

# Pathology of Intestinal Motility

E. L. Gerring

Royal Veterinary College, University of London

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## Introduction

The control of equine bowel motility is multifactorial. In addition to the classical concept of a cybernetic mechanism between the two elements of the autonomic nervous system, there is a complex intramural system often referred to as the „gut brain“. The parasympathetic system mediated by the vagus nerve and the splanchnic nerves mediating sympathetic activity do have an important role, probably in setting tone in the bowel. Loss of the extrinsic input due to destruction of autonomic ganglia remote from the gut results in complete stasis in grass sickness.

Within the bowel wall are two intercommunicating neuronal nets, the submucous plexus and the intramural plexus. These nets consist of groups of neurones which interconnect both longitudinally and circumferentially within the bowel wall. It is this neuronal net which is frequently referred to as the gut brain.

A range of neurotransmitters has been identified within the intrinsic neural network. In addition to acetylcholine and noradrenaline, dopamine, 5HT and a number of neuropeptides have been identified. A case has also been made for opioids, at least in the operation of the caecocolonic pacemaker.

Coordination of gut movement appears to reside in pacemaker centres. The most rostral of these, in the gastroduodenal junctional area, controls the well described patterns of activity which pass aborally along the small intestine. These patterns are superimposed upon an omnipresent basal electrical rhythm which maintains a state of tone. In intermittent meal feeders like dogs and man, these patterns of activity are present in the interdigestive periods but are disrupted in the post-prandial phase which follows a meal. In ruminants, the patterns are continuous and unaffected by feeding but, in the case of the horse, the position is somewhat between these two. In the fasting state the horse behaves like the dog but feeding does not completely disrupt phasic activity.

Normal coordination ensures that the duodenum is relaxed when antral contractions drive chyme into the intestine. Chyme is subsequently mixed by combined aboral and oral movements and propelled aborally by propagated fronts of contractile activity. These fronts carry the chyme boluses

## Summary

The control of equine bowel motility is complex and results from interaction of neural, humoral and endocrine factors. Disorder may result from interference with any part of these processes. Disorders of gastrointestinal motility fall broadly into four groups. Firstly, constipation when the bowel is hypoactive. This group includes pelvic flexure and caecal impactions and meconium retention in the foal. These conditions may be associated with reduced activity in the caecocolonic and pelvic flexure pacemakers. In diarrhoeic conditions the bowel may be hypermotile, allowing insufficient time for large gut water resorption. In the foal it may simply be due to large bowel water overload. Cessation of propulsive gut motility results in ileus. This is commonly encountered after abdominal surgery. In the idiopathic form the disruption of gastroduodenal coordination is mediated by a dopaminergic mechanism. Horses suffering endotoxaemia associated with severe ischaemic bowel disease have a frequently fatal form of ileus mediated via tumour necrosis factor alpha and eicosanoids. In grass sickness, gut hypomotility and eventual stasis results from a ganglionopathy believed to be due to an as yet unidentified neurotoxin.

## Pathologie der Darmmotorik beim Pferd

Die Regulation der Darmmotorik des Pferdes ist komplex. Neurale, humorale und endokrine Faktoren wirken zusammen. Störungen können durch Interferenz mit einem oder mehreren dieser Regelmechanismen entstehen. Sie können grob in 4 Gruppen eingeteilt werden. Einmal gibt es Verstopfung bei herabgesetzter Darmmotorik. Dieser Zustand kann mit herabgesetzter Aktivität der Schrittmacher für das Caecum und craniale Colon bzw. in der Beckenflexur verbunden sein. Bei Durchfall andererseits kann der Darm hypermotorisch sein, so daß nicht ausreichend Zeit für die Wasserabsorption im Dickdarm zur Verfügung steht. Bei Fohlen kann dies ganz einfach Folge einer Überladung des Dickdarms mit Wasser sein. Ein völliges Sistieren der Darmmotorik führt zum Ileus, z. B. häufig nach chirurgischen Eingriffen in der Bauchhöhle. An der idiopathischen Form, der Unterbrechung der gastroduodenalen Koordination, ist ein dopaminerges Mechanismus als Mediator beteiligt. Tritt als Folge einer schweren Ischämie des Dickdarms eine Endotoxinämie auf, so kommt es häufig zu einem letalen Ileus, der über den alpha-Tumornekrosefaktor und Eicosanoide induziert wird. Der herabgesetzten Darmmotorik und dem möglicherweise eintretenden Darmstillstand bei der „Graskrankheit“ liegt eine Ganglionopathie zugrunde, die einem noch nicht identifizierten Neurotoxin zugeschrieben wird.

into the complexes. Caecocolonic electromechanical activity is much less clearly defined but long and short bursts of activity both mix and propel ingesta. These movements are coordinated by a pacemaker in the ileocaecal colonic area and another in the region of the pelvic flexure. No pacemaker has yet been identified for the small colon.

## Disturbances of Normal Motility

### Constipation

In the foal, failure to pass the meconium is a common clinical entity. There is no evidence to suggest any disturbance of normal motility and it seems likely to be purely a mechanical problem.

In the adult, impaction of the pelvic flexure of the large colon is common. It is frequently associated with a change of diet, particularly when changing to dry feeding from

grass. Impaction also occurs at the end of the winter stabled period. Movement of the central part of the large colon is coordinated by a pacemaker located in the region of the pelvic flexure. Normal mixing and propulsive activity is disturbed, perhaps by formation of an ectopic pacemaker. This leads to uncoordinated activity between left dorsal and left ventral colon and impaction results (Sellars et al., 1980).

There is evidence for an inhibitory mechanism operating via the caecocolonic pacemaker, believed to be located in the caecal cupola. The inhibition appears to be mediated by endorphins since naloxone, a specific opioid antagonist, increased large bowel activity in experimental ponies (Roger et al., 1985). This pacemaker will also respond to cholinomimetic drugs. Coordinated activity results from administration of carbachol, which will induce defaecation. Failure of colonic motility is also an important feature of post-operative ileus. In a pony model of this condition (Gerring and Hunt, 1986), it was shown that colonic motility was the last feature to be restored in that self-curing model. In addition to carbachol, the large bowel pacemaker will respond to metaclopramide and to cisapride and domperidone. It is not easy to define the mechanisms by which pacemaker activity is mediated. Domperidone is a dopamine (DA<sub>2</sub>) antagonist, metaclopramide is a DA<sub>2</sub> antagonist but also has serotonin S<sub>3</sub> antagonist properties in addition to weak cholinergic effects. The mechanism of action of cisapride is not fully understood but it is believed to result in the facilitation of acetylcholine action at interneurons within the gut wall.

Recent histological evidence confirms the presence of neurone aggregations in the pelvic flexure area (Burns and Cummings, 1991). These workers also showed a ten-fold increase in the density of neurones staining positive for vasoactive inhibitory peptide (VIP) in the pacemaker region when compared to the rest of the colon wall. The suggestion exists that lesions in these neurones may affect the release of such neurotransmitters in cases of disordered motility.

Caecal impaction is fortunately less common than pelvic flexure obstruction in Europe, but is a common condition in North America. Less is known of the control mechanisms although the motility of the organ has been studied in fistulated animals (Sellars et al., 1980). Increases in caecal activity in response to naloxone and carbachol were observed (Ruckebusch and Roger, 1988). These workers suggested that one pacemaker was responsible for coordination of both colonic and caecal activity.

Studies with the acaricide Amitraz, which causes large bowel stasis and impaction, suggest that an  $\alpha_2$  adrenoceptor mechanism is evoked in these cases. Xylazine has similar but shorter-acting effects. The effect of both these drugs on the caecum can be reversed by the specific antagonist yohimbine.

Chronic bowel obstruction also occurs due to hypertrophy of the muscular wall of the ileum (Edwards, 1981). There is

no evidence of a motor disorder in these cases but it has been suggested that chronic obstruction of the ileocaecal valve may predispose to ileal hypertrophy. Heavy burdens of the tapeworm *Anoplocephala perfoliata* have been associated with some cases.

#### *Diarrhoea*

Acute diarrhoea occurs in foals associated with oestrus in the dam and due to specific infections, notably rotavirus. In the adult, salmonellosis is a potent cause, together with idiopathic colitis. Chronic diarrhoea in the adult is a rare but intractable disease which is associated with large intestinal malfunction. Current opinion suggests that malabsorption is the primary lesion, particularly failure of water resorption. There is little information on motility in diarrhoea but one report in an experimental pony showed reduction in gastric activity and an increase in both small and large intestinal motility (Hunt and Gerring, 1985). This case showed some initial response to the  $\alpha$  adrenoceptor blocker phenoxybenzamine but the result was not sustained.

Paradoxically, the effect of acepromazine on transport through an isolated intestinal loop was to increase transit. The action of acepromazine is complex, it is an  $\alpha$  adrenoceptor blocker with parasympatholytic actions and was suggested to act in that model by decreasing motility and tone in the gut tube, so facilitating flow (Davies and Gerring, 1983). The action of  $\alpha_2$  adrenoceptor agonists such as xylazine is to reduce motility in normal animals.

The case for generally increased motility in diarrhoea is strengthened by efficacy of codeine phosphate in reducing diarrhoea. Opioids in general produce an initial increase in segmental contractions followed by an increase in tone and slowing of intestinal transit (Phaneuf and Ruckebusch, 1983).

In the foal, diarrhoea is believed to be the result of hypersecretion and/or malabsorption in the small intestine resulting in fluid overload on the caecum and colon. It is suggested that the infant large bowel has a ceiling of waterresorptive capacity which is capable of being exceeded. When this occurs, diarrhoea results. There is no evidence to suggest the nature of the maturation process or its time course, but the adult large gut appears to be incapable of being overloaded (Merritt, 1991).

Small intestinal hypersecretion results from enterotoxins of certain species of bacteria. The action of an enterotoxigenic strain of *E. coli* has been demonstrated in explants of foal intestine in culture (Batt et al., 1989). Malabsorption results when the villous architecture of the small intestine is temporarily damaged as in infection with rotavirus. In this disease, villus tips are shed and the intestinal surface area for absorption greatly reduced. Unfortunately there is, as yet, no information on motility changes in either of these states. It could be expected that an increase in luminal fluid volume would increase segmental activity but confirmation is lacking.

### Colic

Colic strictly means pain emanating from the abdomen but the term has come to mean a group of conditions affecting the abdominal portion of the alimentary tract that produce pain. Pain in the early stages is due to distension of the bowel by fluid and gas. In addition to evoking pain, distension activates a local intestinal reflex which inhibits gut motility. Stretching of the bowel wall reduces blood perfusion, resulting in local ischaemia. This also produces pain and reduces motor activity. A specific colic motor complex has been described which occurs in segments of small bowel adjacent to an ischaemic segment (King and Gerring, 1989a). These large amplitude phasic contractions may contribute to the tendency of small intestine to migrate through natural and acquired openings in the abdomen, leading to strangulation.

In so-called spasmodic colic, bowel sounds are excessively loud and it is assumed that pain results from excessive gut activity although there is no supporting evidence. Spasmodic drugs usually bring about rapid resolution, however. When blood supply to the bowel is severely compromised by strangulation, the highly metabolically active mucosa is the first to suffer ischaemic injury. Bowel stasis and ischaemia in strangulated segments favour the overgrowth of endotoxin-producing bacteria and the concentration of lipopolysaccharide in the gut lumen increases. Ischaemic mucosa is no longer an efficient barrier to endotoxin and it leaks into the peritoneal fluid and then gains access to the general circulation (King and Gerring, 1988).

The mechanisms by which endotoxin exerts its effects are complex and several mediators have been implicated. There is evidence from in vitro studies that the macrophage is capable of being stimulated by endotoxin to release tumour necrosis factor (TNF), tissue factor (TF) and plasminogen activity factor (PAI<sub>2</sub>) (Henry et al., 1991). Studies in horses support the contention that eicosanoids are released by endotoxin and the effect on bowel motility closely resembled that due to prostaglandin E<sub>2</sub>. This effect was blocked by phenylbutazone and flunixin (King and Gerring, 1989b). It is also reported that interleukin 6 activity is increased in horses given endotoxin (Morris et al., 1991). This may explain the systemic effects such as pyrexia and leucocytosis which are not very effectively blocked by cyclo-oxygenase inhibitors.

### Post-Operative Ileus (POI)

Post-operative ileus is defined as failure of coordinated propulsive activity in the alimentary tract. It does not necessarily imply complete cessation of motility. One survey (Hunt, et al., 1986) showed POI to be the most important cause of death in horses following colic surgery. They reported an incidence of 16% and mortality exceeding 95%.

An experimental model of POI was developed in ponies (Gerring and Hunt, 1986) which was self-curing over a period of 72–96 hours. In the model, the crucial role of antroduodenal coordination was demonstrated and the long refractoriness of the colon was an important feature.

By a process of pharmacological elimination, these workers defined the central role of dopamine in antroduodenal coordinated movement. The effectiveness of dopamine blockade by domperidone and metaclopramide was demonstrated in the model in which motility was rapidly restored to normality. These workers also defined the utility of the prokinetic drug, cisapride, in restoring normal motor events. This drug has since been proven in a multi-centre clinical trial involving some 250 cases (Gerring et al., 1991). Unfortunately, cisapride is no longer available for veterinary use.

It has been suggested that dopamine-mediated POI occurs in the absence of endotoxaemia. In cases of strangulating obstruction, however, endotoxaemia is also present and the effects of eicosanoids, TNF and other mediators also produce profound effects on gastrointestinal motility. Prostaglandins are most effectively blocked by phenylbutazone but no effective antagonists have yet been found for the other mediators.

### Grass sickness (Equine dysautonomia)

This disease was first reported in Scotland some 70 years ago. The disease is now regularly reported throughout the United Kingdom but only sporadically elsewhere. The condition has a wide variety of presenting signs but the most important feature is failure, to varying degrees, of motility in the alimentary tract. Dysmotility of the oesophagus results in difficulty in swallowing and lower oesophageal ulceration due to reflux of acid gastric contents. In most cases, the stomach and small intestine are dilated and distended by fluid and gas. The large intestine, in all but peracute cases, appears quite empty and contracted. This is the result of motility failure allowing resorption of almost all the water content of the chyme.

The consistent histological lesion is a vacuolating ganglionopathy affecting the caeliacomesenteric ganglia which mediate the sympathetic system to the bowel. It is suggested that the causal agent of grass sickness is associated with grazing but its nature remains obscure (Doxey et al., 1991).

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Dr. E. L. Gerring  
Edgehill  
Little Badminton Lane  
Lea, Malmesbury  
Wiltshire SN16 9NG, UK  
Great Britain