Chirurgische Gastro Interdisziplinär enterologie

Originalarbeit · Original Article

Chir Gastroenterol 2004;20:61–65

Randomized Clinical Trial of Itopride for the Treatment of Postoperative Ileus after Laparoscopic Cholecystectomy

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Key Words
Electrogastrography · Itopride hydrochloride · Postoperative ileus · Laparoscopic cholecystectomy

Summary
Background. Postoperative ileus is a distressing and frequent adverse effect after laparoscopic cholecystectomy (LCE). The goal of this prospective study was to evaluate if the new prokinetic drug itopride hydrochloride (Ganaton®, Abbott GmbH Co. KG, Wiesbaden, Germany) may ameliorate the gastric motility in the early post-operative period after LCE. Transcutaneous electrogastrography (EGG), a noninvasive diagnostic method allowing a monitoring of gastric myoelectric activity, was used to evaluate changes of gastric motility. **Methods.** 50 patients undergoing LCE were observed for 3 days beginning with the day of surgery. The patients were perorally treated with itopride hydrochloride (50 mg per day) or placebo (sacharose) in a randomized double-blind manner. EGG records were done 6, 24, and 48 h after surgery. EGG was performed in a fasting state and after stimulation with a liquid bolus. The EGG data were recorded by a Microdigitrapper device and analyzed using spectral analysis and Fourier transformation. **Results.** When comparing both groups (itopride and placebo), nausea was found significantly more frequently in the placebo group at the day of surgery as well as on postoperative days 1 and 2. The incidence of vomiting did not differ between both groups. Moreover, there are some differences in the EGG records. On the day of surgery, 40 and 56% of the patients in the placebo and the itopride group showed a physiological EGG curve, respectively. On the 1st postoperative day it was 56 and 68% and on the 2nd postoperative day 80 and 88%. However, these differences failed to reach a significance level of $p < 0.05$, most likely because of the relative small group sizes. **Conclusion.** The perioperative use of itopride accelerates the normalization of the EGG curve after LCE. Itopride was well tolerated, and we did not observe serious adverse effects during therapy. Our data suggests that itopride can be a useful accelerator of postoperative ileus restoration after LCE. However, other studies will be necessary to unequivocally prove the beneficial effect of itopride after LCE also in comparison with other commonly used drugs.

Schlüsselwörter
Elektrogastrographie · Itopride HCl · Postoperativer Ileus · Laparoskopische Cholezystektomie

Zusammenfassung
Hintergrund: Der postoperative Ileus ist eine Besorgnis erregende und häufige unerwünschte Nebenwirkung nach laparoskopischer Cholezystektomie (LCE). Das Ziel der vorliegenden prospektiven Studie ist die Evaluation eines potentiellen Benefits des neuen prokinetischen Medikaments Itopride HCl (Ganaton®, Abbott GmbH Co. KG, Wiesbaden, Deutschland) in Hinblick auf die gastrische Motilität in der frühen postoperativen Phase nach LCE. Zur Untersuchung von Veränderungen der gastrischen Motilität wurde die transkutane Elektrogastrographie (EGG), eine noninvasive diagnostische Methode zur Beobachtung der gastrischen myoelektrischen Aktivität, verwendet. **Methoden:** In einem randomisierten doppelblinden Design wurden 50 Patienten über einen Zeitraum von 3 Tagen nach LCE peroral mit Itopride HCl (50 mg/Tag) oder Placebo (Saccharose) behandelt. Die EGG-Aufnahmen erfolgten 6, 24 und 48 h nach der Operation jeweils im nüchternen Zustand und nach Stimulation mit einem flüssigen Bolus. Die EGG-Daten wurden mittels eines Microdigitrappers erfasst und mit Hilfe der Spektralanalyse und der Fourier-Transformation analysiert. **Ergebnisse:** Verglichen mit der Itopride-Gruppe kam es in der Placebogruppe sowohl am Tag der Operation als auch am 1. und 2. postoperativen Tag signifikant häufiger zu Übelkeit. Die Inzidenz für Erbrechen unterschied sich hingegen nicht zwischen den beiden Gruppen. In Bezug auf die EGG-Aufnahmen ergaben sich folgende Unterschiede zwischen den beiden Gruppen: Eine physiologische EGG-Kurve ließ sich in der Placebo- bzw. Itopride-Gruppe am Tag der Operation in 40 bzw. 55%, am 1. postoperativen Tag in 56 bzw. 68% und am 2. postoperativen Tag in 80 bzw. 88% der Patienten nachweisen. Vermutlich aufgrund der zu geringen Gruppengrößen erreichten die Unterschiede zwischen der Itopride- und der Placebogruppe in der vorliegenden Untersuchung jedoch nicht das 0,05%-Signifikanzniveau. **Schlussfolgerung:** Der perioperative Einsatz von Itopride beschleunigt die Normalisierung der EGG-Kurve nach LCE. Itopride wurde gut vertragen, schwerwiegende unerwünschte Nebenwirkungen während der Therapie wurden nicht beobachtet. Die hier gezeigten Ergebnisse lassen vermuten, dass Itopride ein hilfreicher Beschleuniger der postoperativen Ileuswiederherstellung nach LCE ist. Allerdings sind weiterführende Studien zur Absicherung eines Benefits der Itopride-Behandlung im Vergleich mit anderen bei dieser Indikation gebräuchlichen Medikamenten notwendig.

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Introduction

Postoperative ileus (POI) is an inevitable frequent adverse consequence of surgical procedures. POI is defined as an impairment of gastrointestinal motility after abdominal or other surgery and is commonly characterized by abdominal distension, lack of bowel sounds, accumulation of gas and fluids in the bowel, and delayed passage of flatus and defecation [1]. Gastrointestinal symptoms include nausea, vomiting, and stomach cramps. Signs of ileus are thus major contributory factors of postoperative discomfort.

Recovery of the various sections of the gastrointestinal tract occurs at different rates. The duration of paralytic state usually vary from a few hours to 24 h in the small bowel, from 24 to 48 h in the stomach, and from 48 to 72 h in the colon [2]. The effective duration of ileus is therefore mainly dependent on the time until restoration of colon motility.

POI contributes to a number of undesirable consequences. Discomfort related to POI contributes to postoperative pain and may increase morbidity, especially pulmonary morbidity [3]. In addition, prolonged POI delays enteral feeding which otherwise has been shown to enhance immune function and decrease the risk of infectious complications [4].

POI occurs in 25–42% of patients without antiemetic treatment after laparoscopic cholecystectomy (LCE) [5]. Conventional strategies to avoid or treat POI include nasogastric suction, prokinetic agents, early mobilization, early enteral feeding, use of opioid-free or opioid-reduced analgesia, and the use of less invasive surgical procedures. However, the effect of these conventional procedures is limited. Results of a meta-analysis of more than 30 trials [6] suggested that gastroenteral intubation should not be used routinely in the prevention of POI.

Metoclopramide and cisapride are the most commonly studied prokinetic agents used in the management of POI. As shown by several authors [7, 8], metoclopramide has no effect on the duration of POI. For cisapride mixed results were obtained. The effectiveness of cisapride on POI may depend on the route of administration. A positive effect of cisapride on POI was demonstrated after intravenous administration. Cisapride administered rectally did not affect POI. Cisapride has recently been withdrawn from clinical use because of adverse cardiovascular effects [6]. The application of another prokinetic drug, erythromycin, failed to demonstrate any effect on the duration of POI [9].

Itopride hydrochloride is a new prokinetic agent with ancillary antiemetic properties. Itopride has a synergistic dual mode of prokinetic action: It selectively antagonizes peripheral dopamine D_2-receptors and reduces the endogenous breakdown of acetylcholine via inhibition of acetylcholinesterase. Thus, itopride stimulates endogenous acetylcholine release and additionally cause the released acetylcholine to accumulate at cholinergic receptor sites by inhibiting its degradation [10].

Table 1. Patients' demographics

	LCE	
	placebo	itopride
Median age (range), years	37 (25–59)	38 (27–55)
Sex (men/women)	9 / 11	8 / 12
Body mass index, kg/m^2	29.6 ± 3.7	28.5 ± 4.2
Duration of operation, min	52 (20–110)	48 (24–95)
Duration of anesthesia, min	65	67

Table 2. Dose scheme of itopride or placebo

	Dose applied, mg		
	6:00	12:00	20:00
1 day before surgery	0	0	50
Day of surgery	0	0	50
1st postoperative day	50	50	50
2nd postoperative day	50	50	50

Electrogastrography (EGG) is a method providing information on the motility of gastrointestinal tract or, more specifically, the stomach by recording the myoelectric activity of the smooth muscles of the gastrointestinal tract [11]. The noninvasive EGG allows a frequency analysis of gastric contractions, their regularity and amplitude. Moreover, the reaction of the stomach to certain external stimuli, e.g. food or drugs, could be investigated.

In this study, noninvasive EGG was used to evaluate early postoperative changes of gastric motility in patients during the perioperative period of LCE. The goal of this prospective study was to evaluate the efficacy of itopride with respect to gastric motility changes in the early postoperative period after LCE.

Patients and Methods

The prospective study was realized on the 1st Department of Surgery of the 1st Medical Faculty of Charles University in Prague between 2001 and 2002. The ethical committee of the faculty approved the study. Each patient signed the informed consent before being enrolled to the study.

50 patients with planned LCE were included. In the first group, 25 patients were randomized to receive itopride hydrochloride (Ganaton®, Abbott GmbH Co. KG, Wiesbaden, Germany) 50 mg/day. The second group consisted of 25 patients receiving placebo (saccharose 50 mg/day). The demographic characteristics are given in table 1. The patients did not have any serious concomitant disease (preoperative ASA I–II) of the gastrointestinal tract and did not take any other drugs affecting the gastrointestinal motility.

A randomization list was generated and identical tablets containing itopride or sacharose were prepared by personnel not involved in this study. Anesthesia was induced with intravenous administration of thiopental 5 mg/kg and intravenous suxamethonyl 0.75–1.25 mg/kg. After trachea intubation, anesthesia was maintained by sufentanyl 8 µg/kg and nitrous

Table 3. Patients' symptoms (placebo/itopride)

	Day of surgery							
	–1		0		+1		+2	
	placebo	itopride	placebo	itopride	placebo	itopride	placebo	itopride
Nausea	0	0	4	3	3	1	1	0
Retching	0	0	2	2	1	0	0	0
Vomiting	0	0	2	1	1	0	0	0

oxide. Relaxation was achieved by atracurium as required. Nasogastric tube was not inserted. At the end of surgery, atropine 0.5 mg and neostigmine 0.5 mg were administered for reversal of muscle relaxation, and the trachea was extubated. The basic principle of anesthesia was the same for both groups. Postoperative analgesia was provided by pethidine 15 mg intramuscularly.

All episodes of emetic symptoms (nausea, retching, vomiting) were recorded by a registrar who did not know which medication was given to the patients. Nausea was defined as a subjective unpleasant sensation associated with awareness of the urge to vomit, retching was defined as the labored spasmodic, contraction of the respiratory muscles without the expulsion of gastric contents, and vomiting was defined as the forceful expulsion of gastric contents from the mouth [12].

Both groups received the study medication (50 mg itopride or sacharose) in the morning of the day of surgery and a 2nd dose 12 h later. On the 1st postoperative day the study medication was given to both groups each 8 h (table 2).

Electrogastrography

Microdigitrapper® (Abbott) and the adhesive ARBO electrodes were used for EGG examination. The placement of electrodes respected the antral axis – one recording electrode was situated in the middle of the line connecting xiphoid process and navel, the 2nd electrode was placed approximately 5 cm from the first one in an angle of 45 degrees with horizontal line, right below the left rib curve. This location respected the direction of the antrum axis. The 3rd one was a reference electrode and was placed approximately 10 cm from the navel, right below the horizontal line coming through the navel.

The examined person lies on his back completely relaxed. During the investigation he must not speak, eat and drink, and he should breath normally. This fact requires a high level of patient's cooperation, especially in the early postoperative period. EGG recording was done as a stimulation test after 2 h of fasting and lasted 30 min. Then, 30 min, after drinking of 150 ml unsweetened tea we continued the recording for the same period of time. EGG recordings were performed 24 h before operation as well as 5, 24, and 48 h after surgery.

Patients' demographic data were analyzed by a variance test with Bonferroni's correction for multiple comparison and by χ^2 test. The EGG data obtained were analyzed using Fourier transformation and spectral analysis.

Results

With respect patient demographics both treatment groups showed comparable results (table 1).

When comparing both groups (itopride and placebo), nausea was found significantly more frequently in the placebo group at the day of surgery as well as on postoperative days 1 and 2 (table 3). The incidence of vomiting did not differ between both groups. No case of vomiting could be detected after the 1st postoperative day, neither in the itopride nor in the placebo group (table 3). Moreover, there are some differences in the EGG records. On the day of surgery, 40 and 56% of the patients in the placebo and the itopride group showed a physiological EGG curve, respectively. On the 1st postoperative day it was 56 and 68% and on the 2nd postoperative day 80 and 88% (table 4).

Table 4. Physiological EGG curves in patients after LCE

	Day of surgery			
	–1	0	+1	+2
Placebo, %	84	40	56	80
Itopride, %	80	56	68	88

The treatment of itopride was generally well tolerated. In this study we did not observe adverse effects such as anxiety, nervousness, insomnia, confusion, hallucinations and dystonic reactions as they were described for some other dopaminergic antagonists.

Discussion

The pathogenesis of POI is complex and depends on a variety of factors, including type of surgery, anesthetic technique and postoperative care. Patient-related factors are age, sex, obesity, menstrual cycle, a history of previous POI [13]. Experimental and clinical studies described the relation of ileus to the degree of surgical manipulation and the magnitude of the inflammatory response [1].

The inflammatory response to surgery is a potential pathogenic mechanism, resulting in POI. The degree of ileus reflects the intensity of the surgical trauma and the magnitude of the intestinal inflammatory response. Experimental studies [14] showed that several inflammatory mediators (e.g. cytokines, neurotransmitters) were released at the site of surgical injury. Although known to contribute to ileus, the definite roles of these mediators in the pathogenesis of POI remained unclear [1].

As demonstrated in experimental as well as in clinical studies, inhibitory sympathetic neural reflexes are an important mechanism to reduce gastrointestinal motility [15]. Consequently, several clinical randomized studies showed continuous, local thoracic epidural anesthetic blockade to reduce ileus [15].

As etiology of POI is multifactorial, POI may be reduced by a combined multimodal therapy including:
– early mobilization and early enteral feeding,
– laparoscopic surgical technique, and prokinetics.

Early mobilization has not been shown to shorten the duration of POI [15]. However, prolonged immobilization may lead to other postoperative complications. Therefore, early postoperative mobilization is encouraged.

A few studies showed a positive impact of early enteral feeding on POI. However, since the incidence of POI was only slightly reduced by early enteral feeding, it may be of little clinical significance [16, 17].

Another method to reduce POI is laparoscopic surgery. When compared to open procedures, laparoscopic surgical techniques were accompanied more rarely by inflammatory responses [18]. Applying these techniques, gastric emptying and fasted state of gastrointestinal motility were improved and the rate of POI was reduced [19].

The use of opioid-free or opioid-reduced analgesic regimens such as nonsteroidal anti-inflammatory drugs or other agents have been demonstrated to reduce POI [3].

The goal of this prospective study was to evaluate if itopride has a beneficial effect on gastric motility in the early postoperative period after LCE. In contrast to metoclopramide, itopride (due its high polarity and relatively high protein binding) does not readily penetrate the hematoencephalic barrier. In contrast to metoclopramide, itopride therefore did not show any relevant central nervous effects at commonly effective doses. Homeostatic reflex centers might be accessible to itopride and its dopamine D2-antagonizing effects. Nevertheless, itopride at therapeutic prokinetic doses has no effect on vital respiratory and cardiovascular function. Several clinical studies have confirmed that itopride, in contrast to cisapride, has no proarrhythmic potential [20].

As an objective indicator of the disappearance of POI, the assessment of electrical activity has widely been used, focusing on either the return of the migrating myoelectric complex (MMC) or on qualitative changes in MMC patterns. However, the MMC reflects mostly fasted-state activity, and some investigators found no correlation between return of the MMC and the clinical disappearance of POI [1]. Correlations between some of the widely used clinical endpoints, such as bowel sounds, passage of flatus and stool, and the disappearance of POI are also controversial.

The method of EGG evaluation of the gastric motility is not new, but it has been used only in experimental studies. It did not become a standard testing method yet. In our department the EGG method has been used for 6 years as supporting diagnostic method in early detection of postoperative motility disorders [21].

The transcutaneous EGG curve is usually obtained by leads attached to the abdominal wall. Curves obtained from measuring the electric potential between two abdominal electrodes have bipolar character, and this setup provides the qualitatively best signal. On the other hand, we cannot distinguish which of both leads detects a change in the electric potential. This is unproblematic if we are focused only on the frequency of the signal and if we do not analyze the shape of the separate peaks or the phase shift of curves [21, 22].

All anesthetics used for general anesthesia may depress gastrointestinal motility. However, the choice of the general anesthetic technique as well as the duration of general anesthesia were shown to have only minor (nonsignificant) effects on the frequency of POI [23].

On the other hand, the patient groups in our study did not differ with respect to patient demographics, surgical procedures, administered anesthetics and postoperatively given analgesics. Therefore, the differences between both groups can be attributed to the study drug administered. In the postoperative course, a physiological EGG curve was found significantly earlier in the itopride group when compared with the placebo group. This also correlates with an earlier disappearance of side effects such as nausea and vomiting in the itopride group. Itopride was well tolerated. In our relatively small group of 25 patients treated, we did not find any clinically major adverse effects as they were described for other routinely used antidopaminergic drugs.

Conclusion

The perioperative use of itopride decreases the incidence of nausea and vomiting after LCE. Moreover, it shortens the restoration of a physiologic EGG curve even though these differences failed to reach the significance level of $p < 0.05$. This may be due to the relatively small size of the groups investigated. Itopride was well tolerated, and we did not observe any serious adverse events. These results suggest that the itopride accelerates the restoration of POI after LCE. Itopride may therefore a useful supplementing of complex POI treatment in surgical practice. However, other studies will be necessary to unequivocally prove the beneficial effect of itopride after LCE also in comparison with other commonly used drugs.

POI has multiple pathogenetic mechanisms. As no single technique has been demonstrated to eliminate POI, the multimodal intervention with combined continuous epidural local anesthetics, opioid-free or opioid-reduced analgesics, and immediate enteral nutrition seems to be a logically consistent approach.

Acknowledgement

This work was supported by a grant IGA MZ CR ND 6868–3/2001.

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