacharids (King and Gerring, 1992).

The "colic motor complex" is an example of a defective motility pattern that can be registered during experimental extra-luminal obstruction of the small intestine. It represents spastic contractile activity that is expressed by small intestinal segments located

orally to the obstruction zone. How and why these colic motor complexes are generated by the intestine is not known, though they probably represent a local reflex of the intestine in an attempt to evacuate the obstruction (Phaneuf *et al.*, 1972; Davies and Gerring, 1985; MacHarg *et al.*, 1986). Similar colic motor complexes have been found in sheep (Ruckebusch and Bueno, 1975). When these intestinal spasms linger long enough, they substantially increase the intestinal metabolism and can compromise normal intestinal vascularization, which has a detrimental effect on the viability of the intestine. Therefore it has to be mentioned that the administration of prokinetic medication to horses suspected of mechanical obstruction of the small intestine, like volvulus, is not advisable. On the contrary, it should be kept in mind that in these cases intestinal dilation and necrosis can be aggravated.

Besides the colic motor complexes that are registered during extra-luminal obstruction of the jejunum, there is also a concomitant hyperactivity to be observed at the level of the left dorsal colon, which is unique in horses and has never been found in any other species in association with small intestinal obstruction (King and Gerring, 1989). There is probably a resemblance with the human gastro-colonic reflex, where accommodation of a meal in the stomach is accompanied by an increased contractile activity in the colon (King and Gerring, 1989). In horses, the pronounced dilation of the stomach, as in cases of over-feeding or accumulation of reflux, leads to a total loss of myoelectrical and contractile activity of the stomach and small intestine. Hence the importance of a thorough stomach decompression and complete evacuation of reflux in colic horses.

PHARMACOLOGICAL MODULATION OF EQUINE GASTRO-INTESTINAL MOTILITY

Imagine the enormous body fluid shift that takes place in horses during the production of reflux. Rapid dehydration and extensive ionic losses are the result. Inevitably shock and GI hypoperfusion will follow. Therefore it is important to monitor gastro-intestinal motility in colic horses and to start-up supportive prokinetic treatment in time (Table 2). Depending on the location of the GI problem, different types of prokinetic drugs should be used.

Macrolids

As a member of the macrolid antibiotics, erythromycin stimulates the occurrence of MMC complexes in the horse. This is achieved through stimulation of motilin receptors localized on cholinergic neurons (Fiorucci *et al.*, 1993; Tomomasa *et al.*, 1986; Peeters *et al.*, 1989). In horses, motilin immunoreactive cells are found at the level of the duodenum, the jejunum, the cecum and the pelvic flexure. As in rabbits, there is a decreasing density of motilin receptors in the aboral direction (Kitamura *et al.*, 1984). In humans, the endogenic peptide motilin is produced by granular cells localized in the mucosal layer of the antrum, the proximal duodenum, the jejunum and the ileum (Weber *et al.*, 1993). Intravenous administration of motilin to the dog induces the occurrence of a phase 3 of the MMC, which starts in the stomach and propagates all the way to the ileum (Itoh *et al.*, 1984; Yamada *et al.*, 1997). Likewise, intravenous administration of motilin to horses (0.6 µg/kg) induces the occurrence of a phase 3 of the MMC at the level of the proximal jejunum. However, in contrast with the dog, the contractile waves do notreach the ileum (Sasaki and Yoshihara, 1999). In cases of experimentally induced postoperative ileus, the administration of motilin triggers an increased phase 3 activity of the MMC and enhances the solid phase emptying of the stomach. However, although important in horses with reflux, no acceleration of the gastric liquid phase emptying rate can be achieved (Coatney and Adams, 1988; Doherty *et al.*, 1998). This lack of effect on the liquid emptying of the stomach is probably linked to the specific prokinetic properties of erythromycin in horses, which are predominantly focused on the gastric antrum, a part of the stomach that is mainly important for the expulsion of solid food.

The prokinetic activity of erythromycin shows clear species variability. In monogastric animals like humans, cats and dogs, it is mainly the stomach and small intestine that are stimulated, whereas in horses it is also the colon that is clearly activated (Peeters, 1993; Itoh *et al.*, 1984). For example, slow intravenous administration of erythromycin (3.3 mg/kg, 20 min) to healthy horses induces the occurrence of CMMC's at the pelvic flexure (Masri *et al.*, 1991). Erythromycin doses of 0.10, 1.0 and 10 mg/kg administered to healthy ponies stimulate cecal emptying and myoelectrical spiking activity in the colon (Lester *et al.*, 1998a). However, in horses, like in other species, the rate with which the erythromycin is administered intravenously is very important. Slow infusion (60 min) will eventually lead to a pronounced sup-

Table 2. A practical overview of the use of prokinetic drugs in horses.
POI = post operative ileus; ACH = acetylcholine

Prokinetic drug	Route of action	Dose regimen	Disadvantages
Erythromycin lactobionate	Stimulation of motilin receptors	0.5 à 1mg/kg iv TID/QID	Colic symptoms Frequent use "downregulation" of motilin receptors Fatal cases of enteritis
Lidocaine hydrochloride	Sympatic antagonism Direct stimulation of enteral smooth muscle cells Anti-inflammatory	Bolus: 1.3mg/kg iv Maintanance: 0,05mg/kg/min iv of a 2% solution	In case of overdosing: Ataxia during post-operative recovery
Metoclopramide	Alpha 2 receptor antagonist Antagonism of central and peripheral dopaminergic receptors Stimulation of cholinergic neurotransmission	0.04 mg/kg/h iv 0.05 mg/kg IM QID 0.1 à 0.25 mg/kg sc TID/QID 5 mg/kg po TID	Extrapyramidal side effects
Domperidone	Peripheral dopaminergic receptor antagonist	1mg/kg po QID	In a model of POI only stimulation of the gastroduodenal junction
Neostigmine methylsulfate	Cholinesterase inhibitor	0.022 mg/kg iv or sc every 2 to 4h on effect	Pronounced signs of colic
Bethanechol chloride	Parasympaticomimetic drug	0.025 mg/kg sc or 0,25 mg/kg iv in 10ml of 0,9%NaCl every 3 to 4h	Signs of colic Salivation Sweating
Yohimbine	Alpha 2 receptor antagonist	0.15 mg/kg iv BID/TID	No pronounced effect
Acepromazine maleate	Alpha 2 receptor antagonist	0.01 mg/kg IM every 4 to 6h	Blood pressure ? Peripheral vasodilation
Cisapride	Stimulates the release of ACH at the level of cholinergic neurons	1mg/kg po QID	Not available
Tegaserod	Stimulates the release of ACH At the level of cholinergic neurons	0.02mg/kg iv BID	Not available

pression of myolectrical activity, despite an initial increase. As in humans, this is probably due to the reactive down regulation of motilin receptors. During bolus administration (0.10 mg/kg iv, 30 secs), these down regulating mechanisms are not triggered. Therefore, in horses it can be stated that mainly low, subtherapeutic non-anti-microbial doses given as a bolus are most suitable for obtaining prokinetic effects (Ringger and Lester, 1996). However, the possible detrimental effects of the repetitive use of motilin agonists in horses has not been evaluated. In humans, the earlier mentioned tachyphylaxia or receptor down regulation is thought to be responsible for the failure of clinical trials of several motilides, which clearly hampers the development of clinically useful compounds (Thielemans *et al.*, 2005). This should be kept in mind when repetitive dosing is applied in horses.

However, it is not only the amount and administration rate that are important, but also the indication for which the erythromycin is used. Research has demonstrated the expression of different gastro-prokinetic effects by erythromycin in healthy horses in comparison with horses with experimental post-operative ileus. In the latter group, the administration of erythromycin (0.5 mg/kg iv, 1 min) leads to increased myolectrical activity at the level of the ileum and the pelvic flexure, during both the post-recovery (24h) and the post-operative (8 days) periods. In the cecum, however, the stimulating effects are limited to the post-recovery period, which can be interpreted as a less favorable feature for prokinetic purposes (Roussel *et al.*, 2000). In conclusion, it can be stated that in cases of experimental post-operative ileus, the erythromycin induced prokinetic effects are mainly focused on the colon, although some reports mention the successful treatment of clinical cases with small intestinal ileus (Roussel *et al.*, 2000).

Last but not least, there is the alarming possibility of the occurrence of fatal colitis due to the use of erythromycin lactobionate as a gastro-prokinetic agent. Several case reports in the literature, as well as experience with the product in the Large Animal Internal Medicine Clinic of our faculty, show that administration of the antibiotic erythromycin to adult horses can lead to hyperthermia and fatal enteritis due to imbalance of the enteric flora (Prescott and Hoffman, 1993). In order to bring about a minimal antibiotic effect, a minimal receptor down-regulation and a maximal prokinetic effect, it is advised to use 0.5 to 1 mg/kg erythromycin lactobionate in 60 ml of 0.9% NaCl, administered IV three to four times a day as a bolus and not as a slow infusion.

Lidocaine hydrochloride

In human abdominal surgery, lidocaine hydrochloride is used peri-operatively as a pain killing drug and to minimize the duration of naturally occurring post-operative gastro-intestinal stasis (Groudine and Fisher, 1998). With respect to ileus in horses, it is believed that the activation of pain receptors localized in the peritoneum has an inhibitory effect on gastro-intestinal motility (Gerring and Hunt, 1986). Hence the widespread veterinary use of lidocaine in horses suffering from postoperative ileus or proximal enteritis (Malone *et al.*, 1990). It is thought that lidocaine exerts its prokinetic effects through direct stimulation of enteric smooth muscle cells and through suppression of sympathetic inhibitory reflexes (Rimback *et al.*, 1990). There are indications that lidocaine has anti-inflammatory properties. Furthermore, it suppresses both the net transport of fluid into the intestinal lumen and the extravasation of albumin (Nellgard *et al.*, 1996). In vitro motility tests on intestinal smooth muscle strips have demonstrated that lidocaine increases contractility, mainly at the level of the mid-jejunum (Nieto and Rakestraw, 2000a). Very few studies evaluate the in vivo efficacy of lidocaine as a gastro-prokinetic agent. Through the use of abdominal ultrasound, Brianceau and co-workers have demonstrated a decrease in both the mean jejunal diameter and the amount of abdominal fluid accumulation in colic horses that were postoperatively treated with lidocaine. However, when controls were compared with the treatment group, no significant difference in the time-interval to first defecation, production of reflux and number of small intestinal contractions per minute could be demonstrated (Brianceau *et al.*, 2002). Lidocaine is also thought to have anti-endotoxine effects, which could be interesting in countries without easy access to specialized medicines such as polymixin B and pentoxyphylline (Barton *et al.*, 2004; Piero *et al.*, 2000 a,b).

Per rectal application of lidocaine (15 ml of a 2% solution in 45 ml of tap water) can be considered to accomplish rectal relaxation, which can be a helpful tool to prevent the occurrence of rectal tears during abdominal palpation (Sanchez and Merritt, 2005). However, the sensitivity of the rectum to dilation is not influenced and IV administration of Buscopan® is without any doubt just as efficient and less time consuming.

In order to obtain optimum effect, lidocaine is administered per-operatively, starting with a bolus of 1.3 mg/kg of a 2% solution, followed by a continuing infusion of 0.05 mg/kg of the same 2% solution. When recovery is completed and the horse is standing stable on its feet, the bolus regimen is again applied, followed by continuous infusion during minimal 24h. Use of higher per-operative doses can lead to muscle twitching and pronounced ataxia, which can seriously hamper a safe recovery. Overdosing can lead to profuse sweating and fast breathing, sometimes resembling the clinical picture of a horse with a ruptured viscus. Sudden collapse of the horse can also occur. Finally, it has to be mentioned that the use of lidocaine can mask early signs of founder. Therefore, careful monitoring of the colic patient is important. In some colic horses lidocaine administered in bolus dose creates enough sedation and pain relief to perform a complete clinical examination, without the need for the use of other sedatives, which often have long-term suppressing effects on gastro-intestinal motility.

Benzamides and butyrofenones

One of the first benzamides discovered, ***Metoclopramide*****,** is widely used both in human and veterinary medicine to treat gastrointestinal symptoms related to impaired motility and to tackle emesis. One of the features of the "older" drugs is that they are less specific and therefore often stimulate a wide array of enteric receptor types. The down side of this aspecificity is the numerous side effects that are often encountered with these drugs. Hence the tremendous diligence with which researchers are trying to develop receptor-specific blocking and activating agents.

Metoclopramide stimulates serotonergic 5-HT_4 receptors, which in turn enhance the release of acetylcholine at the level of postsynaptic cholinergic neurons. The drug acts on central dopaminergic receptors, where it has an antagonizing effect. Although there is little evidence for the presence of dopaminergic receptors on enteric smooth muscle cells, some researchers propose that metoclopramide has a suppressing effect on the inhibitory effect of dopamine on enteric smooth muscle cells (Tonini, 1996). Finally, it blocks serotonergic 5-HT_3 receptors and adrenergic alpha 2 receptors (Alibibi and McCallum, 1983).

Gerring classifies idiopathic and thus non-endotoxemic ileus in horses as dopaminergic mediated. Hence the advice to use metoclopramide as a gastroprokinetic agent in these horses (Gerring, 1982).

In vitro contractility tests on enteric smooth muscle strips demonstrate that metoclopramide stimulates contractile activity of the equine pylorus, the proximal duodenum and the mid-jejunum. Progressively increasing doses are required to stimulate contractile activity from proximal to distal. This specific feature of metoclopramide is probably linked with its ability to actually coordinate motility in the stimulated intestinal segments rather than simply inducing increased, but random, contractile activity (Nieto and Rakestraw, 2000).

In healthy ponies, metoclopramide (0.125 mg/kg iv) accelerates the gastric liquid phase emptying rate. When applied as an IV bolus of 0.03 mg/kg, no significant changes in the MMC and motoric activity of the jejunum and the pelvic flexure could be demonstrated (Sojka and Adams, 1988). However, used as a continuous infusion (0.5 mg/kg/h iv) in ponies with experimentally induced post-operative ileus, there is a clear increase of the contractile activity of the jejunum, the cecum and the colon. Moreover, metoclopramide is able to re-establish good coordination of disturbed MMC activity in these ponies (Gerring and Hunt, 1986). Standard postoperative administration of metoclopramide as a continuous infusion (0.04 mg/kg/h) seems to suppress the occurrence of postoperative ileus (Dart *et al.*, 1996).

However, overall clinical use of metoclopramide in colic horses is hampered by the frequently encountered extra-pyramidal side effects, which are encountered even with low dosing protocols. The reason for this is the ease with which the drug passes the blood-brain barrier. Especially skinny horses with limited body fat stores seem to be prone to showing these extra-pyramidal side effects. Although continuous low dose infusion (0.04 mg/kg/h) will create more stable blood levels of the drug than will bolus administration, nervous side effects can still occur. Even with IM administration, the extrapyramidal effects have been reported. Sometimes symptoms will occur immediately after the administration of metoclopramide, and sometimes only 36 h after starting the continuous infusion. The horses are fearful and nervous. They show a continuous propensity to sit on their hindquarters. There is profuse sweating and signs of abdominal discomfort are often seen. These symptoms can linger for more than 12h after discontinuation of the metoclopramide treatment. Sometimes walking the horse for 15 min can quickly improve the situation, though this will only be possible in those cases where safe handling is still an option. In most cases, however, the

administration of sedatives will be necessary, accompanied by all the negative effects on gastro-intestinal motility. Other proposed dosing regimens are: 0.05 mg/kg IM QID; 0.1 - 0.25 mg/kg sc TID or QID and 5 mg/kg PO QID.

Domperidone has a widespread use as gastroprokineticum and anti-emetic drug in human medicine. The veterinary use, however, is rather limited. Domperidone will not pass the blood-brain barrier and therefore is free from any extra-pyramidal side effects. Little is known about its pharmacological action. However, experimental evaluation of its efficacy as a prokinetic drug in horses is not very encouraging. In ponies with experimentally induced postoperative ileus, domperidone (0.2 mg/kg IM QID) seems only to be able to stimulate contractility at the gastroduodenal junction. No prokinetic effect could be observed at the level of the colon (Gerring *et al.*, 1991). Domperidone is only available for per oral use. The proposed dose regimen is: 1 mg/kg PO QID.

Cholinergic agonists

Neostigmine methyl sulphate antagonizes the breakdown of the neurotransmitter acetylcholine by the enzyme acetylcholinesterase. The drug can be used successfully in horses with impactions of the cecum or right dorsal colon, refractory to treatment with laxatives. When administered to healthy ponies (0.025 mg/kg sc), neostigmine methyl sulphate induces the occurrence of premature phase 3 complexes of the MMC at the level of the ileum, acceleration of the cecal emptying rate, and the occurrence of CMMC's at the level of the right dorsal colon (Lester *et al.*, 1998c). Its prokinetic activity is mainly focused on the hindgut. On the contrary, neostigmine methyl sulphate seems to have an inhibitory effect on the proximal part of the gastro-intestinal tract, which is quite important for horses suffering from ileus. In healthy ponies, both the gastric liquid phase emptying rate (0.022 – 0.044 mg/kg sc) and the contractile activity of the jejunum are clearly suppressed (Adams *et al.*, 1984; Adams and Margaret, 1985). Despite these observations, there are some reports of successful treatment of horses with postoperative ileus that were refractory to treatment with lidocaine, metoclopramide and erythromycin (Van Hoogmoed and Snyder, 1997). The proposed dosing regimen is: 0.022 mg/kg iv or sc every 2 to 4 hours. Horses treated with neostigmine methyl sulphate can show signs of abdominal discomfort directly after administration of the product.

Bethanechol chloride mimics the action of the neurotransmitter acetylcholine. Acetylcholine stimulates muscarinic receptors, which are found all over the body, including the muscle that surrounds the gastro-intestinal tract. Bethanechol chloride has a pro-contractile effect on both stomach and small intestine. In healthy ponies it stimulates the gastric evacuation of both liquids and solids (Thompson *et al.*, 1994). When administered at a dose of 0.05 mg/kg sc, there is also a clear increase of the contractile activity of the colon which lingers for more than 80 minutes (Roger *et al.*, 1985). In a model of experimentally induced postoperative ileus, there is a discrete increase of the propulsive activity of the stomach and small intestine (2.5 mg/kg sc). The co-administration of bethanechol and yohimbine triggers more distinct prokinetic effects (Gerring and Hunt, 1986). The proposed dosing regimen for bethanechol chloride is: 0.025 mg/kg sc every 3 to 4 hours. Due to the parasympaticomimetic features of bethanechol, side effects like profuse salivation and abdominal discomfort can hamper its use in colic cases. Bethanechol is not available in Belgium as an over-the-counter drug.

Alpha adrenergic receptor antagonists

Alpha adrenergic receptor antagonists inhibit the motility suppressing effects of the sympathetic nervous system on gastro-intestinal motility. As mentioned previously, adrenergic hyperactivity is thought to be part of the complex of factors that can trigger postoperative ileus in horses (Gerring and Hunt, 1986; Eades and Moore, 1993). Gastro-intestinal stasis in horses is often complicated by the onset of endotoxemia, which in turn induces increased release of sympathetic neurotransmitters. Hence, the research that has been done on the possible use of adrenergic antagonists for treatment of ileus and endotoxemia in horses. In healthy ponies, only little if any propulsive effect could be elicited through the use of adrenergic antagonists. Administration of the alpha 2-receptor antagonist yohimbine (0.15 mg/kg iv) even elicits a significant slow-down of the gastric liquid phase emptying rate, both in healthy ponies and in ponies with experimentally induced endotoxemia (Doherty *et al.*, 1998; Meisler *et al.*, 1997). On the whole, this is a rather surprising observation, since one would expect an increased release of acetylcholine and a concomitant increase of contractile activity as a result of antagonizing adre-

nergic alpha 2 receptors localized on cholinergic neurons (Drew, 1978). On the other hand, it has been demonstrated that the use of yohimbine in cases of experimental endotoxemia specifically stimulates cecal vascularization and myoelectrical activity (Eades and Moore, 1993). In a model of experimental postoperative ileus, yohimbine (0.15 mg/kg iv) stimulates the propulsive activity of the jejunum. As mentioned previously, best results were obtained when co-administration of yohimbine (0.15 mg/kg iv) and bethanechol chloride (0.014 – 0.022 mg/kg sc) was applied (Gerring and Hunt, 1986).

Acepromazine is primarily used as a sedative drug in horses. As a neuroleptanalgetic agent, this drug is part of the chemical class known as phenothiazines. It antagonizes several neurotransmitters, including: acetylcholine, 5-hydroxytryptamin, catecholamines and histamine (Rang *et al.*, 1995). Administration of acepromazine to healthy ponies (0.05 mg/kg iv) elicits a significant suppression of the gastric liquid phase emptying rate. However, the solid phase emptying rate is not influenced (Doherty and Adams, 1999; Sutton *et al.*, 2002). Contractility experiments with experimentally intra-abdominally isolated jejunal segments (better known as "Thiry-Vella loops) show that although acepromazine suppresses the myoelectrical activity in these segments, the throughput of liquids is clearly stimulated (Davies and Gerring, 1983 b). However, these observations could not be confirmed by Lester and co-workers during in vivo experiments (Lester *et al.*, 1998c). The overall conclusion, based on all these experimental results, is that acepromazine as a sedative drug, in contrast to many other sedatives, seems to have only minor negative effects on gastrointestinal motility. In some cases it even seems to stimulate contractile activity, without triggering spastic contractions. Therefore it seems to be a good choice as a sedative drug in colic horses without obstruction of the proximal part of the gastro-intestinal tract. However, the detrimental effects of this drug on blood pressure should always be kept in mind. Lowering blood pressure in colic horses suspected of having compromised bowel or in candidates for surgical intervention should be avoided at all times. Finally, acepromazine can be used in low doses (0.01 mg/kg IM every 4 to 6 h) as part of a founder prevention plan.

Serotonergic agonists

Cisapride stimulates presynaptic, myenterically localized 5-HT_4 receptors, which in turn trigger an increased release of the excitatory neurotransmitter acetylcholine. The drug has a blocking effect on 5-HT_2 and 5-HT_3 receptors and influences 5-HT_1 and motilin receptors (Briejer *et al.*, 1995). In humans and dogs, cisapride stimulates the release of endogenous motilin (Song *et al.*, 1997). Whether this is also the case in horses has never been investigated. Finally, as in humans, cisapride acts on K^+-ERG channels localized in the equine GI tract. These ion channels have been identified immunohistochemically in the equine duodenum, the jejunum and the colon (Lillich *et al.*, 2003). Not surprisingly they have also been identified in the equine heart. In humans, it is known that stimulation of these cardiac ion channels is partially responsible for the cardiologic side effects of cisapride, such as life-threatening arrhythmias, that have been reported in some patients (Cools *et al.*, 2001). Whether these side effects might also occur in the horse, is not clear.

There is a lot of controversy about the therapeutic efficacy of cisapride for stimulating GI motility in horses (King and Gerring, 1988; Ruckebusch and Roger, 1988; Levy and Sojka, 1991; Baker and Gerring, 1994). The overall conclusion of the clinical trials performed is that the drug should mainly be used as part of the prophylactic plan. However, once a status of postoperative ileus and endotoxemia exists, little if any effect should be expected from the use of cisapride (Gerring and King, 1989; Gerring *et al.*, 1991; De Geest *et al.*, 1991; Van der Velden and Klein, 1993; Sasaki and Yoshihara, 2000). Although in a model of experimentally induced endotoxemia, a significant acceleration of the gastric liquid phase emptying rate was accomplished, the profound inhibiting effects of prostaglandin E_2 and E coli on jejunal contractile activity could not be antagonized (Valk *et al.*, 1998; King and Gerring, 1992). In January 2005 the decision was made to fully withdraw the licenses of cisapride because the benefits of the drug did not outweigh the cardiologic risks of treatment. In horses, we can only confirm that measured therapeutic blood levels are high enough to trigger cardiac arrhythmias (Finley *et al.*, 2002).

Tegaserod is a more specific serotonergic receptor agonist than cisapride, and it mainly stimulates myenterically localized 5-HT_4 receptors (Chey, 2004). On the basis of the results of in vitro studies, it can be concluded that this receptor is mainly found in the hind-

gut of the horse (Weiss *et al.*, 2002). Tegaserod is available in the US as a per oral drug for the treatment of obstipation predominant irritable bowel syndrome (IBS), and it will be soon available in Europe. In vivo investigations in healthy horses (0.02 mg/kg Tegaserod iv BID) have demonstrated an acceleration of the oro-anal transit of barium filled particles, administered by naso-gastric intubation (Lippold *et al.*, 2004). Whether the drug will find any application in the treatment of postoperative ileus in horses is very questionable, since up until now, little if any evidence has been found to localize the target 5-HT_4 receptor of Tegaserod in the equine stomach and small intestine (Nieto *et al.*, 2000b; Delesalle *et al.*, 2005a,b).

Other drugs

It is interesting to note that the administration of 10 to 20 x 10^6 IU ***K^+-penicillin*** to healthy horses will elicit an increase of myoelectrical activity at the level of the pelvic flexure that will linger for no longer than 15 to 45 min. The observed effect is somewhat comparable with the increased contractile activity seen after administration of erythromycin lactobionate (Roussel *et al.*, 2003). The prokinetic effects of K^+-penicillin cannot be attributed to the K^+ ions, since no myoelectrical changes are observed after the sole application of KCl. However, how the pro-motile effects of K^+ penicillin can be explained, is not clear. The mentioning of this special feature of K^+ penicillin is far from being a plea for standard use of the drug in colic horses. It should always be borne in mind that several studies have reported an increased risk for diarrhea in colic horses treated with this antibiotic (Gustafsson *et al.*, 2004).

As in humans, it is thought that also in horses the release of endogenous endorphins contributes to the onset of ileus. Therefore, efforts are being made to investigate possible beneficial effects of the use of opioid antagonists, like ***naloxone***, in colic horses. One clinical trial reports favorable results after the treatment of colic horses with naloxone (Sciorsci *et al.*, 2000).

CONCLUSION

Gastro-intestinal hypomotility in horses can be triggered by a multitude of factors and should always be considered a complex pathologic condition. Successful treatment of ileus requires a systematic approach, during which all possible problems are addressed in a swift and precise way. A thorough clinical examination is important to identify the type of ileus (mechanical or adynamic). On the basis of these findings, the possible use of prokinetic agents can be justified. The localization of the motility problem has important implications for the type of prokinetic drug that has to be used. In summary, it can be stated that for the treatment of hypomotility of the proximal part of the equine GI tract, lidocaine, metoclopramide and erythromycin are the main drugs of choice. Naloxone, neostigmine, erythromycin and lidocaine are important for the treatment of stasis of the hindgut. In cases showing signs of endotoxemia, the use of adrenergic antagonists can be a helpful tool. It should be noted that the production of reflux in horses represents an enormous loss of body fluids, leading to rapid dehydration, ionary imbalances and hypoproteinemia. The correction of these imbalances is as important as the choice of the right prokinetic drug for successful treatment of ileus in horses. Finally, it is clear that up to the present time a generally efficacious prokinetic drug for the treatment of ileus in horses has not yet become available. Clinical efficacy reports are often very contradictory, which makes it sometimes difficult to justify the use of these often very expensive agents. More fundamental research is needed to reveal enteric receptor populations that are important for GI motility and that can be used as pharmacological targets for prokinetic drug use in horses.

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Uit het verleden

OS, BARG, RUIN EN KAPOEN

Castreren was van oudsher een van de belangrijkste taken van de voorlopers van de dierenartsen. Gespecialiseerde veesnijders bleven hun bedrijf uitoefenen tot in de jaren vijftig van de vorige eeuw, lang nadat de universitair gevormde veeartsen op het toneel verschenen. De woorden waarmee gecastreerde dieren aangeduid worden, zijn zeer oud. Hier een korte samenvatting van hun etymologie.

Het castreren van stieren was zo algemeen dat het woord *os* zelfs synoniem was voor rund. Niemand zal er aan twijfelen dat de oeros in staat was zich voort te planten en dat ossenhaas van niet-gecastreerde runderen lekker is. Het woord is verwant met het Gotische *auhsus* en het Oudin dische *uksan.*

De andere namen van castraten vinden hun oorsprong in het castreren zelf. De term *barg* is waarschijnlijk verwant aan het Germaanse werkwoord *beran*: slaan. 'Oudtijds werden de testikels van het varken murw geklopt', leest men in het 'Etymologisch Woordenboek' van de Vries en Tollenaere. Niet-taalkundige vaklui zullen hier wel een wenkbrauw bij optrekken. Het woord *ruin* laat in het midden hoe de operatie gebeurde. Het is verwant aan het werkwoord rooien. Bij *kapoen* moet men niet ver zoeken. In de term zit de Indo-Europese stam *(s)kap*, zoals in kappen.

Luc Devriese