THE USE OF LIDOCAINE IN EQUINE POSTOPERATIVE ILEUS

by

KAROLIEN MERCHIERS
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Literature review as part of the Master's Dissertation

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PREFACE

First of all, I would like to express my gratitude to Professor Cathérine Delesalle and Professor Gunther Van Loon for giving me the opportunity to write this literature review about equine postoperative ileus, a topic which has always intrigued me. Also I would like to thank Miss Xanthippe Boulougouris for revising the first draft, but most of all Professor Delesalle for her insightful and in-depth remarks on the final version.

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ABSTRACT

Postoperative ileus (POI) is a highly prevalent, but often severe complication in horses after colic surgery. It leads to production of reflux, abdominal pain, distention of the small intestine, absence of defecation and is the most common cause of short-term death after colic surgery in horses. This review aims to provide a state the art overview of current research regarding the pathophysiology and treatment options for POI, focusing on the use of systemic lidocaine. The past ten years evidence has accumulated that intravenous lidocaine may have several beneficial effects on gastrointestinal motility after bowel surgery in horses. However, some authors also warn about possible disadvantages and dangers associated with its use.

Although in general, research points towards beneficial effects on GI motility associated with lidocaine use, we must be cautious, because many blind spots remain to be elucidated concerning the therapeutic effects of lidocaine in POI. In addition, many research results are clouded by a lack of uniformity, both with respect to the criteria defining POI as to the experimental approach. A more standardized approach would highly benefit the value of research results, hopefully leading to the validation of lidocaine as a valuable asset in the treatment and even prevention of POI.

KEY WORDS

Horse - Ileus - Lidocaine - Motility - Postoperative
INTRODUCTION

Postoperative ileus (POI) is a very common but serious complication in horses after colic surgery. Stricto sensu it occurs briefly in all horses that underwent abdominal surgery, often without causing prolonged problems. Most authors, however, use the term 'POI' in the sense of 'prolonged POI', indicating those cases of POI lasting longer than 1 or 2 days after surgery and leading to the expression of a range of serious clinical symptoms. Not only does (prolonged) POI have a very high incidence in horses, but on top of that it is the most important cause of death after colic surgery.

Its enormous medical, emotional and economical impact renders POI an important subject of study. However, also from a scientific point of view, it is a truly fascinating topic: due to the lack of potent and effective prokinetic drugs in horses, many clinicians and researchers are triggered to find solutions to tackle this problem. It is a question that many researchers have tried to answer. Although we now know a lot more about the risk factors and pathogenesis of POI than 10 years ago, there is still no consensus on this matter, let alone on treatment and prevention.

Many forms of treatment have been examined in extenso, and some of them have proven to be very useful in a clinical setting, such as the use of NSAIDs and several prokinetic drugs. However, a quite recent and exciting area of research is the use of IV lidocaine, possibly leading to a significant shortening of the duration of POI and even reduced odds of developing POI in the first place.

In this review, we will start by defining the pathophysiology of equine POI, followed by offering an overview of currently applied therapeutic approaches and finalizing with a focus on lidocaine. Main goal of the current work is to provide a State of the Art overview on the subject of POI, its management and to focus on the pro’s and con’s associated with systemic use of lidocaine as a prokinetic agent in POI horses.
LITERATURE REVIEW

1. POSTOPERATIVE ILEUS

1.1 (Lack of) definition

The word 'ileus' originates from the Greek word εἰλεός (eileos) derived from the verb eilein, meaning 'to twist' or 'to squeeze' 1. It is commonly used to indicate functional (as opposed to mechanical or physical) peristalsis problems in the small intestine 2. There are 3 types of ileus: adynamic ileus, paralytic ileus, and postoperative ileus 3.

Postoperative ileus or POI is a very common, but serious complication in equine colic surgery. The term is used to indicate problems of transient impairment of gastrointestinal (GI) motility occurring shortly after abdominal surgery that is not caused by any mechanical obstruction 4. According to most authors, primarily the small intestinal motility is decreased in POI, generating intestinal reflux into the stomach. However, according to some, the large intestine can also be affected, causing generalized ileus. Various stimuli can cause POI to affect different intestinal tract segments. That is why POI can lead to such a wide range of clinical symptoms 5.

Clinically POI is characterized by signs of abdominal pain, absence of defecation, distention of the small intestine, thirst because of dehydration, increase of packed cell volume (PCV), and reflux of small intestinal fluids into the stomach resulting in nasogastric reflux upon intubation 6,7. The symptoms usually start to show 2 days after surgery.

However, the absence of GI borborygmi (also called 'silent abdomen') is a too subjective parameter to be used as a conclusive diagnostic tool. Therefore the most commonly used diagnostic factor is the volume of gastric reflux removed during nasogastric intubation 3,4. More recent studies often use a cut-off volume of nasogastric reflux of >20 L retrieved during a 24 hour period following surgery or >8 L retrieved at any single intubation time after surgery 8.

There is still no real consensus concerning the exact cut-off volume of nasogastric reflux to be associated with pathological POI. Differences in used criteria to define POI between studies explain the great difference in reported prevalence of POI between studies 4. Despite this lack of consensus, a survey among diplomates of the ECEIM and ECVS revealed that the presence of reflux on nasogastric intubation remains the number one criterion used by clinicians to define POI 9.

Some authors claim percutaneous abdominal ultrasound to be a more definite and accurate detection tool for POI than nasogastric reflux. Reference ranges have been defined regarding the diameter and wall thickness of the visualized loops. On average a jejunal diameter of more than 3 centimeters is considered distended. However, according to some, a more accurate prognostic parameter to evaluate the need for surgery is the number of distended loops that can be visualized. POI is defined by transabdominal ultrasound when more than 3 distended loops of small intestine with decreased contractility are detected 10.
It remains clear that there is no standardized and objective clinical definition of POI in horses. Another important factor is, that just like in humans and rodents a “normal” physiological episode of POI occurs after every abdominal surgery. It is difficult to identify early the transition of physiological POI to pathological POI. To avoid confusion, researchers should clearly distinguish between 'normal POI', 'prolonged POI' (which continues more than 3 to 6 days postoperatively) and 'recurrent POI' (occurring after an apparent resolution of earlier POI). This is important as the latter two have major medical and economical impact. In 2006 a Clinical Consensus Committee attempted to standardize the definitions of different types of POI, however, only a minority of studies being published afterwards took into account these consensus definitions.

1.2 Incidence

According to various studies, approximately 10-47% of horses undergoing abdominal surgery develop POI. As mentioned previously, reported prevalences show a large range due to the fact that many studies apply different criteria to define POI.

In human medicine, POI has a much lower incidence of <10%, because the pathophysiological mechanisms involved are quite different when compared to horses. Moreover, associated mortality in humans is very low. Human POI is mainly a socio-economical problem leading to extra costs. In the US, the annual costs related to complications and prolonged hospital stay due to POI are estimated around 1.46 billion dollars. But in equine surgery, POI not only has significant economical consequences, but also serious medical ones. POI in horses is a highly lethal complication. Studies report mortality rates from 13% up to 86.7%.

It represents the most important cause of death after colic surgery in horses. Even in horses surviving colic surgery, long term risks of complications such as confirmed adhesions are higher in horses that developed POI than in horses that did not.

1.3 Risk factors

POI is a complex multifactorial condition associated with many risk factors. It is beyond the scope of the current review to provide an exhaustive overview of factors predisposing horses to develop POI.

A widely acknowledged risk factor for development of POI is the presence of reflux at admission: horses with preoperative reflux upon intubation at admission are 3 times more likely to develop POI. Also, performance of resection and anastomosis during surgery of the small intestine is strongly associated with an increased risk for POI. This is in contrast with the human situation in which POI is most often associated with descending colon dysfunction.

Not only the location, but also the type of small intestinal anastomosis performed may increase the incidence of POI: in one study the side-to-side stapling anastomosis technique significantly shortened the duration of POI when compared to hand sewed or stapled end-to-end anastomosis techniques.

Other risk factors are high heart rate and high PCV (> 45) at admission, due to impaired cardiovascular state and hypovolemia, elevated serum albumin (>3.3 g/dl) and total protein (>8 g/dl) levels at admission, and
the duration of anesthesia and surgery (the risk of POI increases almost twofold for each hour). According to the authors, this effect is mainly due to the duration of surgery, as the effect of anesthesia alone disappears 9 hours after cessation. Mechanical intestinal manipulation can lead to intestinal inflammation, even in non-manipulated areas, and might therefore lead to an increased risk for POI.

In one study, 88% of POI cases were associated with a strangulating obstruction. In particular strangulating pedunculated lipoma obstructions (PLO) represent an important risk factor for development of POI. Horses suffering from PLO are 3 times more likely to develop POI than horses suffering from other intestinal lesions, possibly because of the sudden and complete nature of strangulation that occurs with this type of strangulation compared to other causes of strangulation.

Endotoxemia and serum electrolyte imbalances are also associated with a higher risk of POI. For example: horses that develop POI have significant hypomagnesemia after surgery. In one rodent study, the susceptibility to POI increased with advancing age.

1.4 Pathophysiology of POI

The neuronal and inflammatory responses that are triggered during peroperative intestinal manipulation, are deemed as important triggering factors in the pathophysiology of POI. In an early phase, the autonomic motor activity - mediated through neural reflexes - is inhibited by an overreactive sympathetic nervous system. This first phase is followed by a prolonged inflammatory phase caused by the manipulation of the intestine. Recent studies complete these findings with supplementary factors, as it becomes increasingly clear that POI is a multifactorial condition with a very complex etiology.

Apart from autonomic neural dysfunction and inflammation (as primary and/or surgical stress response factors), other iatrogenic factors such as agonism by exogenous narcotics on gut opioid receptors can function as catalyzers for the development of POI. Besides that, also modulation of GI hormone activity and electrolyte derangements are key elements in the pathogenesis of POI, all leading to impaired contractility and gut wall edema. Of course one has to bear in mind that the intestinal motility can also be affected directly by the disruption of enteric neural continuity in case of resection and subsequent anastomosis, which can directly impair downstream intestinal motility.

1.4.1 Early neurogenic phase of POI

During and immediately following abdominal surgery, neural reflexes are activated. The enteric nervous system (ENS) consists of two plexuses: an inner submucosal plexus (Meissner), which controls local secretion and absorption, and an outer myenteric plexus (Auerbach), which controls gut motor activity. Sympathetic stimulation causes contraction of blood vessels and sphincters, and inhibition of GI secretion and motor activity. Incision of the abdominal wall briefly interrupts GI motility completely through adrenergic pathways, but activation of nociceptors by mechanical and/or chemical stimuli ceases once the abdomen is closed. After this first short phase, other factors such as pro-inflammatory mediators, are released by tissue damage, prolonging the POI into a second, inflammatory phase.
1.4.2 Inflammatory response

The second phase starts approximately 3-4 hours after surgery and is clinically the most relevant one. Peritoneal breach and bowel handling lead to a release of pro-inflammatory mediators triggered by different cell types. Not all cell types involved in this mechanism are currently known, but the most important ones seem to be mast cells and monocytes/macrophages.

Mast cells in the peritoneum, the mesentery, the muscularis propria and the serosal side of the intestinal wall are probably involved in the inflammatory phase: a murine model showed that manipulation-induced inflammation was reduced in mice pretreated with mast cell stabilizers as well as in mast-cell deficient mice. Even gentle inspection of the intestine at the beginning of the surgery already triggers the release of mast cell mediators, starting a whole inflammatory cascade leading to increased intestinal permeability, infiltration, release of oxygen free radicals and reduced gut motility. Triggered mast cells degranulate and release vasoactive and pro-inflammatory substances such as histamine and proteases in the peritoneal cavity. In mice, mast cell activation during abdominal surgery disrupts the epithelial barrier function and causes inflammation of the muscularis externa of the bowel. Mast cells are likely to play a role in the bacterial translocation to the mesenteric lymph nodes after intestinal surgery, contributing to the development of POI and possibly endotoxemia.

The innate immune system with its circulating monocytes and resident macrophages in the intestinal wall is thought to play a key role in the inflammatory process of POI. Under normal conditions, resident
macrophages form a sentinel network in the myenteric plexus between the longitudinal and circular muscle layer of the intestinal wall. However, surgical manipulation causes an increase in their number and leads to their activation, via mechanisms that are still not exactly known 27. These resident macrophages are activated by mast cell mediators, by alarmines or danger associated molecular patterns (DAMPs) released after mechanical cellular injury caused by manipulation of the gut. They can also be activated by pathogen associated molecular patterns (PAMPs) of intestinal bacteriae translocating through the intestinal wall in case of increased permeability caused by inflammation 12. Activation of these resident macrophages by mast cell mediators or by DAMPs leads to so called 'idiopathic' POI, whereas activation by PAMPs results in 'endotoxemic' POI 6. Activated macrophages release pro-inflammatory cytokines (TNFa, IL1 and IL6) and chemokines leading to the upregulation of endothelial adhesion molecules and the progressive influx of leukocytes into the tunica muscularis of the intestine (predominantly monocytes, neutrophils and mast cells). This influx starts 3-4 hours after surgery and reaches a maximum 18-24 hours post-surgery 12,27. Finally, the activated resident macrophages release NO and prostaglandins, respectively through inducible nitric oxide synthase (iNOS) and cyclo-oxigenase-2 (COX-2) 28. PGE2 and NO are potent smooth muscle relaxants with a direct inhibiting effect on contractility 12. NO is one of the most important regulators of intestinal motility, being released from the enteric nervous system (ENS) in a controlled manner to modulate motility patterns 27.

Conversely, inhalation anesthesia with NO does not appear to cause any inhibition of intestinal motility 25. Furthermore, relative intestinal ischemia caused by the inflammation or by direct decrease in arterial blood flow can lead to oxidative stress in the intestinal cells, perturbing the gut integrity and motility 24. In these intestinal ischemia- reperfusion lesions in horses, neutrophil granulocytes are the predominant cell type associated with inflammation 29. Neutrophils are mainly located in the blood circulation, but can be recruited in response to various inflammatory stimuli, such as the release of reactive oxygen metabolites (ROM) during reperfusion of an ischemic area. This release of ROM is caused by the fact that during ischemia, ATP is broken down to hypoxanthine, which subsequently accumulates in the tissues. Activation of local proteases converts xanthine dehydrogenase into xanthine oxidase (XO). As new oxygen is brought to the tissues by reperfusion, it functions as an electron donor during the breakdown of the accumulated hypoxanthine, leading to the formation of superoxide anion radicals. These free radicals cause further damage to the tissues and trigger the formation of neutrophil attracting chemokines, such as IL8 and leukotrienes. Neutrophils may also compromise the intestinal barrier solely by their physical infiltration across tight junctions. This infiltration causes an increase in permeability and a decrease in transepithelial resistance 30.

Eosinophilic granulocytes residing in the equine intestinal mucosa and submucosa are also capable of initiating and maintaining a local inflammatory reaction in response to mucosal injury in vitro as well as in vivo after mechanical manipulation of the colon by releasing toxic secondary granule proteins 20,31. However, the eosinophil redistribution towards the luminal surface in response to manipulation of the intestine seems less pronounced than the neutrophilic response.
Experimental mechanical manipulation of the jejunum in horses showed the weakest inflammatory reaction to enterotomy alone, and the strongest response to the use of Doyen forcepses, causing a severe local inflammatory reaction. Neutrophils also infiltrated the circular muscle layer after manual emptying of the jejunum – a procedure typically performed during colic surgery in horses with jejunal distention (stripping of the jejunum). It is thought that this neutrophil infiltration in the circular muscle layer may contribute to the development of POI \(^{20,29}\). In a mouse model, neutrophil infiltrates inhibit contractile activity both locally - via the release of NO - and globally by activating sympathetic inhibitory neural reflexes \(^{26}\). Neutrophilic inflammation in equine jejunal myenteric layers seems to peak around 18 hours after surgery, and coincides with the moment in which POI is clinically identified \(^{32}\).

However, POI goes further than only affecting the intestine locally: it is a generalised phenomenon that also impacts intestinal segments distal from the zone of manipulation or injury. This knowledge is quite recent. This can be explained by the fact that activation of inhibitory adrenergic neural pathways also impairs neuromuscular function in distant areas, and by the fact that distant resident macrophages can also be activated by circulating cytokines and endotoxins \(^{12}\). In rats it has been shown that selective manipulation of jejunum results in panenteritis \(^{33}\).

1.4.3 Hormonal disturbances
Gastrointestinal hormones and neuropeptides such as motilin, substance P (SP) and vasoactive intestinal peptide (VIP) play a role in normal gut motility, but their levels are prone to alterations because of the surgical insult on itself, and the lack of early oral intake afterwards. Motilin is a hormone with cyclic increases in the normal gut, thus enhancing gut motility, but seems to be absent or diminished in animals with POI. SP normally stimulates GI motility through direct action on smooth muscle cells and neurons in the enteric nervous system (ENS), but also is an important mediator of the inflammatory response to intestinal tissue injury. VIP is a smooth muscle relaxant that could possibly slow down post operative motility recovery \(^{24}\).

1.4.4 Pharmacological (iatrogenic) factors
Narcotic analgesics have a negative effect on GI motility. Opioids do not only have an impact on the central nervous system, but also on the peripheral \(\mu\)-opioid receptors, thereby inhibiting acetylcholine release at the myenteric plexus and thus impairing gut motility. Because of this, the use of exogenous opioids is discouraged in colic patients. However, the stress of surgery triggers the release of endogenous opioids such as enkephalins and dynorphins, which contribute considerably in the pathogenesis of POI as they have an agonism on gastrointestinal \(\delta\)-, \(\mu\)- and \(\kappa\)-receptors. Keeping in mind the very low profile pain killing drug management that is applied in colic horses, when compared to humans, these endogenous opioids are an important factor to be tackled. On top of that, opioids potentiate iNOS induction and NO-release from phagocytes \(^{34,28}\).
1.4.5 Electrolyte imbalance

Perioperative disturbances in electrolyte balance due to intestinal luminal fluid loss may constitute an important factor in the pathophysiology of POI, causing myenteric dysfunction, impaired contractility and gut wall oedema. On the other hand, they may also be the result of gastrointestinal fluid shifts during POI 24. Production of large amounts of reflux during POI for example represents an important fluid shift in these patients. Keeping in mind that a 500 kg horse has a circulation volume of 50 liters, production of 20L of reflux every 4 hours represents an important burden for the horse. This fluid shift is quite an important factor that leads to the high lethality associated with POI in horses.

2. MANAGEMENT OF POI

Most risk factors of POI cannot be controlled or are inevitable. Proper and effective management is crucial to alleviate the horse's suffering and to increase its odds of survival. The primary focus for treatment includes fluid/electrolyte supplementation and anti-inflammatory drug therapy, but given the fact that POI is a complex multifactorial condition, a whole series of measures can be taken. In this chapter we list the most important ones.

2.1 Supplementation of fluids and electrolytes

The administration of IV fluids is a widespread practice in equine POI patients to replace intestinal luminal fluid loss. Compound sodium lactate solution is the most popular choice, but it is not ideal for long term therapy because of its elevated sodium and low potassium concentrations. If the duration of the POI exceeds 2-3 days, extra supplementation with potassium is required 3. Hypocalcemia in colic horses is highly correlated with an elevated risk of ileus and even mortality. Supplementation of calcium improves clinical outcome for these patients 35.

2.2 Anti-inflammatory drug therapy

Non-steroidal anti-inflammatory drugs (NSAIDs) are pivotal for treatment of POI, as inflammation plays a crucial role in its pathogenesis. However, most nonselective NSAIDs do have an antiplatelet effect and increase the risk for gastrointestinal ulceration and prolonged hemorrhage at the surgical site. More recent specific COX-2 inhibitors lack this mechanism and can shorten POI without these side effects 25. Flunixin meglumine appears to be the most commonly used NSAID in the management of POI horses, although there is little scientific evidence of it being more efficient than other NSAIDs 9. In fact, flunixin even seems to inhibit the recovery of the transepithelial barrier function in ischemia-injured jejunum 36,37. A comparison between flunixin meglumine and meloxicam in horses with small intestinal lesions...
showed no difference in survival rates or incidence of POI, although those receiving meloxicam showed more signs of pain and higher neutrophil counts. The delaying effect of flunixine on jejunal mucosal recovery can be countered by the concurrent administration of lidocaine. This topic will be discussed in the next part of this review.

2.3 Sham feeding and early feeding

In human POI patients, chewing gum is used as sham feeding, which is thought to stimulate early recovery of GI motility after surgery. It is thought that sham feeding stimulates vagal activity, and shortens the time to first flatus and bowel movement. In humans, sham feeding has a similar stimulating effect on gastric motility to regular feeding, but the increase in gastric myoelectric activity returns to normal after only 2 minutes, whereas in regular feeding it remains increased for 30 minutes after ingestion. In analogy to the use of chewing gum in human patients, studies focusing on sham feeding have been performed in horses, using the visual presence of a hay net. Other researchers have evaluated the effect of bit chewing on gastrointestinal motility, and learned that chewing on a simple snaffle bit significantly an rapidly increases the frequency of borborygmi in the horse's abdomen.

Early enteral feeding has become a priority in the management of human POI patients, as it significantly shortens the time to first passage of stool, compared to parenteral nutrition. Conversely, patients receiving parenteral nutrition showed a significant increase in anastomotic leak rate. Total parental nutrition is thought to have a similar effect on the intestinal mucosa to malnourishment by inducing mucosal atrophy, which leads to increased bacterial translocation due to decreased gut barrier function.

While early feeding only seems to have a modest shortening effect on the duration of POI, it does not increase the incidence of complications, and it does enhance anastomotic and wound healing. This is why initiating early oral intake is commonly started before clinical resolution of POI. In horses the onset moment of refeeding has evolved the past few years, coming from a situation in which horses were withheld from all food at least 48h after surgery, to current practices, providing drinking water within hours after surgery and providing food within 24 hours after surgery.

2.4 Nasogastric decompression

Regular gastric decompression by means of nasogastric intubation is a crucial management factor to tackle POI since, if it is not performed in the face of active reflux production, gastric rupture will occur. However, this procedure also has its downsides. Studies have demonstrated that preventive intubation may impair recovery by causing fever and atelectasis. A randomized study in 200 human patients showed that nasogastric intubation made no difference with regard to anastomotic or wound complications. Patients without a NGT were more comfortable and mobile, and those with a NGT tended to have a slightly higher incidence of atelectasis and pneumonia. A review of 26 clinical trials confirmed these findings.
Complications such as fever, atelectasis and pneumonia were significantly fewer in patients managed without a NGT, although they experienced more abdominal distention and vomiting. No difference was noted in the incidence of wound or anastomotic complications or in length of hospital stay. Only 1 out of every 20 patients actually required regular gastric decompression \textsuperscript{43}. Another study of human patients revealed that the time to first passage of flatus occurred earlier in patients without NGT \textsuperscript{2}. However, in equine medicine nasogastric decompression is still widely used, which of course is essential in the face of active reflux production.

2.5 Opioids (pain management)

As mentioned in the previous chapter, both exogenous and endogenous opioids have an adverse effect on GI motility. They increase resting tone to the point of spasm and decrease prevalence of peristaltic waves. This is also the case with endogenous released morphine, the effect of which can be inhibited by the administration of naloxone \textsuperscript{41}. A study in human patients with an investigational selective opioid antagonist with extremely limited oral bioavailability has shown that GI opioid receptors play an important role in recovery from POI \textsuperscript{34}. Although it has been recommended in human medical literature to avoid the use of opioids for peri-operative analgesia in order to preserve GI motility, a recent survey demonstrated that the majority of clinicians still do not perceive pre-, intra- and postoperative opioid administration as being an important risk factor for POI. As mentioned previously, post operative pain management is as important in the prevention of POI. 87\% of respondents reporting a POI incidence above the median range used opioids perioperatively \textsuperscript{9}. To antagonise the effect of both endogenous and exogenous opioids on peripheral receptors, there are two promising drugs: alvimopan and methylaltrexone \textsuperscript{44}. They will be discussed in the following section focusing on prokinetic drugs.

2.6 Prokinetic drug therapy

The use of prokinetic drugs is common practice, but there is much debate about their efficacy. There is still no solid clinical evidence that prokinetics can overcome the powerful inhibitory effect of surgery on GI motility \textsuperscript{12}. A large number of studies has demonstrated the GI-stimulating effect of prokinetics in healthy subjects, but these do not seem to be easily applicable to POI patients. This is a difficulty often encountered in studies on healthy subjects: healthy intestine is likely to respond differently to drugs than injured or ischemic intestine \textsuperscript{45}. Also, there is still no evidence that the expensive human prokinetics may have the same or indeed even any effect in horses. For example, the identified pattern of equine serotonergic receptor population does not seem to correspond with the one in humans \textsuperscript{46}. This is important to keep in mind, since all new generation human prokinetic drugs focus on the modulation of intestinal 5-HT4 receptor populations.
Prokinetics act through various different pathways. Some increase the release or availability of acetylcholine, others increase activity at dopamine and serotonin receptors, while yet others antagonize inhibitory neurotransmitters, simulate molecules that promote contractile activity, or reduce the release of norepinephrine. The list of drugs used as prokinetics is very long, and for a large number of them there is still no solid clinical evidence of their beneficial effects in POI in horses. This chapter will only address the most frequently used ones. The most commonly used prokinetic drug in horses with POI is lidocaine, followed by metoclopramide, erythromycin and neostigmine, but these are considerably less frequently used.

a. Local anesthetics

The sympathetic reflex during the first neurological phase of POI can be blocked by the use of epidural local anesthetics, reducing the duration of POI substantially. Epidural anesthesia has been used for decades as a form of sympathectomy in POI treatment. Local anesthetics inhibit depolarization potentials by binding to sodium channels and interfering with sodium transfer through axonal membranes. Nowadays, they are also used intravenously in colic surgery because of their prokinetic effects. According to the most recent survey IV lidocaine remains the most frequently used drug with prokinetic effects in POI in horses. This will be discussed in extenso in the next chapter. The effects of lidocaine were compared in vitro to those of mexiletine, bupivacaine, tetracaine and procaine, all structure-related drugs. All of these caused a specific increase in contractility, but only lidocaine and mexillitine reduced creatine kinase release (caused by augmented muscle cell membrane permeability), as well as shortened recovery time of tissue contractility. These findings lead to the conclusion that prokinetic effects of lidocaine are based on interactions with smooth muscle cell membranes modulated by the specific structural and lipophilic features shared by lidocaine and mexiletine. Mexiletine may even have a stronger prokinetic effect in POI patients compared to lidocaine, but it lacks the analgetic, anti-inflammatory and sympathicolytic properties of lidocaine. On top of that, mexiletine can have significant GI side effects, so it is rarely used clinically. Bupivacaine is not administered intravenously because of its narrow therapeutic range.

b. Opioid antagonists

To antagonise the effect of both endogenous and exogenous opioids on peripheral receptors, there are two promising drugs: alvimopan and methylnaltrexone. Alvimopan is a peripherally acting selective µ-receptor antagonist, that does not easily cross the blood-brain barrier because of its polarity. Clinical tests in human patients taking postoperative opioid analgesics show that the use of alvimopan significantly accelerates GI recovery and promote early hospital discharge. Alvimopan does need to be administered orally before the surgery to occupy the receptors before the administration of opiates. Metylnaltrexone (NMN) is formed by adding a methyl group to naltrexone, making it less lipophilic and therefore preventing its crossing the blood-brain barrier. It is a peripheral opioid antagonist that ameliorates delayed gastric emptying and prolonged intestinal transit in healthy horses that received morphine. However, in rodents it fails to influence POI after intestinal manipulation.
c. Cisapride
Cisapride is a serotoninergic agonist that increases the release of acetylcholine in the myenteric plexus by stimulating preganglionic serotonin receptors, affecting all segments of the GI tract. It has shown good results promoting gastric emptying and small intestinal motility, but triggers potential severe cardiac side effects in humans. It also has shown excellent results in horses with POI when used in a prophylactic manner, but due to lack of IV formulations it is not being used very often. Moreover, because of the human cardiac side effects, it has been withdrawn from the market and its use is only allowed in very specific medical situations.

d. Neostigmine
Neostigmine is a reversible cholinesterase inhibitor that may have some stimulating effects on the myoelectrical activity in certain sections of the intestine by increasing parasympathetic stimuli. Based upon clinical studies, it could effectively reduce POI symptoms in horses, in particular when the large colon is involved. It is therefore the most common drug choice for treatment of large colon impactions. However, it also delays gastric emptying and causes abdominal pain. In addition, it increases the risk for developing intestinal volvulus or strangulation through its strong prokinetic effects. Occurrence of more adverse effects such as blurred vision, cramps and fatigue have greatly reduced the clinical use of neostigmine as a prokinetic in human patients.

e. Yohimbine
Alpha 2-antagonist yohimbine decreases expression of iNOS and attenuates the effect of intestinal manipulation on transit and intestinal smooth muscle contraction. It also blocks the delay in gastric emptying caused by endotoxins. It moderately improves myoelectric and mechanical activity in equine POI, but without restoring normal motility. The effect of yohimbine may be enhanced by concurrent administration of metoclopramide. There is too little information about the effectiveness of yohimbine for treatment of equine POI to recommend it. It should in any case be administered as a slow infusion to avoid excitement and tachycardia.

f. Erythromycin
Erythromycin is a macrolide antibiotic acting as a motilin receptor agonist. Motilin is an intestinal hormone of which the release is triggered by vagal influences and the passage of feed. Motilin receptors are mainly situated in the proximal part of the GI tract, but can also be found more distally. Erythromycin significantly increases myoelectrical activity in the ileum and pelvic flexure in healthy horses, but does not have a real prokinetic effect in horses with POI. Still, erythromycin is widely used as a prokinetic agent in horses, because prokinetic choice in equine medicine is limited by the lack of available drugs due to high cost or exclusivity to human medicine. Use of erythromycin can lead to severe dysbacteriosis and fatal diarrhea in horses.
All things considered, postoperative prokinetic drug treatment appears to be ineffective in horses suffering from POI, even if some of them show beneficial effects on GI motility in healthy horses. On the other hand, intraoperative profylactic administration of local anesthetics may be beneficial, as well as alpha 2-antagonists that prevent NO-release.

3. THE USE OF LIDOCAINE IN POI

3.1 General

Lidocaine (IUPAC name: 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide) is an amide type local anesthetic also used as antiarrythmic drug because of its cardiac depressant activity. It stabilizes the neuronal membrane by binding to its voltage-gated sodium channels, thereby inhibiting the ionic fluxes required to initiate an impulse.

![Molecular structure of lidocaine](image)

A few decades ago, lidocaine was used epidurally in order to decrease the duration of POI. However, when it was noticed that the use of epidural local anesthetics also resulted in significant increases in plasma levels through systemic absorption, it was hypothesized that lidocaine could have a similar beneficial effect when administered intravenously through continuous rate infusion (CRI). In the early nineties, the use of lidocaine infusion during and/or immediately after surgery was tested in human patients undergoing abdominal surgery. It significantly reduced pain, it's use was associated with a significantly shorter duration of hospital stay, and a significantly earlier return of bowel function without adverse reactions 57, 58.

Clinical trials in horses suggest that IV lidocaine has a positive effect on short-term survival, because of its protective effect against the development of POI after small intestinal colic surgery 17. It's main route of action is believed to be promotion of GI motility by blocking the sympathetic inhibitory reflexes involved in the pathophysiology of ileus, rather than a direct action on the intestine itself (as is seen in humans for example with the use of 5-HT4 agonists). It decreases sympathetic nervous system activity and has a direct excitatory effect on intestinal smooth muscle cells 59.
However, in humans the beneficial effects of lidocaine seem to be significantly more pronounced when administered epidurally than when infused intravenously. Unfortunately, epidural administration of local anesthetics does not only block sensory but also motor fibre conduction, possibly resulting in hindlimb paralysis, which obviously is to be avoided in horses. Indeed, hindquarter paralysis may be manageable in small animals, but not in horses.

There is no consensus on the prophylactic and therapeutic effects of systemic lidocaine use or even on the optimal time frame for its administration. In some studies, lidocaine was only administered postoperatively and in other studies it was administered in a prophylactic fashion which entails administration either only during, or also upfront surgery. This explains the lack of consensus. However, there is one clear message: the best results with lidocaine are obtained when it is administered perioperatively, rather than only in the postoperative period.

Most commonly, treatment with systemic lidocaine starts with the administration of a bolus or loading dose, followed by CRI (continuous rate infusion). Some authors suggest however that the use of a bolus as loading dose might be useless, and that without it the effects would be the same. Even if the vast majority of studies on the use of systemic lidocaine in colic surgery are quite positive about the results, there are a few important downsides associated with the use of the product, which should be kept in mind. The aim of the summary below is to provide a concise overview of both benefits and downsides associated with the use of lidocaine.

3.2 Benefits of systemic lidocaine to prevent POI

The use of systemic lidocaine is felt to be quite safe to start with. None of the articles we reviewed mention adverse effects, provided that toxic dose limits were not exceeded. The use of IV lidocaine at therapeutic infusion rates does not seem to provoke any changes in heart rate, respiratory rate or body temperature. Only occurrence of sudden dizziness and instability of the horse is reported when the initial loading bolus is administered at high speed.

One of the most important beneficial effects of systemic lidocaine in the context of POI is its prokinetic effect. This effect can be both direct, by stimulating intestinal smooth muscle contractility, or indirect, by reducing pain and inflammation. The direct prokinetic effects of systemic lidocaine have already been discussed in the previous part about prokinetics. A recent in vitro study showed that lidocaine enhances contractility of intestinal smooth muscle even after the ENS has been completely blocked with a powerful neurotoxin. This finding proves that lidocaine is able to affect smooth muscle cells in a direct way, and not necessarily through the myoelectric plexus. Still, this direct excitatory effect on intestinal smooth muscle cells cannot explain the prokinetic effects of lidocaine in POI horses, as propulsive motility generally only returns many hours after the lidocaine infusion.
In addition, lidocaine does not show prokinetic effects in healthy horses, but it does so in horses with POI. Therefore its impact on motility is thought to be an indirect one via its analgetic and anti-inflammatory properties. This point of view is supported by a study evaluating the small intestinal myoelectrical activity in normal horses after surgery. The results of this study did not show any increase in smooth muscle contractility after administration of systemic lidocaine. The authors estimate that possible prokinetic effects of lidocaine are more indirect, acting by decreasing inflammation or suppression of inhibitory sympathetic reflexes.

It is even quite possible that, in clinical cases, systemic lidocaine may be effective through a mechanism not present in normal horses. In vitro tests on non-injured equine jejunal smooth muscle and in vivo tests on ischemia-reperfusion injured smooth muscle tissues support this idea by showing that the frequency of lidocaine-stimulated contractility is far stronger in ischaemia-reperfusion injured tissue than in noninjured smooth muscle. Contractility was even recovered to the level recorded in noninjured control samples. This suggests that lidocaine may improve smooth muscle contractility by certain cellular repair mechanisms. The anti-inflammatory effects of systemic lidocaine probably are the most important in the context of POI. Lidocaine inhibits prostaglandin synthesis and migration of granulocytes. It puts a brake on the release of neutrophilic lysosomal proteases, phagocytosis and the production of free radicals and therefore reduces the significant neutrophilic inflammation occurring in the equine jejunum after colic surgery. It also attenuates production of prostaglandins, leukotrienes and thromboxanes by leukocytes. Pre-treatment with lidocaine decreases plasma PGE2 metabolite concentration and mucosal COX-2 expression in ischemia-reperfusion injury.

Systemic lidocaine also decreases endothelial ICAM-1 expression, thus inhibiting neutrophil migration. By this mechanism it is able to prevent oedema of the equine gut wall in ischemia-reperfusion lesions. Oedema of the gut wall is on itself a possible cause of hypomotility of the intestine. Hypoxia results in increased neutrophilic and endothelial adhesion molecule expression. Reperfusion after a period of ischemia leads to increased blood vessel filling and sloughing of the mucosa and submucosal layers away from the muscular layers. Lidocaine significantly reduces this sloughing and decreases leakage of vessels, thus preventing occurrence of interstitial oedema. Similarly it attenuates the endotoxin-induced increase of leukocyte adherence and macromolecular leakage in case of sepsis, preventing endothelial damage.

Lidocaine also seems to counteract the adverse effect of flunixin meglumine on intestinal mucosal barrier recovery. Ischemia-reperfusion injuries are very common in colic patients. Flunixin meglumine is a powerful NSAID and therefore a popular NSAID to treat colic patients, as mentioned in the previous chapter. However, flunixin does have a delaying effect on the recovery rate of mucosal barrier function after ischemic injury. Ischemia-injured jejunum of horses treated with flunixin shows an increase in neutrophil influx compared to jejunum from horses treated with saline solution. Flunixin lowers the transepithelial resistance, leading to a loss of mucosal barrier function due to loss of epithelial cells and failure to close paracellular spaces. These
paracellular spaces are unable to close because flunixin reduces the production of the prostaglandins required to stimulate their closure. Nevertheless, if lidocaine is coadministered with flunixin, the ischemia-injured jejunum recovers. This effect is due to the fact that lidocaine reduces mucosal inflammation by directly inhibiting neutrophilic infiltration. Infiltrating neutrophils travelling through paracellular spaces between epithelial cells into the small intestinal mucosa disrupt mucosal repair 68.

Another important indirect prokinetic effect of systemic lidocaine is the fact that, thanks to its analgetic properties, it lowers the required dose of general anesthetics and post-operative opioids, both of which have their own motility-suppressing effects 71. However, caution is needed because this analgetic effect is not equally efficient in different types of surgery 72. In humans, IV lidocaine lowers the use of sevoflurane by 16%, leading to more haemodynamic stability post intubation 73. When administered epidurally, it even appears to lower sevoflurane requirements by 35% 74. In horses, the use of a continuous IV infusion of lidocaine allowed for a 25% reduction of the isoflurane requirement 75 and a 26.7% reduction of the sevoflurane requirement 76. The latter study emphasises however the variability among horses: the MAC reduction varied from 6.3% to 44.6%. A test with halothane in ponies showed that the magnitude of MAC reduction with lidocaine is dose dependent. Small doses of lidocaine provoke a 20% reduction, whereas greater doses can reduce the MAC by up to 70% 77. This reduction of anesthetic requirements has no negative effect on the cardiovascular system 78. Because of all these beneficial effects, the use of systemic lidocaine results in a shortening of the duration of POI and also of hospital stay. According to one review, intra-operative administration of lidocaine can possibly even be associated with reduced odds of POI in horses, although the authors caution that the association in their review was only marginally significant, and that there might be an influence by differences in experience of hospital staff 8.

Treatment with IV lidocaine tends to shorten the duration of hospital stay quite significantly, both in humans and in horses. In one study, horses treated with lidocaine spent on average 12 days in hospital, whereas the others stayed over 17 days 62. The same effect is noted in human hospital stay duration: on average POI patients treated with lidocaine during the first 24 hours post-op can leave the hospital over a day earlier when compared to non lidocaine treated patients 58, 79, 80.

3.3 Risks and downsides of systemic lidocaine

Still not all researchers agree on the mere beneficial properties of IV lidocaine. Even though lidocaine has a short half-life, its pharmacokinetic properties can be influenced by general anaesthesia, leading to higher plasma levels and slower elimination. These prolonged and elevated lidocaine levels can lower the quality of recovery 79. Therefore it is recommended to discontinue the infusion of lidocaine 30 minutes before the end of surgery to reduce ataxia during recovery 81. Alternative ways to overcome the adverse effects of lidocaine on recovery quality are decreasing the infusion rate over time during surgery, or delaying the horse’s first attempt to stand up by administering sedation 48. Other authors recommend the use of romifidine and ketamine to sedate the horse once it is placed in the
recovery box. This approach allowed them to avoid lidocaine related problems during the recovery of approximately 2,000 horses 48.

In general, a good alternative to achieve a more stable plane of anesthesia during surgery and a significantly better quality of recovery is the intraoperative use of medetomidine instead of lidocaine 82. On the other hand, this would not have the beneficial prokinetic effects of lidocaine in POI situations. Other studies fail to measure any negative effects of intraoperative lidocaine infusion on recovery quality 83.

Another problem with lidocaine is that it can be locally irritating and may temporarily suppress immunity. In mice, chronic exposure to lidocaine can lead to impaired lymphocyte function 62. It is recommended to avoid the use of systemic lidocaine in patients with gross bacterial contamination, as it may slightly decrease the bactericidal capacity of neutrophils. This effect occurs at concentrations exceeding the average therapeutic dose, but still the risk had to be kept in mind 48.

In horses, systemic lidocaine treatment increases the thermal threshold significantly, demonstrating that it does provide efficient changes in somatic nociception. This effect does not occur in humans 48. However, systemic lidocaine does not seem to have a noteworthy effect on visceral nociception. Its visceral analgetic properties may be less pronounced than often assumed 84. The downside of the strong somatic analgetic properties of lidocaine is that it also may have analgetic effects in laminitic horses, masking the symptoms and delaying the detection of laminitis. Clinicians should be very attentive to increased heat and digital pulses even if there is no significant lameness 62.

Serum levels of lidocaine can be significantly altered by other drugs administrated in parallel. The in vitro protein binding of lidocaine in equine plasma is moderate, but highly portein bound drugs such as ceftiofur may displace lidocaine, increasing unbound lidocaine concentrations with the risk of lidocaine toxicity 85. In horses lidocaine is metabolized via the cytochrome P450 system, and excreted in the urine. General anaesthesia alters lidocain kinetics: plasma lidocaine concentrations under general anaesthesia are increased because of a decrease in clearance. This effect is due to competition for metabolization by the CYP450. Also, sevoflurane can cause a decrease in hepatic blood flow, which decreases lidocaine clearance 48.

Neonates, elderly or debilitated individuals may also have impaired or insufficient liver function, resulting in elevated plasma lidocaine levels 86.

As lidocaine has a short half life, serum concentrations of lidocaine increase rapidly when the loading dose is administered, and decrease rapidly once the maintenance infusion is discontinued. The disposition pattern of lidocaine does not seem to be affected by the effects of GI tract disease. In colic horses, it shows the same pharmacokinetics as it does in healthy horses. Even the effects of general anaesthesia seem to be effaced. This can probably be expained by the fact that horses with GI tract disease maintain a higher circulating blood volume and cardiac output during anaesthesia than healthy horses 87. If therapeutic dose limits are exceeded, lidocaine can have toxic effects. Lidocaine toxicity is a gradual,
concentration-dependent phenomenon, at first affecting the central nervous system, followed by the cardiovascular system at higher concentrations. In conscious horses, IV lidocaine overdose causes muscle tremors and ataxia. These signs do not necessarily occur as a continuum in all horses. The toxic threshold in the horse is 2-3 times the target therapeutic level ⁸⁵.

![Fig. 3: clinical signs of lidocaine toxicity with increasing plasma concentrations of lidocaine. From Torfs et al, 2009 ⁸⁶](image)

In horses, the nervous and musculoskeletal systems are more sensitive to the effects of systemically administered lidocaine than the cardiovascular system. Recovery from the effects of lidocaine overdose is rapid.
DISCUSSION

The use of systemic lidocaine in horses suffering from postoperative ileus has already shown many promising results in a large number of trials and studies, particularly when administered intraoperatively. Nevertheless, there remain several blind spots in what is actually known about its exact mechanisms of action. Additionally, a minority of adverse effects cannot be ignored and need further research. It is difficult to draw straightforward conclusions from this literature review, for a number of reasons.

First, the lack of a standardized definition of POI makes it very difficult to compare different studies. Very few authors make a clear and uniform distinction between 'physiological' and prolonged POI, or between different forms of POI caused by different mechanisms (such as strangulation, resection or even simple manipulation of the intestine) and therefore possibly following different pathogenic pathways. Sometimes even the distinction between human, murine and equine POI becomes unclear.

Second, most animal models only focus on POI following intestinal manipulation, not on POI following resection and anastomosis, even if this procedure is very common in colic surgery. The question remains to which extent the results of these experimental studies can be extrapolated to other cases of POI.

Another difficulty in comparing many clinical studies is the wide variety in administration protocols of lidocaine. In some trials lidocaine is administered perioperatively, whereas in others it is only administered postoperatively or both intra- and postoperatively.

A large number of clinical trials are based on rodent research models used as a template for human research, however more research is needed in order to know to what extent these findings can be extrapolated to horses. Undoubtedly there are interspecies differences, even if the major underlying mechanisms are quite similar in most species. For example, in humans POI is situated mainly in the distal part of the gastrointestinal tract (colon), whereas in horses it consists most often of small intestinal dysmotility.

Unfortunately we have no other option as to include reviews and studies from human medicine in this review, given the fact that there are not enough equine studies to provide a solid basis on the subject. The lack of equine studies is partly caused by the enormous financial endeavours that are needed when executing such studies. On the other hand, it is quite difficult to induce pathological POI experimentally in a reproductive fashion. Last but not least, there are the ethical issues associated with such studies. An elegant, however of course less accurate way to study the effects of lidocaine on POI in horses is the execution of large scale multi-centre studies during which many patients are monitored longitudinally. These studies are less reliable as they cannot take place in scientifically controlled circumstances, and often depend on the cooperation of both clinicians and horse owners; Moreover, in these type of studies the double blinded placebo controlled approach is impossible. In case these studies are executed in a retrospective fashion, the quality of the archiving system of participating equine centres is of key importance as well.
Another pitfall is the discrepancy between *in vitro* and *in vivo* trials. In vitro trials often use higher concentrations of lidocaine than the plasma levels allowed *in vivo*. This might distort conclusions on the effectiveness of lidocaine in live subjects.

When we were researching the exact mechanisms of action of lidocaine, we noticed that a vast majority of the reviews we found, referenced one single source, namely Rimbäck *et al* (cfr. reference 56) dating from 1990 – which is more than 25 years ago. Ironically, most of these authors conclude their articles suggesting that further research on the precise mechanisms of lidocaine is needed. However, browsing through the current literature we discovered that very few scientists actually have done so.

Articles on the possible harmful effects of systemic lidocaine on recovery quality often appear to originate from the same group of researchers. While relatively small in number, these dissonant voices cannot be ignored, as their research methods appear to be scientifically sound.

However, despite these confusing messages coming from scientific literature, there are a few clear lines to be seen. It becomes more and more apparent that lidocaine probably is beneficial for the treatment of POI. The possible downsides that have been reported so far are either not very important, or can be largely avoided/compensated. At this point the balance tilts towards the positive side, but as long as there is no certainty on the exact mechanisms of lidocaine in POI, it is impossible to draw final conclusions.

We are convinced, however, that research on the use of lidocaine in POI could make a huge step forward if a consensus would be formulated on protocols and definitions to be used by researchers focusing on that subject.

We think it would be useful to examine the similarities between the pathophysiology of POI in humans, rodents and horses and to which extent human drugs might be applicable in horses in order to let equine medicine benefit from the vast research possibilities in human medicine. Or this could even work the other way round: human medicine might also gain knowledge from research in equine POI. Ironically, lidocaine is a good example, as it was used in the treatment of equine POI long before being deployed in the treatment of human POI, at least when it comes to the systemic administration route.

Given the enormous amount of new knowledge concerning the pathophysiology of POI gathered in the past decade, renewed and further research on the precise mechanisms of lidocaine is paramount. We would also like to recommend that a more thorough distinction would be made between different types of POI based upon their etiology. For instance, we think that POI caused by intestinal manipulation may follow slightly different pathways than POI caused by intestinal resection, and therefore most probably both of them need a different pharmacotherapeutical approach.
LIST OF REFERENCES


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SAMENVATTING

Postoperatieve ileus (POI) is een frequent voorkomende, maar vaak ernstige complicatie na koliekoperaties bij paarden. De sterk verminderde of afwezige darmmotilititeit leidt tot gastroduodenale reflux, abdominale pijn, distentie van het jejenum en de afwezigheid van defecatie. POI is dan ook belangrijkste oorzaak van sterfte kort na koliekoperaties. Deze literatuurstudie heeft tot doel een stand van zaken op te maken van wat onderzoekers tot nog toe hebben ondertekt over de pathofysiologie en behandelingsopties van POI, met een bijzondere focus op de effecten van systemisch toegediende lidocaïne. Dit lokaal anesthesicum is namelijk een hot topic in het onderzoek naar nieuwe behandelingsopties voor POI. Nogal wat in vitro en in vivo studies hebben het voorbije decennium diverse gunstige effecten aangetoond van lidocaïne op de intestinale motilitie van paarden die een koliekoperatie ondergingen.

Mits correcte dosering is het immers een zeer veilig geneesmiddel, dat bij paarden met POI een duidelijk prokinetisch effect heeft zowel door zijn directe inwerking op de gladde spiercellen van de dunne darm als door zijn indirect anti-inflammatoire en visceraal analgetisch effect. Bovendien kan lidocaïne de nefaste effecten counteren van flunixine meglumine - zeer vaak gebruikt als analgeticum bij paarden met koliek - op de barrièrefunctie van de darmmucosa. Door al deze effecten kan men met behulp van lidocaïne niet alleen de overlevingskansen van koliekpaarden na abdominale chirurgie significant verhogen, maar ook hun gemiddelde hospitalisatieduur met enkele dagen verkorten.


Uit de voorzichtige balans in deze studie tussen voor- en nadelen van systemisch lidocaïne, blijkt duidelijk dat er wellicht heel wat toekomst zit in lidocaïne als middel in de strijd tegen POI bij paarden. Maar even duidelijk blijkt dat er behoefte is aan verder onderzoek om de vele blinde vlekken in de kennis over de precieze pathofysiologie van POI en in de werkingsmechanismen van systemisch lidocaïne op te helderen. Jammer genoeg is het gebrek aan uniformiteit in de precieze definiëring van POI en de diagnose ervan een
fundamenteel probleem, dat het vergelijken van heel wat onderzoeken erg moeilijk tot zelfs onmogelijk maakt. Ook een meer gestandaardiseerde aanpak van experimentele studies zou dit onderzoeksdomein een enorme stap vooruit helpen.