Hyperamylasemia and pancreatitis following spiral enteroscopy

Christopher W Teshima MD[1], Huseyin Aktas MD[1], Ernst J Kuipers MD PhD[1,2], Peter B Mensink MD PhD[1]

CW Teshima, H Aktas, EJ Kuipers, PB Mensink. Hyperamylasemia and pancreatitis following spiral enteroscopy. Can J Gastroenterol 2012;26(9):603-606.

BACKGROUND: Acute pancreatitis is a significant potential complication with double-balloon enteroscopy. Hyperamylasemia is frequently observed after both double-balloon enteroscopy and single-balloon enteroscopy but often without associated pancreatitis. Whether the same phenomenon occurs with spiral enteroscopy is currently unknown.
AIMS: To determine the incidence of pancreatitis and hyperamylasemia following spiral enteroscopy.
METHODS: A prospective cohort study of consecutive patients undergoing proximal spiral enteroscopy was conducted. Serum amylase levels were measured immediately before and following the procedure, combined with observation for clinical signs of pancreatitis.
RESULTS: A total of 32 patients underwent proximal spiral enteroscopy, with a mean total procedure time of 51 min (range 30 min to 100 min) and mean depth of insertion of 240 cm (range 50 cm to 350 cm). The diagnostic yield was 50%, with 31% of all procedures being therapeutic. While no patients exhibited signs that raised suspicion of pancreatitis, hyperamylasemia was common (20%). Hyperamylasemia was not significantly associated with procedure duration or depth of insertion but was linked to patients with Peutz-Jeghers syndrome and with the use of propofol sedation, suggesting that it may be more common in difficult cases.
CONCLUSIONS: Postprocedural hyperamylasemia occurred frequently with proximal spiral enteroscopy, while no associated pancreatitis was observed. This finding suggests that hyperamylasemia may not necessarily reflect pancreatic injury nor portend a risk for pancreatitis.

Key Words: *Hyperamylasemia; Pancreatitis; Small bowel; Spiral enteroscopy*

L'hyperamylasémie et la pancréatite après une entéroscopie spiralée

HISTORIQUE : La pancréatite aiguë est une complication potentielle importante de l'entéroscopie à double ballonnet. L'hyperamylasémie est fréquente après une entéroscopie à simple ou à double ballonnet, souvent sans pancréatite associée. On ne sait pas si le même phénomène se produit en cas d'entéroscopie spiralée.
OBJECTIF : Déterminer l'incidence de pancréatite et d'hyperamylasémie après une entéroscopie spiralée.
MÉTHODOLOGIE : Les auteurs ont effectué une étude de cohorte prospective de patients consécutifs ayant subi une entéroscopie spiralée proximale. Ils ont mesuré les taux d'amylase sérique prospective immédiatement avant et après l'intervention, de même que l'observation des signes cliniques de pancréatite.
RÉSULTATS : Au total, 32 patients ont subi une entéroscopie spiralée proximale, pour une durée d'intervention moyenne de 51 minutes (plage de 30 minutes à 100 minutes) et une profondeur d'insertion moyenne de 240 cm (plage de 50 cm à 350 cm). Le rendement diagnostic était de 50 %, et 31 % de toutes les interventions étaient d'ordre thérapeutique. Aucun patient n'a présenté de signes évocateurs d'une pancréatite, mais l'hyperamylasémie était courante (20 %). L'hyperamylasémie ne s'associait pas de manière significative à la durée de l'intervention ou à la profondeur de l'insertion, mais était liée au syndrome de Peutz-Jeghers et à la sédation au propofol, laissant supposer qu'elle serait plus courante dans des cas difficiles.
CONCLUSIONS : L'hyperamylasémie est fréquente après une entéroscopie spiralée proximale, mais les auteurs n'ont observé aucune pancréatite connexe. Cette observation laisse croire que l'hyperamylasémiene reflète pas nécessairement une lésion pancréatique ou un risque de pancréatite.

Spiral enteroscopy (1,2) is the most recent form of small bowel endoscopy to join the techniques of single-balloon enteroscopy (SBE) (3) and double-balloon enteroscopy (DBE) (4,5) for the investigation of small intestinal diseases. Large series have been performed, with DBE demonstrating that the most common, significant adverse events with the procedure are bleeding (0.2% to 0.8%), perforation (0.3% to 0.4%) and pancreatitis (0.2% to 0.3%) (6,7). While considerable attention has focused on the occurrence of post-DBE pancreatitis, asymptomatic hyperamylasemia remains quite common (8). In the first study reporting complications with SBE (9), there were no cases of pancreatitis, but again, hyperamylasemia was frequently encountered. Currently, there are no published studies regarding complications following spiral enteroscopy, and the risks of pancreatitis and hyperamylasemia remain unknown. Accordingly, the aim of the present study was to determine the incidence of pancreatitis and hyperamylasemia after proximal spiral enteroscopy.

METHODS

Study design

Consecutive patients undergoing proximal spiral enteroscopy at Erasmus MC University Medical Center, a tertiary referral university hospital in Rotterdam, The Netherlands, were prospectively included in the study after providing written informed consent. Demographic and clinical data were recorded, as were insertion depth, duration, sedation requirements, diagnostic and therapeutic outcomes, and adverse events. Blood samples were collected immediately before and 2 h to 4 h following proximal spiral enteroscopy for measurement of serum amylase and C-reactive protein (CRP) levels. All patients were clinically evaluated 2 h to 5 h after the procedure to assess for abdominal complaints that could be suggestive of pancreatitis. Any need for overnight hospital stay or readmission was noted. All patients were contacted the following day for evaluation of complaints. Referring physicians and/or the general physician were asked to report adverse

[1]*Department of Gastroenterology and Hepatology;* [2]*Department of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands*
Correspondence: Dr Christopher W Teshima, Division of Gastroenterology, University of Alberta Hospital, 1-51 Zeidler Ledcor Centre, Edmonton, Alberta T6G 2X8. Telephone 780-248-1673, fax 780-492-9416, e-mail teshima@ualberta.ca
Received for publication September 27, 2011. Accepted January 10, 2012

TABLE 1
Clinical and endoscopic data (n=32)

Patient characteristics	
Age, years, mean (range)	64 (32–86)
Female sex	19 (59)
Indication for enteroscopy	
Anemia	26 (81)
Peutz-Jeghers syndrome	4 (13)
Other*	2 (6)
Enteroscopy data	
Conscious sedation	20 (63)
Propofol sedation	12 (37)
Insertion depth, cm, mean (range)	240 (50–350)
Procedure time, min, mean (range)	51 (30–100)
Diagnostic yield	16 (50)
Angiodysplasia	7 (22)
Polyp(s)	4 (13)
Tumour	3 (9)
Ulcer(s)	2 (6)
Therapeutics†	10 (31)

*Data presented as n (%) unless otherwise indicated. *Abdominal pain with abnormal imaging (n=2); †Polypectomy (n=4; removed 24 polyps), argon plasma coagulation (n=6)*

outcomes within 30 days of the procedure. The study was approved by the institutional review board of Erasmus MC University Medical Center.

Spiral enteroscopy procedure

Spiral enteroscopy was performed using the Discovery SB spiral overtube (Spirus Medical Inc, USA) in combination with either the Olympus SIF-Q160Y SBE endoscope (Olympus Optical Co, Japan) or the Fujinon EN-450P5 or EN-450T5 DBE endoscopes (Fujinon Inc, Japan) without attached balloons. The spiral overtube has raised helices at its distal end, a locking device to fix the overtube to the endoscope and two foam handles at its proximal end to facilitate overtube rotation. Clockwise rotation of the spiral overtube acts in a manner similar to that of a screw, advancing the endoscope while pleating the bowel onto its surface (1). The procedure was performed by two physicians: an endoscopist with considerable small bowel enteroscopy experience (PM) together with an advanced endoscopy fellow (CT or HA). The endoscope was inserted into the proximal esophagus in the usual fashion, after which further advancement was achieved by rotation of the overtube by twisting the foam handles. While the first operator rotated the overtube, the second operator steered the endoscope tip. Withdrawal of the endoscope was achieved by counterclockwise overtube rotation. The depth of insertion was estimated during endoscope withdrawal according to a previously described and accepted spiral enteroscopy method (1,2).

All patients completed bowel preparation with 4 L of a polyethylene glycol solution and an overnight fast, which is the standard practice for small bowel enteroscopy at the institution due to the belief that improved mucosal views are obtained once deep insertion reaches the ileum. Most procedures were performed under conscious sedation (midazolam and fentanyl) while selected cases were performed using anesthesiologist-administered propofol. Propofol was selected for cases expected to be prolonged or more difficult (eg, multiple polypectomies in Peutz-Jeghers syndrome patients), as well as for cases performed during live endoscopy courses. With few exceptions, spiral enteroscopy was performed without previous capsule endoscopy, which is not performed at the centre, and was chosen in favour of DBE or SBE according to the endoscopist's discretion. All procedures were performed on an outpatient basis.

Definition of hyperamylasemia and pancreatitis

Hyperamylasemia was defined as a twofold or greater increase in serum amylase (ratio of postprocedure to preprocedure amylase ≥2) to a level exceeding the upper limit of normal (>99 U/L). Clinical pancreatitis was defined according to the revised 2008 version of the Atlanta Classification of acute pancreatitis, which consists of typical abdominal pain strongly suggestive of acute pancreatitis, serum amylase level at least three times greater than the upper limit of normal and/or characteristic findings of acute pancreatitis on contrast-enhanced computed tomography scan (10). Radiological imaging was not routinely performed in all patients, but instead was reserved for cases in which pancreatitis was suspected based on clinical grounds (abdominal pain with abnormal amylase levels between 100 U/L and 299 U/L that was less than three times the upper limit of normal). An abnormal preprocedure serum amylase level ≥100 U/L in combination with the absence of postprocedural abdominal pain was considered to be sufficient to exclude pancreatitis and suggest macroamylasemia. The normal values for serum amylase and CRP levels were 0 U/L to 99 U/L, and <9 mg/L, respectively.

Statistical analysis

Stata version 10.1 (Stata Corp, USA) was used to analyze the data. Means and ranges were used to summarize data for continuous variables and percentages were used to summarize data for categorical variables. Continuous data were compared using the Student's *t* test (with Welch's approximation to correct for unequal variances) while categorical data were assessed using the χ^2 test. A two-sided $P<0.05$ was considered to be statistically significant. Univariable and multivariable logistic regression analyses were planned but not performed because the number of positive outcomes was too low to draw reliable conclusions.

RESULTS

Patient characteristics

Between November 2008 and March 2010, 32 patients with a mean age of 64 years (range 32 to 86 years) underwent proximal spiral enteroscopy; 19 (59%) were women. The most common indications for small bowel enteroscopy were anemia (81%) and Peutz-Jeghers syndrome (13%) (Table 1). Two patients with anemia had undergone previous video capsule endoscopy, whereas two of the Peutz-Jeghers syndrome patients previously underwent DBE. None of the included patients had a medical history of acute or chronic pancreatitis. While six (19%) patients consumed two or more units of alcohol per week, no patient consumed more than five units.

Spiral enteroscopy procedure

The mean depth of insertion beyond the ligament of Treitz was 240 cm (range 50 cm to 350 cm) with an average total procedure time of 51 min (range 30 min to 100 min). Conscious sedation was used for 20 patients (62%) while anesthesiologist-administered propofol was used in 12 (38%). All Peutz-Jeghers syndrome patients received propofol compared with 29% of the remaining cohort. The majority of patients (91%) underwent the proximal procedure only, while three (9%) underwent both a proximal and a distal spiral enteroscopy. Among these three patients, total enteroscopy with complete visualization of the small bowel was not achieved. The proximal spiral enteroscopy was diagnostic in 50% of cases, identifying angiodysplasia in seven (22%), polyps in four (13%), a tumour in three (9%) and ulcerations in two (6%) patients. Spiral enteroscopy was therapeutic in 10 (31%) patients, with argon plasma coagulation used to treat angiodysplasia in six (19%) (performed when angiodysplasias were considered clinically significant, defined as 'large' lesions or those that bled when probed by a catheter) and polypectomy performed in four (13%) cases, removing a total of 24 polyps.

Hyperamylasemia and pancreatitis

Serum samples were taken at a mean of 175 min (range 130 min to 270 min) after the spiral enteroscopy procedure. Two patients had an elevated amylase level before the procedure (101 U/L and 112 U/L, respectively), without any signs or symptoms suggestive of pancreatitis. Neither of these patients developed an elevation in serum

amylase level after the procedure greater than two times the baseline value, rising to 112 U/L and 167 U/L, respectively. Both were considered to have macroamylasemia and were excluded from subsequent analysis. Six (20%) patients developed hyperamylasemia, with a mean ratio of post- to preprocedure amylase of 2.9 and a mean postprocedure amylase level of 210 U/L (range 104 U/L to 510 U/L), reflecting an average increase in amylase of 139 U/L (range 56 U/L to 403 U/L). These changes significantly exceeded those among the 24 (80%) patients without hyperamylasemia, who had a mean postprocedure amylase level of 73 U/L (P<0.01) and an average increase of only 21 U/L (P<0.01). The mean CRP levels did not increase after the spiral procedures and did not differ significantly between patients with normal amylase levels and those with hyperamylasemia. Comparing the patient group with postprocedural hyperamylasemia with the normal amylase group, the only significant differences were the indication for the procedure (P=0.01) and the type of sedation used (P=0.01) (hyperamylasemia was more likely with Peutz-Jeghers syndrome patients and propofol sedation; normal amylase levels were more likely with anemia as the indication and conscious sedation). There were no significant differences in terms of demographic features or endoscopic outcomes, including both depth of insertion and procedure time (Table 2). In addition, there was no significant linear relationship between the duration of the enteroscopy procedure and the subsequent change in serum amylase level (P=0.34).

There were no cases of acute pancreatitis. In fact, none of the patients experienced postprocedural abdominal pain that raised suspicion for possible pancreatitis and, therefore, no imaging studies were performed. Furthermore, no adverse events were recorded at follow-up.

TABLE 2
Comparison of normal amylase and hyperamylasemia groups

Patient characteristic	Normal amylase (n=24)	Hyperamylasemia (n=6)	P
Age, years	65 (32–86)	60 (34–83)	0.59
Female sex	15 (63)	3 (50)	0.58
Indication (ie, anemia)	22 (92)	3 (50)	**0.01**
Enteroscopy data			
Conscious sedation	18 (75)	1 (17)	**0.01**
Propofol sedation	6 (25)	5 (83)	**0.01**
Insertion depth, cm	233 (50–350)	250 (200–300)	0.43
Procedure time, min	50 (30–100)	62 (30–80)	0.26
Diagnostic yield	11 (46)	4 (67)	0.36
Therapeutic yield	7 (29)	3 (50)	0.17
Serum measurements			
Amylase, U/L			
Pre	52 (28–98)	71 (27–113)	0.08
Post	73 (28–130)	210 (104–510)	**<0.01**
Absolute Δ (post – pre)	21 (−3–44)	139 (56–403)	**<0.01**
Post/pre ratio	1.4 (0.9–2.3)	2.9 (2.0–4.8)	**<0.01**
C-reactive protein, mg/L			
Pre	17 (1–190)	5 (1–16)	0.17
Post	17 (1–206)	6 (1–20)	0.23
Clinical pancreatitis*	0	0	–

*Data presented as mean (range) or n (%) unless otherwise indicated. Bolded values indicate statistical significance. *Defined according to the revised (2008) Atlanta Classification for acute pancreatitis (10).* Δ Change; *Post Postprocedure; Pre Preprocedure*

DISCUSSION

Acute pancreatitis is a concerning potential complication with DBE. Large, multicentre, retrospective studies reported the risk of pancreatitis after diagnostic DBE procedures to be 0.2% to 0.3% (6,7,11). Two prospective studies demonstrated a much higher frequency of hyperamylasemia (up to 50%) after DBE than the observed rate of pancreatitis (nearly 5%) (12,13). This has been interpreted as evidence of a causative link among oral DBE, hyperamylasemia and pancreatic injury. However, multiple theories have been proposed speculating about the mechanism by which DBE leads to pancreatitis, with no clear consensus (14). Recently, we performed two prospective studies involving DBE (8) and SBE (9) demonstrating that after modifying the insertion technique to delay balloon inflation until beyond the ligament of Treitz, the incidence of pancreatitis was very low: 0.7% and 0% for DBE and SBE, respectively. However, hyperamylasemia remained relatively common, 17% and 16% for DBE and SBE, respectively, although significantly less common when compared with earlier reports (12,13). It is unclear whether this persistent hyperamylasemia results from injury to the pancreas or if it is caused by other factors such as local strain or mucosal injury to the small bowel itself.

In the present study, 20% of patients developed hyperamylasemia after proximal spiral enteroscopy, with no patients developing suggestive abdominal pain symptoms and no cases of pancreatitis. Interestingly, the development of hyperamylasemia was not associated with the duration of the procedure as has been suggested by previous DBE studies (8,13). However, the development of hyperamylasemia was significantly associated with Peutz-Jeghers syndrome and with propofol sedation. Because propofol was specifically selected for cases anticipated to be more technically challenging and, because Peutz-Jeghers syndrome patients underwent multiple polypectomies (a mean of six polyps per patient), it is interesting to speculate that the development of hyperamylasemia may be more closely linked to difficult procedures, which may not necessarily take longer than other cases but may involve more strain on the pancreas or on the small bowel itself.

Chief among the several limitations in the present study was the small sample size. We observed a high frequency of hyperamylasemia without associated pancreatitis, but the sample was insufficient to capture these events. Indeed, only multicentre registry data are likely capable of identifying complications as infrequent as pancreatitis. In fact, a large, multicentre registry has reported (in abstract form) the early experience with spiral enteroscopy and found no cases of pancreatitis after 1750 spiral procedures (15). While amylase levels were not reported, the absence of pancreatitis after such a considerable number of procedures implies that the risk is low with spiral enteroscopy and suggests that the hyperamylasemia observed in our study was not necessarily a harbinger of pancreatitis. A second notable limitation was our lack of measurement of serum lipase or fractionation of pancreatic and salivary amylase isoenzyme levels, which may have been useful for differentiating the origin of the elevated amylase levels. Although other series examining DBE and hyperamylasemia have shown a strong correlation between serum amylase and lipase measurements (12,13), it is regrettable that these were not measured in our study to provide more definitive evidence as to the source of hyperamylasemia.

Nevertheless, the findings of the present study begin to shed more light on the etiology of hyperamylasemia observed after deep enteroscopy. Because the spiral method does not involve the inflation of balloons nor the same degree of stretching of the small bowel with repetitive insertion and shortening of the endoscope and overtube, a number of previously considered causative theories seem less likely given the persistent observation of hyperamylasemia after spiral enteroscopy. In particular, duodenal hypertension from balloon inflation (16), mechanical strain on the pancreas from repetitive stretching of the endoscope and overtube (17-19), irritation of the pancreatic sphincter from the inflation of the overtube balloon or compression of the sphincter from the back-and-forth movements of the overtube (20), seem much less likely. However, the suggestion of mechanical strain on the pancreas from the profound straightening of the duodenum at the ligament of Treitz (11) as well as the ischemic vascular injury theory due to compression or stretching of the peripancreatic vessels (18,20) remain. In addition, it is still possible that overtube-induced strain on the small bowel itself is responsible for the hyperamylasemia (21).

SUMMARY

The present study is the first to report the incidence of hyperamylasemia following proximal spiral enteroscopy, being a frequent finding occurring after one in five procedures despite no cases of pancreatitis. Thus, we hypothesize that while DBE can clearly cause pancreatitis, patients who develop elevated amylase levels after deep enteroscopy do not necessarily incur injury to the pancreas or elevated risk for pancreatitis. In fact, patients with significant abdominal pain after enteroscopy, even in the context of an elevated amylase level, should first be evaluated for other, possibly more serious complications, such as intestinal perforation, before considering pancreatitis, particularly in light of reports of perforations resulting from spiral enteroscopy (15,22) and the growing realization that pancreatitis is an unlikely event for which hyperamylasemia may be a nonspecific finding.

MEETING PRESENTATIONS: Poster presentation at the 2011 Canadian Digestive Disease Week (CDDW) in Vancouver, British Columbia, February 26 to March 1, 2011.

GRANT SUPPORT: Investigator-initiated, unfunded study.

DISCLOSURES: CW Teshima, H Aktas, EJ Kuipers and PB Mensink have no financial disclosures or conflicts of interest to declare.

REFERENCES

1. Akerman PA, Agrawal D, Cantero D, et al. Spiral enteroscopy with the new DSB overtube: A novel technique for deep peroral small-bowel intubation. Endoscopy 2008;40:974-8.
2. Akerman PA, Agrawal D, Chen W, et al. Spiral enteroscopy: A novel method of enteroscopy by using the Endo-Ease Discovery SB overtube and a pediatric colonoscope. Gastrointest Endosc 2009;69:327-32.
3. Tsujikawa T, Saitoh Y, Andoh A, et al. Novel single-balloon enteroscopy for diagnosis and treatment of the small intestine: Preliminary experiences. Endoscopy 2008;40:11-5.
4. Yamamoto H, Sekine Y, Sato Y, et al. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc 2001;53:216-20.
5. Yamamoto H, Kita H, Sunada K, et al. Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases. Clin Gastroenterol Hepatol 2004;2:1010-6.
6. Mensink PBF, Haringsma J, Kucharzik T, et al. Complications of double balloon enteroscopy: A multicenter survey. Endoscopy 2007;39:613-5.
7. Gerson LB, Tokar J, Chiorean M, et al. Complications associated with double balloon enteroscopy at nine US centers. Clin Gastroenterol Hepatol 2009;7:1177-82.
8. Aktas H, Mensink PBF, Haringsma J, et al. Low incidence of hyperamylasemia after proximal double-balloon enteroscopy: Has the insertion technique improved? Endoscopy 2009;41:670-3.
9. Aktas H, de Ridder L, Haringsma J, et al. Complications of single-balloon enteroscopy: A prospective evaluation of 166 procedures. Endoscopy 2010;42:365-8.
10. Acute Pancreatitis Classification Working Group. Revision of the Atlanta classification of acute pancreatitis (3rd revision). <www.pancreasclub.com/resources/ AtlantaClassification.pdf> (Accessed May 1, 2010).
11. Möschler O, May A, Müller MK, et al. Complications in and performance of double-balloon enteroscopy (DBE): Results from a large prospective DBE database in Germany. Endoscopy 2011;43:484-9.
12. Honda K, Itaba S, Mizutani T, et al. An increase in the serum amylase level in patients after peroral double-balloon enteroscopy: An association with the development of pancreatitis. Endoscopy 2006;38:1040-3.
13. Kopácová M, Rejchrt S, Tachecí I, et al. Hyperamylasemia of uncertain significance associated with oral double-balloon enteroscopy. Gastrointest Endosc 2007;66:1133-8.
14. Kopacova M, Tacheci I, Rejchrt S, et al. Double balloon enteroscopy and acute pancreatitis. World J Gastroenterol 2010;16:2331-40.
15. Akerman PA, Cantero D. Severe complications of spiral enteroscopy in the first 1750 patients. Gastrointest Endosc 2009;69:AB127 (Abst).
16. Groenen MJ, Moreels TG, Orlent H, et al. Acute pancreatitis after double-balloon enteroscopy: An old pathogenetic theory revisited as a result of using a new endoscopic tool. Endoscopy 2006;38:82-5.
17. Heine GD, Hadithi M, Groenen MJ, et al. Double-balloon enteroscopy: Indications, diagnostic yield, and complications in a series of 275 patients with suspected small-bowel disease. Endoscopy 2006;38:42-48.
18. Matsushita M, Shimatani M, Uchida K, et al. Mechanism of acute pancreatitis after peroral double-balloon enteroscopy. Endoscopy 2007;39:480; author reply 481.
19. Jarbandhan SVA, Van Weyenberg SJB, van der Veer WM, et al. Double balloon endoscopy associated pancreatitis: A description of six cases. World J Gastroenterol 2008;14:720-4.
20. Lo SK, Simpson PW. Pancreatitis associated with double-balloon enteroscopy: How common is it? Gastrointest Endosc 2007;66:1139-41.
21. Monkemuller K, Fry L, Malfertheiner P. Double-balloon enteroscopy: Beyond feasibility, what do we do now? Endoscopy 2007;39:229-31.
22. Li X-B, Gu L-Y, Song Y, et al. Small-bowel perforation in a patient with Roux-en-Y anatomy for Peutz-Jeghers polyps after spiral enteroscopic investigation. Endoscopy 2011;43:E85.