

Double-Contrast Barium Enteroclysis as a Patency Tool for Nonsteroidal Anti-Inflammatory Drug-Induced Enteropathy

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Abstract

Background Evaluating small bowel patency is recommended for capsule endoscopy in patients suspected of nonsteroidal anti-inflammatory drug-induced (NSAID) enteropathy.

Aims The aim of this investigation was to examine whether radiography is a candidate of patency tool in NSAID enteropathy.

Methods We reviewed double-contrast barium enteroclysis in 21 patients with NSAID enteropathy diagnosed either by capsule endoscopy or balloon-assisted endoscopy. The endoscopic findings were classified into circular ulcers, linear ulcers and small mucosal defects. The radiographic signs of the corresponding endoscopic findings were retrieved and the depiction rate was calculated.

Results Of the 21 patients, endoscopy detected circular ulcers, linear ulcers, and small ulcers in 12, 3 and 12 patients, respectively. Small bowel radiography depicted circular narrowing as pseudo-folds in 10 patients (83%) and linear ulcers as eccentric rigidity in 2 patients (67%). However, radiography was able to depict small mucosal defects in only 3 patients (17%). Two of 5 patients with pseudo-folds experienced retention of the capsule.

Conclusion “Pseudo-folds” is a sign corresponding to circular ulcer in NSAID enteropathy, which may be predictive of capsule retention.

Keywords Nonsteroidal anti-inflammatory drug · Small bowel · Capsule endoscopy · Balloon-assisted enteroscopy · Radiography

Introduction

It has become evident that patients taking nonsteroidal anti-inflammatory drugs (NSAID) are at high risk of small bowel mucosal lesions [1, 2]. In observational studies by means of video-capsule endoscopy (VCE) or balloon-assisted endoscopy (BAE), more than 50% of patients under long-term NSAID use had small bowel ulcers [3–6]. The endoscopic findings of NSAID enteropathy vary widely, from diminutive mucosal defects to sharply demarcated ulcers [3, 4, 7–9]. Amongst various types of mucosal lesions, severe and concentric strictures of the small bowel, referred to as diaphragms, are the most characteristic of NSAID enteropathy [10, 11].

In the early period after the introduction of CE, cases of NSAID enteropathy with the diaphragms were examined by the procedure, and as a consequence, those cases suffered from capsule retention [12, 13]. It has subsequently been reported that NSAID enteropathy is one of the major causes of the retention of the capsule. In a single center analysis, Li et al. [14] reported that 8 of 14 patients who experienced capsule retention had NSAID enteropathy. In an extensive review by Liao et al. [15], NSAID enteropathy has been shown to be the third most frequent cause of capsule retention, accounting for 18.4% of such cases.

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In order to avoid capsule retention, a patency capsule system has been developed and become clinically available [16–18]. However, the patency system is time-consuming, requiring 5 days for final decisions at most [18]. Furthermore, it is a historical fact that diaphragms could be diagnosed by small bowel radiography in the 1990s [19–22]. We thus made a retrospective analysis of our patients with endoscopically diagnosed NSAID enteropathy to assess the role of double-contrast barium enteroclysis as a procedure for luminal patency in the disease.

Methods

Patients

We reviewed patients with small bowel ulcers detected by VCE or BAE at our institutions during the period 2003–2011, and identified 53 patients who fulfilled the following criteria for NSAID enteropathy. The criteria included (1) presence of small bowel mucosal lesions, (2) NSAID intake for at least a week just prior to enteroscopy, and (3) ulcer healing after discontinuance of the NSAID without any specific treatment. Among the patients, we recruited 21 who had been examined by double-contrast barium enteroclysis (DCBE) prior to enteroscopy for the present investigation. Written informed consent was obtained from each subject with regards to the purpose and the method of each examination. This retrospective study was undertaken according to the Helsinki Declaration.

There were 7 females and 14 males, and the ages at the time of enteroscopy ranged from 46 to 88 years (mean, 68 years). The indication for enteroscopy was overt obscure gastrointestinal bleeding (OGIB) in 13 patients, abdominal pain in 5, and occult OGIB in 3. Seventeen patients had been taking a single NSAID, while 4 patients were under two species of NSAID. The species of NSAID were loxiprofen (7 patients), diclofenac (6), low-dose aspirin (4), indomethacin (2), meloxicam (2), ibuprofen, naproxen, ampyroxicam and celecoxib (each in 1 patient). The indication for NSAID use was osteoarthritis in 10 patients, rheumatoid arthritis in 6, other arthralgia in 2, and cardiovascular diseases in 3. Time duration from the start of NSAID until the diagnosis of the enteropathy ranged from 0.2 to 240 months with a mean of 52 months.

Enteroscopy

VCE was performed by either PillCam SB system (Given Imaging, Yoqneam, Israel) or EndoCapsule system (Olympus, Tokyo, Japan), according to the manufacturer's recommendation. After an overnight fast, patients were prepared by simethicone with tap water or 900 ml of

magnesium citrate prior to the examination [23]. Patients were then instructed to ingest the capsule and the images for the subsequent 8 h were recorded. The VCE images were reviewed by one of the authors (M.E.), who was informed of the patients' characteristics including NSAID use. Capsule retention was regarded as a case of retained capsule for more than 3 days, which required subsequent endoscopic or surgical procedure for removal.

Oral and anal BAEs were performed with Double Balloon Enteroscopy System (Fujifilm, Tokyo, Japan) under fluoroscopy [24]. After an overnight fast, the patients were prepared by 2 l of electrolyte lavage solution in cases of anal BAE. The route for BAE was determined by the endoscopists on the basis of the patients' characteristics. The patients were prepared by continuous intravenous infusion, and examined by enteroscopy under a light sedation by intravenous midazolam. The scope was advanced as far as possible with reciprocal insertion of the scope and the overtube.

The VCE and BAE findings were classified into circular ulcers, linear ulcers, and small mucosal defects [7]. A severe, concentric stenosis with diaphragm was regarded as circular ulcers. Small mucosal defects included red spots and small ulcers.

Double-Contrast Barium Enteroclysis

Small bowel radiography was performed with a double-contrast technique as has previously described [25]. In brief, patients were prepared by an insertion of a naso-jejunal tube under fluoroscopy. The tube was fixed at the ligament of Treitz by a pneumodilatation of the balloon at the tip of the tube. Then, 200–300 ml of 70% v/w barium sulphate was slowly injected through the tube until the terminal ileum was filled with the contrast material. The small intestine was then inflated with 800–1,000 ml of air injected through the tube. When a sufficient inflation was achieved, 40 mg of scopolamine butyl bromide was injected intravenously to inhibit peristalsis and to obtain double-contrast images.

Assessment

We first compared clinical features between patients with and without each endoscopic finding. Radiographic images were then reviewed by two enteroscopists (T.M. and M.E.) with a reference to each enteroscopic finding. The depiction rate of each enteroscopic finding was calculated.

Statistical Analyses

When comparing two groups, Mann–Whitney test, chi-squared test or Fisher's exact probability test were used

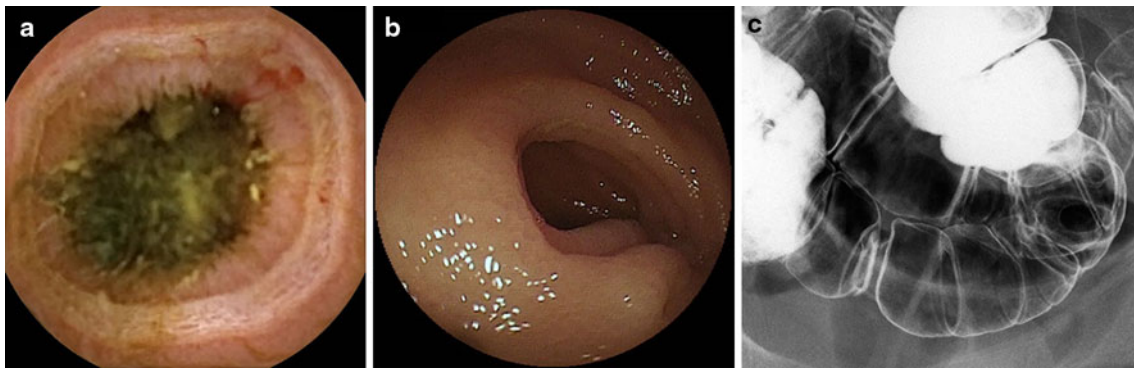


Fig. 1 Enteroscopic and radiographic findings of a case of circular ulcers in the ileum. A 78-year-old female who had been diagnosed as rheumatoid arthritis and had been under celecoxib was examined because of anemia. Under VCE (a) and oral BAE (b), multiple

circular ulcers were found. Double-contrast barium enteroclysis depicted the ulcers as concentric and multiple stenoses in the ileum (c). The findings are compatible with “pseudo-folds”

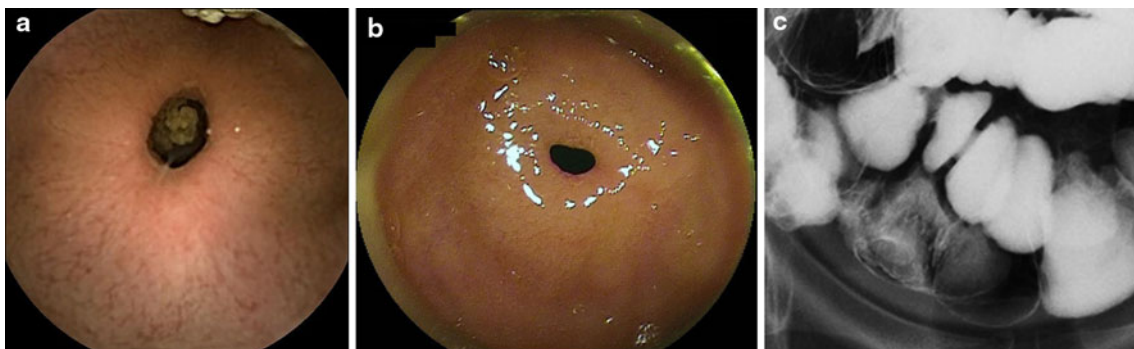


Fig. 2 Enteroscopic and radiographic findings of a case of diaphragms in the ileum. A 72-year-old female had been taking diclofenac for rheumatoid arthritis for 24 months, during which repeated abdominal pain occurred. VCE (a) and anal BAE

(b) detected concentric stenosis in the ileum. Double-contrast barium enteroclysis showed concentric stenosis in the lower part of the ileum (c). The findings are compatible with condensed “pseudo-folds.” This case experienced capsule retention

where appropriate. Probabilities less than 0.05 were considered to be significant.

Results

Enteroscopic Findings

The subjects were examined by 13 anal BAEs, 8 oral BAEs, and 10 VCEs. Eleven subjects were examined by BAE alone, and 3 patients by VCE alone. The remaining 7 subjects were examined by both BAE and VCE.

Circular ulcers (Fig. 1a, b), linear ulcers and small mucosal defects were found in 12, 3 and 12 patients, respectively. The predominant site of involvement within the small bowel was the jejunum in 3 subjects, the ileum in 6 and both the jejunum and the ileum in 8. Three subjects had both circular ulcer and small mucosal defects. The other 3 subjects had both linear ulcer and small mucosal defects, while 6 subjects had small mucosal defects alone.

Six of 12 subjects with circular ulcers had diaphragms (Fig. 2a, b). Among 10 subjects examined by VCE, 2 experienced capsule retention, which was treated by endoscopic balloon dilatation under BAE.

Table 1 compares clinical features between patients with circular ulcers and those without. While neither gender, age at the time of diagnosis of NSAID enteropathy, predominant site of involvement nor duration of NSAID use was different between the two groups, overt OGIB was less frequent in patients with circular ulcers than those without the ulcers (11 vs. 42%, $P = 0.037$). There was also a trend towards less frequent cardiovascular disease in patients with circular ulcer as the indication of NSAID use. Four of 12 patients with circular ulcers had been taking two NSAID species while patients without circular ulcer had been taking a single species of NSAID (33 vs. 0%, $P = 0.08$). Laboratory data including serum protein, hemoglobin and C-reactive protein values were not different between the two groups.

Table 1 Comparison of clinical features between patients with and without circular ulcers

Clinical features	Patients with circular ulcers (<i>n</i> = 12)	Patients without circular ulcers (<i>n</i> = 9)	Probability
Sex (female/male)	4/8	3/6	1.0
Age (range, median) (years)	46–88, 68.5	47–87, 80	0.26
Indication of NSAID use			
Arthropathy/CVD	12/0	6/3	0.06
Indication for enteroscopy			
Overt OGIB/others	5/7	8/1	0.037
Predominant site			0.81
Jejunum	2	1	
Jejunum and ileum	5	3	
Ileum	5	5	
Laboratory data (range, median)			
Hemoglobin (g/dl)	4.9–13.7, 8.5	5.6–13.5, 8.8	0.36
Serum protein (g/dl)	3.9–7.8, 9.2	4.3–7.9, 8.8	0.52
C-reactive protein (mg/dl)	0.01–11.6, 0.12	0.10–3.88, 0.73	0.10
Use of two NSAIDs species	4	0	0.08
Duration of NSAID use (range, median) (months)	0.2–240, 30	1–192, 12	0.55
NSAID species			
Loxiprofen	4	3	
Diclofenac	4	2	
Aspirin	1	3	
Indomethacin	2	0	
Others	5	1	

OGIB Obscure gastrointestinal bleeding, CVD cardiovascular diseases

Table 2 indicates a comparison between subjects with small mucosal defects and those without. As summarized in the table, subjects with small mucosal defects were taking multiple NSAID less frequently than those without (0 vs. 44%, $P = 0.02$). In addition, hemoglobin value was higher in subjects with small mucosal defect than in those without. There was also a trend towards higher serum protein value in the former than in the latter.

Radiography

Review of the radiographic images in 12 subjects with circular ulcers revealed that concentric narrowing with extremely short width was depicted in 10 patients (Figs. 1c and 2c). The narrowing apparently mimicked normal-appearing folds of the jejunum. Such “pseudo-folds” was found in multiplicity. However, the longitudinal alignment of the pseudo-folds was irregular, and the distance in-between the folds was not uniform. The proximal part of the bowel was not dilated in any subject with circular ulcers. In 2 of 3 subjects with linear ulcers, radiography revealed eccentric rigid area with converging folds.

Radiography failed to depict any significant findings in 10 of 12 subjects with small mucosal defects. In 2 subjects,

compression images showed tiny barium flecks in the lower part of the ileum. The depiction rate of NSAID enteropathy was thus 83% for circular ulcers, 67% for linear ulcers and 17% for small mucosal defects.

Among 10 patients examined by VCE, 2 of 5 subjects with pseudo-folds experienced capsule retention. The capsule was not retained in the other 5 subjects without the radiographic signs.

Discussion

Our retrospective investigation revealed that DCBE could depict circular ulcers in NSAID enteropathy, while it failed to depict small mucosal defects. We could also show that patients with circular ulcers complained of overt OGIB less frequently than those without, and they tended to have been under two species of NSAID. These observations suggest that radiography together with clinical manifestations may be a tool for patency in patients suspected of having NSAID enteropathy.

In the 1980s and 1990s, diaphragms of the small bowel drew much attention as the characteristic lesion of NSAID enteropathy. The diaphragms were histologically characterized by

Table 2 Comparison of clinical features between patients with and without small mucosal defects

Clinical features	Patients with mucosal defects (n = 12)	Patients without mucosal defects (n = 9)	Probability
Sex (female/male)	5/7	2/7	0.11
Age (range, median) (years)	47–87, 75	46–88, 67	0.30
Indication of NSAID use			
Arthropathy/CVD	9/3	9/0	0.23
Indication for enteroscopy			
Overt OGIB/others	9/3	4/5	0.17
Predominant site			0.48
Jejunum	1	2	
Jejunum and ileum	4	4	
Ileum	7	3	
Laboratory data (range, median)			
Hemoglobin (g/dl)	5.6–13.7, 9.7	4.9–10.1, 8.8	0.036
Serum protein (g/dl)	4.3–7.9, 6.2	3.9–7.2, 5.4	0.051
C-reactive protein (mg/dl)	0.01–3.9, 0.72	0.01–11.6, 0.06	0.12
Use of two NSAID species	0	4	0.02
Duration of NSAID use (range, median) (months)	1–240, 18	0.2–240, 24	0.97
NSAID species			
Loxiprofen	3	4	
Diclofenac	3	3	
Aspirin	3	1	
Indomethacin	0	2	
Others	3	3	

OGIB Obscure gastrointestinal bleeding, CVD cardiovascular diseases

marked fibrosis with shallow ulcers at the tip of the Kerckring's folds [10, 11]. While 6 of our 21 subjects actually had diaphragms, we also found circular ulcers in those 6 patients as well as in another 6 patients without apparent diaphragms. It is thus suggested that circular ulcers are the most typical and representative mucosal lesions in NSAID enteropathy. However, it is a fact that there have been cases of diaphragms, which were missed by small bowel radiography and diagnosed by enteroscopy [26–28]. In those reports, small bowel radiography probably failed to depict extremely thin narrowing without dilatation of the proximal bowel.

In the literature, the radiographic features of NSAID-induced diaphragms have been discussed in symptomatic patients who were examined by barium follow-through study [19, 21, 22]. Zalev et al. [22] analyzed four symptomatic cases of diaphragms and found that lifesaver-like stricture and babel-like configuration were depicted by small bowel radiography. Although those descriptions were heterogeneous with regards to the width of the narrow septae, they are in concert with respect to concentric and multiple stenoses [19–22]. Our results indicated that the circular ulcers, as well as diaphragms, were depicted as apparently normal folds when the affected small bowel was insufflated with an appropriate amount of air under DCBE. It thus

seems likely that the radiologic finding referred to as “pseudo-folds” sign may be applicable and specific to the diagnosis of NSAID enteropathy.

It has been reported that VCE detected small mucosal defects even in healthy subjects after short-term NSAID use [29–31]. However, DCBE failed to depict most of small mucosal defects in our subjects with NSAID enteropathy. With this regard, VCE or BAE is the procedure of choice for the diagnosis of the disease. Even though VCE has advantages as to safety and convenience, it has also been shown that NSAID enteropathy is one of the major conditions associated with capsule retention [14, 15]. A conspicuously high incidence of capsule retention in NSAID enteropathy seems to be a consequence of undiagnosed diaphragms. Small bowel radiography thus seems to have a role as a patency tool for VCE in patients suspected of having NSAID enteropathy. In fact, capsule retention did occur in 2 of our 5 patients with pseudo-folds sign, while none of the subjects without the sign experienced the adverse event.

Despite a worldwide, huge population exposed to NSAID, cases of diaphragm are encountered infrequently. In addition, clinical features predisposed to diaphragms are poorly understood except for long-term NSAID use [10–13, 19–22, 26–28]. Although the difference did not

reach statistical significance, our analyses of the subjects' demographics revealed that the simultaneous use of two NSAID species was associated with the occurrence of circular ulcers. In addition, subjects with circular ulcers experienced overt OGIB less frequently than those without. Conversely, subjects with small mucosal defects had less severe anemia and hypoproteinemia, and they had been taking only a single NSAID. These observations strongly suggest that circular ulcers are the consequence of chronic and repeated exposure to NSAID. Accordingly, the history of NSAID intake and clinical manifestations seem to be predictive of circular ulcers, and presumably, of diaphragms.

Recently, patency capsule system for patients at a high risk of capsule retention has become available [16–18]. Although the system has been shown to be a sensitive procedure [16–18], it requires at least 30 h for the final decision. There are also difficulties in determining the localization of the patency capsule under radiographs or by the scanners [17]. Even though Postgate et al. [17] reported that small bowel radiography was normal or minimally abnormal in patients in whom the patency capsule was retained, they did not include any case of NSAID enteropathy. It thus seems possible that DCBE with a special reference to pseudo-folds sign may be a convenient tool for the determination of luminal patency in patients taking NSAID.

Maglinte et al. [32] proposed double-contrast enteroclysis to be equal or superior to VCE for the evaluation of mucosal details such as aphthous lesions and scarred ulcers in Crohn's disease. Our results showed that this was not the case for NSAID enteropathy, probably due to the difference in the number and the depth of diminutive lesions between Crohn's disease and NSAID enteropathy. In addition, CT- and MR-enterographies have become alternative to and more informative than small bowel radiography for the evaluation of transmural or stenotic lesions in Crohn's disease [33–37]. Since CT- and MR-enterographies are also able to depict mucosal alterations, these procedures may be other candidates as a patency tool for NSAID enteropathy.

In conclusion, an analysis of clinical and radiographic features of 21 patients with NSAID enteropathy revealed DCBE to be applicable as a patency tool prior to VCE for subjects suspected of having the disease. On that occasion, the pseudo-folds sign may be suggestive of circular ulcers and the diaphragms. Given such circumstances, BAE with a preparation of endoscopic balloon dilatation would be practically preferred to VCE [9, 38]. The value of small bowel radiography in comparison with patency capsule should be examined in the area of widespread use of NSAID including aspirin.

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