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A study on the significance of postoperative ileus

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Abstract

Postoperative ileus (POI) is a temporary impairment of gastrointestinal (GI) motility occurring universally after major abdominal surgery. For the majority of affected surgical patients, POI is transient, lasting approximately 3 to 5 days. The adverse effects of POI are composed of not only physiologic effects such as reduced bowel function, exacerbation of nausea and vomiting, and increased postoperative pain, but also other clinically related effects such as delay of oral feeding, prolonged hospitalization, and increased use of human and material resources.

Determination of the end of POI is somewhat controversial. The studies in the literature have used varying end points, and each has its own weakness. Bowel sounds are sometimes used as an end point, but they require frequent auscultation, their presence does not necessarily indicate propulsive activity, and they can be the result of small-bowel activity and not colonic function.

Keywords: postoperative, ileus, patient

Introduction

Flatus also is not the ideal end point. It requires a conscious patient who is comfortable reporting its occurrence to the investigator. Also, there is some question as to the correlation between flatus and bowel movements (Waldhausen, *et al*., 1990). Bowel movements are seemingly the most reliable end point. The migrating myoelectric complex (MMC) is the basal level of activity in the bowel in the fasting state, serving a "housekeeping" function (Szurszewksi, 1969). The resumption of this myoelectric complex after surgery is responsible for recovery from POI.

In humans the MMC can be recognized from the lower oesophagus to the distal small intestine, but it is most prominent in proximal jejunum. This enteric rhythm usually exhibits three phases: Phase I when only slow waves are observed without spike bursts (without actual muscle contractions); phase II when spike bursts are observed on slow waves irregularly (the occurrence of intermittent muscle contractions); and phase III with spike bursts on every slow wave for a few minutes (the contractions with the maximal contractile frequency). Rats are particularly suited for studying the MMC as the cycling period is only about 15 min in the conventional state.

Motility of the GI tract is temporarily impaired after surgery and is characterized by disorganized electrical activity and lack of coordinated propulsion (Behm & Stollman, 2003) [3]. In the stomach, studies have consistently demonstrated a postoperative period of gastric hypomotility associated with irregular and disorganized electrical activity (Clevers *et al*., 1991) [7]. Gastric propulsion may be orad, and there may also be increased pyloric tone that contributes to abnormal gastric emptying (Dauchel *et al*., 1976) [10].

Motor activity is similarly disorganized in the small bowel. Morris *et al*. (1983) observed the disappearance of phase III contractions 2 days after the operation. Miedema *et al*. (2002) also detected retrograde contractions, leading to significant delays in small bowel transit. Normal colonic motility is typically the last to return after surgery. Studies evaluating postoperative colonic motility frequently have found a period of relative hypomotility that is generally associated with random, disorganized bursts of electrical activity (Wilson, 1975; Condon *et al*., 1986) [8].

The type of surgical procedure performed can have significant effects on postoperative GI motility. Skin incision has no effect on the MMC activity of the bowel, whereas opening the peritoneum will completely inhibit the MMC (Livingston & Passaro, 1990). Some controversies exist over the timing of the MMC return after abdominal surgery.

Benson *et al*. (1994) [4] have shown that MMCs are present in the small bowel within a few hours after surgery. On the contrary, others investigators found that MMCs were abolished for 1 or 2 days after surgery, taking from 3 to 7 days for normal pattern to reestablish (Smith *et al*., 1977; Morris *et al*., 1983; Schippers *et al*., 1991).

Experimental study of postoperative ileus

We investigated the possible role of cholinergic, adrenergic, dopaminergic, serotonergic, nitrergic mechanisms, and also local anaesthetics in POI. Objective: To investigate altered gastrointestinal motility in POI and effects of potential etiological agents on the GI electrical activity to determine a cause for the development of POI and treatment. We were solving the following questions: 1) Whether the administration of different pharmacological agents stimulate the MMC or its separate phases; 2) Which pharmacological agents will induce early recovery of the MMC from POI?

Materials and methods

Experimental animals and grouping

Fifty four male Wistar rats weighing 300-350 g were used. Animals were divided into nine groups. Control group (n = 6) which included the rats with implanted three bipolar electrodes and an infusion cannula in that the electrical activity was measured on the 10th day post-surgery (after recovery). LAP

group (n = 6) in which an exploratoty laparotomy, implantation of three bipolar electrodes and an infusion cannula were considered as trauma and the study measurements were conducted on the 1st – 6th days postoperative. Other seven LAP groups in which an exploratoty laparotomy, implantation of three bipolar electrodes and an infusion cannula were considered as trauma and the study measurements were conducted on the 1st – 6th days postoperative.
These rats received from the 1st trough 3rd postoperative days neostigmine 0,2 mg/kg (n = 6), or propranolol 0,15 mg/kg (n = 6), or metaclopramide 0,5 mg/kg (n = 6), or cisapride 0,2 mg/kg (n = 6), or domperidone 0,5 mg/kg (n = 6), or L-NAME 0,1 mg/kg (n = 6), or trimebutine 2,86 mg/kg (n = 6).

Laparotomy
The rats were anesthetized with 5% ketamine solution i.p. in the dose of 0.3 ml/100 g body weight, and the operation was performed aseptically. After shaving the hair on rat abdomen, an incision (about 4 cm in length) was made. One of the three bipolar stainless steel electrodes were implanted into the muscular wall of the antrum, and the other two were implanted into the muscular wall of the small intestine at 3 cm (duodenum) and 30 cm distally to the pylorus (jejunum).
An infusion cannula for drug administration was inserted into the jejunum (5cm proximal to the jejunal electrode). The wires of the electrodes and the infusion cannula were tunneled subcutaneously in the rat's tail and drawn outside at 5-6 cm of the tail tip. The incision was sutured with silk in double layers. Approximately 2 h was required from start to end of the operation. Post-operatively, the rats are kept in individual cages with a special tether allowing the animal to move freely within the cage.
This cage design enabled to manipulate with the infusion cannula for drug administration during experiment and to connect the electrodes for recording the electrical activity. The animals were housed in an air-conditioned room at 22˚C with a 12-h light cycle, fed standard laboratory diet and given water ad libitum. The animals were fasted for 24 h before surgery (ad libitum intake of water was permitted).

Gastrointestinal motility recordings
The rats were given no food or water during the recording of gastrointestinal motility. In the control group, a 10-day recovery period was provided post-surgery. The recording of antroduodenojejunal electromyograms was performed after the animals had been fasted for 24 h with free access to water. Fasting gastrointestinal motility was recorded for 1 h.
In the other groups gastrointestinal motility was recorded for 6 days after the operation. Fasting gastrointestinal motility was recorded for 1 h before- and for 2 h after administration of the drugs. The electrodes were connected to the amplifier with the sensitivity of 0.1 mV and the frequency band of 0, 03 - 100 Hz. The signals are entered in the computer IBM PC for the review, analysis and storage. The evaluation of the GI electrical activity is performed using the spectral analysis (the assessment of slow waves) and non-linear filtration algorithm (assessment of spike potentials). Percentage of slow waves on which spike bursts were superimposed at the levels of stomach, duodenum and jejunum was calculated. In addition, a visual analysis of electromyograms is performed, i.e. the calculation of time parameters of electrical activity that characterize the MMC.
The main feature of the MMC, the activity front or phase III, was identified as a period of clearly distinguishable intense spiking activity. The amplitude should be at least twice that of preceding baseline, and propagating aborally through the whole recording segment and followed by a period of quiescence, phase I of the MMC. Phase II was characterised as a period of irregular spiking activity preceding the activity front. Periods with no detectable spike potentials were considered as quiescence. Characteristics of the MMC, such as period of the MMC, percentage of duration of the MMC phases, duration and propagation time of phase III of the MMC were evaluated.

Statistical analysis
Results were expressed as the Me (25; 75)%. The parameters of GI electrical activity were evaluated with the Mann–Whitney U-test and Friedman –ANOVA. P values less than 0.05 were considered significant.

Drugs and other chemicals
L-NAME were purchased from ICN Biomedicals Inc. Propranolol (Anaprilin) was obtained from ICN Medicinal (Moscow, Russia), cisapride (Coordinax) and domperidone (Motilium) from Janssen Pharmaceutica (Beerse, Belgium), neostigmine (Proserini) from Pharmstandard-October (Moscow, Russia), metoclopramide (Cerucal) from AWD pharma (Germany), trimebutine (Tambutin) from Dae Han New Pharm. Co. (Corea). All compounds were dissolved in saline. All drugs were administered intraintestinally in volumes of 0.2 ml. All the protocols and procedures were approved by the Institutional Review Board for Experimental Studies.

Results
The interdigestive motility pattern, the MMC, recorded in the duodenum and proximal jejunum, was observed in all animals (control group). Approximately 5 MMC was noted during 1 h. Period of the MMC in the duodenum and in the jejunum were 700 (620; 810)s and 710 (680;770)s, respectively. Percentage of slow waves on which spike bursts were superimposed for 1 h recording at the levels of stomach, duodenum and jejunum was 12,0 (9,8; 12,2)%; 40,5 (38,9; 42,4)% and 44,0 (42,1; 46,4)%, respectively. The MMC consisted of three distinct phases: phase I is period quiescence (only slow waves are observed without spike bursts); phase II is period of irregular activity (when spike bursts are observed on slow waves irregularly); and phase III is period of regular activity (spike bursts on every slow wave). Characteristics of the MMC are presented in Table 1

Table 1: Characteristics of the MMC

	Duodenum	Jejunum
percentage of duration of phase I, %	37,3 (35; 41,5)	35,6 (31,5; 40,1)
percentage of duration of phase II, %	37,4 (36,8; 45)	43 (35; 44,1)
percentage of duration of phase III, %	22,9 (20; 25,2)	23,1 (21,1; 24,9)
phase III duration, s	175 (150; 180)	170 (160; 180)
phase III migration time from duodenum to jejunum, s	410 (320; 490)	

Discussion

To observe the gastrointestinal motility under awake conditions of the rats, we implanted the infusion cannula and three electrodes at various points in the gastrointestinal tracts. Therefore, it took about 2 h from start to end of the operation and physical damage to gastrointestinal tract from the operation was greater than after laparotomy alone. In a our study, we found that suppression of the MMC and weak irregular contractions were observed in all segments of the small intestine on the 1st postoperative day after laparotomy in rats. The time of first occurrence of phase III in the jejunum and the duodenum without drug administration was, respectively, on the 2nd and the 3rd day after laparotomy. Full recovery of GI electrical activity and the MMC of small intestine we obtained on the 5th postoperative day after laparotomy.

Clinically, the disorders of gastrointestinal motility referred to as ileus are generally present after laparotomy and require several days for recovery. During the period of post-operative ileus after laparotomy, problems arise with feeding, control of body fluids and wound healing because patients cannot eat. Early recovery from post-operative ileus would thus be beneficial. In addition, ileus after laparotomy is a major impediment to patient recovery, since it necessitates the use of a nasal tube for drainage of retained intragastric fluid and for parenteral feeding.

Attempts have, therefore, been made to reduce the duration of postoperative ileus in order to permit removal of the nasal gastric tube as early as possible and to enable oral nutritional eating. It is thought that food residues and secretions remaining in the gastrointestinal tract during ileus cause abdominal distention and disorders (Tsukamoto *et al*., 2000). The primary objective of pharmaceutic intervention is to augment the pathways that stimulate motility or attenuate the inhibitory neurons that predominantly suppress activity.

Studies evaluating cholinergic agonists in the setting of POI have often produced conflicting results. Acetylcholine is released from the enteric nervous system and causes increased gut wall contractility. Acetylcholine is degraded in the synaptic cleft by acetylcholinesterase. Neostigmine is a reversible inhibitor of acetylcholinesterase and as such has been investigated as a potential treatment for postoperative ileus (Luckey *et al*., 2003). Neostigmine is the first-line treatment for colonic ileus (De Giorgio & Knowles, 2009) [11]. Kreis *et al*. (2001) found that neostigmine therapy significantly increased colonic motility in the early postoperative period in patients undergoing colorectal surgery. In three randomized, placebo-controlled trials, the success rates were 85% to 94% after the first dose (Ponec *et al*., 1999; Amaro & Rogers, 2000; van der Spoel *et al*., 2001) [1].

Conclusion

We investigated altered gastrointestinal motility in POI and effects of potential etiological agents on gastrointestinal electrical activity to determine a cause for the development of POI and treatment. Our results are consistent with the hypothesis that small intestinal motility is under tonic inhibition by adrenergic, dopaminenergic, nitrergic and nociceptive mechanisms, and release from this inhibition results in phase III activity. The main role in disappearance the MMC after surgery belongs to the activation of nonadrenergic noncholinergic mechanisms.

In the early postoperative period, endogenous NO is a major inhibitory component that seems to constitute the common final pathway of mediators and the neural pathways inhibiting the MMC in rats. The administration of almost all drugs on the 1st through the 3rd postoperative day reversed recovery of GI electrical activity. All drugs, except for neostigmine induced early recovery of the MMC from POI. Our finding demonstrated that cisapride, domperidone, metaclopramide, propranolol, L-NAME, trimebutine may be useful as prokinetic agents to induce early recovery of the MMC from POI.

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