ORIGINAL ARTICLE

Efficacy of an activated charcoal–simethicone combination in dyspeptic syndrome: Results of a placebo-controlled prospective study in general practice

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Summary

Aim. – The aim of this prospective, multicenter, randomized, placebo-controlled trial was to evaluate the efficacy of a commercial combination of simethicone and activated charcoal (Carbosylane®) on dyspeptic symptoms in patients consulting a general practitioner.

Patients and methods. – A total of 132 patients were studied. Treatment duration was 3 months, followed by a 2 month follow-up period.

Results. – At the end of the treatment period, the percentage of patients with a reduction of at least two points on the symptom intensity scale was significantly higher with Carbosylane® than with a placebo ($P = 0.043$). Compared with placebo, the intensity of three symptoms (abdominal fullness, bloating and the sensation of slow digestion) was significantly decreased after 90 days of Carbosylane® ($P < 0.05$). At the end of the post-treatment follow-up, the percentages of patients with moderate or severe global complaints were 6.78% and 21.43% in the Carbosylane® and placebo groups, respectively ($P < 0.03$).

Conclusion. – Among patients consulting a general practitioner for dyspeptic syndrome, 3 months of treatment with Carbosylane® resulted in significant symptomatic improvement. The improvement was still evident 2 months after the end of treatment.

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Introduction

In France, dyspeptic syndrome is a common complaint requiring significant attention by general practitioners because of its frequency (affecting about one in three adults) and its major impact on the quality of life. In one population-based study, abdominal pain and a sensation of slow digestion were the most commonly reported complaints [1]. While only 50% of sufferers consult a physician (either a generalist or specialist), management practices should nevertheless target individualized efficacy.

According to the Rome III criteria, dyspeptic syndrome is defined as the association of diverse digestive symptoms of variable intensity in the epigastric region that, particularly after meals and over a period of at least 6 months, become chronic and permanent, or recurrent and episodic, occurring within the past 3 months. Dyspeptic syndrome probably arises from a multifactorial mechanism. Elements that are probably involved include impaired gastric motility, gastric hypersensitivity and bloating and inflammatory phenomena associated with Helicobacter pylori infection [2]. The diagnosis of functional dyspepsia is generally one of exclusion as there is no specific biological or morphological test for it. Nevertheless, in the context of general practice, a pragmatic attitude is the rule, involving a test using medical treatment [3].

Currently, there is no agreed-upon standard treatment for dyspeptic syndrome. The use of antisecretory drugs, H2-receptor antagonists (anti-H2) or proton pump inhibitors (PPI) may provide improvement in a minority of patients, but only for off-label indications [4] and with a high number of patients-to-treat to cure one (NPT), or around eight or nine [4]. Considering its low efficacy (NPT = 18) [5], systematic eradication of H. pylori is not recommended for this indication [6]. Although several studies have demonstrated that prokinetic drugs such as D2 dopamine receptor antagonists or cisapride [4] are more effective than placebo, the risk of serious adverse effects with cisapride greatly limits its use.

In the course of dyspeptic syndrome, the sensations of bloating or abdominal fullness are probably related, in part, to the accumulation of air, an anomaly demonstrated in patients with irritable bowel syndrome [7]. Simethicone is widely used to reduce the amount of air in the digestive tract. Two studies have also demonstrated that simethicone is more effective than either cisapride or placebo in those with functional dyspepsia [8,9].

A commercial combination of simethicone and activated carbon (Carbosylane®) has had marketing approval in France for dyspeptic syndrome since 1981 and is widely prescribed. However, its efficacy should be reassessed in the context of the new, recently issued guidelines [10].

The purpose of the present multicenter, randomized, placebo-controlled study was to assess the efficacy of Carbosylane® in patients consulting a general practitioner for dyspeptic syndrome.

Patients and methods

Patients

This study included patients, aged 18 to 49 years, who complained of at least one of the following symptoms: abdominal fullness; bloating; nausea; slow digestion. These symptoms were present every day for a period of at least eight consecutive days prior to consultation and were the main reason for seeking care from a general practitioner.

The presence of symptoms of gastroesophageal reflux and/or irritable bowel syndrome was tolerated as long as these symptoms were not predominant at history taking. Patients who had a history of gastrointestinal cancer, surgery involving the gastrointestinal tract, recent weight loss, anemia or an inflammatory syndrome were not included. Similarly, patients with a long-standing dyspeptic syndrome who had undergone endoscopic and/or imaging explorations within the past 2 years for this reason, or taken prior treatment within the last 10 days for dyspeptic symptoms or...
treatment with an anxiolytic agent or antidepressant were not included.

Considering the age of the patients included (18—49 years), no complementary biochemical or morphological test was required for inclusion. Similarly, a search for *H. pylori* was not deemed necessary [11].

The patients gave their informed consent to participate in the study protocol, which had been approved by the ethics committee Comité de protection des personnes se prêtant à une recherche biomédicale (CPPRB) of the Saint-Germain-en-Laye hospital.

**Treatment**

On inclusion in the trial, patients were treated with either Carbosylane® or a placebo. The usual formulation of gastrosoluble and gastroresistant capsules was used for Carbosylane®. Each capsule of Carbosylane® contained 140 mg of activated charcoal and 45 mg of simethicone and could not be distinguished from the capsules containing the placebo. Two capsules taken three times a day during meals were prescribed.

**Study design**

This was a multicenter, double-blind, placebo-controlled study comparing two treatment arms of 3 months’ duration, followed by an observation period of 2 months with no treatment (Fig. 1). Patients were recruited and followed by the general practitioner investigators and asked to consult their physician if, for any reason, they were dissatisfied. Physicians were free to order any complementary explorations they considered necessary and/or to prescribe another treatment to achieve symptom relief.

**Symptom intensity**

The overall and individual symptom intensities (abdominal fullness, bloating, sensation of slow digestion, nausea) were determined by each patient using a self-assessment diary that was completed every day for 7 days prior to the clinical visit. These were scored using a scale from 0 to 3, where 0 = absence of symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms. Clinical outcome was defined as the symptom score on day 0 minus the symptom score at the end of treatment and recorded as improved (positive difference), unchanged (no difference) or worsened (negative difference). Major improvement was defined as a positive difference of more than two points.

**Outcomes**

The main outcome was the change in overall patients’ complaints. Secondary outcomes were the percentage of patients with major improvement and the outcome of each of the four key symptoms of the dyspeptic syndrome. The need for complementary explorations and/or the initiation of another treatment for dyspepsia because of persistent symptoms was also taken into consideration.

**Statistical analysis**

An intention-to-treat analysis was performed using data from all patients who had received at least one capsule in one of the study arms and had undergone an outcome assessment. Results are expressed as percentages or as means ± standard deviation.

A Cochran—Mantel—Haenszel test, stratified by symptom intensity on day 0, was used to analyze changes in overall complaints and dyspepsia symptoms. The relative risk of improvement (RRI) and the relative risk of major improvement (RRMI), with 95% confidence intervals (95%CI) were also calculated to assess the effect of treatment.

The number of prescriptions for complementary explorations and new treatments because of therapeutic failure were compared between the two groups using the Chi² test or, for sample sizes inferior to 5, Fisher’s exact test.
Results

Altogether, 132 patients — predominantly female and with a mean age of 39.0 ± 8.8 years — were included in the study. Demographic data, symptom distribution and symptom intensity recorded on day 0 were similar for the two treatment arms (Table 1). On average, patients had had the symptoms for 7.1 ± 21.5 months, with a non-significant trend for a longer course in the placebo group (P=0.91).

Symptoms at end of treatment

Global complaints

At the end of treatment, there was no significant difference in overall complaints between the placebo group and the Carbosylane® group (P=0.115; RRI = 1.10, 95% CI = 0.91—1.33) (Fig. 2). However, the RRMI (two or more points on the intensity score) was greater in the Carbosylane® group than in the placebo group (Fig. 3). Improvement from mild intensity to complete relief and from severe intensity to mild intensity was noted in 56.6% of patients in the Carbosylane® group versus 33.3% in the placebo group (P < 0.01). The RRMI with Carbosylane® was 1.54 (95% CI = 1.05—2.26).

Abdominal fullness

Compared with placebo, the fullness symptom was significantly improved in the Carbosylane® group (P = 0.004; RRI = 1.2, 95% CI = 0.9—1.6 versus RRMI = 1.9, 95%

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Included population.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Gender ratio (F/M)</td>
<td>70%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40 ± 9</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>10 ± 29</td>
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<tr>
<td>Overall complaint (%)</td>
<td>0:0</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
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<tr>
<td></td>
<td>2:68</td>
</tr>
<tr>
<td></td>
<td>3:27</td>
</tr>
<tr>
<td>Abdominal fullness (%)</td>
<td>0:5</td>
</tr>
<tr>
<td></td>
<td>1:8</td>
</tr>
<tr>
<td></td>
<td>2:65</td>
</tr>
<tr>
<td></td>
<td>3:21</td>
</tr>
<tr>
<td>Bloating (%)</td>
<td>0:5</td>
</tr>
<tr>
<td></td>
<td>1:6</td>
</tr>
<tr>
<td></td>
<td>2:56</td>
</tr>
<tr>
<td></td>
<td>3:33</td>
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<tr>
<td>Slow digestion (%)</td>
<td>0:14.5</td>
</tr>
<tr>
<td></td>
<td>1:9.5</td>
</tr>
<tr>
<td></td>
<td>2:56</td>
</tr>
<tr>
<td></td>
<td>3:21</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>0:51</td>
</tr>
<tr>
<td></td>
<td>1:24</td>
</tr>
<tr>
<td></td>
<td>2:17</td>
</tr>
<tr>
<td></td>
<td>3:8</td>
</tr>
</tbody>
</table>

F/M: female/male.

<sup>a</sup> 0: never; 1: mild; 2: moderate; 3: severe.

![Improvement in overall complaints between day 0 and day 90.](image)

Rate of major improvement in overall complaints between day 0 and day 90.

CI = 1.2–33). With Carbosylane®, 68% of patients experienced symptom improvement versus 58% in the placebo group. The proportion of patients with major improvements was two-fold greater in the Carbosylane® group: 44% versus 23% with placebo (Fig. 4).

**Bloating**

Compared with placebo, the intensity of bloating was significantly lower in the Carbosylane® group (P = 0.045; RRI = 1.2, 95% CI = 1.0–1.4 versus RRMI = 1.4, 95% CI = 0.9–2.2). Thus, with Carbosylane®, 89% of patients reported symptom improvement versus 71% with placebo. As for major improvements, the difference was greater: 67% in the Carbosylane® group versus 43% in the placebo group (Fig. 4).

**Sensation of slow digestion**

Similarly, compared with placebo, there was a significant improvement in the slow digestion symptom with Carbosylane® (P = 0.022; RRI = 1.3, 95% CI = 1.0–1.5 versus RRMI = 1.4, 95% CI = 0.9–2.2). Overall, 76% of the Carbosylane® patients reported improvement in the slow-digestion symptom compared with 59% in the placebo group. The difference between the Carbosylane® group and the placebo group was larger for major improvement: 45% and 29%, respectively (Fig. 4).

**Nausea**

Few patients complained of nausea (Table 1). There was a relative improvement (RRI = 1.04) with Carbosylane® (95% CI = 0.8–1.3), but the difference compared with the placebo was not significant (P = 0.26).

**Prescriptions (complementary tests, new treatment)**

During the treatment period (days 0–90), complementary tests were ordered because of persistent dyspeptic symptoms for eight patients in the placebo group versus three in the Carbosylane® group. Abdominal ultrasound was ordered for eight patients and an endoscopic procedure for three (two colonoscopies and one video capsule ultrasound). The initial treatment was considered unsuccessful (because a new treatment was prescribed) for 11 patients in the placebo group versus six patients in the Carbosylane® group. These differences were not statistically significant (P = 0.12 for complementary tests and P = 0.19 for treatment failure).
Efficacy of Carbosylane in dyspepsia

A significant difference favoring Carbosylane® (P < 0.03) in the Carbosylane® group (Fig. 5). Also, symptom improvement persisted from day 90 to day 150 for abdominal fullness, bloating and sensation of slow digestion, with a significant difference favoring Carbosylane® (P < 0.05).

Tolerability

During the trial, 70 patients (54%), including 36 (54%) in the Carbosylane® group, reported 150 undesirable events (Table 2). These adverse events were, in the order of decreasing incidence: pharyngitis (n = 12; eight [10%] in the Carbosylane® group and four [5.6%] in the placebo group); bronchitis (n = 9; seven [9%] in the Carbosylane® group and two [3%] in the placebo group); and cystitis (n = 9; six [7.6%] in the Carbosylane® group and three [4%] in the placebo group). The differences were not significant and none of these events were considered to be related to the treatment under study.

Discussion

The results of this randomized placebo-controlled trial demonstrate a favorable action of Carbosylane® taken daily for a period of 3 months for the treatment of dyspeptic syndrome managed by a general practitioner. Significant symptom relief was noted for the three key symptoms characteristic of the syndrome. Improvement in overall complaints was not demonstrated unless an improvement of at least two points in the symptom intensity score was seen.

In the present study, the inclusion criteria were defined pragmatically to take into consideration the routine practices used by general practitioners in managing patients with dyspeptic syndrome. The participating patients had all reported recent symptom onset (7 months on average) and were consulting for symptoms that had persisted for at least 8 days. Although, theoretically, the diagnosis of functional dyspeptic syndrome is a diagnosis of exclusion, requiring upper gastrointestinal endoscopy to rule out other causes [12], the recent onset of symptoms and the characteristics of the population (18—49 years) authorized the pragmatic attitude used in the present study, reflecting the daily practices of general practitioners [3,11]. Furthermore, patients with dyspeptic syndrome who required complementary tests were not included, which should have eliminated patients with long-standing or resistant symptoms. Retrospective analysis showed that the symptoms reported by the patients included in the study complied with the Rome III criteria.

The fact that the significant symptom relief observed in the Carbosylane® group (significant improvement in three of the four symptom scores and significantly favorable relative risk of major improvement) was associated with a lack of improvement in overall complaints is, however, difficult to interpret. One explanation might be the inherent subjectivity of global assessments. The small sample size may also be relevant. Designing a study to assess subjective functional symptoms is especially difficult [10]. Assessment scales specifically designed for dyspeptic symptoms such as the Nepean dyspepsia index are probably more sensitive, but also rather complex and difficult to implement in a therapeutic trial conducted in the context of general practice. Prescriptions for complementary tests and new treatments, considered to be markers of patient dissatisfaction, were thus noted to obtain a set of objective data. The fact that general practitioners in France prescribe few complementary tests in young patients with recent dyspeptic symptoms [3] did not allow demonstration of any significant differences. Nevertheless, the results of the present study suggest that effective symptomatic treatment of dyspepsia can avoid costly investigations and multiple therapeutic prescriptions. The medico-economic impact of this strategy should be evaluated in the context of the French healthcare system.

Recent classifications have identified two subgroups within the dyspeptic syndrome population: pseudoulcerative syndromes, during which abdominal pain predominates; and motor syndromes [12]. This distinction is not based on any precise pathophysiological considerations and was not taken into account in this study.

In the absence of specific treatment for an identified pathophysiological target, first-line symptomatic treatment can be recommended [2,11]. If patients with associated signs of gastroesophageal reflux are carefully excluded, then antisecretory, anti-H2 or PPI can provide relief for, at best, 10—20% of patients [4]. Use of prokinetic agents such as domperidone, cisapride, metoclopramide or erythromycin are warranted on the basis of a pathophysiological rationale.

Table 2 Adverse effects.

<table>
<thead>
<tr>
<th>Field</th>
<th>Carbosylane® (67 patients)</th>
<th>Placebo (71 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>ENT/stomatological</td>
<td>18</td>
<td>26.9</td>
</tr>
<tr>
<td>Pain in general</td>
<td>16</td>
<td>23.9</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>13</td>
<td>19.4</td>
</tr>
<tr>
<td>Gastrointestinal, biliary</td>
<td>12</td>
<td>17.9</td>
</tr>
<tr>
<td>Lung</td>
<td>10</td>
<td>14.9</td>
</tr>
<tr>
<td>Urogenital</td>
<td>7</td>
<td>10.4</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>Neurological/psychiatric</td>
<td>1</td>
<td>0.25</td>
</tr>
</tbody>
</table>
However, this therapeutic option has proven disappointing [4]. Itopride, a D2-dopamine antagonist with cholinergic properties, has shown efficacy in a phase-II trial but was not confirmed in two later, phase-III trials [13], thus illustrating the difficulties inherent in the development of new compounds.

The results of the present study confirm those of a controlled-trial comparing simethicone and cisapride with placebo in which simethicone was significantly more active than placebo, with a slight advantage compared with cisapride [8]. However, the mechanism of action of simethicone remains unclear. This agent, which is not absorbed, reduces air production in the gastrointestinal tract [14] and may favor clearance of gastrointestinal air [8] and also has an antibacterial effect on *H. pylori* [15]. Its association with activated charcoal may favor the elimination of gastrointestinal air which probably plays an important role in the generation of functional symptoms [7].

In conclusion, the results of this double-blind, placebo-controlled study confirm the favorable effects of the combination of activated charcoal with simethicone (Carbosylane®) for patients with recent dyspeptic disorders managed by a general practitioner. The improvements achieved with this simple first-line treatment may even bring about a reduction in the need for costly investigations that are also unpleasant for the patient.

Conflicts of Interest

Michel Lecuyer was the study coordinator. Thierry Cousin and Marie-Noëlle Monnot are employed by the clinical research department of Grimberg laboratories. Benoit Coffin was in charge of rereading the French manuscript.

References
