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Itopride in the Treatment of Functional Dyspepsia in Chinese Patients

A Prospective, Multicentre, Post-Marketing Observational Study

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Abstract

Background: Prokinetic agents are commonly used in the symptomatic treatment of functional dyspepsia (FD). Safety or efficacy issues associated with the use of available prokinetics, such as metoclopramide, domperidone, cisapride and mosapride, mean there is a need for an effective and well tolerated prokinetic agent. Itopride is a novel prokinetic agent with a dual mode of action, good safety profile and documented efficacy in placebo-controlled trials.

Objective: The objective of this study was to assess the effectiveness and safety of itopride in the management of FD.

Methods: This was a prospective, multicentre, post-marketing observational study carried out in private outpatient clinics throughout China. The study included patients with symptomatic FD aged ≥18 years. Patients were prescribed itopride 50 mg three times daily before meals for 4 weeks, after which there was a 2-week follow-up period during which they did not take itopride. Effectiveness and tolerability data obtained from patients who completed 4 weeks of therapy were analysed. The treatment response rate after 4 weeks was measured by patient global assessment; scores at the end of treatment were compared with baseline scores. Response rate based on symptom scoring was also measured after 4 weeks, with an effective treatment being defined as a symptom improvement of ≥50%.

Results: In total, 587 patients with FD were enrolled. The mean ± SD difference in the total symptom score before and after the 4-week treatment period was −5.62 ± 3.27, corresponding to a 69.23 ± 26.53% reduction from baseline ($p < 0.001$). The treatment response rates in patients who fulfilled Rome I, II and III criteria for FD were 33.68%, 34.71% and 35.50%, respectively, after 1 week of treatment; 52.82%, 54.61% and 56.51%, respectively, after 2 weeks; 66.67%, 67.23% and 68.64%, respectively, after 3 weeks; and 72.82%, 73.54% and 75.15%, respectively, after 4 weeks. Response rates were significantly different at 1 week versus 4 weeks of treatment. Nine patients (1.54%) had adverse events: four were probably related to the study drug, three were

possibly related and two were not related. Of the nine patients with adverse events, two discontinued the study drug, two suspended (i.e. temporarily discontinued the drug until the adverse event subsided) the study drug, and five continued the study drug. Seven of the nine patients with adverse events had adverse reactions (defined as adverse events considered causally related to the study drug): two improved, three recovered and two showed no change. No adverse reactions were serious enough to warrant discontinuation of therapy. **Conclusion:** Itopride was an effective and well tolerated drug in the management of FD in this patient population.

Introduction

Dyspepsia refers to a heterogeneous group of upper abdominal symptoms, including pain, discomfort, bloating, early satiation, post-prandial fullness and nausea. The term dyspepsia includes all relevant abdominal symptoms of the upper gastrointestinal tract, regardless of the underlying cause. In contrast, the term functional dyspepsia (FD) is used when dyspeptic symptoms are present in the absence of structural or biochemical abnormalities detected by routine diagnostic work-up, which would otherwise account for the symptoms. Specifically, FD is defined as the presence of symptoms thought to originate in the gastroduodenal region in the absence of organic, systemic or metabolic disease that is likely to explain the symptoms.[1] It is now well documented, however, that in FD patients there might be abnormalities such as minimal mucosal inflammation or disordered sensory or motor function that are not routinely diagnosed. Interestingly, a structural abnormality can be found in less than 50% of patients with dyspeptic symptoms.[2] An organic cause is found in only a minority of investigated patients.[3,4] The underlying pathophysiology of FD is as yet not fully understood. The widely proposed mechanisms include gastroduodenal dysmotility, visceral hypersensitivity, gastroduodenal acid exposure, autonomic/central nervous system (CNS) dysfunction and psychosomatic factors, whereas *Helicobacter pylori* infection, in the absence of ulcers, is unlikely to explain symptoms.[2,5-7]

Itopride is a novel prokinetic agent. It activates gastrointestinal motility through synergism of its dopamine D_2 receptor antagonistic action and its acetylcholine esterase inhibitory action. Itopride also has an antiemetic action through interaction with D_2 receptors located in the chemoreceptor trigger zone. Since 1995, itopride has been shown to be safe and effective in clinical studies conducted in Japan,[8,9] India,[10] China[11] and Germany.[12]

The optimum therapeutic strategy for FD has not been well established owing to the poorly defined pathogenesis of the condition, although prokinetic agents, including itopride, are often prescribed and systematic analyses clearly suggest the efficacy of these treatments.[13] This post-marketing surveillance study was designed to obtain clinical data related to the use of itopride for the treatment of FD patients in real-world settings.

There have been no clinical studies of itopride using Rome III criteria (see Methods section).[14] Thus, it is unclear how many patients with FD in actual practice fulfil the criteria for the various subgroups, how these subgroups overlap, and how the symptom patterns predict response to therapy.[15] In clinical trials, itopride treatment periods varied from 2–8 weeks; however, there are no data on the different response times to itopride treatment nor the differences in times to response or relapse of symptoms among the subgroups.

The present study was undertaken to document the effectiveness and safety of itopride in the routine clinical management of FD in patients attending private outpatient clinics throughout China.

Methods

This was a prospective, multicentre, post-marketing study in which itopride was prescribed in the usual manner in accordance with the terms of the local authorities regarding dose, population and indication. Because this study was observational, its follow-up was not interventional. Any intervention was left to the judgement of the gastroenterologist during the 6-week study period. This included six patient visits (after the initial baseline visit) that were scheduled to occur at weekly intervals over the 4-week treatment period and the 2-week post-treatment follow-up period (table I).

Objectives

The primary objective of the study was to evaluate the efficacy of itopride in the overall FD patient population and to compare treatment responses in this population with those in different symptom pattern subgroups (i.e. Rome I, Rome II and Rome III FD populations). The secondary objective of the study was to describe the overall safety of itopride.

Patient Population

Inclusion Criteria

Patients were included in the study if they were: (i) seeking treatment for FD symptoms; (ii) aged ≥18 years; (iii) diagnosed with FD, based on one or more symptoms (post-prandial fullness, early satiation, epigastric pain, epigastric burning, nausea or vomiting, bloating, burping, heartburn, regurgitation with or without constipation and/or diarrhoea with a feeling of incomplete evacuation), with no lesions on endoscopy and no intake of drugs (such as nonsteroidal anti-inflammatory drugs, antiarrhythmic drugs, etc.) that could have side effects that mimic the symptoms of FD, and duration of symptoms >6 months; (iv) found to have no evidence of structural disease likely to explain their symptoms; (v) assigned to treatment with itopride monotherapy; and (vi) not taking any prokinetic or other gastrointestinal drugs for at least 15 days before commencement of study treatment. Furthermore, patients could be included in the study only if they reported failure of their previous FD therapy.

Table I. Study schedule and recorded parameters

Item	Day 0 (V1)	Treatment period (days 1–28; V2–5)	Follow-up period (days 29–42; V6–7)
Demographic information[a]	×		
Medical history[b]	×		
Diagnosis	×		
FD subtype	×		
Symptom score	×	×	×
Patient global assessment		×	×
Compliance		×	
Adverse events		×	×

a Age, sex, height, body weight, co-morbidities and educational level.

b FD course, previous treatment, co-morbidities and concomitant medicines, systematic review of medical history and physical examination.

FD = functional dyspepsia; **V** = visit.

Exclusion Criteria

The exclusion criteria were: (i) contraindications described in the product label; (ii) known cases of gastrointestinal haemorrhage, mechanical obstruction, perforation and other cases in which enhanced gastrointestinal motility could adversely affect the patient's condition; (iii) known hypersensitivity to itopride; and (iv) investigators' assessment that the patient was ineligible for itopride treatment.

Patient Subgroups

Patients were categorized into three groups according to the Rome criteria for FD: a = post-prandial fullness; b = early satiation; c = epigastric pain; d = epigastric burning; e = nausea and/or vomiting; f = bloating; g = burping; h = heartburn; i = regurgitation; j = constipation and/or diarrhoea with the feeling of incomplete evacuation.[14] Rome I criteria were fulfilled if a patient had one or more of the symptoms a–i; Rome II if a patient had one or more of the symptoms a–g, but none of the symptoms h or i; and Rome III if a patient had one or more of the symptoms a–d, and possibly symptom e, but none of the symptoms f–i.[14]

Dosing Regimen

Patients fulfilling the inclusion criteria were prescribed itopride 50 mg three times daily before meals for a maximum of 4 weeks, with a 2-week

follow-up period after stopping itopride treatment. The patients' diet was as per normal during the trial, with no specific restrictions. A patient could withdraw from the study at any time without prejudice. The physician could discontinue any patient's participation for any reason, including failure to comply with the protocol. If a patient withdrew or was withdrawn from the study, this was noted, along with the reason for withdrawal, on the case report form. Compliance was measured in terms of the pills returned at patient visits during the treatment period. Taking less than 80% or more than 120% of the study drug medication defined in the protocol was defined as poor compliance.

Outcome Measures

Effectiveness and tolerability data obtained from patients who completed a minimum of 4 weeks of itopride treatment were considered for analysis. The treatment response rate after 4 weeks was measured by comparing patient global assessment scores at the end of treatment with baseline scores. Response rate based on symptom scoring was also measured after 4 weeks, with an effective treatment being defined as symptom improvement of ≥50%.

Effectiveness

For the patient global assessment, patients were asked to respond to the question: "Please rate the severity of your upper abdominal complaints, compared to the condition at the outset of treatment. How much have they changed? Please mark the statement that best applies to you: 1 = symptom free, 2 = markedly improved, 3 = slightly improved, 4 = unchanged, 5 = worse." As stated in the previous section, a patient who reported ≥50% symptom improvement was defined as a responder. The symptom pattern, severity and change in severity of symptoms after 4 weeks were measured by the following scoring criteria applied to each symptom: 3 = serious – symptoms were severe and daily activities were severely affected; 2 = moderate – symptoms present and daily activities were mildly affected; 1 = mild – symptoms present but did not affect daily activities; 0 = no symptoms. The symptoms scored were the upper abdominal symptoms listed in the Rome criteria for FD (see Patient Subgroups section). All symptom scores were summed to obtain a total symptom score.

Safety

An adverse event was defined as any untoward medical occurrence in a patient, regardless of whether it was considered to be causally related to use of the treatment. An adverse event could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product. Adverse events data were collected throughout the study and until 30 days after the last dose. All adverse events, including symptoms, signs or diseases, were evaluated. Information recorded concerning the adverse events occurring during the trial period included their nature, whether serious or not, their intensity, any treatment given, the outcome and an opinion about the causal relationship with the study medication. The incidence (%) of adverse events was calculated and analysed according to the guidelines for statistical analysis issued by the State Food and Drug Administration (SFDA) of China. The seriousness of the adverse event and its causal relationship with treatment were also tabulated. Furthermore, information on adverse reactions, defined as adverse events considered to be causally related to use of the study drug, was recorded in detail. A list of all adverse events was compiled.

Results

Study Enrolment and Disposition

Total study enrolment was 587 patients from 19 sites throughout China (listed in the Acknowledgements section). Between 20 and 40 patients were enrolled in each centre, with enrolment being consecutive. Participation in the study was approved for every centre by the independent ethics committee. All patients gave their informed consent to participate in the study. The first visit of the first patient occurred on 27 June 2007, and the last visit of the last patient was on 26 July 2008. Twelve

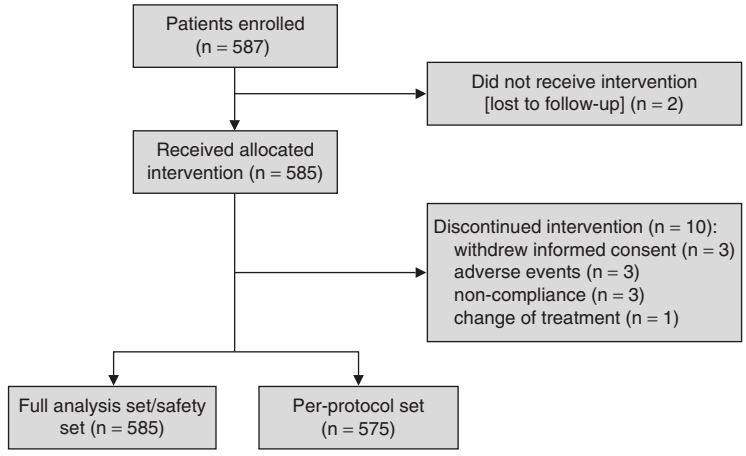

Fig. 1. Study flow chart.

patients were discontinued from the study: ten withdrew and two were lost to follow-up. As a result, the full analysis set (FAS) and safety set included 585 patients (figure 1). Of the ten patients who withdrew from the study, three discontinued because of withdrawal of informed consent and seven discontinued treatment but were not discontinued from the trial (three because of adverse events, three because of poor adherence, and one because of treatment change). These ten patients were excluded from the per-protocol set (PPS), which included 575 patients.

Demographic and Baseline Characteristics

Of the 585 patients, 44.27% were males (table II). The patients' ages ranged from 18 to 90 years. The patients' mean height was 164.64 cm and their mean body weight was 62.63 kg.

The mean duration of FD was 8.13 months (table III). Overall, 38.80% of the patients were of junior college (i.e. between high school and university/college) education level or higher, whereas 38.63% had a high school or career education. Overall, 48.03% of the patients had taken medication for the treatment of gastrointestinal diseases within 6 months before the study. Only 22.74% of the patients were currently taking concomitant medicines. Overall, 106 patients (18.12%) had postprandial distress syndrome and 175 (29.91%) had epigastric pain syndrome (table IV).

Rome I (n = 585) had 412 patients overlapping with Rome II and 338 patients overlapping with Rome III, whereas 338 patients in Rome II overlapped with Rome III (figure 2).

Treatment Compliance

According to the definition of poor compliance stated in the Dosing Regimen section (taking less than 80% or more than 120% of the study drug

Table II. Summary of demographic characteristics[a]

Characteristic	Value
Sex [n (%)]	
males	259 (44.27)
females	324 (55.38)
missing information	2 (0.34)
Age (y)	
mean ± SD	46.83 ± 15.4
median	45
range	18–90
Height (cm)	
mean ± SD	164.64 ± 10.59
median	164
range	145–184
Body weight (kg)	
mean ± SD	62.63 ± 21.47
median	61
range	40–99

a Full analysis set (n = 585).

Table III. Summary of medical history and educational level[a]

FD duration (mo)	
mean ± SD	8.13 ± 3.16
median	8
range	1–25
Education level [n (%)]	
masters and above	6 (1.03)
university	122 (20.85)
junior college	99 (16.92)
high school/career education	226 (38.63)
primary/middle school and below	122 (20.85)
illiterate	6 (1.03)
missing information	4 (0.68)
Medication for treatment of GI diseases within previous 6 mo [n (%)]	
no	304 (51.97)
yes	281 (48.03)
Current concomitant medicine [n (%)]	
no	452 (77.26)
yes	133 (22.74)

a Full analysis set (n = 585).

FD = functional dyspepsia; **GI** = gastrointestinal.

medication), 14 patients (2.39%) had poor compliance.

Effectiveness Analysis

Total Symptom Score

The mean ± SD total symptom scores for the FAS before and after 4 weeks of treatment were 8.13 ± 3.16 and 2.51 ± 2.62, respectively (table V). This represented a mean ± SD difference in total symptom score between pretreatment and after 4 weeks of treatment of 5.62 ± 3.27, a reduction of 69.23 ± 26.53%. The mean total symptom score following treatment was significantly lower than before treatment for both the FAS and the PPS ($p < 0.001$). Mean scores for all individual symptoms also decreased significantly after 4 weeks of treatment compared with pretreatment in both the FAS and the PPS ($p < 0.001$).

Response Rates

In the FAS, 27.17% of patients were classified as non-responders after 4 weeks of observation.

For the FAS of Rome I, II and III patients, the treatment response rates were 33.68%, 34.71% and 35.50%, respectively, after 1 week of treatment; 52.82%, 54.61% and 56.51% after 2 weeks; 66.67%, 67.23% and 68.64% after 3 weeks; and 72.82%, 73.54% and 75.15% after 4 weeks of treatment. Response rates after 1 week of treatment and post-treatment for the subsequent 3 treatment weeks were all significantly different compared with pretreatment ($p < 0.001$).

Analysis of Response Rate by Functional Dyspepsia Subtype

For the post-prandial distress syndrome subgroup, the response rate increased from 31.68% after 1 week of treatment to 73.49% after 4 weeks of treatment. For the epigastric pain syndrome subgroup, the response rate increased from 33.71% after 1 week of treatment to 70.86% after 4 weeks of treatment. Response rates after 1 week of treatment and 4 weeks of treatment were all significantly different compared with pretreatment ($p < 0.001$).

Time to Response

Time to response was measured using the patient global assessment performed on a weekly basis until the end of the 2-week post-treatment follow-up period. For the FAS, the median time to response was 10 days, with a median response rate of 53% during that time.

Table IV. Summary of functional dyspepsia (FD) subtype and ECG findings[a]

Item	n (%)
PDS	
no	464 (79.32)
yes	106 (18.12)
missing information	15 (2.56)
EPS	
no	364 (62.22)
yes	175 (29.91)
missing information	46 (7.86)
ECG findings	
normal	314 (53.68)
not performed	30 (5.13)
abnormal without clinical significance	238 (40.68)
abnormal with clinical significance	3 (0.51)

a Full analysis set (n = 585).

EPS = epigastric pain syndrome; **PDS** = post-prandial distress syndrome.

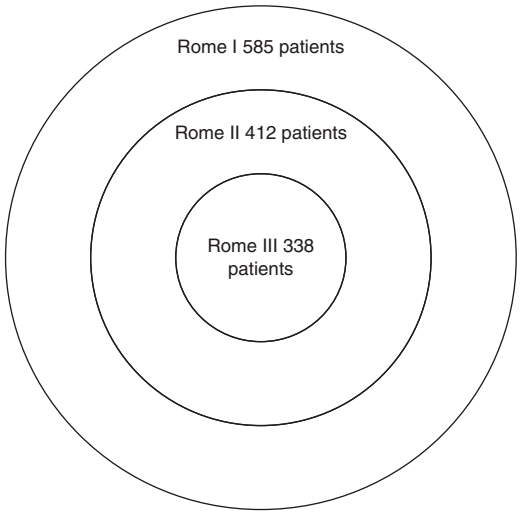

Fig. 2. Diagrammatic representation of the symptom pattern according to the Rome criteria[14] in 585 patients with functional dyspepsia.

Relapse Rates

The symptom relapse rate was 7.75% at the 1-week post-treatment follow-up visit and 11.50% at the 2-week post-treatment follow-up visit.

Patients who discontinued the study drug did not have significantly different relapse rates to those who continued the study drug after 1 week of treatment. However, after 2 weeks of treatment, a significant difference in relapse rates was seen ($p = 0.01$).

Adverse Events

There were nine patients with adverse events during this study: four were probably related to the study drug, three were possibly related and two were not related. The incidence of adverse events was 1.54%. Of the nine patients, two discontinued the study drug, two suspended (i.e. temporarily discontinued the drug until the adverse event subsided) the study drug, and five continued on treatment. Seven of these nine patients had adverse reactions (i.e. considered to be causally related to use of the study drug): two improved, three recovered and two had no change (table VI). No adverse reaction was serious enough to require discontinuation of therapy.

Discussion

The safety profiles of available prokinetic agents (metoclopramide, domperidone, cisapride and mosapride) are a major concern when selecting drugs for FD treatment. Metoclopramide, the only prokinetic agent available in the US, has undergone only limited clinical evaluation for FD. Metoclopramide is also associated with a high incidence of adverse CNS effects, especially extrapyramidal symptoms (dystonic-dyskinetic reactions, parkinsonism and tardive dyskinesia).[16] Domperidone is a peripherally acting dopamine receptor antagonist that does not cross the blood-brain barrier; thus, unlike metoclopramide, it does not lead to extrapyramidal symptoms.[17] However, domperidone has been shown to produce elevations in serum prolactin levels and may cause gynaecomastia and ga-

Table V. Summary of total symptom scores before and after treatment

Variable	FAS (n = 585)	PPS (n = 575)
Before treatment		
mean ± SD	8.13 ± 3.16	8.12 ± 3.15
median	8	8
range	1–25	1–25
After 4 weeks of treatment		
mean ± SD	2.51 ± 2.62	2.42 ± 2.47
median	2	2
range	0–18	0–18
Difference[a]		
mean ± SD	5.62 ± 3.27	5.70 ± 3.22
median	5	5
range	–2 to 23	–2 to 23
p-value[b]	<0.001	<0.001
Difference (%)[c]		
mean ± SD	69.23 ± 26.53	70.22 ± 25.37
median	75	75
range	–14.29 to 100	–14.29 to 100
p-value[b]	<0.001	<0.001

a Mean total symptom score before treatment – mean total symptom score after 4 weeks of treatment.

b Wilcoxon signed-rank test.

c Mean total symptom score before treatment – mean total symptom score after 4 weeks of treatment/mean total symptom score before treatment × 100.

FAS = full analysis set; **PPS** = per-protocol set.

Table VI. Adverse reactions[a] in the safety population (n = 585)

Adverse reaction	Related to study drug	Outcome	Serious
Diarrhoea	Possibly	Improved	No
Diarrhoea	Probably	Did not change	No
Dizziness	Possibly	Recovered	No
Diarrhoea	Probably	Recovered	No
Diarrhoea	Possibly	Did not change	No
Drug eruption	Probably	Recovered	No
Mammary and abdominal pain	Probably	Improved	No

a Adverse events considered to be causally related to use of the study drug.

lactorrhoea with long-term therapy. Cisapride has been reported to have the potential to prolong the QT interval and, thus, predispose patients to serious cardiac arrhythmias. Therefore, its use has been restricted in India, and it has been withdrawn in the US.[18] Mosapride, which belongs to the cisapride group (substituted benzamide) of drugs, is mainly metabolized by the cytochrome P450 (CYP) 3A4 enzyme. Coadministration of the CYP3A4 inhibitor erythromycin with mosapride has been shown to increase plasma concentrations of mosapride.[19] Thus, drug interactions are likely to occur if mosapride is administered along with other drugs that are metabolized by the CYP3A4 enzyme (e.g. histamine H_2 receptor antagonists, clarithromycin, ketoconazole, etc.). Ventricular arrhythmias have also been reported with mosapride.[20] However, some studies have shown that although there was a pharmacokinetic interaction between mosapride and erythromycin, their coadministration did not affect the ECG findings.[21] Thus, in view of these safety issues with the existing prokinetic agents, there is a need for an effective and well tolerated prokinetic drug.

Itopride is highly polar, and therefore barely penetrates the brain and the CNS, unlike other gastroprokinetic agents.[22] CNS-related adverse events and increases in prolactin levels caused by the antidopaminergic effect of itopride are, therefore, less pronounced and less frequent than those seen with other dopamine receptor antagonists.[23] Itopride does not prolong the QT interval, and, therefore, unlike cisapride, is not considered likely to cause arrhythmias.[24,25] Because itopride is metabolized by the flavine-containing monooxygenase, metabolic competition is not expected with the majority of drugs, which are converted by the CYP family.

In the present study, the effectiveness and safety of itopride therapy was evaluated in 585 symptomatic FD patients. The mean ± SD difference in the total symptom score before and after 4 weeks of treatment was 5.62 ± 3.27, equating to a mean reduction in total symptom score over this period of 69.23 ± 26.53%. The mean total symptom score decreased significantly between pretreatment and 4 weeks of treatment ($p < 0.001$). The symptom relapse rate was 7.75% at 1-week post-treatment follow-up and 11.50% at 2-week post-treatment follow-up.

When drawing conclusions about the efficacy of treatment in patients with FD, it is important to consider the possible role of the placebo effect. The overall response rate with itopride in the current study was about 75% with no placebo control for comparison. Given the substantial placebo effect in FD, the question of whether the current results included this placebo effect needs to be considered. One double-blind study of omeprazole for FD patients revealed that the response rate with placebo was 23–27%.[26] Another study showed the remission rate was 41% in the placebo group compared with 57–64% in the itopride group.[12] In previous publications, a placebo response rate of 23–49% in FD has been reported.[27] Although the current study did not include a control arm, itopride was associated with a much higher response rate than the response rates for placebo reported in previous publications. The current study results are also consistent with those of a trial conducted in China in 2003.[11] The overall response rate with

itopride in that trial was 89.1% after 2 weeks of treatment whereas the response rate in the placebo group was 62.5%. The difference between the two groups was clinically significant. Clinical experience suggests that the symptoms of FD patients often significantly improve when normal endoscopic results are disclosed. However, since this study was a post-marketing study and all patients included in the study had not responded to previous treatment, this possible effect of disclosure of normal endoscopic findings can be discounted. In other clinical studies conducted in India[25] and Japan,[9] itopride has been documented to produce moderate to complete symptomatic relief in 67–100% of patients with FD (chronic gastritis, non-ulcer dyspepsia) after 2 weeks of treatment. Sumil et al.[28] conducted an open-label, non-comparative study and found moderate improvement in 72.2% of patients. Thus, the efficacy results obtained in the present post-marketing surveillance study are similar to those observed in other studies conducted in India and Japan.

Similarly, itopride was well tolerated by the majority of patients in the above-mentioned post-marketing surveillance study conducted in India; only 76 patients (3.61%) reported 87 adverse events.[25] The most common adverse events reported were diarrhoea (31), headache (9), dizziness/giddiness (9), constipation (7) and itching/rash (5). Of the adverse events reported, 60 (69.0%), 24 (27.6%) and 3 (3.4%) were of mild, moderate and severe intensity, respectively. Only 21 adverse events were judged to be related to itopride therapy. The incidence of adverse events in the current study was 1.54%, lower than reported for other similar clinical studies. The seven adverse reactions consisted of diarrhoea (n = 4), dizziness (n = 1), drug eruption (n = 1) and mammary and abdominal pain (n = 1). No serious adverse events were reported in the study, and no cardiovascular adverse events were observed.[29] This further supports the belief that itopride does not produce significant cardiovascular adverse effects. Thus, the tolerability data obtained in the present study confirm that itopride is a relatively well tolerated drug.

This clinical study categorized the patients in terms of three Rome FD criteria, and showed that 412 of the 585 FD cases meeting Rome I criteria overlapped with patients meeting Rome criteria II, and that 338 patients with Rome II criteria had Rome III criteria. This study indicated that the FD patients fulfilling Rome III criteria enjoyed the highest response rate, reflecting the fact that the Rome III criteria excluded those false FD patients diagnosed by Rome II criteria. The Rome III criteria made the diagnosis of FD more convenient for clinicians; prior to publication of these criteria, FD had been defined as upper abdominal pain or discomfort, which was considered too general and ambiguous for doctors in clinical practice. The sense of discomfort referred to included many non-pain symptoms, such as upper abdominal distention, early satiation, bloating and nausea, which were influenced by a variety of factors, including the cultural and educational background of the patient. In cases like this, Rome III defined FD as 'at least one of the following: early satiation, post-prandial fullness, upper abdominal pain or upper abdominal burning' instead of the less precise description of continuous or repeated dyspepsia (upper abdominal pain or discomfort). The Rome III criteria for FD are more clinically practical and facilitate the correct diagnosis of FD.

The symptoms of FD may overlap with other functional gastrointestinal disorders (FGIDs), meaning that various FGIDs might occur in one patient. Studies have found that up to half of patients with FD also suffer from irritable bowel syndrome (IBS), and a number of epidemiological and pathophysiological similarities between the two conditions have been shown to exist.[29-31] In consideration of this, Rome III removed the item 'no evidence for alleviation of dyspepsia after bowel movement or the association of dyspepsia with the frequency of bowel movement or the nature of feces (e.g. not IBS)', which meant Rome III did not rule out the possibility of the coexistence of two FGIDs (which was not the case with the Rome II criteria). A proportion of the patients whose abdominal pain was relieved after bowel movement or was associated with the frequency of bowel movement or the nature of faeces, excluded by Rome II, were still classed as FD in Rome III, but the possibility of a combi-

nation with IBS could not be excluded. There is also evidence to suggest significant overlap between gastro-oesophageal reflux disease (GORD), particularly non-erosive reflux disease, and FD.[32] Our study did not analyse the response rate of FD in combination with other FGIDs. Therefore, future studies should focus on the efficacy of itopride in the treatment of the patients with FD overlapping with GORD or IBS. Furthermore, since psychological distress appears to be more prevalent in those with FD compared with the general population,[33] the influence of psychological distress on the treatment of FD is also of interest to the physician.

Conclusion

This is the first study of the use of itopride in FD using Rome III criteria. The study results indicate that itopride is safe and effective in the treatment of Chinese patients with symptomatic FD. The incidence of adverse events and adverse reactions was low, which is consistent with the results of previous reports.

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