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ORIGINAL ARTICLE

Effects of tegaserod and erythromycin in upper gut dysmotility: a comparative study

Issam Nasr · Satish S. C. Rao · Ashok Attaluri · Syed M. A. Hashmi · Robert Summers

Abstract

Objectives Tegaserod may enhance upper gut transit, but, its prokinetic effects on antral/small bowel motility and how this compares with erythromycin is unknown. We prospectively assessed and compared the effects of tegaserod and erythromycin on upper gut motility.

Methods In an open label, non-crossover study, 22 patients (M/F=4/18; mean age=37 years) with symptoms of upper gut dysmotility underwent 24-hour ambulatory antroduodenojejunal manometry with a six-sensor solid state probe. The effects of 12 mg oral tegaserod were compared with 125 mg intravenous erythromycin by quantifying pressure wave activity and assessing motor patterns.

Results Motor activity increased ($p<0.05$) in antrum, duodenum and jejunum with both drugs when compared to baseline period. The motor response with tegaserod was higher ($p<0.05$) in jejunum and occurred during the second or third hours, whereas with erythromycin, it was higher ($p<0.05$) in antrum and occurred within 30 minutes. After tegaserod, a 'fed-response' like pattern was seen whereas after erythromycin, large amplitude (>100 mmHg) antral contractions at 3 cycles per minute were seen. Following tegaserod and erythromycin, phase III MMCs occurred in 12 (55%) and 8 (36%) patients respectively ($p>0.05$).

Conclusions Both drugs increase upper gut motility and induce MMC's, but exert a differential response. Tegaserod produces a more sustained prokinetic effect in the duodenum/jejunum, whereas erythromycin predominantly increases antral motor activity.

Keywords Dysmotility · erythromycin · small bowel manometry · tegaserod

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Introduction

Functional gastrointestinal symptoms are common in the general population, with a reported prevalence of 25–40%.[1] They are responsible for up to 33% of gastroenterology office consultations in Great Britain and 40% in the United States.[2] These patients present with a variety of symptoms that include fullness, bloating, nausea, vomiting, abdominal pain, diarrhea, constipation or weight loss. These symptoms suggest an upper or lower gastrointestinal dysfunction that may be caused by a sensory or mixed sensori-motor disorder.

Physiological studies of patients with symptoms of upper gastrointestinal dysmotility have demonstrated delayed gastric emptying, abnormal small bowel motility, and visceral hypersensitivity.[3,4] Because there is no approved treatment, and the pathophysiology continues to evolve, current therapies largely consist of empirical trials of anti-secretory agents, anti-*Helicobacter pylori* therapies, antidepressants, antinausea and prokinetic agents.[4]

Recently, 5-Hydroxytryptamine (5-HT), acting through 5-HT_1, 5-HT_3 and 5-HT_4 receptors has been shown to play a significant role in gastrointestinal motility, sensation and secretion.[5–9] Stimulation of 5-HT_4 receptors has been shown to trigger the peristaltic reflex in animals.[10,11] Tegaserod, a selective 5-hydroxytryptamine-4 (5-HT_4) receptor partial agonist has been shown to stimulate motility throughout the gastrointestinal tract.[10,11] In healthy subjects, tegaserod had no effect on gastric emptying, but accelerated orocecal and colonic transit.[12] Another clinical study demonstrated

that tegaserod enhanced fasting gastric compliance and significantly accelerated gastric emptying and gut transit in healthy subjects.[13] Large controlled trials have shown that it improves abdominal pain, bloating, stool frequency and consistency in female patients with constipation-predominant irritable bowel syndrome,[12] and in chronic constipation.[14] However, very little is known regarding the effects of tegaserod on antral and small bowel motor activity in humans.

Erythromycin, a macrolide antibiotic and a motilin agonist, is widely used as a promotility agent.[15,16] Clinical trials have demonstrated that erythromycin improves gastric emptying in diabetic gastroparesis.[17–19] However, a recent randomized controlled trial showed that erythromycin was not effective as a prokinetic agent when compared to placebo in the treatment of postoperative ileus after urological surgery.[20] Furthermore, its prokinetic effects on the upper gut have not been compared with another promotility agent such as tegaserod.

We tested the hypothesis that tegaserod increases pressure activity in the stomach and small bowel, and that its motor effects are similar to those of erythromycin. The aim of our study was to examine and compare the effects of tegaserod and erythromycin on the motor activity of the antrum, duodenum and jejunum in subjects with symptoms of upper gastrointestinal dysmotility.

Methods

Subjects

Consecutive patients referred to a tertiary care center with unexplained and persistent (>6 months) symptoms, suggestive of upper gastrointestinal dysmotility, were invited to participate in this study. For at least 12 weeks, during the previous year, all of these patients reported at least two of the following symptoms: abdominal pain, fullness, bloating, nausea, vomiting, diarrhea, indigestion, or weight loss. Within 2 months prior to the study, all patients underwent standard investigations that included esophagogastroduodenoscopy (EGD), right upper quadrant ultrasound or CAT scan, routine hematology, liver biochemistry, and *H. pylori* testing to exclude any luminal pathology or secondary causes for their symptoms. Additional exclusion criteria were pregnancy or breast-feeding; abdominal surgery other than appendectomy and cholecystectomy, and use of drugs that affected motility such as opiates and anticholinergics. Each participant completed a medical interview, received a full physical examination, and responded to a symptom questionnaire. All subjects gave written informed consent for the study which was approved by the Human Investigation Review Board.

Questionnaire

An upper GI-dysmotility symptom questionnaire was administered to all subjects prior to the study. It enqui-red about the presence or absence of the following eight symptoms in the preceding 2 weeks: fullness, bloating, nausea, vomiting, abdominal pain, diarrhea, indigestion and chest pain. If present, they were asked to rate its frequency, intensity, and duration on a 0–3 Likert-like scale; 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe symptoms. On this scale, the total score for each symptom could range from 0 to 9. A mean total score was calculated for each symptom. A comprehensive drug history, including dosage and duration of use of any anticholinergic or prokinetic medications (metoclopramide, erythromycin, tegaserod, domperidone), and any unintentional weight loss in the preceding 6 months were also recorded.

Manometric assembly

We used a 250-cm long elastic catheter that was custom built with six solid state pressure transducers (Konigsberg Instruments, Pasadena, CA, USA). The probe was connected to a six-channel portable solid-state digital datalogger (MicroDigitrapper 4 Mb, Medtronics; Minneapolis, MN, USA) with a sampling frequency of 4 Hz, A-D conversion, temporary storage up to 4 Mb and event markers. Upon completion of the study, data were downloaded to an IBM-compatible personal computer for analysis (Gastrosoft version 6.3; Multigram, Synectics Medical Inc., Minneapolis, USA).

Study protocol

We performed antroduodenal jejunal manometry using the following protocol (Fig. 1): Following an overnight fast, a six-sensor solid-state manometry probe was placed under endoscopic and fluoroscopic guidance such that two sensors that were located 5 cm apart were placed in the antrum, two sensors 15 cm apart were located in the duodenum, and two sensors 15 cm apart were located in the jejunum. The recorder was placed in a shoulder bag and the patients slept at home and were free to ambulate throughout the study. One and a half hour after probe placement, all patients, in the fasted state, received 125 mg of intravenous erythromycin lactobionate. Four hours later, all patients ate a standard 500 kcal meal consisting of a chicken sandwich, 6 oz (180 mL) of milk, a cookie and a banana. The macronutrient composition was 52% carbohydrates, 25% protein and 23% fat. The following morning they were instructed

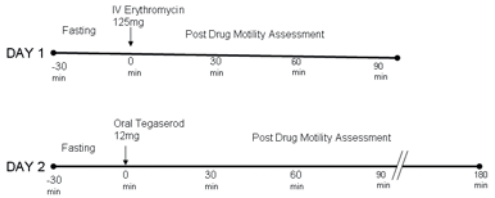

Fig. 1 Schematic diagram of the study protocol

to wake up at 6 am. At 8 am, they were asked to take 12 mg of oral tegaserod (Zelnorm, Novartis pharmaceuticals, NJ, USA). The motility recording was continued until 11 am and thereafter the probe was removed. An event marker was attached to the recorder, and the patients were encouraged to use this and mark the time of events such as eating, walking, and sleeping or to indicate the occurrence of symptoms such as abdominal pain, passing flatus, etc. They were also provided with a diary, in which they described any event(s) or symptom(s), and recorded its time and duration.

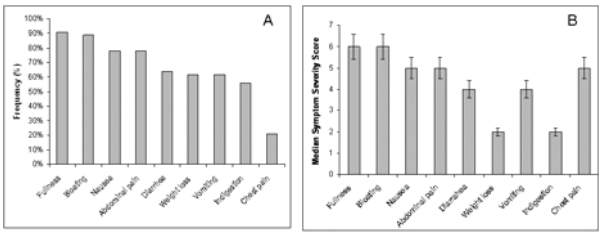

Fig. 2 Prevalence of dyspeptic symptoms (panel A) and the median total severity score of each symptom at baseline (panel B)

Data analysis

After completion of the recording, the data stored in the portable recorder was transferred to a personal computer for visual display and analysis. Tracings were analyzed by visual inspection for motility patterns such as phase III MMCs, and for quantitative assessment of pressure activity such as area under the curve (AUC) of the pressure waves. Pressure waves that occurred simultaneously in several channels with similar amplitude and duration of ≤3 seconds were identified as artifacts and excluded from the analysis. Phase III MMCs were defined as propagating cluster of repetitive contractions with a frequency of 3/minute in the antrum and 11–13/minute in the duodenum and with a duration of at least 3 minutes that was followed by a period of motor quiescence.[21] Their incidence, duration, propagation velocity and site of origin were calculated. The pressure activity data from each of the two sensors located in the antrum, duodenum, and jejunum were averaged and were used as an overall index of motility for each segment. Motor activity in the first half hour prior to ingestion of each drug was used as the baseline period. Data were analyzed for 90 minutes after erythromycin, and for 180 minutes following tegaserod.

Statistical analysis

The data were found to be non-parametric and were therefore analyzed using the Mann–Whitney *U*-test and ANOVA with Kruskal–Wallis analysis of rank, where appropriate, using a commercially available software package (Prism 3.0; GraphPad Software, Inc., San Diego, CA, USA). A p-value <0.05 was considered significant. The data are expressed as the median ± interquartile range (q_u-q_L).

Results

Demographics and symptom patterns

Twenty-two subjects (four men) with a mean age (SD) of 37 (12) years were recruited for the study. The prevalence of dysmotility-like symptoms is shown in Fig. 2A. Fullness and bloating were the most common symptoms, but over 50% of subjects reported one or more of the other five symptoms that are commonly described by patients with upper gastrointestinal dysmotility. The median total score revealed that most of the symptoms were not only frequent but also moderately severe in intensity and duration (Fig. 2B). Fig. 2B also summarizes the median total score for each symptom in this group of patients.

Nausea was reported after erythromycin and tegaserod administration in five and six patients respectively. However, all of these subjects reported significant nausea at baseline prior to the study.

Effects of tegaserod on antroduodenal and jejunal motility

Tegaserod increased (p<0.02) motor activity in all three segments of the upper gut when compared to the baseline period (Table 1). The effect of tegaserod on upper gut motor activity extended into the third hour of recording. This increased motor activity peaked between 120 and 150 minutes in 10 patients, and between 150 and 180 minutes in 12 patients. In addition, the increased motor response was higher (p<0.05) in jejunum when compared to the duodenum or

Table 1 Comparison between baseline median area under the curve (AUC) of pressure wave before every drug and median peak AUC induced by that drug

	Erythromycin			Tegaserod		
	Baseline	Peak	p	Baseline	Peak	p
Antral AUC (mmHg s)	20751	31610	0.001	24186	29345	0.02
Duodenal AUC (mmHg s)	21739	27989	0.001	21658	34766*	0.001
Jejunal AUC (mmHg s)	17757	23819	0.001	17428	31825*	0.001

*p<0.05; tegaserod *vs.* erythromycin

antrum, and occurred mostly during the second and third hours (Fig. 3).

The pattern of motor response was similar to a 'fed-response' with intermittent, phase II-like pressure waves that occurred at two to three cycles per minute in the antrum and 10–14 cycles per minute in the small bowel (Fig. 4). A single phase III MMC was observed in 12 subjects, two phase III MMCs were seen in four subjects and three phase III MMCs in one subject. Seven of the 17 MMCs originated in the antrum, and 10 in the duodenum. Most of the phase III MMCs occurred in the first 2 hours (six in the first, and nine in the second hour), and only two were observed in the third hour. The average duration of MMCs in the antrum, duodenum and jejunum were 5.1 (SD 2.3), 6 (2.7) and 7 (2.7) minutes, and the propagation velocities were 7.5, 5.2 and 4.4 cm/minute, respectively.

Effects of erythromycin on antroduodenal and jejunal motility

Erythromycin also increased ($p<0.01$) motor activity in the antrum, duodenum and jejunum when compared to the baseline period (Table 1). The increase in motor activity was short lived, and typically lasted up to 1 hour after infusion. It was significantly higher ($p<0.05$) in the antrum during the first 30 minutes and in the duodenum and jejunum during the next 30 minutes (Fig. 5).

Erythromycin also induced large amplitude (>100 mmHg) antral contractions usually at three cycles per min (Fig. 6). Following erythromycin infusion, a phase III MMC-like response was seen immediately in eight subjects (36%). All phase III MMC-like responses originated in the antrum with an average response duration in the antrum of 15.25 minutes (SD 9.7), duodenum of 5.5 minutes (SD 2.0) and jejunum of 6.6 minutes (SD 2.9). The propagation velocity of the MMC response was 3.3 cm/minute in the antrum, 4.2 cm/minute in the duodenum and 7 cm/minute in the jejunum.

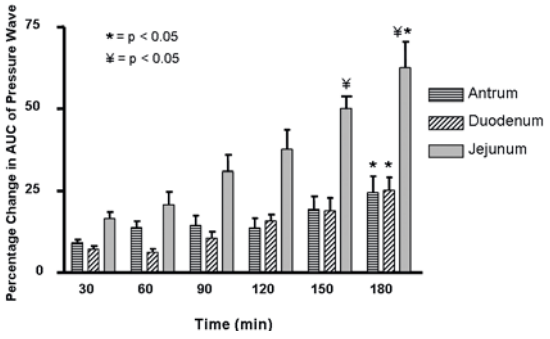

Fig. 3 Effects of tegaserod on antral, duodenal and jejunal motility Data represent % change of median AUC from median control period *$p<0.05$ *vs*. baseline; ¥$p<0.05$ jejunum *vs*. antrum or duodenum

Comparison of effects of erythromycin and tegaserod on antroduodenal and jejunal motility

The pressure activity in the antrum, duodenum, and jejunum during the baseline period (half an hour prior to drug administration) were similar for erythromycin and tegaserod (Table 1). After tegaserod, the maximum increase in motor activity (peak) was observed in the third hour whereas after erythromycin it was observed in the first hour. When we compared the peak motility effects that were induced by each drug, we found that the effects of tegaserod on duodenal and jejunal motor activity were higher ($p<0.05$) than that induced by erythromycin (Table 1). Also, in the third hour, the tegaserod induced increase in antral motor activity was similar to that of erythromycin ($p=0.3$) (Table 1).

Discussion

In this prospective, open label study, we evaluated and compared the effects of erythromycin and tegaserod in patients with persistent symptoms of upper gastrointestinal dysmotility. To our knowledge, this is the first study that has examined the prokinetic effects of tegaserod on upper gut motility in humans, particularly in patients with dysmotility.

We found that tegaserod increased motor activity in the antrum, duodenum and jejunum by inducing a 'fed-response' like pattern that was most pronounced in the jejunum. The effects lasted for at least 3 hours. Because the recording was discontinued after 3 hours, we were unable to fully quantify the motor effects of this drug. This increase in motor activity together with the induction of MMCs in several subjects most likely represented a prokinetic effect

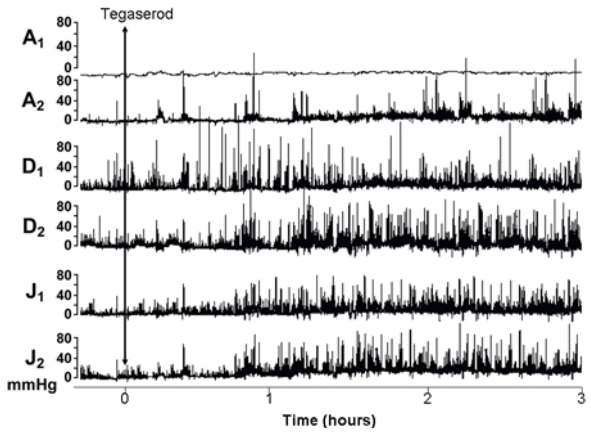

Fig. 4 Typical upper gut motility response to tegaserod. A1 and A2 represent the antral motility channels, D1 and D2 duodenal motility channels and J1 and J2 Jejunal motility channels. Arrow=time of tegaserod administration. As can be seen, a fed-response like pattern is induced in the antrum, duodenum and jejunum, starting approximately 1 hour after ingestion of tegaserod. The response appears to last for at least 3 hours

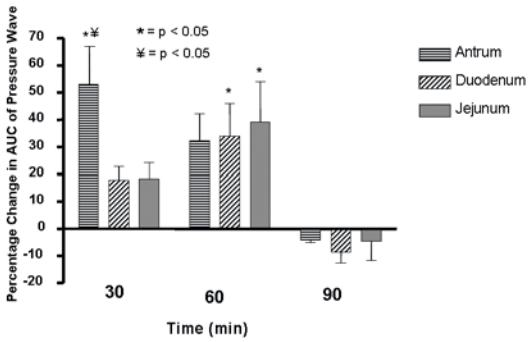

Fig. 5 Effects of erythromycin on antral, duodenal and jejunal motility. Data represent % change of median AUC from median control period. *p<0.05 *vs*. baseline; ¥p<0.05 antrum *vs*. duodenum or jejunum

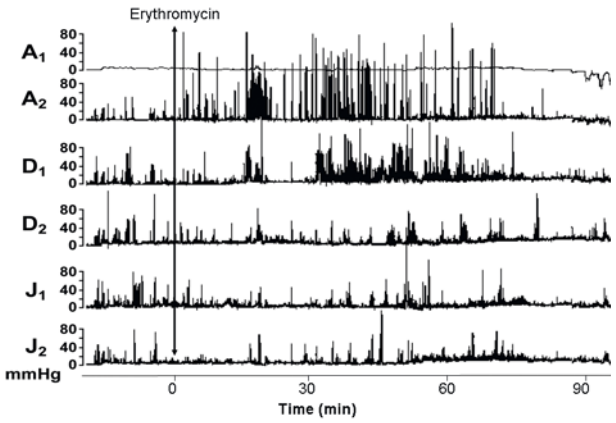

Fig. 6 Typical upper gut motility response to erythromycin. A1 and A2 represent the antral motility channels, D1 and D2 duodenal motility channels and J1 and J2 Jejunal motility channels. Arrow = time of erythromycin administration. Within 5 minutes after erythromycin infusion, strong, high amplitude (>100 mmHg) contractions can be seen in the antrum, and at 30 minutes some increase in the duodenal and jejunal motor activity

with improved peristaltic activity in the upper gut. This observation was consistent with previous reports that showed an acceleration of gastric emptying and small bowel transit with tegaserod.[14,16]

Erythromycin also enhanced motor activity in the antrum, duodenum and jejunum when compared to the baseline period. During the first 30 minutes there was over 50% increase in the AUC of pressure waves in the antrum. During the next 30 minutes there was a similar and approximately 33% increase in motor activity over baseline. However, this effect was short lived and was significantly higher in the antrum than in the duodenum or jejunum. In addition, erythromycin induced a phase III MMC-like response in more than one-third of subjects. These findings are in agreement with the known prokinetic effects of erythromycin that include accelerated gastric emptying, increased antral contractions and enhanced antroduodenal coordination.[16,19,22]

Erythromycin is a potent gastric prokinetic,[16,17] but clinical studies of motilin receptor agonists such as erythromycin and ABT-229 have been disappointing in the treatment of patients with upper GI dysmotility symptoms.[23] This is partly due to the suppression of the gastric accommodation and presumed antral distension by motilides which may negate promotility benefits. Despite limited or negative impact on dyspeptic symptoms, intravenous erythromycin is widely used as a prokinetic agent particularly in patients with gastroparesis and as demonstrated by this study can be useful. Long-term use, however, is limited by its anti-bacterial action, development of tolerance to the drug and drug–drug interactions.[22]

In contrast, tegaserod not only appears to increase gastric and small bowel motility, but also has been reported to improve gastric accommodation.[24,25] Thus, in selected patients with persistent symptoms of upper gastrointestinal dysmotility, tegaserod by improving upper gut motility may be clinically useful. However, in a large randomized controlled trial, only a modest therapeutic effect was seen with tegaserod in patients with functional dyspepsia.[26] This inadequate therapeutic response may in part be due to the heterogenous population that was examined. In a more recent open label study, tegaserod was shown to be useful in improving dyspepsia and reflux symptoms in patients with chronic constipation.[27]

The limitations of our study include the smaller sample size, and the acute nature of our assessment. Whether these acute prokinetic effects translate into long-term clinical benefit, merits further appraisal. In addition, there was a lack of blinding to the drug administered; however, the motility data were analyzed by one investigator who was blinded to the nature of the clinical problem. Because of the comparative, exploratory and mechanistic nature of the study, a placebo control was not feasible. Patients were ambulatory during the recordings and this may have affected their motility. However, during the data analysis, artifacts were identified and eliminated and the motility index following each drug administration was compared to the baseline activity from the same subject. While erythromycin's half life is 1–2 hours,[28] tegaserod's is estimated to be 11 hours.[29] This difference in pharmacokinetics together with the route of administration (intravenous *vs*. oral) may also explain some of the differences that were observed in the study with regards to the onset and duration of motor effects on the upper gut. We chose two different routes of administration for each drug to simulate their usage in routine practice.

In conclusion, we found that both drugs can increase upper gut motility, and induce MMC's, but exert a differential response. Erythromycin predominantly increases antral motor activity but its effect is short lived, either because of the

pharmacokinetic effect of the drug or its intravenous route of administration or both. Tegaserod induces a more pronounced prokinetic effect in the jejunum as well as the antrum and duodenum and causes a more sustained increase in upper gut motor activity. These data suggest that tegaserod may be useful as a prokinetic agent for the treatment of gastric and small bowel dysmotility. The differential effects observed in this study may allow clinicians to better tailor the prokinetic drugs, based on the nature of upper gut dysfunction.

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IMAGE

Blind pouch syndrome following enterocolic anastomosis – multidetector computed tomographic findings

A 60-year-old man with complaints of diarrhea and a previous history of colonic carcinoma which was operated several years back underwent a multidetector computed tomographic (MDCT) scan of the abdomen which revealed a subtotal colectomy status with preservation of the sigmoid colon and the rectum. A side-to-side anastomosis between the ileum and the sigmoid colon was noted (Fig. 1). The blind end of the anastomosed ileal loop was dilated and contained mottled contents suggestive of retained fecal matter. There was surrounding minimal mesenteric fat stranding (Fig. 2) and mesenteric lymphadenopathy. The CT features were suggestive of post-surgical blind pouch of the small bowel.

Blind pouch syndrome is a well-recognized complication of small bowel anastomosis. Abnormal peristalsis results in filling of the pouch, with stagnation, bacterial overgrowth and subsequent diarrhea.[1] These are most commonly seen after side-to-side anastomosis.[1] It is important to identify them as complications such as small bowel obstruction. enteroliths, ulceration, bleeding and anemia are known to occur.[1] Distinguishing a diverticulum from a blind pouch may be difficult on CT. However identification of adjacent surgical clips helps to confirm the diagnosis.[1] The maximum sac diameter in proven cases of blind pouch syndrome in a previous study[1] ranged between 3.7 cm to 11 cm. In our case the maximum sac diameter was 4.4 cm. The mesenteric fat stranding and the enlarged mesenteric lymphnodes support the diagnosis of bacterial infection within the pouch[1] and are not seen in an otherwise uncomplicated case of side-to-side anastomosis.

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Reference

1. Sandrasegaran K, Maglinte DD, Rajesh A, *et al.* CT findings for postsurgical blind pouch of small bowel. *AJR Am J Roentgenol* 2006;186:110–3.

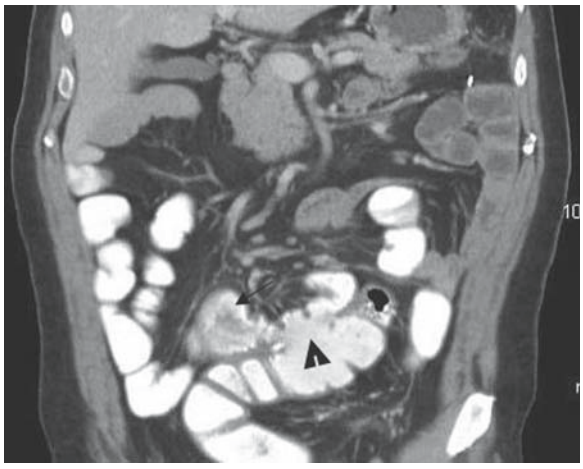

Fig. 1 Coronal reformatted MDCT study of the abdomen reveals post enterocolic anastomosis (black arrow head). The blind end of the anastomosed ileal loop is dilated containing fecal residue (black arrow)

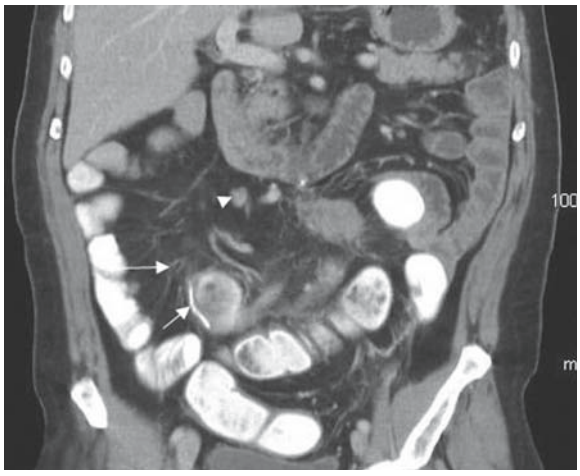

Fig. 2 Coronal reformatted MDCT study reveals surgical suture at the distal end of the blind pouch (short white arrow). There is associated mesenteric fat stranding (long white arrow) and lymphadenopathy (white arrowhead)