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A randomized placebo-controlled trial of simethicone and cisapride for the treatment of patients with functional dyspepsia

G. HOLTMANN*, J. GSCHOSSMANN*, P. MAYR† & N. J. TALLEY‡
*Division of Gastroenterology and Hepatology, University of Essen, Germany; †Private Clinic, Stockach, Germany; and ‡Department of Medicine, University of Sydney, Nepean Hospital, Penrith, NSW, Australia

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SUMMARY

Aim: To compare the efficacy of simethicone with placebo and the prokinetic cisapride in patients with functional dyspepsia.

Methods: One hundred and eighty-five patients with functional dyspepsia were randomized and treated in a double-dummy technique with simethicone (105 mg t.d.s.), cisapride (10 mg t.d.s.) or placebo (t.d.s.). The primary outcome measure was the O'Brien global measure of the patients' rating of 10 upper gastrointestinal symptoms (graded as absent = 0, moderate = 1, severe = 2 or very severe = 3). Outcome measures were assessed at baseline and after 2, 4 and 8 weeks of treatment (intention-to-treat).

Results: At 2, 4 and 8 weeks, treatment with simethicone and cisapride yielded significantly (all P values < 0.0001) better improvement of symptoms compared to placebo. Simethicone was significantly better than cisapride after 2 weeks ($P = 0.0007$), but the differences were not statistically significant after 4 and 8 weeks. Patients treated with simethicone judged the efficacy of their treatment as very good in 46% of cases, compared to 15% and 16% receiving cisapride and placebo, respectively.

Conclusions: Simethicone and cisapride were significantly better than placebo for symptom control in patients with functional dyspepsia after 2, 4 and 8 weeks of treatment. Simethicone was also superior to the prokinetic cisapride in the first 2 weeks of treatment.

INTRODUCTION

Dyspepsia is highly prevalent in the population, but structural (or organic) lesions causing dyspepsia symptoms are only found in a minority of patients. Dyspepsia in the absence of a clinically identifiable structural lesion causing symptoms is referred to as functional dyspepsia.[1, 2] Because a structural explanation is lacking, disturbed gastrointestinal function is believed to play a role in the development of symptoms.[3] Pharmacological treatments for patients with functional dyspepsia remain unsatisfactory,[4] and hence the search for convincingly efficacious treatment options is an important goal. Unfortunately, the results of *Helicobacter pylori* eradication studies have generally been disappointing, although there may be a small, albeit controversial, benefit long term.[5] Some controlled trials have demonstrated a superiority over placebo for H_2-receptor antagonists[6] and proton pump inhibitors,[7] but benefits have been modest. A number of randomized controlled trials have demonstrated the superiority of cisapride over placebo and this has been confirmed in systematic reviews and meta-analyses;[8–10] however, the use of cisapride is now restricted in most countries because of rare cardiac side-effects.

In patients with functional dyspepsia, fullness and bloating are believed to be gas related,[11] and gas retention has been demonstrated in the irritable bowel

Correspondence to: Dr G. Holtmann, University of Essen, Department of Internal Medicine, Division of Gastroenterology and Hepatology, Hufelandstr. 55, 45122 Essen, Germany.
E-mail: g.holtmann@uni-essen.de

syndrome.[12] In addition, functional dyspepsia is linked to disturbed gastrointestinal sensation[13] or dysmotility.[14] Simethicone is an agent widely taken to reduce gastrointestinal gas, although it is generally considered to be of no specific value in functional dyspepsia. However, in a recent randomized controlled trial,[15] simethicone somewhat unexpectedly was observed to be superior to cisapride in terms of the global improvement of symptoms in functional dyspepsia. As no placebo arm was included, it was not possible to conclude that simethicone is efficacious in patients with functional dyspepsia. For this reason, the present trial was conducted.

Another contentious issue is the relevance, if any, of symptom patterns in identifying the response to therapy. It has been suggested that patients with functional dyspepsia can be subdivided into dyspepsia subgroups based on the pattern of symptoms.[1] However, as these subgroups overlap,[16, 17] and lack stability over time,[18] the clinical relevance of this approach is uncertain. Moreover, it is uncertain whether the symptom subgroups predict treatment outcomes, although this has been observed to occur with acid suppression in some but not all studies.[7, 19]

Thus, this study aimed to compare the efficacy of simethicone with placebo and cisapride in patients with functional dyspepsia. We also aimed to identify specific symptoms that may respond to treatment with simethicone and cisapride. Because cisapride has been considered the standard treatment for patients with functional dyspepsia, and simethicone was superior to cisapride in a recent trial, we hypothesized that simethicone would not only be superior to placebo but would also at least not be inferior to cisapride in terms of the improvement of dyspeptic symptoms in these patients.

MATERIALS AND METHODS

Study design and patients

Patients with a suspected diagnosis of functional dyspepsia were eligible for this trial. They were recruited by 16 physicians in private practice. Prior to inclusion into the trial, a physical examination, laboratory testing (i.e. white and red blood count, sedimentation rate, fasting blood sugar, liver function tests), abdominal ultrasound and upper gastrointestinal endoscopy were performed to exclude a structural cause for the symptoms.

Functional dyspepsia was diagnosed if the subjects had suffered from upper abdominal pain or discomfort (i.e. a negative feeling in the upper abdomen that did not reach the level of pain and was characterized by one or more symptoms, including early satiety, postprandial fullness, bloating or nausea) for at least 3 months without an identifiable structural or biochemical abnormality as a cause of the symptoms. Predominant reflux symptoms (retrosternal pain, burning or regurgitation) were considered to be part of gastro-oesophageal reflux disease rather than functional dyspepsia. Thus, patients with reflux symptoms only or patients with predominant reflux symptoms were not eligible for participation in the study. In addition, patients with concomitant symptoms of the irritable bowel syndrome were not allowed to enter the trial.

All patients with a history of cardiac disease, electrolyte disturbances, intake of medication that potentially interacts with cisapride (e.g. antifungals or macrolides) or an abnormal electrocardiogram at baseline were excluded from participation in the study.

After establishing a diagnosis of functional dyspepsia, any medication potentially affecting the gastrointestinal tract was withdrawn. After at least a 7-day wash-out, gastrointestinal symptoms were re-evaluated and patients were only recruited if they had a minimum of three symptoms judged to be at least of moderate or severe intensity. Other patients and those not compliant with the study protocol at the first follow-up visit were not eligible for trial participation. Patients were randomized to receive simethicone (105 mg t.d.s.), cisapride (10 mg t.d.s.) or placebo at the end of the baseline run-in period. Study medication was blinded by means of the double-dummy technique (Figure 1).

The study was approved by the local study centres' ethics committees, and all patients gave written informed consent.

Assessment of symptoms

At baseline and after 2, 4 and 8 weeks of treatment, the intensity of symptoms was measured. The severity of 10 upper abdominal symptoms (upper abdominal fullness, upper abdominal pain, borborygmus, belching, early satiety, nausea, vomiting, regurgitation, heartburn/retrosternal discomfort, loss of appetite) was assessed in a standardized interview. The intensity of the respective symptoms was scored as 0 (absent), 1 (moderate), 2

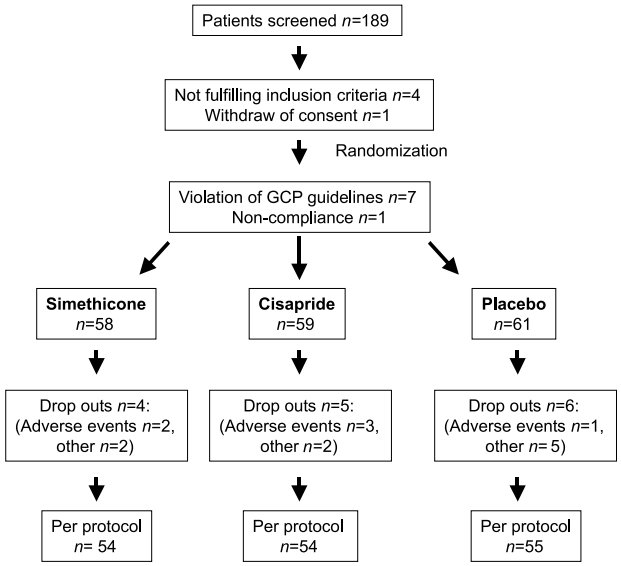

Figure 1. Sample sizes and drop-outs before and after randomization. After diagnostic work-up and a wash-out period of at least 7 days without medication, the patients were randomized and treated in a double-dummy technique with placebo (t.d.s.), cisapride (10 mg t.d.s.) or simethicone (105 mg t.d.s.). Prior to treatment and after 2, 4 and 8 weeks of treatment the intensity of the target variables was assessed. Subjective symptoms were documented daily by the patients in a diary throughout the study. GCP, good clinical practice.

(severe) or 3 (very severe), and a global symptom severity score was calculated that served as the primary outcome variable. A visual analogue scale was used to determine the patients global judgement of the intensity of discomfort (0 = no complaints, 100 = most intense complaints).

Furthermore, patients were asked to judge the efficacy of treatment 8 weeks after the start of medication as 'very good', 'good', 'moderate' or 'no effect'.

Assessment of compliance

At each visit, patients returned the containers of medication and pill counts were performed. A patient who took between 80% and 120% of the prescribed pills was considered to be compliant.

Calculation of sample size

Sample sizes were determined to show the superiority of simethicone compared with placebo in an a priori ordered sequence of tests after 8, 4 and 2 weeks of treatment. Based on a previous trial,[15] we assumed a difference of 3.5 points in the symptom score to be clinically relevant. Assuming a standard deviation of 5.5, a power of $1 - \beta = 0.9$ and $\alpha = 0.05$ as significant, a sample size of 43 patients per group was needed.

In the second step of the analysis, the sample sizes were determined to show the non-inferiority of simethicone compared with cisapride in an a priori ordered sequence of tests after 8 and 4 weeks of treatment, and to show the superiority of simethicone compared with cisapride after 2 weeks of treatment. The equivalence limit was $\sigma/2$, where σ is the standard deviation of the target parameter. A slightly lower sample size was needed in the second step to show significance. Therefore, $n = 43$ was used as the minimum sample size per group needed in this study. Assuming 25% drop-outs and non-valid patients, 58 patients per group were planned.

Data analyses

The primary target variable for the assessment of the treatment response was the O'Brien sum score[20, 21] of 'adjusted' changes from baseline in the gastrointestinal symptoms after 2, 4 and 8 weeks of treatment. These adjusted changes, or so-called delta values, were essentially differences in the 'symptom score at the control visit – the symptom score at baseline', but optimized by means of separate analyses of covariance for each item to eliminate the variation of the differences explainable by the variation of the corresponding baseline values. After adjustment, the delta values were normalized, i.e. transformed to variables with mean '0' and standard deviation '1', and added up to obtain the O'Brien sum score. The scoring was based on factor analysis and previously validated.[15]

The sum scores were compared among trial groups to establish the following objectives: the superiority of simethicone compared to placebo after 2, 4 and 8 weeks (one-sided *t*-test; $\alpha = 0.025$); the superiority of simethicone compared to cisapride after 2 weeks (one-sided *t*-test; $\alpha = 0.025$); the non-inferiority of simethicone compared to cisapride after 4 and 8 weeks (test of non-inferiority by means of the confidence interval inclusion method; $\alpha = 0.025$). To control for the potential β error, all of these comparisons were conducted hierarchically.

Additionally, the superiority of cisapride compared to placebo after 2, 4 and 8 weeks was tested to establish cisapride as the positive standard (internal validation).

A secondary target variable was the visual analogue scale for the intensity of discomfort. Adjusted changes in visual analogue scale values were analysed as described above to verify the superiority of simethicone and cisapride compared to placebo, and to show the non-inferiority of simethicone compared to cisapride. Tests of non-inferiority were carried out with $\sigma/2$ as the equivalence limit, where σ represents the standard deviation derived from the respective underlying analysis.

In a recent study utilizing the same questionnaire,[15] the following five symptom factors were identified: (i) fullness with upper abdominal fullness as the only item; (ii) pain and satiety with upper abdominal pain, early satiety and loss of appetite as items; (iii) bloating with peristaltic motions/borborygmi and passing of gas as items; (iv) nausea with nausea and vomiting as items; (v) reflux with heartburn/retrosternal discomfort and regurgitation as items. In an additional exploratory analysis, the efficacy of the various treatments with regard to these five factors was tested utilizing the O'Brien sum score.

All data analyses were performed based on an intention-to-treat population ($n = 175$) as well as a per protocol population, excluding major violations of the protocol. Missing data during the course of treatment were analysed by means of the 'last observation carried forward'. No substantial differences were obtained between the analyses in the two populations. Therefore, per protocol results are not shown. Statistical analyses were performed utilizing the Statistical Analysis System (SAS release 6.12).[22, 23]

RESULTS

Study population

One hundred and eighty-nine out-patients with a suspected diagnosis of functional dyspepsia were screened. Four subjects were excluded prior to randomization for violation of entry criteria ($n = 1$) or withdrawn consent ($n = 3$). Seven patients from one trial centre were excluded after randomization for major violation of good clinical practice (GCP) guidelines in this trial centre ($n = 6$) or insufficient compliance ($n = 1$), leaving a study population of 178 subjects (58 simethicone, 59 cisapride and 61 placebo).

Overall, 52.8% of the patients were female. The age ranged from 19 to 74 years with a mean ± s.d. of 49.6 ± 13.8 years. There were no significant differences between the trial groups with regard to baseline characteristics in the study population (Table 1).

In the simethicone group, four patients did not complete the 8 weeks of treatment (adverse events: $n = 2$), whilst five patients in the cisapride group (adverse events: $n = 3$) and six patients in the placebo group (adverse events: $n = 1$) terminated the trial prematurely.

Response to treatment

Symptom scores. The baseline adjusted 'raw' symptom summary scores of the 10 abdominal symptoms are depicted in Figure 2. At entry, the majority of patients reported moderate to severe symptom intensities. Thus,

Table 1. Characteristics of the study populations

Parameter	Simethicone ($n = 58$)	Cisapride ($n = 59$)	Placebo ($n = 61$)
Gender female (%)	62.1	45.8	50.8
Age (years) (mean ± s.d.)	46.9 ± 13.9	50.0 ± 14.3	51.8 ± 13.0
Weight (kg) (mean ± s.d.)			
Female	65.4 ± 8.4	67.1 ± 10.0	68.8 ± 14.2
Male	82.2 ± 13.8	83.9 ± 14.4	80.4 ± 10.5
Height (cm) (mean ± s.d.)			
Female	164 ± 6	165 ± 7	162 ± 6
Male	175 ± 7	178 ± 5	176 ± 6
Duration of symptoms (years) (median)	2.1	2.6	2.2
Alcohol consumption (never or rarely) (%)	87.9	93.2	86.9
Smoking (active nicotine consumption) (%)	17.2	22.0	24.6
Absence of any gastric mucosal lesion (%)	41.4	47.5	41.0
Absence of any duodenal mucosal lesion (%)	82.8	79.7	73.8
H. pylori positive (histology or urease test) (%)	10.3	8.5	8.2

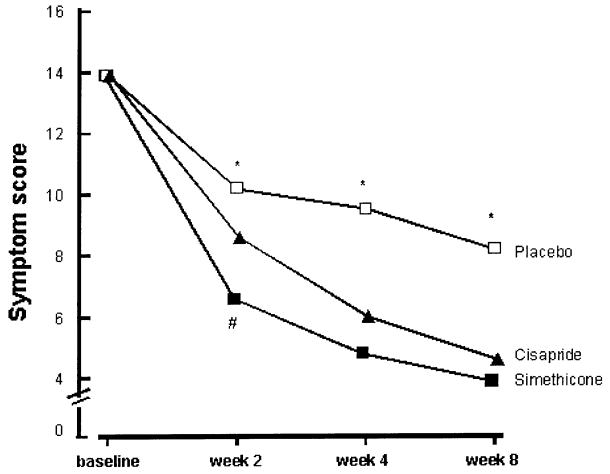

Figure 2. Baseline adjusted raw symptom scores after 2, 4 and 8 weeks of treatment. (*$P < 0.0001$ placebo vs. simethicone or cisapride; #$P = 0.0007$ simethicone vs. cisapride).

83% of patients reported moderate to severe fullness, whilst upper abdominal pain was judged to be mild to moderate by 76% of the study population. Confirmatory statistics were carried out on the basis of the O'Brien sum scores (Figure 3). After 2, 4 and 8 weeks of treatment, the sum scores were significantly lower with

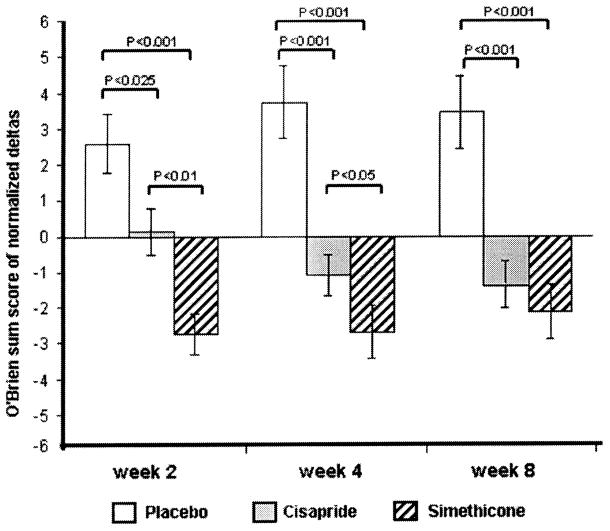

Figure 3. O'Brien sum score of normalized symptom changes from baseline (± S.E.M.) after 2, 4 and 8 weeks of treatment. For each separate week, the delta values of the symptoms are normalized based on the assumption that the overall effect equals zero. Therefore, the overall effect of the cumulated sum score also equals zero (e.g. after 2 weeks, improvement of symptoms in patients treated with cisapride reflects the average effect of the total population; placebo was less effective, but improvement of the symptom score was best during therapy with simethicone).

simethicone or cisapride compared to placebo. Simethicone was not inferior vs. cisapride after 4 ($P < 0.0001$) and 8 weeks ($P = 0.0004$), and was superior vs. cisapride after 2 weeks ($P = 0.0007$). The sum scores were lower in simethicone-treated vs. cisapride-treated patients after 4 and 8 weeks, but the differences were not significant at the 2.5% level.

Effects of treatment on specific symptom factors. Compared with placebo, treatment with simethicone and cisapride resulted in a significant improvement of virtually all symptom subgroups as defined by factor analysis. Throughout the 8-week trial, simethicone resulted in a numerically better improvement of symptoms than cisapride, and the differences were significant at the 2.5% level for the first 2 weeks for fullness, pain/satiety and nausea (data not shown).

Visual analogue scale. After 2, 4 and 8 weeks, visual analogue scale scores were significantly ($P < 0.025$) lower for patients treated with simethicone or cisapride compared to placebo (Table 2). Differences between simethicone and cisapride, however, were not significant.

Patients' judgement of treatment efficacy. At the end of the 8-week treatment period, 45.5% (95% confidence interval (CI), 31.9–59.5%) of patients treated with simethicone judged the efficacy of their treatment as very good, compared to 14.8% (95% CI, 6.6–27.1%; $P = 0.0005$) treated with cisapride and 16.1% (95% CI, 7.2–28.3%; $P = 0.0008$) treated with placebo.

Influence of H. pylori *status on response.* Only 9.0% of the study population were infected with *H. pylori*. Response to treatment was not associated with *H. pylori* status ($P = 0.50$ after 2 weeks, $P = 0.33$ after 4 weeks and $P = 0.79$ after 8 weeks of treatment).

Duration of symptoms and response. The median duration of symptoms ranged from 2.1 to 2.6 years for the respective treatment groups (see Table 1). The influence of the duration of symptoms on response was evaluated by means of analysis of variance (ANOVA) using a dichotomized version of duration (≤ median, > median) as a cofactor, and by means of a non-parametric Spearman correlation analysis of duration and O'Brien sum scores in the total intention-to-treat population. ANOVA yielded no association of response with disease duration ($P = 0.88$ after 2 weeks, $P = 0.98$ after

Table 2. Baseline adjusted means of the visual analogue scale for the intensity of discomfort

Week	Simethicone	Cisapride	Placebo	Simethicone vs. placebo	Cisapride vs. placebo
0	56.3	56.3	56.3		
2	33.5	34.1	43.1	$P = 0.0102$	$P = 0.0145$
4	23.5	25.3	38.1	$P = 0.0002$	$P = 0.0011$
8	22.0	22.6	37.1	$P < 0.0001$	$P = 0.0003$

4 weeks and $P = 0.54$ after 8 weeks of treatment), and no statistically significant interactions of disease duration and study therapy were detected. The Spearman correlation coefficients were $r_s = 0.03$ ($P = 0.72$) after 2 weeks, $r_s = 0.063$ ($P = 0.41$) after 4 weeks and $r_s = -0.02$ ($P = 0.80$) after 8 weeks of treatment.

Adverse events. All treatments were generally well tolerated. Adverse events were reported in 11.5%, 16.9% and 20.7% of patients treated with placebo, cisapride and simethicone, respectively. The differences between treatment groups were not statistically significant (chi-squared test, $P = 0.391$). The most frequently affected body system was the gastrointestinal tract, which accounted for 4.9%, 8.6% and 8.5% of the adverse events for placebo, simethicone and cisapride, respectively. Diarrhoea and pain were most frequently reported. Most adverse events were of mild or moderate intensity and had resolved by the end of the study. One patient experienced an atrioventricular node re-entry tachycardia as a serious adverse event during treatment with cisapride. There were no further relevant abnormalities of laboratory parameters in either treatment group.

DISCUSSION

This is the first prospective, placebo-controlled, double-blind trial to compare simethicone with placebo and a prokinetic agent in patients with functional dyspepsia. During the 8-week study period, simethicone was significantly better than placebo in improving dyspeptic symptoms. Simethicone had a more rapid onset of action than the prokinetic cisapride and was superior to cisapride after 2 weeks and similar in efficacy to cisapride at 4 and 8 weeks. Patients treated with simethicone judged the efficacy of their treatment as very good in 46% of cases; however, this was only the case in 15% and 16% of patients receiving cisapride and placebo, respectively.

Simethicone has been used for many years in various countries for the treatment of patients with otherwise unexplained abdominal symptoms that are believed to be gas related.[11] Indeed, there is now evidence that disturbed clearance of gas may be one mechanism related to symptoms in a subgroup of patients with functional gastrointestinal disorders.[12]

Simethicone is not absorbed from the lumen of the gut. For this reason, the observed benefits are unlikely to be due to any systemic effects of the compound. Simethicone has been shown to reduce the amount of H_2 eliminated in breath during a lactulose challenge in healthy subjects.[24] This suggests that either gas production or gas clearance (absorption from the gut or venting of the gas via the mouth or rectum) may be modulated by simethicone. Preliminary experimental studies from our own laboratory have shown that the acute administration of simethicone may stimulate upper gastrointestinal motility via unknown pathways, and thus may accelerate the propulsion and expulsion of gas (Holtmann 2000, unpublished results). However, in our study, improvement of symptoms was not confined to bloating, as pain and early satiety also significantly improved. Whilst the addition of simethicone to antacid therapy may improve some symptoms in patients with gastro-oesophageal reflux disease,[25] this disease was an exclusion parameter in this trial.

Simethicone exerts an antibacterial effect on *H. pylori*[26, 27] and thus may influence faecal flora, although this has not yet been studied. Simethicone also suppresses urea hydrolysis.[28] However, in our study, there were no differences in the response to treatment with regard to *H. pylori* status. No effects of simethicone on other Gram-negative bacteria have been observed.[27] Dietary fibre may influence the amount of hydrogen produced in the gut. Thus, dietary habits could have influenced the outcome. In the present study, we did not record dietary habits. However, treatment was randomly allocated and thus dietary factors should have had the same influence in all treatment arms.

It has been recommended that the treatment of patients with functional dyspepsia should be based on the pattern of symptoms.[1] Cisapride, for example, has

been typically evaluated in patients with a specific spectrum of dysmotility-like symptoms.[29] However, in epidemiological studies, the symptom subgroups identified have been shown to overlap.[30, 31] In the present study, several symptoms were assessed and treatment effects based on specific symptom clusters, as identified by factor analysis, were analysed. Interestingly, simethicone and cisapride both improved the various symptom subgroups, and treatment effects were not limited to specific symptoms.

Patients recruited for this trial were treated for their symptoms by general practitioners. Thus, these patients most likely represent typical patients with functional dyspepsia and are not restricted to patients seen at tertiary referral centres. Thus, our data should be relevant for the majority of patients with functional dyspepsia. Nevertheless, the efficacy of simethicone in patients with functional dyspepsia seen at tertiary referral centres, who probably have more resistant symptoms, needs to be confirmed separately.

In the current study, simethicone was compared with placebo and cisapride. The use of cisapride is now restricted in most countries because of the rare side-effects of prolonged QT interval, cardiac dysrhythmias and sudden death. Due to the number of clinical trials that have documented the efficacy of cisapride in patients with functional dyspepsia, this compound can still be considered as the prokinetic 'gold standard',[8–10] and thus was selected as an active comparator before prescribing restrictions were implemented.

In summary, in this placebo-controlled, 8-week trial, simethicone and cisapride were significantly better than placebo in controlling symptoms in patients with functional dyspepsia. In addition, during the first 2 weeks, simethicone was superior to cisapride. As simethicone is not absorbed from the gut and lacks systemic effects, the data imply that a luminal factor (e.g. gaseous distention in the setting of visceral hyperalgesia) may be involved in the development of symptoms in patients with functional dyspepsia. Further clinical studies exploring potential mechanisms of action are needed.

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