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Randomised double-blind comparison of simethicone with cisapride in functional dyspepsia

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SUMMARY

Aim: To compare the efficacy of simethicone with cisapride in patients with functional (non-ulcer) dyspepsia.

Methods: After standardized diagnostic work-up and at least 6-days wash-out of medication, 177 patients with functional dyspepsia were enrolled; 173 of them (age 19–71 years) were randomized and treated using a double-dummy technique with simethicone (84 mg t.d.s.) or cisapride (10 mg t.d.s.). At baseline and after 2 and 4 weeks, the intensity of the symptoms was scored from 0 (absent) to 3 (severe) using a standardized symptom questionnaire. Efficacy of the treatment was judged by the patients as 'very good', 'good', 'moderate' or 'no effect'.

Results: A total of 166 patients completed the trial. After 2 and 4 weeks, 34% and 46% (respectively), of the patients treated with simethicone judged the improvement in symptoms to be excellent compared to 13% and 22% (respectively) of patients treated with cisapride ($P < 0.01$). After 2 weeks the difference in the improvement in the global symptom score was significantly better ($\Delta 30.7\%$, $P < 0.001$) for simethicone than for cisapride, while this difference failed statistical significance after 4 weeks ($\Delta 10.2\%$, $P = 0.11$).

Conclusions: In patients with functional dyspepsia, simethicone relieves symptoms during the first 2 weeks of treatment significantly better than cisapride.

INTRODUCTION

Dyspepsia is a frequent reason for medical consultation in primary and secondary care. It is now well recognized that structural (or organic) lesions are only found in a minority of patients with dyspepsia. Dyspepsia, in the absence of a clinically identifiable structural lesion causing symptoms, is referred to as functional (non-ulcer) dyspepsia.[1] Because a structural explanation is lacking, disturbed GI function is believed to play a role in the development of symptoms. Pharmacological treatment for patients with functional dyspepsia remains unsatisfactory even though at least some controlled trials demonstrate a superiority over the placebos for H_2-receptor antagonists, proton pump inhibitors, and prokinetics.[2–4]

In patients with functional dyspepsia, fullness or bloating are believed to be gas-related, linked to disturbed GI motility, or reflect heightened perception of gas or disturbed motility. For this reason agents that may affect gastrointestinal gas (e.g. simethicone or a prokinetic) are used for treatment of these patients. However, so far no data are available that compare simethicone with a standard prokinetic.

Another contentious issue is the relevance of symptom pattern in the response to therapy. It has been suggested that patients with functional dyspepsia can be subdi-

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vided into dyspepsia subgroups based on the pattern of symptoms.[1] However, as these subgroups overlap and lack stability over time, the clinical relevance of this approach is uncertain.[5–7] Moreover, it is unknown whether the symptom subgroups identify treatment outcomes.

Thus, this study aimed to compare the efficacy of simethicone with the standard prokinetic cisapride in patients with functional dyspepsia, and identify symptoms that respond to treatment with simethicone. Therefore, because cisapride is considered the standard treatment for patients with non-ulcer dyspepsia, we hypothesized that simethicone is not inferior to cisapride regarding improvement of dyspeptic symptoms in patients with non-ulcer dyspepsia.

MATERIALS AND METHODS

Study design and patients

After approval by the Ethical Committees of the study centres, 177 outpatients with predominantly upper abdominal pain or discomfort and the diagnosis of non-ulcer (functional) dyspepsia were recruited for the study by 17 physicians in private practice. Prior to inclusion in the study, a standardized diagnostic work-up was performed in all patients. Functional dyspepsia was diagnosed if the subjects had upper abdominal pain, or discomfort (i.e. a negative feeling in the upper abdomen that does not reach the level of pain, characterized by one or more symptoms including early satiety, postprandial fullness, bloating or nausea) for more than 3 months without an identifiable structural or biochemical abnormality causing the symptoms. Predominant reflux symptoms (retrosternal pain, burning or regurgitation) were considered to be part of the gastro-oesophageal reflux disease rather than being part of functional dyspepsia. Thus, patients with reflux symptoms only or patients with predominantly reflux symptoms were ineligible for participation in the study. In addition, patients with concomitant symptoms of irritable bowel syndrome that dominated the clinical picture were not allowed to enter the trial.

Prior to inclusion in the trial, physical examination, laboratory testing (i.e. white and red blood count, sedimentation rate, fasting blood sugar, liver function tests), abdominal sonography and upper gastrointestinal endoscopy did not find evidence for a structural cause of the symptoms. Patients with either a positive histology or urease test were considered to be *H. pylori*-positive. After establishing the diagnosis of functional dyspepsia medication potentially affecting the GI tract was withdrawn. After at least 7 days of wash-out of medication, gastrointestinal symptoms were re-evaluated and only patients with at least three individual symptoms judged to be at least moderate or severe were recruited. All other patients were ineligible for inclusion in the trial. In addition, patients who did not comply with the first follow-up visit were also ineligible for participation in the trial.

Thereafter, patients were randomized to receive either simethicone (84 mg t.d.s.) or cisapride (10 mg t.d.s.). The patient characteristics of the two study populations are listed in Table 1.

Assessment of symptoms

A standardized questionnaire was used to assess abdominal symptoms. This questionnaire addressed 10 symptoms that served as the primary target variables (upper abdominal fullness, upper abdominal pain, passing of gas, early satiety, nausea, vomiting, regurgitation, heart burn, loss of appetite, perception of small or large bowel movements). The intensity of the respective symptoms was scored as 0 (absent), 1 (low intensity), 2 (moderate intensity) or 3 (severe). In addition, patients were asked to judge the efficacy of the treatment 2 and 4 weeks after the start of medication as being 'very good', 'good', 'moderate' or having 'no effect'. Similarly the physician judged the response to treatment.

Assessment of compliance

After the second and fourth week of treatment, patients returned the medication containers and pill counts were performed. A total of 168 pills were prescribed for the study period. A patient who took more than 80% of the prescribed pills (>135) was considered compliant.

Calculation of the sample sizes

Prokinetics can be considered the standard treatment for patients with non-ulcer dyspepsia. Thus, the current study was designed to test the non-inferiority of simethicone to cisapride rather than targeting the

Table 1. Characteristics of the study populations

	Simethicone $n = 87$ (%)	Cisapride $n = 86$ (%)	P-value
Gender female (%)	41 (47.1)	56 (65.1)	0.017
Age, years (mean ± s.d.)	48.8 ± 11.9	47.2 ± 13.3	0.396
Weight (kg)			
female	67.9 ± 12.3	66.9 ± 11.2	0.684
male	78.7 ± 8.3	80.0 ± 11.1	0.564
Height (cm)			
female	166 ± 5	165 ± 5	0.186
male	173 ± 6	177 ± 8	0.056
First functional dyspepsia episode	23 (26.4)	22 (25.6)	0.898
In case of recurrence: duration of illness (years, median)	4.3	5.3	0.815
Alcohol consumption (never or less than once weekly)	86 (98.9)	82 (95.3)	0.169
Smoking (active nicotine consumption)	17 (19.5)	16 (18.6)	0.876
Absence of any gastric mucosal lesion	48 (55.2)	34 (39.5)	0.039
Absence of any duodenal mucosal lesion	67 (77.0)	63 (73.2)	0.568
H. pylori-positive (histology or urease-test)	6 (6.9)	11 (12.8)	0.193

superiority of one compound over the other. For this purpose half a standard deviation (s.d./2) of the efficacy variable was used as an equivalence margin, and a sample size of 85 patients per group was sufficient to show non-inferiority after 2 and 4 weeks of treatment with an α-value of 0.025 and a β-value of 0.10.

Target variables and data analyses

First, for each individual symptom, a separate analysis of covariance for the differences in symptom intensities during treatment minus symptom intensities at baseline was performed, with medication as the treatment factor and baseline values as the covariate.[8, 9] These analyses yielded adjusted changes in symptom intensities, which eliminated the variation in treatment effects due to differences in the baseline values. Secondly, these 10 adjusted efficacy variables were standardized and, with the exception of upper abdominal fullness, enumerated to give five subgroups of symptoms that were identified to be correlated, based upon a factor analysis performed with the symptoms at entry. Thirdly, upper abdominal fullness and the four factors were analysed as multiple endpoints according to O'Brien's procedure, which uses the standardized sum of the five items as a global efficacy variable.[8]

With regard to the choice of equivalence margins (50% of s.d.), treatment differences (delta) of improvements during treatment with simethicone minus cisapride were also calculated and expressed in terms of percentage of s.d. A negative delta value indicated a better response during treatment with simethicone, whereas a positive value indicated a better response for cisapride. The upper (Cl_u) and the lower (Cl_l) 95% CI values for the deltas were also calculated. $Cl_o < 50\%$ indicated non-inferiority of simethicone compared to cisapride with an $\alpha = 0.025$ value. $Cl_o < 0\%$ indicated a significant superiority of simethicone compared to cisapride with an $\alpha = 0.05$ two-sided. For exploratory purposes, the tests for the non-inferiority of cisapride compared with simethicone were performed using the criterion $Cl_u > -50\%$.

The patient's judgement regarding the efficacy of treatment was used as a secondary target variable.

Mean values and the respective standard deviations were calculated for all numeric variables. In addition, frequencies, proportions and the respective 95% confidence intervals (CI) were determined where appropriate. Data analyses were carried out on the basis of intention-to-treat (ITT). The overall level of significance was controlled by using a closed test procedure and a priori ordered hypotheses.[9] Statistical analyses were carried out utilizing the Statistical Analysis System (SAS version 6.11).[10]

RESULTS

Study population

A total of 177 patients were screened. Four patients were excluded due to protocol deviations (two subjects were excluded prior to randomization: one after randomization and one for violation of entry criteria), leaving a study population of 173 subjects. Eighty-seven patients were randomized to receive simethicone and 86 to receive cisapride. The comparison of the two treatment groups did not reveal significant differences in baseline characteristics. In the cisapride group five patients did not complete the 4-week treatment (side-effects [stomach or abdominal pain, diarrhoea], $n = 4$; insufficient improvement of symptoms, $n = 1$) while two patients (side-effects [stomach pain], $n = 1$; side-effects [stomach pain] and insufficient improvement of symptoms, $n = 1$) in the simethicone group did not complete the trial.

Factors of abdominal symptoms

Factor analysis of nine of the symptoms (the exception being abdominal fullness), yielded a four factorial structure of symptoms (factor 1, pain & satiety; factor 2, bloating; factor 3, nausea; factor 4, reflux) with factor loadings of the individual symptoms ranging from 0.52 to 0.84. The abdominal fullness symptom did not fit into any of the factors in a meaningful manner, hence high negative loadings occurred. Thus, this item is reported and analysed separately.

Response to treatment

Symptom scores. During the 4-week trial, the sum of symptoms significantly decreased in the simethicone group from 14.0 (± 3.7) at baseline to 5.4 (± 3.0) after 2 weeks and 3.3 (± 3.4) after 4 weeks ($P < 0.001$ and $P < 0.001$ vs. baseline, respectively). In the cisapride group, the sum of symptoms decreased from 14.1 (± 3.3) to 7.7 (± 3.4) and 4.4 (± 3.0) after 2 and 4 weeks, respectively ($P < 0.001$ and $P < 0.001$ vs. baseline, respectively). On the basis of the O'Brien global summary score, the difference between simethicone and cisapride was −55.2% (95% CI −85.2% to −25.2%) after 2 weeks and −24.2% (−54.3% to 5.8%) after 4 weeks; percentages of s.d. $Cl_o < 50\%$ indicated a significant non-inferiority of simethicone vs. cisapride after 2 and 4 weeks simultaneously (Bonferoni). Because of $Cl_o < 0\%$, a significant superiority of simethicone was revealed after 2 weeks with regard to the global summary score.

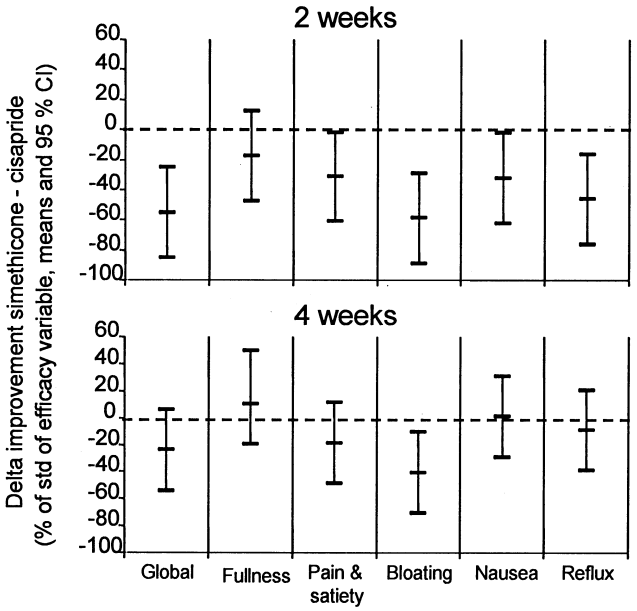

Figure 1. Baseline adjusted differences (simethicone – cisapride) at 2 and 4 weeks of treatment for the ITT population and the respective 95% Confidence Intervals. A negative value indicates the superiority of simethicone while a positive value indicates the superiority of cisapride.

The differences in the improvement of symptoms after 2 and 4 weeks of treatment for the global score and the symptom factors identified by factor analysis are shown in Figure 1. Based upon the ITT analysis, improvement of the global symptom score during treatment with simethicone was not inferior ($P < 0.001$) to cisapride. The reversed tests were not significant except for that of abdominal fullness. Furthermore, significant differences in favour of simethicone were seen with regard to each of the factors pain and satiety, bloating, nausea, and reflux after 2 weeks of treatment. After 4 weeks of treatment significant non-inferiority was obtained for fullness and the other factors ($P < 0.001$ one-sided each), but in contrast to the results after 2 weeks, after 4 weeks a significant superiority of simethicone was seen for bloating only ($P < 0.050$ two-sided).

Patients' and physicians' judgements of treatment efficacy. Based upon the patients' judgements regarding the efficacy of the treatment, significantly (2 weeks

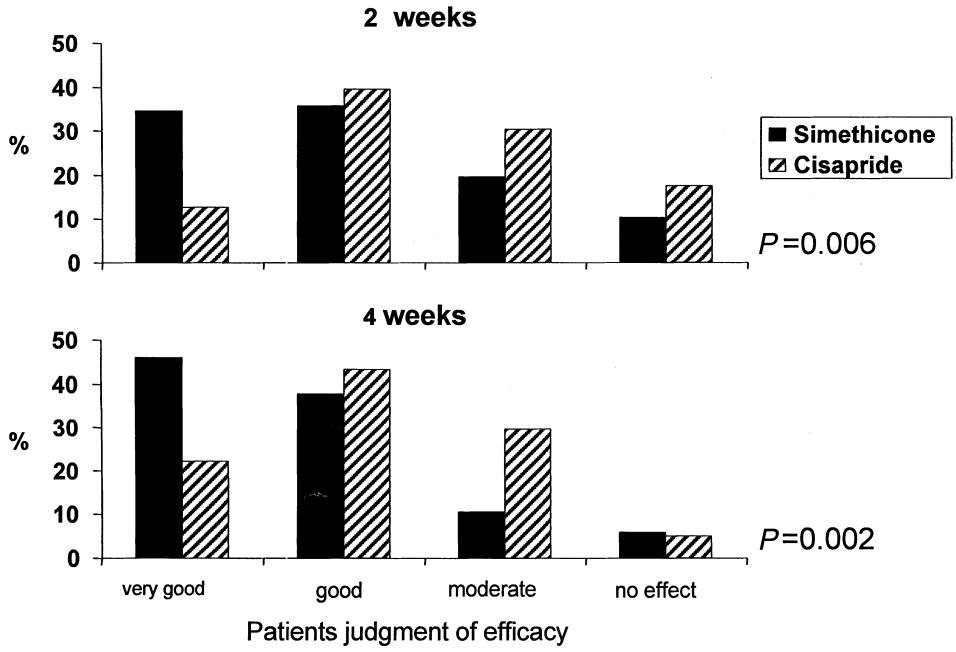

Figure 2. Patients' judgement of treatment efficacy at 2 and 4 weeks.

$P = 0.006$, 4 weeks $P = 0.002$) more patients treated with simethicone reported very good results compared to patients treated with cisapride (Figure 2). Similarly, the physicians judged the response to treatment after 2 and 4 weeks to be very good in 32.2% and 48.2%, respectively, of patients treated with simethicone compared to 14% and 25.9%, respectively, of patients treated with cisapride ($P = 0.002$ and 0.003).

Influence of H. pylori-status on response to treatment. Seventeen out of 156 subjects tested positive for *H. pylori.* Exploratory analysis did not reveal an effect of the *H. pylori*-status on the global improvement or the patient's judgement of treatment efficacy ($P > 0.2$).

Duration of symptoms. Shorter duration of symptoms (> 1 years vs. < 1 years) was associated with a significantly ($P < 0.05$) better global response to treatment with simethicone compared to cisapride (data not shown).

DISCUSSION

In the past, several studies have demonstrated a beneficial effect of acid inhibitory agents or prokinetics for the treatment of patients with functional dyspepsia.[2] These compounds usually provide a therapeutic gain over placebo of between 10% and 30%. A previous controlled study observed more rapid improvement of dyspeptic symptoms compared to placebo.[11] While prokinetics are believed to be the standard treatment for adult patients with functional dyspepsia, simethicone has been used for many years in some countries for the treatment of patients with otherwise unexplained abdominal symptoms that were believed to be gas related. So far there is no controlled trial available that compares a standard prokinetic with simethicone. Thus, this is the first prospective controlled trial that compares the effects of simethicone and cisapride on symptoms in patients with non-ulcer dyspepsia. This study was designed and powered to demonstrate the non-inferiority of both treatment regimens. However, our data are consistent with significantly better improvement of symptoms during the first 2 weeks of treatment in patients treated with simethicone compared to the standard prokinetic cisapride. Nevertheless, it appears necessary that this finding is confirmed in placebo-controlled trials.

A considerable overlap of symptoms of functional dyspepsia and irritable bowel syndrome has been found in previous studies.[6, 7, 12, 13] Thus, it might be argued that the global improvement was not due to dyspeptic symptoms rather than a global effect on various abdominal symptoms. On the other hand, the additionally performed separate analysis of factors derived by factor analysis further demonstrates the superiority for

pure dyspepsia and upper abdominal factors such as pain and satiety or reflux.

Some authors suggest that a distinction be made between excessive gas (which indicates excessive gas production) and feelings of bloating (which are usually unrelated to excessive gas production). Treatment of the former consists of limiting the supply of fermentable material to the colonic bacteria. Symptoms of bloating usually indicate irritable bowel syndrome, and therapy should be directed accordingly.[14] Indeed, evidence for an excess of gas as the cause of the symptoms is as yet insufficient.[15] As yet there is strong evidence that there is not an excess amount of gas but that the presence of 'physiological' amounts of air swallowed and gas produced during the fermentation of carbohydrates by bacteria and an underlying disturbance of visceral nociception may cause the symptoms.[13] Interestingly, the symptom factor bloating responded favourably to simethicone, compared to cisapride; in addition, so far, no effect of simethicone on H_2-production has been found.[16] Thus, the beneficial effect of simethicone is unlikely to be due to a reduced gas production.

Outpatients recruited for this trial were treated for their symptoms by general practitioners. Thus, these patients most likely represent typical patients with non-ulcer dyspepsia rather than patients seen by specialized gastroenterologists or at tertiary referral centres. Since only a small proportion of patients, usually unresponsive to conventional therapy or characterized by psychological or other comorbidity, present at tertiary referral centres or to specialized gastroenterologists, our data have relevance for the majority of patients with non-ulcer dyspepsia. Nevertheless, the efficacy of simethicone in dyspeptics with severe symptoms that are unresponsive to first and second line medication seen at tertiary referral centres needs to be confirmed separately.

The better improvement of symptoms during the first 2 weeks of treatment with simethicone compared to the standard prokinetic cisapride raises the question of the mechanisms of action. In comparison with most other compounds used for the treatment of patients with non-ulcer dyspepsia, simethicone is not absorbed and thus is unlikely to have systemic effects.

Besides the effects on the surface tension, simethicone may stimulate gastrointestinal motility and therefore may accelerate the propulsion and expulsion of gas. As a result, the physiological gas load of the gut might be diminished. On the other hand, simethicone appears to influence symptoms such as pain and satiety or reflux that are not believed to be directly 'gas-related'. Thus, the precise mechanism of action still remains to be elucidated.

In summary, during the first 2 weeks of treatment simethicone appears to be superior to the standard prokinetic cisapride for the symptomatic treatment of functional dyspepsia. The mechanism of action remains to be elucidated.

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