18. D'Haens GR, Vermeire S, Van Assche G, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of CD: a controlled randomized trial. *Gastroenterology*. 2008;135:1123–1129.
19. Blum E, Katz JA. Postoperative therapy for CD. *Inflamm Bowel Dis*. 2009;15:463–472.
20. Peyrin-Biroulet L, Deltenre P, Ardizzone S, et al. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in CD: a meta-analysis. *Am J Gastroenterol*. 2009;104: 2089–2096.
21. Herfarth H, Tjaden C, Lukas M, et al. Z T-1 Study Group. Adverse events in clinical trials with azathioprine and mesalamine for prevention of postoperative recurrence of CD. *Gut*. 2006;55:1525–1526.
22. Domènech E, Mañosa M, Bernal I, et al. Impact of azathioprine on the prevention of postoperative CD recurrence: results of a prospective, observational, long-term follow-up study. *Inflamm Bowel Dis*. 2008;14:508–513.
23. Vermeire S, van Assche G, Rutgeerts P. Review article: altering the natural history of CD—evidence for and against current therapies. *Aliment Pharmacol Ther*. 2007;25:3–12.
24. Yamamoto T, Umegae S, Matsumoto K. Impact of infliximab therapy after early endoscopic recurrence following ileocolic resection of CD: a prospective pilot study. *Inflamm Bowel Dis*. 2009;15: 1460–1466.
25. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents CD recurrence after ileal resection. *Gastroenterology*. 2009;136: 441–450.
26. Rubenstein JH, Chong RY, Cohen RD. Infliximab decreases resource use among patients with CD. *J Clin Gastroenterol*. 2002;35:151–156.
27. Sorrentino D, Terrosu G, Avellini C, et al. Infliximab with low-dose methotrexate for prevention of postsurgical recurrence of ileocolic Crohn disease. *Arch Intern Med*. 2007;167:1804–1807.
28. Poggioli G, Laureti S, Selleri S, et al. Factors affecting recurrence in Crohn's disease. Results of a prospective audit. *Int J Colorectal Dis*. 1996;11:294–298.
29. Sachar DB, Wolfson DM, Greenstein AJ, et al. Risk factors for postoperative recurrence of Crohn's disease. *Gastroenterology*. 1983;85: 917–921.
30. Griffiths AM, Wesson DE, Shandling B, et al. Factors influencing postoperative recurrence of Crohn's disease in childhood. *Gut*. 1991; 32:491–495.
31. Greenstein AJ, Sachar DB, Pasternack BS, et al. Reoperation and recurrence in Crohn's colitis and ileocolitis Crude and cumulative rates. *N Engl J Med*. 1975;293:685–690.
32. Raab Y, Bergström R, Ejerblad S, et al. Factors influencing recurrence in Crohn's disease. An analysis of a consecutive series of 353 patients treated with primary surgery. *Dis Colon Rectum*. 1996;39:918–925.
33. Anseline PF, Wlodarczyk J, Murugasu R. Presence of granulomas is associated with recurrence after surgery for Crohn's disease: experience of a surgical unit. *Br J Surg*. 1997;84:78–82.
34. Wolff BG. Factors determining recurrence following surgery for Crohn's disease. *World J Surg*. 1998;22:364–369.
35. Whelan G, Farmer RG, Fazio VW, et al. Recurrence after surgery in Crohn's disease. Relationship to location of disease (clinical pattern) and surgical indication. *Gastroenterology*. 1985;88:1826–1833.
36. Takagi S, Utsunomiya K, Kuriyama S, et al. Effectiveness of an 'half elemental diet' as maintenance therapy for CD: a randomized-controlled trial. *Aliment Pharmacol Ther*. 2006;24:1333–1340.
37. Ogata H, Hibi T. Does an elemental diet affect operation and/or recurrence rate in CD in Japan? *J Gastroenterol*. 2003;38:1019–1021.
38. Ikeuchi H, Kusunoki M, Yanagi H, et al. Effects of elemental diet (ED) on surgical treatment in CD. *Hepatogastroenterology*. 2000;47: 390–392.

J Gastroenterol (2011) 46:1197–1202
DOI 10.1007/s00535-011-0439-1

ORIGINAL ARTICLE—ALIMENTARY TRACT

Correlation between endocytoscopy and conventional histopathology in microstructural features of ulcerative colitis

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Received: 7 February 2011 / Accepted: 25 June 2011 / Published online: 30 July 2011

Abstract
Background Routine diagnosis of the histopathological activity of ulcerative colitis (UC) requires multiple biopsy samples, and an endocytoscopy system (ECS) provides real-time ultra-magnifying microscopic imaging in vivo.
Methods We have established an ECS score (ECSS) to determine a histopathological activity index of UC. Fifty-five UC patients (mean age 40.7 years; 67% men) were enrolled. A super-magnifying ECS with magnification 450× was used, and sample biopsies were obtained. Matts' histopathological grade was determined, to evaluate disease severity, by two pathologists, with consensus. The ECSS of UC was independently determined by at least two investigators, with consensus. In total, 76 pairs of ECSS and Matts' histopathological grades were independently acquired. To validate the ECSS, inter-observer agreement between three endoscopists, with consensus, and another endoscopist, was calculated as the kappa value. We also evaluated the correlation between the ECSS and Matts' histopathological grade, and between the conventional Matts' endoscopic grade and Matts' histopathological grade.
Results The ECSS of UC intestinal mucosa, i.e., the sum of the indices for shape (0–3) and distance between crypts (0–2), and the visibility of superficial microvessels (0–1), showed a strong correlation with Matts' histopathological grades ($\rho = 0.713$, $P < 0.001$); as well, there was a strong correlation between the conventional Matts' endoscopic grade and Matts' histopathological grade ($\rho = 0.694$, $P < 0.001$). Furthermore, the ECSS showed high reproducibility ($\kappa = 0.79$, 95% confidence interval [CI] 0.71–0.87).
Conclusions Our novel ECSS has good predictive value for the histopathological activity of UC.

Keywords Endocytoscopy · Ulcerative colitis · Mucosal inflammation · Histopathology

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Introduction

Two devices are currently available that allow in vivo microscopic inspection of the microstructural mucosal features of the gastrointestinal tract: confocal laser endomicroscopy (CLE) (Pentax, Tokyo, Japan, and Mauna Kea Technologies, Paris, France) [1–6] and an endocytoscopy system (ECS) with an ultra-magnification light microscopy device (Olympus Medical Systems, Tokyo, Japan) [1, 7–10]. There are two types of each device, probe-based and integrated-scope types [6, 11]. These devices can facilitate the distinguishing of neoplastic from non-neoplastic lesions [3, 4, 7, 8, 11, 12], and also in classifying the severity of inflammatory lesions [9, 13] histopathologically. For CLE, several groups have recently reported its use for the detection of the microstructural features of the mucosa in ulcerative colitis (UC) patients [12, 13], and one group attempted to identify a correlation

between classification by CLE and paired histological sample findings [13]. However, no such studies have been conducted for ECS. ECS can provide a real-time image, as with light microscopy, and facilitate rapid diagnosis [10]. The aims of the present study were: (1) to develop a new UC scoring system based on ECS and (2) to validate the pathological and clinical utility of this scoring system.

Methods

Enrolled patients and ECS procedure

Fifty-five patients with a confirmed diagnosis of UC were prospectively enrolled in this study from April 2009 to April 2010. Written informed consent was obtained from all subjects, and the study was approved by the ethics committee of Keio University Hospital. Six experienced endoscopists (R. B., T. Ka., N. H., T. Ko., N. I., and H. O.) performed total colonoscopy with a conventional colonoscope (CF-Q260AI; Olympus Medical Systems). If patients agreed to participate in this study, the ECS (ECS, CF-Y0001; Olympus Medical Systems) was used to obtain more sensitive, ultra-magnified images of the rectal area. Our ECS was an integrated scope-type ultra-magnifying system and could be switched from conventional and magnifying views to super-magnifying, using a button located at the top of the endoscope. The ECS was used at the representative part of the rectal area that had been detected by conventional and magnifying endoscopy. When differences in endoscopic activities were observed, multiple ECS images and biopsy samples were taken. The rectal mucosa was washed with an excess of water plus simethicone, and stained with 10 mL of 1% methylene blue solution. The excess stain was rinsed off to avoid overstaining the cells. It takes a few minutes to perform dye staining, and approximately 10–20 min to observe the surface of the lesion with the ECS [7]. Ultimately, a targeted biopsy was performed as accurately as possible for histological analysis of the same sites. All biopsy specimens were fixed in 10% formalin and embedded in paraffin, serially sectioned, and stained with hematoxylin and eosin (H&E). Histological examination and scoring were performed by two experienced pathologists, with consensus (between five different pathologists and M. M.).

Scoring system

All reviewers were blinded to the clinical and histological backgrounds of the ECS images. First, 20 ECS pictures were reviewed, and all items relevant to the pathological features of UC were collected by one endoscopist (R. B.). The scoring system thereby created and set by this endoscopist was called the ECS score (ECSS). Then 20 ECS pictures were scored by two experienced endoscopists (T. Ka, N. H.), upon reaching agreement. Pictures other than these were reviewed and scored by three endoscopists (R. B., T. Ka., and N. H.), also in agreement.

To validate the ECSS, inter-observer agreement between three endoscopists (R. B., T. Ka., and N. H.), with consensus, and another endoscopist, was calculated as the kappa value. Next, we evaluated the correlation between the ECSS and Matts' histopathological grade, and that between the conventional Matts' endoscopic grade and Matts' histopathological grade. Furthermore, to assess the clinical utility of the ECSS, correlations between the ECSS and clinical activity factors [C-reactive protein (CRP) level and stool frequency] were evaluated. These data were collected from medical records.

Statistical analysis

Statistical analysis was performed using PASW version 17 software (IBM, Tokyo, Japan). Statistical correlations between two groups were determined using Spearman's rank correlation coefficient. Inter-observer agreements were assessed with kappa statistics. Kappa values were

Table 1 Profiles of enrolled patients

Total number of patients	55
Age (years)	40.7 (15–69)
Male	37 (67.3%)
Disease duration (years)	8.6 (0.5–30)
Type of UC	
Total colitis	23
Left-sided	20
Proctitis	12
Clinical course	
Relapsing–remitting type	45
Chronic continuous type	4
One attack only	6
Treatment	
5-ASA	M/F
SASP	12/8
Mesalazine	37/8
Prednisolone	1/22
6-MP	7/1
AZA	2/2
Tacrolimus	0/1
CAP	1/6
No medication	4/0

UC ulcerative colitis, *5-ASA* 5-aminosalicylic acid, *SASP* salazosulfapyridine, *6-MP* 6-mercaptopurine, *AZA* azathioprine, *CAP* cell apheresis, *M* male, *F* female

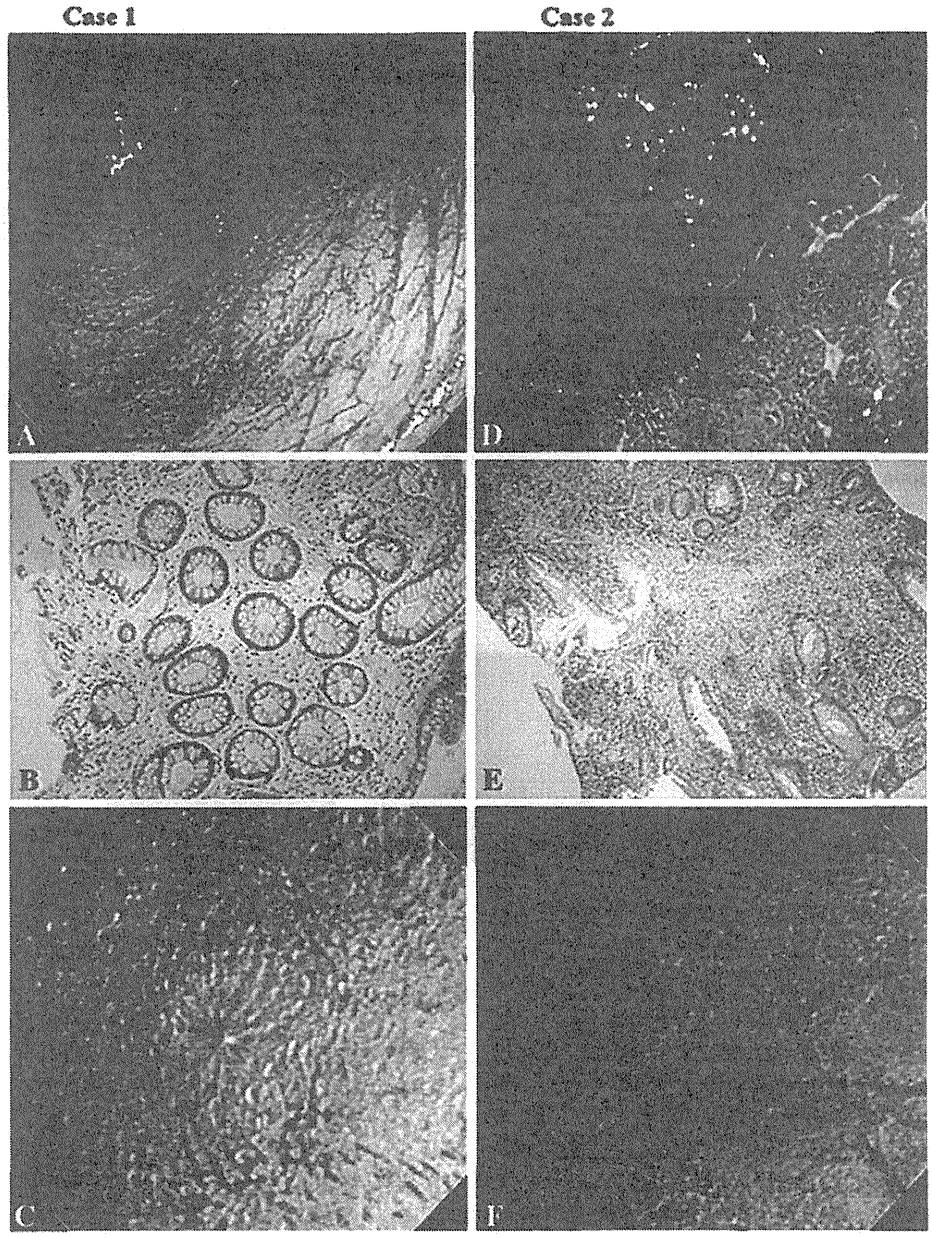

Fig. 1 Representative series of conventional endoscopic, ECS, and histopathological images. **A–C** Case 1: a patient in clinical remission (46 years, female). **D–F** Case 2: a patient with active-stage ulcerative colitis (UC) (42 years, female). **A, D** endoscopic images. **B, E** H&E, ×400. **C, F** ECS, ×450

interpreted as follows: absence of agreement 0, slight agreement <0.20, fair agreement 0.21–0.40, moderate agreement 0.41–0.60, substantial agreement 0.61–0.80, and almost perfect agreement >0.81, as proposed by Landis and Koch [14].

Results

Patient demographics and characteristics are shown in Table 1. The number of enrolled patients was 55, and clinical activity was regarded as remission or mild in 51 patients and moderate in 4. When differences in endoscopic activities were observed in the rectum of the same patient, multiple ECS images and biopsy samples were taken. In total, 76 ECS images were obtained.

We selected three items from the first 20 ECS images. ECSS-A indicates the shape of crypts: 0 normal round; 1 oval, indicating possible crypt distortion; 2 irregular, indicating severe crypt distortion and destruction; and 3 not recognizable, indicating extensive crypt destruction (Fig. 2A). ECSS-B indicates the distance between neighboring crypts: 0 normal, three or more crypts are observed in a visual field; 1 intermediate, 2 ≤ crypts < 3 in a visual field; and 2 elongated, <2 crypts in a visual field (Fig. 2B). ECSS-C indicates the visibility of superficial microvessels: 0 not visible, and 1 visible (Fig. 2C). Even in normal rectal mucosa, ECS occasionally detects microvessels. ECSS-C

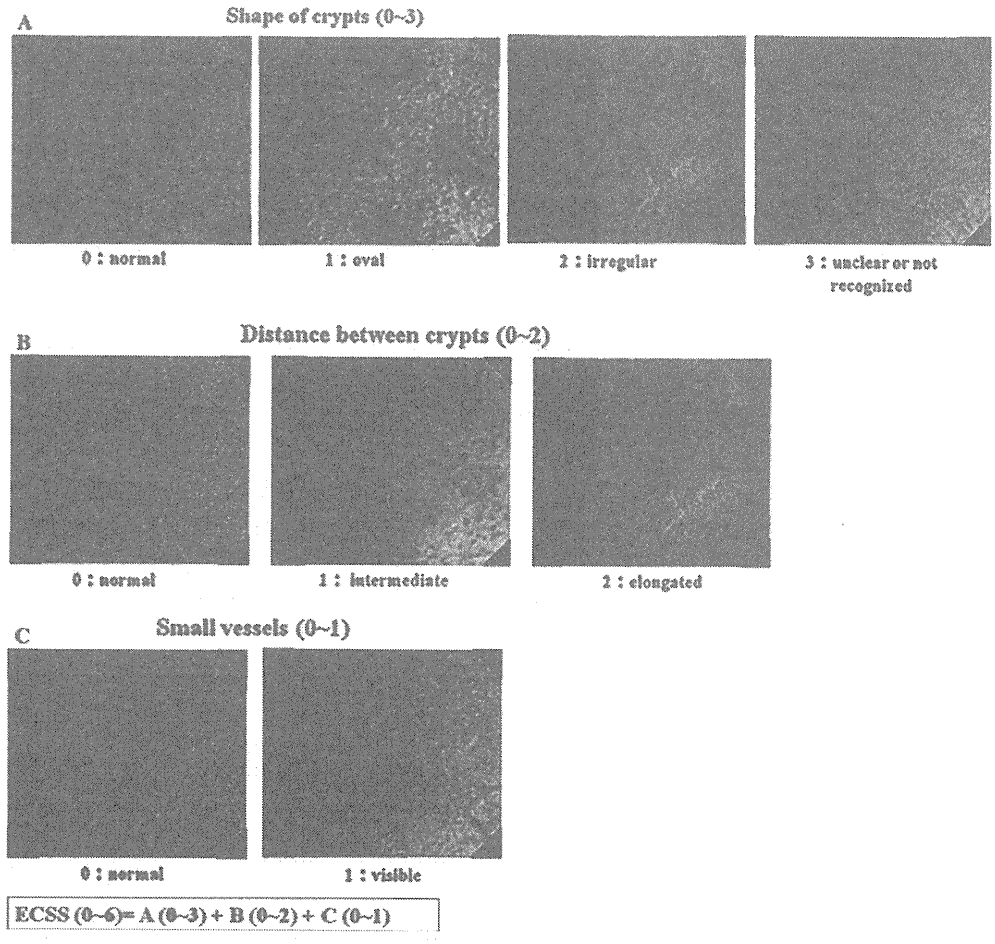

Fig. 2 Endocytoscopy system score (ECSS). Three indices were adopted for the ECSS. ECS score A (ECSS-A): shape of crypts, 0 normal round; 1 oval, indicating possible crypt distortion; 2 irregular, indicating severe crypt distortion and destruction; and 3 unrecognizable, indicating extensive destruction. ECSS-B indicates the distance between neighboring crypts: 0 normal, three or more crypts in a visual field; 1 intermediate, $2 \leq$ crypts < 3 in a visual field, with infiltrating cells in the lamina propria (LP); and 2 elongated, fewer than 2 crypts in a visual field. ECSS-C indicates the visibility of superficial microvessels: 0 not visible, and 1 visible. The total ECSS is the sum of ECSS-A, B, and C (minimum 0, maximum 6)

Table 2 Inter-observer agreement for each evaluation item and total ECSS

	κ value	95% CI	*P* value
ECSS-A (shape)	0.73	0.61–0.85	<0.001
ECSS-B (distance)	0.52	0.34–0.70	<0.001
ECSS-C (vessels)	0.63	0.45–0.81	<0.001
Total ECSS	0.79	0.71–0.87	<0.001

ECSS endocytoscopy system score, *CI* confidence interval

visible vessels were defined as superficial and dilated microvessels. Total ECSS is the sum of ECSS-A, B, and C (minimum 0, maximum 6). As shown in Fig. 1, a representative UC patient in the remission stage (Case 1: 46 years, female) showed almost normal mucosa except for a slightly unclear vascular pattern by conventional colonoscopy (Fig. 1A) and regular crypts with strong staining on H&E pictures (Fig. 1B). In contrast, a representative UC patient in the active stage (Case 2: 42 years, female) showed diffuse inflammation with mucosal erythema, erosion, and purulent mucus by conventional colonoscopy (Fig. 1D) and sparse, irregular crypts and marked infiltration of mononuclear cells in the lamina propria (LP) with

Table 3 Correlation between conventional Matts' endoscopic grade and Matts' histopathological grade

	Matts' histopathological grade					
	1	2	3	4	5	Total
Matts' endoscopic grade						
1	12	1	0	0	0	13
2q	30	8	2	1	0	41
2a	2	0	12	0	0	14
3	0	2	2	1	2	7
4	0	0	0	0	1	1
Total	44	11	16	2	3	76

Spearman rank correlation coefficient $|r| = 0.694$

H&E staining (Fig. 1E). The ECS images of these two cases corresponded to the histological H&E-stained images (Fig. 1C, F). In addition, microvessels were visible in the ECS image in the patient in the active stage of UC.

To assess the reproducibility of the ECSS, kappa values were calculated. As shown in Table 2, moderate to substantial agreements were recognized for each item. Furthermore, substantial agreements between different endoscopists were observed for the total ECSS. Before

Table 4 Correlations of ECSS-A, -B and -C with Matts' histopathological grade

	Matts' histopathological grade						$\|r\|^a$
	1	2	3	4	5	Total	
Shape							
0	32	6	2	1	0	41	0.568
1	12	5	8	0	1	26	
2	0	0	5	0	1	6	
3	0	0	1	1	1	3	
Distance							
0	42	8	3	0	0	53	0.745
1	2	2	6	1	2	13	
2	0	1	7	1	1	10	
Vessels							
0	44	7	8	1	0	60	0.643
1	0	4	8	1	3	16	

[a] Spearman rank correlation coefficient

Table 5 Correlation between ECSS and Matts' histopathological grade

	Matts' histopathological grade					
	1	2	3	4	5	Total
ECSS						
0	31	6	0	0	0	37
1	12	1	4	1	0	18
2	1	1	2	0	0	4
3	0	2	3	0	1	6
4	0	1	3	0	1	5
5	0	0	4	0	0	4
6	0	0	0	1	1	2
Total	44	11	16	2	3	76

Spearman rank correlation coefficient $|r| = 0.713$

investigating the possible application of the ECSS for assessing the histopathological disease activity of UC, we evaluated the correlation between the conventional Matts' endoscopic grade and Matts' histopathological grade, as shown in Table 3. Consistent with previous reports, we found a significant correlation between the two (Spearman's $\rho = 0.694$, $P < 0.001$), although Matts' endoscopic grade (2q) tended to correspond to a broad range of Matts' histopathological grades. Next, we examined whether each ECSS index (ECSS-A, B, and C) correlated with Matts' histopathological grades (Table 4). All were found to show good correlations, with ECSS-B, the indicator of the distance between neighboring crypts, showing the strongest correlation (ECSS-A, $\rho = 0.568$, $P < 0.001$; ECSS-B, $\rho = 0.745$, $P < 0.001$; ECSS-C, $\rho = 0.643$, $P < 0.001$). Finally, we assessed the total ECSS as an indicator of UC histopathological disease activity. As shown in Table 5, there was a strong correlation between the ECSS and Matts' histopathological grades ($\rho = 0.713$, $P < 0.001$).

Correlations between the ECSS and clinical activity factors (CRP and stool frequency) were evaluated. The ECSS and stool frequency showed a weak correlation ($\rho = 0.303$, $P = 0.03$). There was no significant correlation between the ECSS and CRP.

Discussion

This is the first study to show the potential applicability of a newly developed ECS scoring system for the assessment of the histopathological disease activity of UC. First, we confirmed that the ECSS had a high kappa value, i.e., that the ECSS showed high reproducibility. The ECSS involves only three evaluation items, and each has four or fewer categories. This simple process may have contributed to the high inter-observer agreement. Next, we demonstrated a good correlation between the ECSS and Matts' histopathological grade; as well, we demonstrated a good correlation between the conventional Matts' endoscopic grade and Matts' histopathological grade. The distance between neighboring crypts (ECSS-B) ($\rho = 0.745$, $P < 0.001$) was the most reliable of the three indices. Furthermore, other items also showed significant correlations with Matts' histopathological grade. The ECSS is comprised of only three items. It does not allow assessment of conventional histopathological items, such as inflammatory cell infiltration. Thus, the ECSS is not a substitute for routine conventional histopathological examination in the evaluation of UC, but could serve as a simple surrogate for this evaluation.

Employing an approach similar to that used in the present study, Li et al. [13] have shown the benefits of classifying the histopathological activity of UC using CLE. They classified CLE findings based on crypt architecture, microvascular alteration, and fluorescein leakage into

crypts. They also analyzed the correlation between each classified item and the histological index, divided into two categories (Geboes index). On the other hand, we analyzed the correlations between three ECSS items (A, B, C) and Matts' histopathological grade, divided into five categories. Furthermore, we confirmed a strong correlation between the ECSS and Matts' histopathological grade. Therefore, the ECSS is an excellent predictor of the histopathological activity of UC.

Most clinical studies reported to date have used a CLE integrated into the distal tip of a conventional upper endoscope (iCLE: EG-3870CIK; Pentax) or a colonoscope (EC-3870CILK; Pentax) [6]. A smaller number of studies used a probe-based CLE (pCLE) (Mauna Kea Technologies) inserted through the accessory channel of a traditional endoscope [6]. Similar to the classification of CLE, ECS is classified as probe-based ECS (pECS) and integrated-scope type ECS (iECS) [11]. We used an iECS which could be switched from conventional and magnifying views to super-magnifying using a button located at the top of the endoscope. iECS is very useful in that a single scope can obtain images ranging from conventional to super-magnified.

Confocal laser endomicroscopy based on tissue fluorescence uses local and/or intravenous contrast agents and generates images [6]. ECS observation also requires pretreatment with methylene blue or toluidine blue staining [11]. In the present study, the additional time required for ECS observation was approximately 20 min. In other words, with an additional ECS procedure, we were able to predict the histopathological activity of UC.

We found no correlations between the ECSS and clinical activity. There was a weak correlation ($\rho = 0.303$, $P = 0.03$) between the ECSS and stool frequency. These results were attributed to small sample size and bias favoring the enrollment of patients with relatively mild disease activity. To assess the clinical efficacy of the ECSS, further clinical trials with a larger sample will be needed.

In conclusion, our newly developed ECSS is simple to perform and the data obtained provide a good prediction of the histological activity of UC. To confirm the clinical and histopathological usefulness of the ECSS, further clinical study with a larger sample size is needed.

Acknowledgments We sincerely thank Dr. Yasushi Iwao for helpful discussions. This study was supported in part by grants-in-aid for Scientific Research, Scientific Research on Priority Areas, and Exploratory Research and Creative Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology; the Japanese Ministry of Health, Labor and Welfare; the Japan Medical Association; Foundation for Advancement of International Science; and The Japanese Foundation for Research and Promotion of Endoscopy Grant. All authors disclosed no financial relationships relevant to this publication. We are grateful to Olympus Medical Systems Co. Ltd. for providing the ECS.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Inoue H, Kudo SE, Shiokawa A. Technology insight: Laser-scanning confocal microscopy and endocytoscopy for cellular observation of the gastrointestinal tract. Nat Clin Pract Gastroenterol Hepatol. 2005;2(1):31–7.
2. Kiesslich R, Canto MI. Confocal laser endomicroscopy. Gastrointest Endosc Clin N Am. 2009;19(2):261–72.
3. Hurlstone DP, Thomson M, Brown S, Tiffin N, Cross SS, Hunter MD. Confocal endomicroscopy in ulcerative colitis: differentiating dysplasia-associated lesional mass and adenoma-like mass. Clin Gastroenterol Hepatol. 2007;5(10):1235–41.
4. Sakashita M, Inoue H, Kashida H, Tanaka J, Cho JY, Satodate H, et al. Virtual histology of colorectal lesions using laser-scanning confocal microscopy. Endoscopy. 2003;35(12):1033–8.
5. Neumann H, Kiesslich R, Wallace MB, Neurath MF. Confocal laser endomicroscopy: technical advances and clinical applications. Gastroenterology. 2010;139(2):388–92, 392.e1-2.
6. ASGE Technology Committee, Kantsevoy SV, Adler DG, Conway JD, Diehl DL, Farraye FA, et al. Confocal laser endomicroscopy. Gastrointest Endosc. 2009;70(2):197–200.
7. Sasajima K, Kudo SE, Inoue H, Takeuchi T, Kashida H, Hidaka E, et al. Real-time in vivo virtual histology of colorectal lesions when using the endocytoscopy system. Gastrointest Endosc. 2006;63(7):1010–7.
8. Anandasabapathy S. Endoscopic imaging: emerging optical techniques for the detection of colorectal neoplasia. Curr Opin Gastroenterol. 2008;24(1):64–9.
9. Matysiak-Budnik T, Coron E, Mosnier JF, Le Rhun M, Inoue H, Galmiche JP. In vivo real-time imaging of human duodenal mucosal structures in celiac disease using endocytoscopy. Endoscopy. 2010;42(3):191–6.
10. Hosoe N, Kobayashi T, Kanai T, Bessho R, Takayama T, Inoue N, et al. In vivo visualization of trophozoites in patients with amoebic colitis by using a newly developed endocytoscope. Gastrointest Endosc. 2010;72(3):643–6.
11. Neumann H, Fuchs FS, Vieth M, Atreya R, Siebler J, Kiesslich R, et al. Review article: in vivo imaging by endocytoscopy. Aliment Pharmacol Ther. 2011;33(11):1183–93.
12. Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, et al. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology. 2007;132(3):874–82.
13. Li CQ, Xie XJ, Yu T, Gu XM, Zuo XL, Zhou CJ, et al. Classification of inflammation activity in ulcerative colitis by confocal laser endomicroscopy. Am J Gastroenterol. 2010;105(6):1391–6.
14. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159–74.

J Gastroenterol
DOI 10.1007/s00535-011-0501-z

ORIGINAL ARTICLE—ALIMENTARY TRACT

Small bowel injury induced by selective cyclooxygenase-2 inhibitors: a prospective, double-blind, randomized clinical trial comparing celecoxib and meloxicam

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Received: 10 August 2011 / Accepted: 24 October 2011

Abstract
Background Selective cyclooxygenase (COX)-2 inhibitors are less harmful to the small bowel mucosa than non-selective anti-inflammatory drugs. We aimed to compare the severity of small bowel mucosal injury in healthy volunteers induced by two selective COX-2 inhibitors, celecoxib and meloxicam, in a randomized, double-blind trial, using capsule endoscopy (CE).
Methods Twenty-nine healthy subjects were randomized to take either celecoxib (200 mg twice daily) or meloxicam (10 mg once daily) for 2 weeks. The incidence and the number of small bowel mucosal injuries (bleeding, ulcers, and erosions) observed by CE were compared between the two groups.
Results The overall incidence of small bowel mucosal injury was not different between the celecoxib group (6 of 14 subjects, 42.9%) and the meloxicam group (4 of 15 subjects, 26.7%, $P = 0.45$). In subjects with positive CE findings, the number of ulcers was greater in the meloxicam group than in the celecoxib group ($P = 0.02$), while such a trend was not found with regard to erosions ($P = 0.52$). The distribution of mucosal lesions within the small bowel was similar in the two groups.
Conclusions Selective COX-2 inhibitors are not completely safe for the small bowel. The mucosal lesions may be less severe with celecoxib than with meloxicam.

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Keywords Selective cyclooxygenase-2 inhibitor · Small bowel mucosal injury · Capsule endoscopy

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) frequently show gastrointestinal (GI) toxicity. For instance, gastroduodenal ulcers occur in 20–30% of chronic NSAID users [1–3]. It has also been shown that colonoscopy detects ulcers in the lower GI tract in 3% of chronic NSAID users [4, 5]. Although it had become evident in the 1980s that NSAIDs also damaged the small bowel, in practice, the mucosal injury could not be visualized until capsule endoscopy (CE) and double-balloon endoscopy (DBE) became widely used. While a postmortem examination identified small bowel ulcerations in 21 (8.4%) of 249 NSAID users [3], it has subsequently become evident in CE and DBE studies that NSAIDs cause small bowel mucosal injury more frequently, with a prevalence of up to 70% [6–8].

Recent clinical studies have shown that the incidence of upper GI injury was lower in subjects treated with selective cyclooxygenase (COX)-2 inhibitors than in those treated with non-selective NSAIDs [9–12]. Furthermore, celecoxib, one of the selective COX-2 inhibitors, has been shown to cause small bowel mucosal injury and lower GI events less frequently than non-selective NSAIDs [12–14]. Meloxicam, an agent synthesized as a traditional NSAID, also has a selective inhibitory action against COX-2 [15, 16]. In vitro studies showed that meloxicam had less potent inhibitory action on the synthesis of prostaglandin E, 6-keto-prostaglandin $F_{1\alpha}$, and thromboxane B_2 in human gastric mucosa when compared to indomethacin [17]. Ex vivo analysis of monocytes obtained from meloxicam-pretreated humans revealed that the drug had a five- to tenfold higher inhibitory

Published online: 15 December 2011

effect on COX-2 than on COX-1 [18–20]. In clinical trials, meloxicam was associated with a lower incidence of upper GI toxic events when compared to other traditional NSAIDs [21–23]. However, small bowel mucosal injury caused by meloxicam has not been examined to date.

In order to examine whether selective COX-2 inhibitors are protective against small bowel injury in humans, and to investigate possible differences between the small bowel toxicity of two selective COX-2 inhibitors, celecoxib and meloxicam, we performed a prospective, double-blind, randomized, controlled study.

Methods

Study design

This study was a prospective, double-blind, randomized trial. Prior to randomization, all subjects underwent laboratory tests (complete blood cell count, serum chemistry, and detection of *Helicobacter pylori* antibody), an electrocardiogram (ECG), and a baseline CE. Any subjects who had abnormal laboratory test results or an abnormal ECG were excluded from the study. Subjects who had small bowel erosions or ulcers at baseline CE were also excluded. All remaining subjects were then randomized, by a computer-generated randomization system, to receive either celecoxib (200 mg twice daily) or meloxicam (10 mg once daily) for 2 weeks. The dose of each drug was determined on the basis of the dose approved by the Japanese Ministry of Health and Welfare and applied to other clinical trials [24, 25]. In both groups, omeprazole (20 mg once daily) was given in consideration of possible gastric mucosal injury. Celecoxib and meloxicam were prepared in dummy capsules and the subjects were instructed to take a capsule twice per day for 2 weeks. The use of other NSAIDs, aspirin, or anti-ulcer drugs was strictly prohibited during the study period. After 2 weeks of medication, the subjects completed a questionnaire about GI symptoms, underwent repeated laboratory tests, and received a second CE.

The study protocol was approved by the institutional review board of the International University of Health and Welfare Fukuoka Sanno Hospital (FS-2-0903-049), and the study was conducted in accordance with the Helsinki Declaration. This trial has been registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as number UMIN000003871. All subjects provided their written informed consent before entry into the study.

Subjects

Healthy volunteers with normal physical examinations and normal laboratory test results were eligible for the present investigation. Exclusion criteria were as follows: (1) a history of peptic ulcers, (2) a history of recent (within a month) use of NSAIDs or aspirin, (3) a history of aspirin-induced asthma, (4) allergy to sulfonamide, (5) recent treatment with anti-ulcer drugs, (6) stenosis of the GI tract, (7) a history of adhesion ileus, (8) pregnant or nursing females, and (9) the presence of other disorders regarded as causing the subject's participation in the present study to be inappropriate.

Capsule endoscopy

The baseline and the second CEs were performed using a PillCam SB (Given Imaging, Yokneam, Israel). After an overnight fast for 12 h, each subject was prepared with sensor arrays and a data recorder, and instructed to swallow the capsule with a small amount of water. CE images were recorded for the subsequent 8 h. All the digital video image streams were downloaded to the Given Imaging Reporting and Processing of Images and Data (RAPID) system.

Two observers (M.E. and Y.M.) independently assessed the CE images. Positive CE findings were classified as mucosal bleeding or mucosal injuries. Mucosal injuries were further divided into ulcers and erosions on the basis of the classification reported by Fujimori et al. [26] and Niwa et al. [27] with slight modifications. Mucosal bleeding was defined as the presence of luminal blood in the small intestine. A large mucosal defect with obvious whitish mucous was defined as an ulcer (Fig. 1a), while a small mucosal break surrounded by redness was regarded as an erosion (Fig. 1b). The small intestine was divided equally into the jejunum and the ileum by the small bowel transit time. If the CE findings were different between the two observers, they then discussed the case until a consensus opinion was reached.

Endpoints

The primary endpoint was the incidence of positive CE findings of any type at the second CE.

The secondary endpoints were the incidence of CE findings in the jejunum and in the ileum, the numbers of each CE finding in subjects with positive CE results, GI symptoms, and the presence or absence of anemia. GI symptoms were assessed at the end of the medication period by using a GI symptom rating scale (GSRS) [28]. Anemia was defined as a decrease in the hemoglobin level by more than 2.0 g/dl from the baseline value.

Statistical analysis

The incidence of small bowel mucosal injury after 2 weeks of celecoxib has been shown to range from 6 to

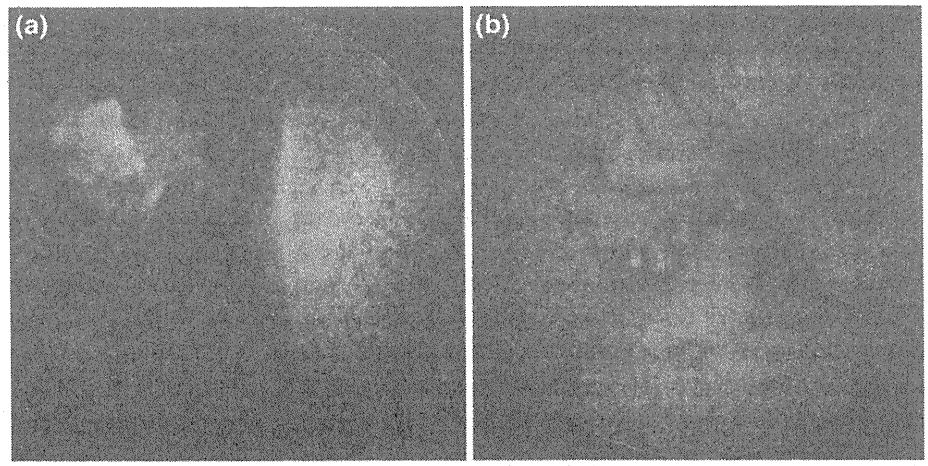

Fig. 1 Examples of mucosal injury observed by capsule endoscopy (CE) (a ulcer, b erosion)

16% [13, 14]. The incidence of small bowel mucosal injury caused by meloxicam was unknown. We thus presumed the incidence to be equivalent to that of non-selective NSAIDs (68–75%) [6, 7]. In the present study, the sample size was calculated on the assumption that the incidence of small bowel mucosal injury would be 10% for celecoxib and 60% for meloxicam. To detect this difference with a 0.05 significance level and a statistical power of 80%, it was calculated that 15 subjects per group would be required.

Parametric data were expressed as medians (ranges). The data were compared between the groups using the Mann–Whitney *U*-test. Non-parametric data were expressed as frequencies, and analyzed by Fisher's exact probability test or the χ^2 test. A P value of <0.05 was considered to be statistically significant for each test.

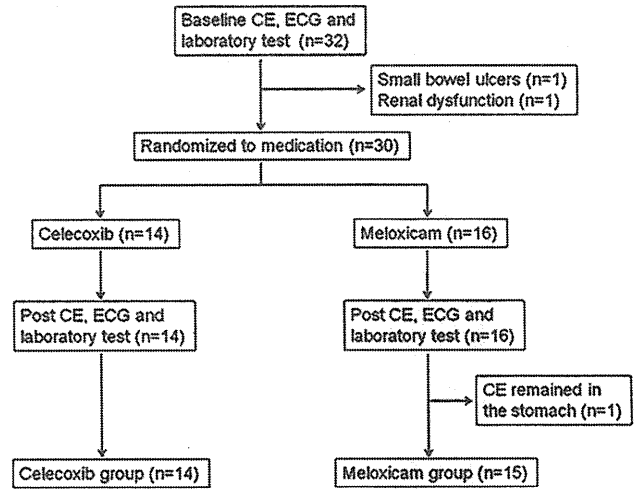

Fig. 2 Flow chart of the study subjects

Results

Subjects

The study was conducted from April to August 2010. During the study period, 32 subjects were enrolled. A flow chart of the study subjects is shown in Fig. 2. Two subjects were excluded, one because of multiple small bowel ulcers and one because of a slight increase in the serum creatinine level (1.2 mg/dl) at baseline. The remaining thirty subjects were then randomized to either the celecoxib or the meloxicam group. The second CE enabled total enteroscopy in 29 subjects, because the capsule remained in the stomach during the second CE in one subject (who had been taking meloxicam). Consequently, the celecoxib and meloxicam groups comprised 15 subjects and 14 subjects, respectively.

Table 1 shows a comparison of the demographic data in the two groups of study subjects. There were no significant differences in age, gender, or body weight between the two groups. *Helicobacter pylori* infection was detected in 3 subjects in the celecoxib group and in one subject in the meloxicam group. The prevalence of the infection was not different between the two groups. One subject in the celecoxib group continued taking concurrent medication for his essential hypertension.

Table 1 Comparison of demographic data between the celecoxib and meloxicam groups

	Celecoxib group	Meloxicam group	*P* value
Number of subjects	14	15	
Age (years)	33 (25–50)	30 (24–46)	0.60
Gender (female/male)	6/8	6/9	0.88
Body weight (kg)	66 (45–79)	59 (39–76)	0.68
Helicobacter pylori infection	3	1	0.33
Concurrent medication	1[a]	0	0.48

Parametric data are expressed as medians (ranges)

[a] The subject continued taking an angiotensin II receptor blocker

In the subjects who completed the full study protocol, we did not encounter any extra-abdominal symptoms or significant changes in laboratory data.

Capsule endoscopy findings

In each subject, the two observers reported a concordant result as to the presence or absence of positive findings at the second CE. However, there were two subjects in whom the determination of an ulcer or erosion was discordant between the two observers, thereby requiring a discussion. As a result of the discussion, a consensus was reached that there were erosions in 6 subjects in the celecoxib group, three of whom also had ulcers. In the meloxicam group, ulcers were found in 4 subjects, three of whom also had erosions. Consequently, the incidence of small bowel mucosal injuries was not significantly different between the two groups (42.9% in the celecoxib group and 26.7% in the meloxicam group, $P = 0.45$) (Fig. 3). When the total number of mucosal injuries was compared, no significant difference was found between the celecoxib group (0 [range 0–14]) and the meloxicam group (0 [range 0–18]). Similarly, neither the number of ulcers nor the number of erosions differed between the two groups.

We then compared the severity of mucosal injuries in the two groups in subjects with positive CE findings (Fig. 4). Six subjects in the celecoxib group and four subjects in the meloxicam group were the subjects for the comparison. The number of ulcers in subjects taking celecoxib was 1 (range 0–1), while the number was higher (3 [range 1–3]) in subjects taking meloxicam ($P = 0.02$). The number of erosions was 6 (range 1–13) in subjects taking celecoxib and 13 (range 0–16) in subjects taking meloxicam ($P = 0.52$). The total number of mucosal injuries was no different between the two groups of subjects (6 [range 1–14] in subjects with celecoxib and 16 [range 3–18] in subjects with meloxicam, $P = 0.18$).

Figure 5 shows a comparison of the incidence of jejunal and ileal injuries in the two groups. Ulcers were found only in the ileum, with an incidence of 21% (3 subjects) in the celecoxib group and an incidence of 27% (4 subjects) in the meloxicam group (Fig. 5a). While the incidence of erosions in the jejunum was not different between the two groups (7.1% in the celecoxib group and 6.7% in the meloxicam group, $P = 1.0$), the incidence of ileal erosions was higher in the celecoxib group (42.9%) than in the meloxicam group (20%). However, the difference did not reach statistical significance ($P = 0.25$).

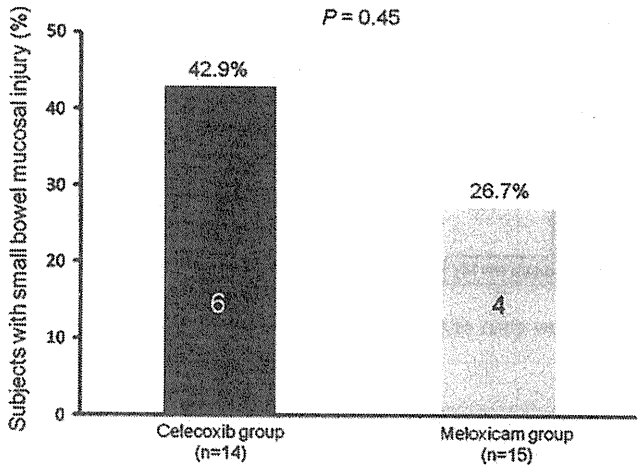

Fig. 3 Comparison of the incidence of small bowel mucosal injury between the celecoxib and meloxicam groups

Symptoms, laboratory data, and complications

One subject in the celecoxib group complained of epigastric pain. In the meloxicam group, two subjects experienced abdominal discomfort and one subject had diarrhea. As shown in Table 2, the GSRS score was 17 (range 15–25) in the celecoxib group and 18 (range 15–26) in the meloxicam group. None of the subjects manifested anemia at the end of the medication period.

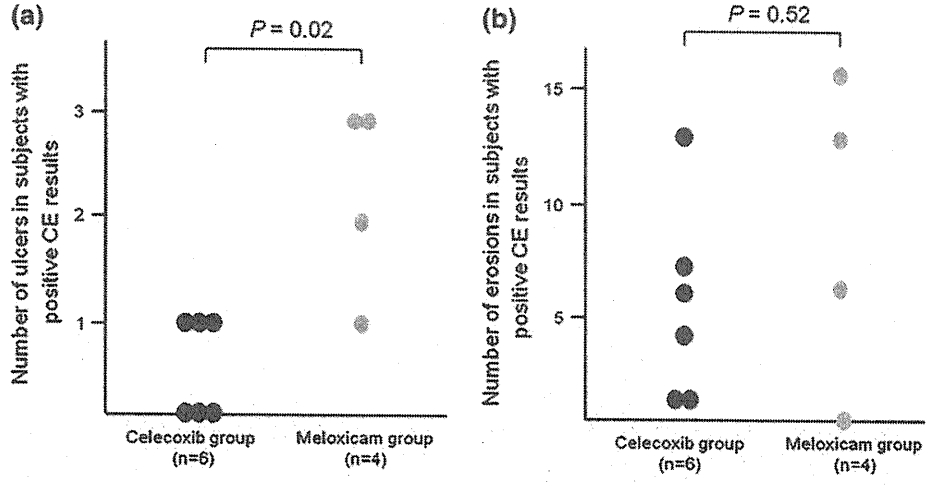

Fig. 4 Comparison of the number of lesions in subjects with positive CE results (**a** number of ulcers, **b** number of erosions)

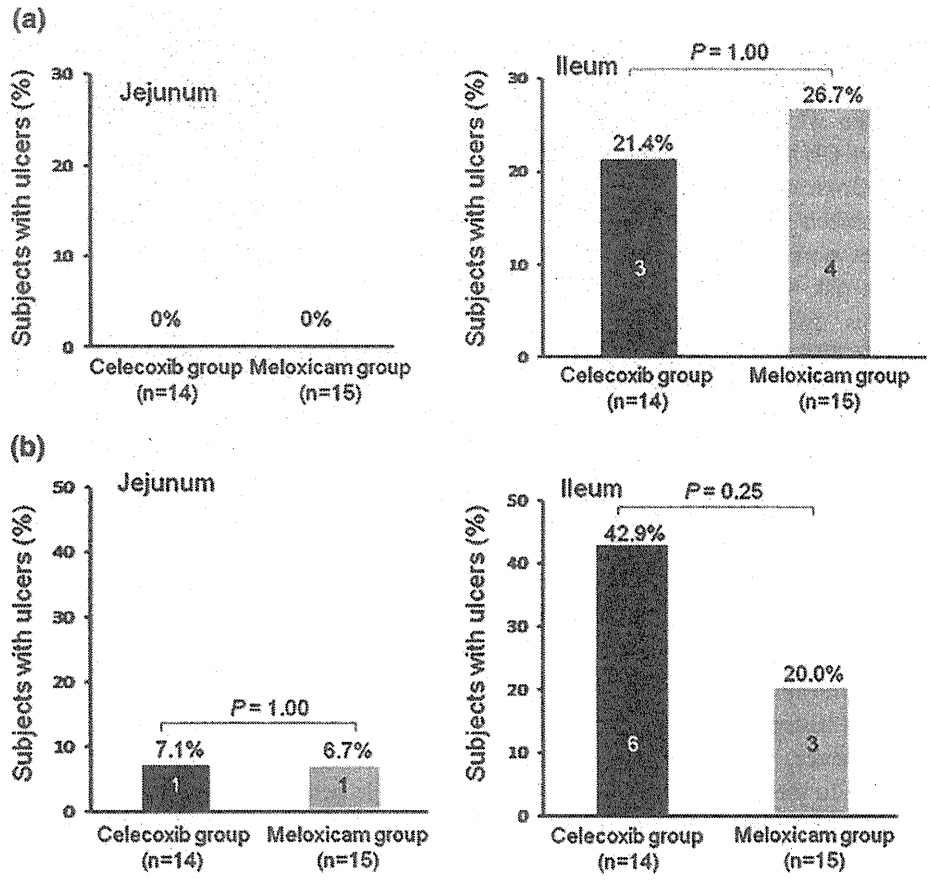

Fig. 5 Comparison of the incidence of small bowel mucosal injuries between the two groups according to their site (a ulcers, b erosions)

Table 2 Abdominal symptoms and laboratory data

	Celecoxib group (n = 14)	Meloxicam group (n = 15)	P value
Symptoms	1	3	0.60
GSRS	17 (15–25)	18 (15–26)	0.52
Anemia	0	0	

Anemia was defined as a decrease in the hemoglobin level of at least 2.0 g/dl from baseline

GSRS gastrointestinal symptom rating scale, *GSRS* data are expressed as medians (ranges)

Discussion

NSAIDs and selective COX-2 inhibitors are generally classified by their COX-2/COX-1 selectivity determined by in vitro or ex vivo experiments. In this regard, meloxicam and celecoxib are classified in the same category of NSAIDs, with selectivity ranging from 5 to 50 [29, 30]. However, the relative risk of upper GI toxicity is threefold higher with meloxicam than with celecoxib [31]. Lanas et al. [32] reported a much higher risk of upper GI bleeding in patients administered meloxicam than in those administered celecoxib in a hospital-based, case–control study. These observations suggest that the in vivo COX-2/COX-1 selectivity of each of these NSAIDs is different from their in vitro and ex vivo selectivities, and that the in vitro and ex vivo selectivities are not predictive of GI toxicity. We thus hypothesized that the incidence and the severity of small bowel damage would be different between celecoxib and meloxicam. In accordance with prior clinical trials, we carried out a double-blind prospective study with healthy subjects treated with short-term NSAIDs [13, 14]. As has been confirmed in other prospective studies treating healthy volunteers [7, 13, 14], we found small bowel mucosal lesions in 3% of our subjects prior to the administration of the test drugs.

Our results indicated that the incidence of small bowel mucosal damage induced by celecoxib (43%) was not different from that induced by meloxicam (27%), with rather a higher value for celecoxib than for meloxicam. Interestingly, the incidence of celecoxib-induced small bowel mucosal damage in our subjects was equivalent to that induced by diclofenac or naproxen in Western and Eastern subjects verified by randomized trials [7, 13, 27, 33] and it was higher than that induced by ibuprofen in Western subjects [14]. It thus seems reasonable to conclude that the selective COX-2 inhibitors available at present are not unequivocally safe for the small bowel. However, because celecoxib and meloxicam have anti-COX-1

properties, it is still possible that COX-1 inhibition contributes to the pathogenesis of the mucosal damage even in subjects treated with selective COX-2 inhibitors.

When we compared the CE findings in subjects with positive CE results, we found a greater number of ulcers in the meloxicam-treated subjects than in the celecoxib-treated subjects. This observation suggests that meloxicam induces more severe mucosal lesions in subjects who are at a high risk of NSAID enteropathy. Possible explanations for this difference between meloxicam and celecoxib include differences in the effects of the two drugs on the enterohepatic recirculation [34], in their effects on bacterial flora and bile acid composition, and presumably, in their effects on in vivo COX-2/COX-1 selectivity. Because severe mucosal damage is likely to cause GI complications such as bleeding and perforation, celecoxib may be safer than meloxicam for the small bowel.

In both our celecoxib and meloxicam groups, most mucosal damage was found in the distal part of the small bowel. It has been confirmed that NSAIDs increase intestinal permeability through enterocytic mitochondrial damage and a decrease in prostaglandin synthesis, and, as a consequence, the intestinal mucosa becomes more susceptible to the actions of luminal agents such as bile acid, bacterial flora, and ingested foods [34–37]. Changes in the composition of bile acids and an increase in bacterial flora in the ileum may explain the more severe mucosal damage at this site [37]. A similar trend in the distribution of mucosal injuries has been confirmed in recent studies using other NSAIDs [26, 38, 39], indicating that the ileum seems to be the predominant site prone to mucosal injury in patients taking NSAIDs or COX-2 inhibitors.

The incidence of small bowel mucosal injuries in our celecoxib group was 43%, which was much higher than was predicted (10%). We predicted the incidence of small bowel mucosal injury in the celecoxib group based on the prospective studies done by Goldstein et al. [13, 14], and this discordant result may therefore have been a consequence of the differences in subjects' ethnicities and physiques between the studies done by Goldstein et al. [13, 14] and our present trial. In fact, the body weight of our subjects (median 59 kg) was much lower than that in the study by Goldstein et al. [14] (73 kg). However, it should also be noted that in an observational study done by Maiden et al. [40] in the United Kingdom, CE detected minute small bowel mucosal injuries in 50% of patients taking COX-2 inhibitors (celecoxib, etoricoxib, rofecoxib, or valdecoxib). It thus seems possible that COX-2 plays a significant role in the preservation of the mucosal integrity of the small bowel, and the inhibition of COX-2 can easily lead to mucosal breaks.

Our present study has some limitations. First, because the predicted incidence of mucosal injury in the celecoxib group was lower than the actual incidence, we should have recruited a larger number of subjects for each group to prove an insignificant difference in the incidence of mucosal injuries between the two groups. We thus cannot deny a significantly higher incidence of injuries in the celecoxib group. However, our conclusion that celecoxib possibly damages the small bowel should not be modified. Second, the small sample size suggests that there may be a type 2 error in the comparison of the severity of mucosal injuries, which means that the number of ulcers was not actually different between the two groups. Finally, subjects in the meloxicam group were administered a 10-mg dose of meloxicam, which is the standard dose in Japan but is lower than that in Western countries (15 mg).

In conclusion, our prospective study indicated that the incidence of small bowel mucosal damage was not different between subjects treated with celecoxib and those treated with meloxicam, suggesting that selective COX-2 inhibitors are not completely safe for the small bowel. Our sub-analysis of subjects with positive CE findings suggested celecoxib to be less harmful than meloxicam, indicating that factors other than in vitro COX-2/COX-1 selectivity may be associated with small bowel toxicity. The conspicuously high incidence of mucosal damage in our subjects treated with celecoxib warrants further studies to establish the role of selective COX-2 inhibitors for the prevention of small bowel injuries in patients scheduled to receive long-term NSAID treatment.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Graham DY, Agrawal NM, Roth SH. Prevention of NSAID-induced gastric ulcer with misoprostol: multicentre, double-blind, placebo-controlled trial. Lancet. 1988;2:1277–80.
2. Collins AJ, Davies J, Dixon SA. Contrasting presentation and findings between patients with rheumatic complaints taking nonsteroidal anti-inflammatory drugs and a general population referred for endoscopy. Br J Rheumatol. 1986;25:50–3.
3. Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. N Engl J Med. 1992;327:749–54.
4. Kurahara K, Matsumoto T, Iida M, Honda K, Yao T, Fujishima M. Clinical and endoscopic features of nonsteroidal anti-inflammatory drug-induced colonic ulcerations. Am J Gastroenterol. 2001;96:473–80.
5. Amano Y, Kushiyama Y, Takahashi Y, Ishihara S, Adachi K, Kinoshita Y. Prevalence of ileo-colonic ulcerative lesions in chronic NSAIDs users. Am J Gastroenterol. 2004;99:1193.
6. Graham DY, Opekun AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. Clin Gastroenterol Hepatol. 2005;3:55–9.
7. Maiden L, Thjodleifsson B, Theodors A, Gonzalez J, Bjarnason I. A quantitative analysis of NSAID-induced small bowel pathology by capsule enteroscopy. Gastroenterology. 2005;128:1172–8.

8. Matsumoto T, Kudo T, Esaki M, Yano T, Yamamoto H, Sakamoto C, et al. Prevalence of non-steroidal anti-inflammatory drug-induced enteropathy determined by double-balloon endoscopy: a Japanese multicenter study. Scand J Gastroenterol. 2008;43:490–6.
9. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. J Am Med Assoc. 2000;284:1247–55.
10. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med. 2000;343:1520–8.
11. Singh G, Fort JG, Goldstein JL, Levy RA, Hanrahan PS, Bello AE, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. Am J Med. 2006;119:255–66.
12. Chan FK, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. Lancet. 2010;376:173–9.
13. Goldstein JL, Eisen GM, Lewis B, Gralnek IM, Zlotnick S, Fort JG. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. Clin Gastroenterol Hepatol. 2005;3:133–41.
14. Goldstein JL, Eisen GM, Lewis B, Gralnek IM, Aisenberg J, Bhadra P, et al. Small bowel mucosal injury is reduced in healthy subjects treated with celecoxib compared with ibuprofen plus omeprazole, as assessed by video capsule endoscopy. Aliment Pharmacol Ther. 2007;25:1211–22.
15. Noble S, Balfour JA. Meloxicam. Drugs. 1996;51:424–30.
16. Kawai S. Cyclooxygenase selectivity and the risk of gastrointestinal complications of various non-steroidal anti-inflammatory drugs: a clinical consideration. Inflamm Res. 1998;47(Suppl 2):S102–6.
17. Tavares IA. The effects of meloxicam, indomethacin or NS-398 on eicosanoid synthesis by fresh human gastric mucosa. Aliment Pharmacol Ther. 2000;14:795–9.
18. Giuliano F, Ferraz JG, Pereira R, de Nucci G, Warner TD. Cyclooxygenase selectivity of non-steroidal anti-inflammatory drugs in humans. Ex vivo evaluation. Eur J Pharmacol. 2001;426:95–103.
19. Panara MR, Renda G, Sciulli MG, Santini G, Di Giamberardino M, Rotondo MT, et al. Dose-dependent inhibition of platelet cyclooxygenase-1 and monocyte cyclooxygenase-2 by meloxicam in healthy subjects. J Pharmacol Exp Ther. 1999;290:276–80.
20. Stichtenoth DO, Wagner B, Frölich JC. Effects of meloxicam and indomethacin on cyclooxygenase pathways in healthy volunteers. J Investig Med. 1997;45:44–9.
21. Hawkey C, Kahan A, Steinbrück K, Alegre C, Baumelou E, Bégaud B, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. Br J Rheumatol. 1998;37:937–54.
22. Dequeker J, Hawkey C, Kahan A, Steinbrück K, Alegre C, Baumelou E, et al. Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies (SELECT) trial in osteoarthritis. Br J Rheumatol. 1998;37:946–51.
23. Singh G, Lanes S, Triadafilopoulos G. Risk of serious upper gastrointestinal and cardiovascular thromboembolic complications with meloxicam. Am J Med. 2004;117:100–6.
24. Sakamoto C, Soen S. Efficacy and safety of the selective cyclooxygenase-2 inhibitor celecoxib in the treatment of rheumatoid arthritis and osteoarthritis in Japan. Digestion. 2011;83:108–23.
25. Shinohara N, Kumagai A, Kanagawa K, Maruyama S, Abe T, Sazawa A, et al. Multicenter phase II trial of combination therapy with meloxicam, a COX-2 inhibitor, and natural interferon-α for metastatic renal cell carcinoma. Jpn J Clin Oncol. 2009;39:720–6.
26. Fujimori S, Gudis K, Takahashi Y, Seo T, Yamada Y, Ehara A, et al. Distribution of small intestinal mucosal injuries as a result of NSAID administration. Eur J Clin Invest. 2010;40:504–10.
27. Niwa Y, Nakamura M, Ohmiya N, Maeda O, Ando T, Itoh A, et al. Efficacy of rebamipide for diclofenac-induced small-intestinal mucosal injuries in healthy subjects: a prospective, randomized, double-blinded, placebo-controlled, cross-over study. J Gastroenterol. 2008;43:270–6.
28. Svedlund J, Sjödin I, Dotevall G. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988;33:129–34.
29. Kato M, Nishida S, Kitasato H, Sakata N, Kawai S. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs: investigation using human peripheral monocytes. J Pharm Pharmacol. 2001;53:1679–85.
30. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proc Natl Acad Sci USA. 1999;96:7563–8.
31. Massó González EL, Patrignani P, Tacconelli S, García Rodríguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. Arthritis Rheum. 2010;62:1592–601.
32. Lanas A, García-Rodríguez LA, Arroyo MT, Gomollón F, Feu F, González-Pérez A, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut. 2006;55:1731–8.
33. Fujimori S, Seo T, Gudis K, Ehara A, Kobayashi T, Mitsui K, et al. Prevention of nonsteroidal anti-inflammatory drug-induced small-intestinal injury by prostaglandin: a pilot randomized controlled trial evaluated by capsule endoscopy. Gastrointest Endosc. 2009;69:1339–46.
34. Reuter BK, Davies NM, Wallace JL. Nonsteroidal anti-inflammatory drug enteropathy in rats: role of permeability, bacteria, and enterohepatic circulation. Gastroenterology. 1997;112:109–17.
35. Matsumoto T, Iida M, Kuroki F, Hizawa K, Koga H, Fujishima M. Effects of diet on experimentally induced intestinal ulcers in rats: morphology and tissue leukotrienes. Gut. 1994;35:1058–63.
36. Koga H, Aoyagi K, Matsumoto T, Iida M, Fujishima M. Experimental enteropathy in athymic and euthymic rats: synergistic role of lipopolysaccharide and indomethacin. Am J Physiol. 1999;276:G576–82.
37. Anthony A, Pounder RE, Dhillon AP, Wakefield AJ. Vascular anatomy defines sites of indomethacin induced jejunal ulceration along the mesenteric margin. Gut. 1997;41:763–70.
38. Chutkan R, Toubia N. Effect of nonsteroidal anti-inflammatory drugs on the gastrointestinal tract: diagnosis by wireless capsule endoscopy. Gastrointest Endosc Clin N Am. 2004;14:67–85.
39. Hayashi Y, Yamamoto H, Kita H, Sunada K, Sato H, Yano T, et al. Non-steroidal anti-inflammatory drug-induced small bowel injuries identified by double-balloon endoscopy. World J Gastroenterol. 2005;11:4861–4.
40. Maiden L, Thjodleifsson B, Seigal A, Bjarnason II, Scott D, Birgisson S, et al. Long-term effects of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective agents on the small bowel: a crosssectional capsule enteroscopy study. Clin Gastroenterol Hepatol. 2007;5:1040–5.

doi:10.1111/j.1440-1746.2011.06635.x

GASTROENTEROLOGY

Diagnosis and treatment of functional gastrointestinal disorders in the Asia-Pacific region: A survey of current practices

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Key words
Asia-Pacific region, diagnosis, functional dyspepsia, irritable bowel syndrome, questionnaire, treatment.

Accepted for publication 24 January 2011.

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Conflicts of interest: Kentaro Sugano declares that he received consulting fee from AstraZeneca plc, Takeda Pharmaceutical Co. Ltd, Dainippon Sumitomo Pharma Co. Ltd., research grants from Takeda Pharmaceutical Co. Ltd, Astellas Pharma Inc, Eisai Co Ltd, Otsuka Pharmaceutical Co., and lecture fee from Takeda Pharmaceutical Co. Ltd, Astellas Pharma Inc, and, Dainippon Sumitomo Pharma Co. Ltd. Other authors report no conflict of interest related to this study.

Abstract

Background and Aims: Functional gastrointestinal disorders (FGIDs), namely functional dyspepsia (FD) and irritable bowel syndrome (IBS) are common disorders important to public health in the Asia-Pacific region. Our objectives were to determine the current practices in diagnosis and management of these disorders in the Asia-Pacific region.

Methods: Forty-three physicians and researchers in FGID who attended the first Asian Pacific Topic Conference at Tokyo in November 2010 were invited to answer a questionnaire. Twenty-three Japanese doctors and twenty doctors from other Asia-Pacific Societies answered the questionnaire, which consisted of 60 multiple-choice questions concerning physician's preferences in diagnosis and management of FGIDs.

Results: Overall, there were similarities in diagnostic approach, such as differential diagnosis, exclusion of organic diseases, psychophysiological assessment, medical advice or medication with psychological drugs, not only among different Asia-Pacific region but also between FD and IBS. Several notable differences were seen. For example, general practitioners did not commonly use the term FD or diagnose FD by themselves, while the term IBS was widely used and frequently diagnosed. Sub-categorization was more common in IBS than FD. There was also a difference between Japan and other Asia-Pacific region; upper GI endoscopy and blood examination were more common in Japan, while eradication of *Helicobacter pylori* was more frequently done in other countries. Anti-secretory drugs for FD and mild laxatives or anti-diarrheal drug for IBS were frequently used, and prokinetics were used for all patients with FD or IBS. Interestingly, drugs developed in Japan and Chinese herbal medicines were more frequently prescribed in Japan.

Conclusion: Information obtained in this survey is useful for understanding the most common clinical approaches for FGIDs in the Asia-Pacific region.

Introduction

On November 26 and 27 in 2010, the first Asian Pacific Topic Conference was held in Tokyo as a joint meeting organized by the Japanese Society of Gastroenterology (JSGE) and Asian Pacific Association of Gastroenterology (APAGE). As emerging common disorders in the Asia- Pacific region, functional gastrointestinal disorders (FGIDs) was chosen as the topic, and more than 40 researchers in this field from different Asia-Pacific region participated in the meeting. Information on experiences of participants was collected by questionnaires.

FGIDs are considered to be important to public health because they are highly prevalent, induce major social and economic burdens, and are associated with impaired health-related quality of life. Since FGIDs are a heterogenous group of chronic conditions, they have different clinical features and probably have different underlying pathophysiologic mechanisms.[1] Although there are established diagnostic criteria such as Rome III,[2–4] the boundary between true abnormality and health remains to be defined, more effective therapy should be challenged on many levels, and establishing effective clinical guidelines specific for the Asia-Pacific (A-P) region is necessary.

It is also important to know how diagnosis and management have been conducted in different regions of Asia because clinical approach to FGID could be largely affected by heterogeneity in disease structure and socioeconomic conditions in each country. We therefore collected data by questionnaires in order to determine the most common clinical approach in diagnosis and treatment (management) of FGID in the A-P region. The information we obtained may be useful for understanding the current situation of diagnosis and treatment of FGIDs in the A-P area.

Methods

In September 2010, questionnaires were sent to 43 physicians and researchers in the field of FGIDs in the A-P region who were scheduled to attend the first Asian Pacific Topic Conference in Tokyo. Twenty faculties and investigators from Asian Pacific Societies of APAGE and 23 faculties from Japan were invited to take part in the questionnaire survey. On October 30, a reminder was sent to those who had not responded.

The questionnaire consisted of 60 multiple-choice questions concerning physician's preference about diagnosis and management of functional dyspepsia (FD) and irritable bowel syndrome (IBS). The questionnaire included 29 items for FD, and 31 items for IBS. A comment could be added next to some questions.

In the questionnaire we excluded questions about definition, pathophysiology, etiology and epidemiology of FGID. Diagnosis section included the following questions: (i) How is FGID diagnosed by a general practitioner (primary care physician) or by a gastroenterologists (GI specialists)? (ii) How are organic diseases or other diseases excluded at diagnosis? (iii) How are FGID patients categorized into subgroups? (iv) How are characteristic symptoms, life styles, and dietary conditions taken into account? and (v) How are psychological and physiological examinations performed at diagnosis? The treatment section included the following questions: (i) How is the disease explained and what advice is given about life style and diet? (ii) When and what kinds of GI drugs are preferentially administered to patients? and (iii) When and what kinds of psychological drugs and psychological therapy are used for patients?

Statistical data were analyzed using the chi-square test, and a P-value of < 0.05 was considered statistically significant.

Results

Diagnosis of FD and IBS (general practitioners *vs* gastroenterologists)

There was a similarity in clinical approaches of the two disorders except for some items. For example, as shown in Figure 1, the term "FD" was used by only 40% of general practitioners (primary care

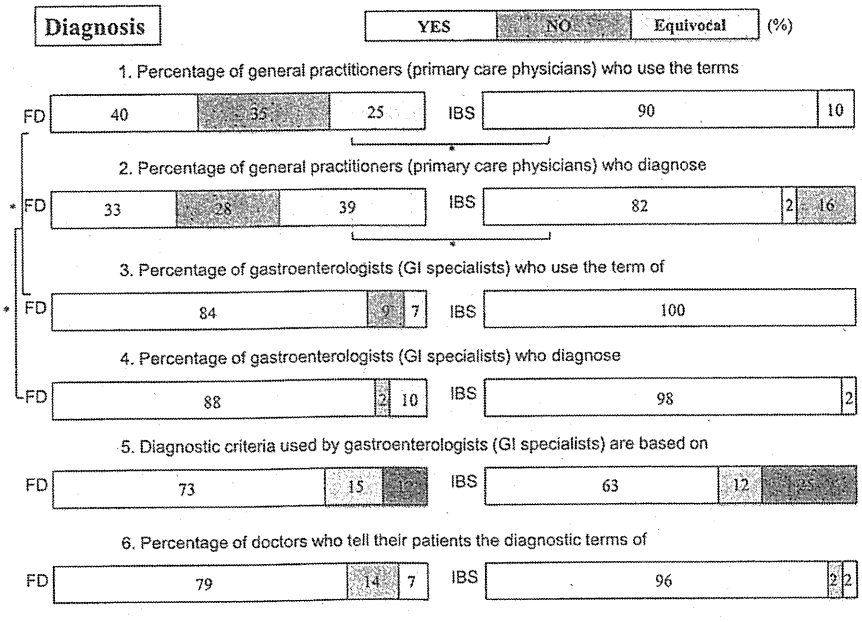

Figure 1 Diagnosis of functional dyspepsia (FD) and irritable bowel syndrome (IBS) (general practitioner *vs* gastroenterologist) in the Asia-Pacific region. Results in answer to items No.1–6 are shown as percentages of doctors except No. 5. No. 5: ▭ Rome III, ▭ Rome II, ▭ others. The left side of the figure shows answers for FD, and the right side shows the answers for IBS. The overall answers from 43 panelist doctors are shown. An open bar indicates the percentage of "yes" answers, a dark-shaded bar indicates the percentage of "no" answers, and a light-shaded bar indicates the percentage of "equivocal" answers. * $P < 0.05$.

physicians) in the A-P region, and only 33% of general practitioners diagnosed FD. Especially in Japan many cases were diagnosed as other disorders such as chronic gastritis. On the other hand, the term "IBS" was used by 90% of general practitioners and 82% of general practitioners diagnosed IBS ($P < 0.05$).

The terms FD and IBS were used by 84% and 100% of gastroenterologist (GI specialists), respectively, and these disorders were diagnosed by 88% and 98% of gastroenterologists, respectively. Diagnosis of FD or IBS by gastroenterologists was based mainly on Rome III criteria (73% for FD and 63% for IBS) and sometimes on Rome II criteria (15% for FD and 12% for IBS). Diagnosis in other cases was usually based on clinical symptoms, criteria that are broader than the Rome criteria, excluding organic diseases. There was no significant difference between Japan and other area in the A-P region in terms of use of the diagnostic criteria. After diagnosis of FD or IBS, most of the panelists told patients the diagnostic term FD (79%) or IBS (96%).

Investigations and alarm signs of FD and IBS

As shown in Figure 2 and 68% of the panelist doctors mandatorily performed upper GI endoscopy for diagnosis of FD. The performance rate was significantly greater among Japanese doctors than other A-P doctors. For those who did not mandatorily perform upper GI endoscopy, the main indications for endoscopy were age (over 50 years) (64%), presence of alarm features (64%), and use of NSAIDs (non-steroidal anti-inflammatory drugs) (57%). The dominant features that panelists regarded as alarm signs in patients with dyspepsia were weight loss (91%), anemia or GI bleeding (86%), age (over 50 years)(81%), family history of gastric cancer (77%), dysphagia (77%), past history of ulcer (72%), and vomiting (67%).

Less than half of the doctors (45%) usually performed imaging studies of the lower GI tract for the diagnosis of IBS. For those who did not perform lower GI examinations, the main indications for colonoscopy were the presence of alarm features (68%), positive fecal occult blood (65%), age (over 45 years) (55%), and family history of colon cancer (55%). The dominant features that panelists regarded as alarm signs in patients with IBS symptoms were blood in stools (98%), presence of anemia (93%), weight loss (86%), family history of colon cancer (76%), age over 45 years (74%), and signs of inflammation (74%).

When panelists diagnosed FD, 75% of the doctors usually performed blood examinations to exclude organic diseases. Interestingly almost all of the Japanese doctors performed blood examinations, while only half of other A-P doctors did ($P < 0.05$).

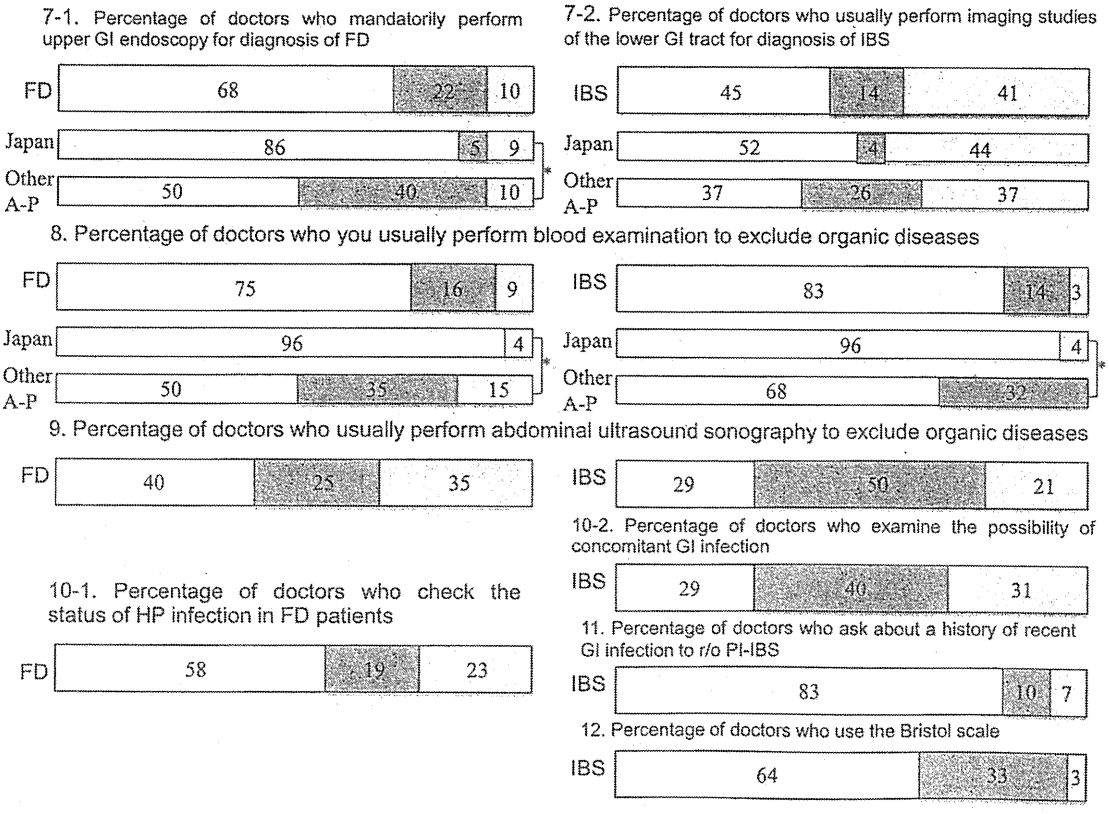

Figure 2 Preferences of panelist doctors in the Asia-Pacific region in diagnosis of FD and IBS (about differential diagnosis). Results in answer to items No.7–12 are shown as percentages of doctors. The overall answers from 43 panelist doctors are shown, except for Japan with answers from 23 doctors, and Other A-P, with answers from 20 doctors. An open bar indicates the percentage of "yes" answers, a dark-shaded bar indicates the percentage of "no" answers, and a light-shaded bar indicates the percentage of "equivocal" answers. A-P, Asia-Pacific region; HP, *Helicobacter pylori*; PI-IBS, Post-infectious IBS. $*P < 0.05$.

The items usually examined were full blood count (86%), AST, ALT and ALP (alkaline phosphatase) (81%), total protein and albumin (65%), CRP (C-reactive protein) or ESR (erythrocyte sedimentation rate) (58%), and others including blood glucose or HbA_1C, thyroid function, renal function and electrolytes, serum amylase especially for Japanese doctors, and serological tests for celiac disease especially for other A-P doctors. In the case of IBS, 83% of doctors usually performed blood examinations of items similar to those for FD, such as full blood count (86%), CRP or ESR (81%), AST, ALT and ALP (79%), and total protein and albumin (64%). Other items examined were thyroid function, renal function, blood glucose or HbA1C, tumor markers such as CEA (carcinoembryonic antigen) especially among Japanese doctors, serological tests for celiac disease, milk intolerance and a test for bacterial overgrowth especially among other A-P doctors. On the other hand, when panelists diagnosed FD or IBS, fewer doctors (40% for FD and 29% for IBS) usually performed abdominal ultrasound sonography to exclude organic diseases.

Differential diagnosis, sub-grouping, and other examinations

It was shown that only 58% of doctors checked the status of *Helicobacter pylori* (HP) infection in FD patients, with no significant difference between Japanese and other A-P doctors. In patients with IBS, only 29% of panelist doctors examined the possibility of concomitant GI infection, although many doctors (83%) asked patients about past history of recent GI infection to rule out post-infectious IBS. Infectious agents considered in IBS patients included *Salmonella, Yersinia, Escherichia coli* and *Mycobacterium* in Japan and *Giardia lamblia*, parasites, and bacterial overgrowth in other A-P region. In the case of FD, other infectious agents than HP were usually not taken into account by panelists.

As shown in Figure 3 when panelists diagnose FD, 54% of doctors subcategorized their patients mostly (87%) by using Rome III diagnostic criteria. There was no difference in sub-grouping between Japanese and other A-P doctors. In the case of IBS, however, subgrouping of patients appeared to be more popular among all panelist doctors (80%) ($P < 0.05$), and most of them (87%) subcategorized their patients into IBS-C, IBS-D or IBS-M according to the Rome III criteria. Bristol stool form scale was used by 64% of doctors when they asked patients about stool pattern.

When panelists diagnosed FD, they usually excluded patients with reflux symptoms (54%), but 29% of the panelists did include these patients. In contrast, when panelists diagnosed FD, they usually included patients with lower GI symptoms suggesting IBS (63%), and only 28% of panelists excluded these patients. For diagnosis of IBS, 71% of doctors took into account other symptoms such as bloating, meal-related abdominal pain, gas, and urgent sensation. About half (52%) of the panelists, especially

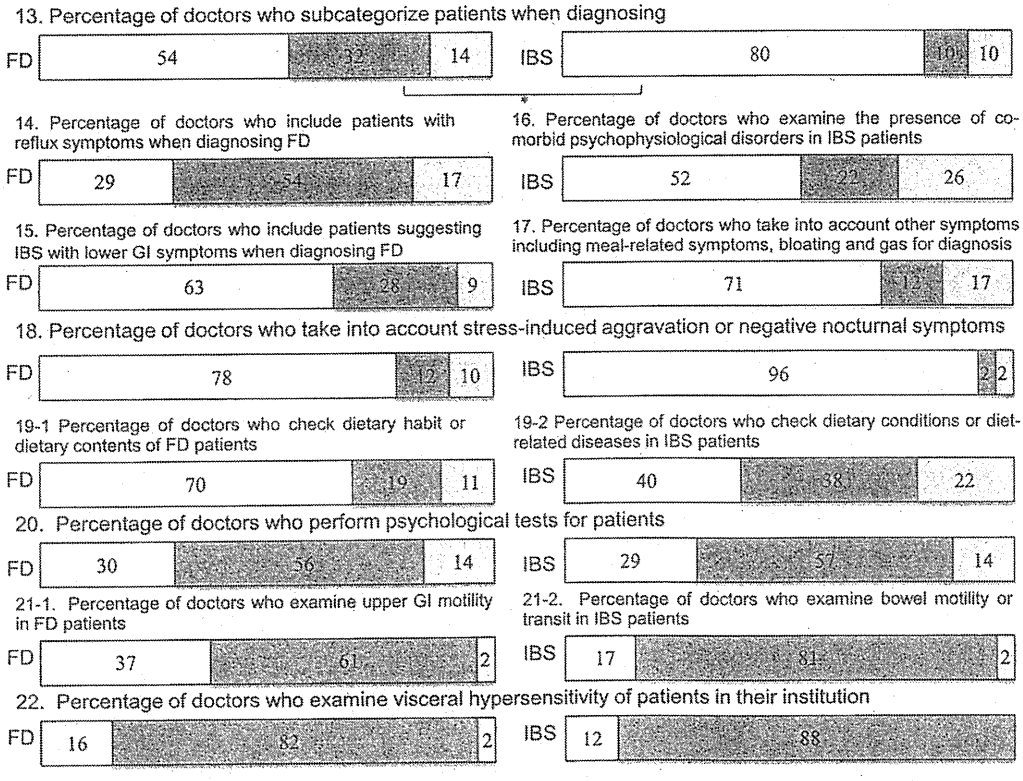

Figure 3 Preferences of panelist doctors in the Asia-Pacific region in diagnosis of FD and IBS (sub-grouping and other examinations). Results in answer to items No.13–22 are shown as percentages of doctors. The overall answers from 43 panelist doctors are shown. An open bar indicates the percentage of "yes" answers, a dark-shaded bar indicates the percentage of "no" answers, and a light-shaded bar indicates the percentage of "equivocal" answers. *$P < 0.05$.

other A-P doctors (74%), examined for the presence of co-morbid psychophysiological disorders in IBS patients.

For diagnosis of FGIDs, most of the panelists took into account stress-induced aggravation or disappearance of nocturnal symptoms, particularly for diagnosis of IBS (96%). Seventy percent of panelist doctors checked the dietary habit or dietary contents in their FD patients, although only 16% of doctors examined food allergies in these patients. Forty percent of panelist doctors checked dietary conditions or diet-related diseases in IBS patients to rule out conditions such as food allergy, or celiac disease. This item tended to be more widely checked among doctors in other A-P regions (53%) than in Japan (30%). Diagnostic tests mainly used for this item were serological tests for celiac disease, hydrogen or lactose breath test, and serum IgE and RAST (radioallergosorbent test).

For specific examinations, about 30% of the panelists performed psychological tests for their FD or IBS patients using various questionnaires concerning depression and anxiety such as HADS (hospital anxiety and depression scale), SDS (self-rating depression scale), PHQ (patient health questionnaire)-9, HAMD (Hamilton rating scale for depression), STAI (state-trait anxiety inventory), and other personality and psychosomatic tests including CMI (Cornell medical index), SCID (structured clinical interview for DSM), MMPI (Minnesota multiphasic personality inventory) and Egogram. Upper GI motility was examined in 37% of FD patients in institutes of panelist doctors by various methods such as ultrasound, ^{13}C-acetate breath test, scintigraphy, marker transit, electrogastrogram (EGG), and manometry. The frequency of bowel movement or bowel transit examination was less (17%) than upper GI, and radio-opaque marker, manometry and breath hydrogen test were mainly used for this examination. Visceral hypersensitivity of FGID patients was examined in only 16% of FD patients by barostat and water drinking test and in only 12% of IBS patients by barostat. However, in some institutions, functional brain activity was also determined by using evoked potential, positron emission tomography (PET), and/or functional magnetic resonance imaging (f-MRI).

Treatment of FGID—Life style and dietary factors

For the treatment of FGID, about 80% of panelist doctors explained the possible pathophysiology of FD or IBS to their patients (Fig. 4), with no difference between Japan and other A-P regions. For treatment of FD, almost all (95%) of the doctors gave advice about improvement of life style (including stress coping) or dietary habit to the patients, and 85% of the doctors taking time for the explanation, and 69% of the panelists thought that the advice given was more important than medication. Similarly, for treatment of IBS, almost all (95%) of the panelist doctors gave advice about improvement of life style (including stress coping), and 79% of the doctors gave advice about improvement of dietary habit or

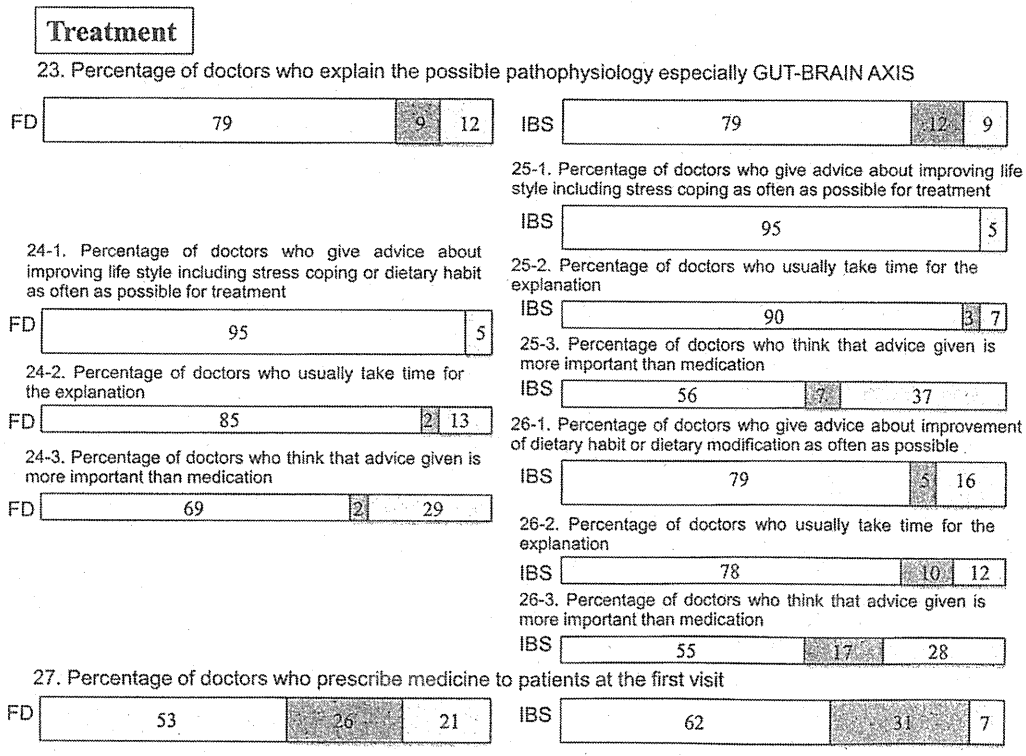

Figure 4 Preferences of panelist doctors in the Asia-Pacific region in management (treatment) of FD and IBS (general aspects). Results in answer to items No.23–27 are shown as percentages of doctors. The overall answers from 43 panelist doctors are shown. An open bar indicates the percentage of "yes" answers, a dark-shaded bar indicates the percentage of "no" answers, and a light-shaded bar indicates the percentage of "equivocal" answers.

dietary modification, usually taking time for the explanation. However, only about half of the panelists thought that advice for life style (56%) or dietary modification (55%) was more important than medication, and less than half of the Japanese doctors thought so (life style, 41%; dietary modification, 48%).

Treatment of FGID—pharmacotherapy

About half of the panelist doctors (53%) usually prescribed medicine to patients complaining of dyspeptic symptoms at the first visit. If not, they prescribed medicine immediately after diagnosis of FD (61%), after communication with patients to keep a good relationship (22%), or according to the patient's request (13%). In the case of IBS, about 2/3 of the panelist doctors (62%) usually prescribed medicine to patients complaining of IBS-like symptoms at the first visit. If not, they prescribed medicine immediately after diagnosis of IBS (54%), after communication with patients to keep a good relationship (23%), or according to the patient's request (15%).

For treatment for subgroups of FD, about 68% of the panelist doctors usually gave different prescriptions to patients with PDS (postpradial distress syndrome: patients with meal-induced dyspeptic symptoms) and patients with EPS (epigastric pain syndrome: patients with epigastric pain) type (Fig. 5). About 3/4 of the doctors prescribed a histamine H2-receptor antagonists (H2RA) to patients with FD, 71% of doctors prescribed H2RA to EPS patients, and 23% of doctors prescribed H2RA to all patients. Most of the panelist doctors (89%) prescribed PPI (proton pump inhibitors) to patients with FD, 49% of doctors prescribed PPI to EPS patients, and 35% of doctors prescribed PPI to all patients. Interestingly, all panelist doctors (100%) prescribed some kind of prokinetics to patients with FD, 66% of doctors prescribed prokinetics to patients with PDS type, and 22% of doctors prescribed ptrokinetics to all patients. Mosapride citrate, domperidone, itopride hydrochloride, and Chinese herbal medicine were frequently used. In some institutes, motilium, levosulpiride, and simethicone were also used.

When HP was positive, about half (53%) of the panelist doctors eradicated HP in their FD patients. Only 35% of the doctors in Japan said yes for HP eradication, and many doctors (39%) answered equivocal, while 75% of other A-P doctors said yes ($P < 0.05$).

Regarding medication for different subgroups of IBS, about half (50%) of the panelist doctors prescribed some common drugs and about 20% prescribed mostly common drugs among IBS subtypes, and only 26% of doctors prescribed totally different drugs between IBS-C and IBS-D. The commonly used drugs among IBS subtypes were probiotics, polycarbophyl calcium, antispasmodic, prokinetics and anti-depressants. Low FODMAP (fermentable oligo-, di- and mono-saccharides, and polyols) diet and fiber supplementation were also recommended in the Oceania regions. Probiotics were widely used (about 3/4) for patients with IBS. Mild laxatives (92%) and anti-diarrheal drugs including loperamide hydrochloride (85%) were also widely used. Polycarbophil calcium was also popular but mainly in Japan (86%). Lubiprostone is not currently available in the A-P area. The use of prokinetics for IBS was 100% as in the case of FD, and anti-spasmodic (76%), trimebutine maleate (60%), 5-HT3 receptor antagonists including ramosetoron (57%), and 5-HT4 agonists including mosapride citrate (48%) were all used, with trimebutine maleate (78%) and the 5-HT3 antagonist ramosetoron hydrochloride (83%) being preferentially used in Japan. Interestingly, traditional herbal medicine was widely used for FD as well as for IBS in Japan and China but not in the other A-P area. Rikkunshito (Liu-Jun-Zi-Tang in Chinese) was very popular for FD, while Daikenchuto (Da-Jian-Zhong-Tang in Chinese) was also very popular for IBS. Other Chinese traditional medicines used were Hangeshashinnto, Simotang for FD, and Keishika-shakuyakuto for IBS.

Treatment of FGID with psychological drugs and psychotherapy

As shown in Fig. 6, for treatment of FGID, most of the panelist doctors prescribed anxiolytic drugs to patients with FD (90%) and to patients with IBS (83%). Most of the doctors prescribed anxiolytic drugs as second-line therapy for FD (72%) and IBS (74%), but others prescribed anxiolytic drugs as third-line therapy. Anxiolytic drugs were prescribed to FGID patients mostly with anxiety signs (70% in FD and 67% in IBS), but about 1/5 of patients were prescribed drugs when they showed anxiety by psychological tests.

A large percentage of panelist doctors also prescribed anti-depressants to patients with FD (84%) and to patients with IBS (76%). Two thirds of the doctors prescribed anti-depressants as second-line therapy for FD (70%) and for IBS (71%), but others prescribed anti-depressants as third-line therapy. Anti-depressants were prescribed to about half of FGID patients mostly with depressive signs (57% in FD and 54% in IBS), but about 1/5 of the patients were prescribed anti-depressants when they were found to have depression by psychological tests. A small percentage of doctors prescribed anti-depressants to all patients (8% in FD and 5% in IBS). When doctors prescribed anti-depressants, most of them prescribed low doses (78% in FD and 83% in IBS), but others prescribed regular doses. The anti-depressants preferentially used were tricyclic anti-depressant (41% in FD and 46% in IBS) and selective serotonin reuptake inhibitors (SSRI) (48% in FD and 39% in IBS). Serotonin & norepinephrine reuptake inhibitors (SNRI) were used for about 10–15% (11% in FD and 15% in IBS) of FGID patients.

Specific psychological treatment besides medication was used for about 24% of FD patients and 26% of IBS patients in the institutions of panelist doctors by several methods including cognitive behavioral therapy (CBT), relaxation, meditation, autogenic training, hypnotherapy, and fasting therapy.

Discussion

In this survey, we were able to compare the clinical approaches to FD and IBS by the panelist doctors. Many aspects of diagnosis and treatment of FD and IBS were quite similar, though there were some differences among APAGE countries. For example, the term FD is less commonly used by general practitioners in the A-P region compared with the term IBS, and general practitioners usually do not diagnose FD, while they often diagnose IBS. On the other hand, it was shown that the terms FD and IBS are both frequently used and that they are equally well diagnosed by gastroenterologist (GI specialists). One reason is that the concept of