Effect of an oral bulking agent and a rectal laxative administered alone or in combination for the treatment of constipation

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SUMMARY

Objectives — The aim of the present study was to search for a synergetic action between psyllium and a defecation-inducing drug, Eductyl®, for symptom relief in patients suffering from chronic constipation.

Methods — Twenty healthy volunteers and 20 patients complaining of chronic constipation were included in a randomized crossover study. The study was divided into four 2-weeks periods: pre-inclusion and three periods of treatment with psyllium, Eductyl®, and Eductyl® + psyllium respectively. Colonic transit time was determined at the end of each period of treatment. During each of the four periods, a self-administered questionnaire was used to assess symptoms of constipation.

Results — For constipated patients, treatment with Eductyl® and Eductyl®-psyllium improved clinical symptoms of constipation: increased stool frequency, resulted in fewer hard stools and less sensation of incomplete evacuation and less straining to defecate. The improvement was associated with a decrease in total and segmental colonic transit time. The Eductyl®-psyllium combination did not exhibit any synergetic effect.

Conclusion — Treatment with Eductyl® alone is more efficient than with psyllium alone in providing symptom relief. Combination with psyllium is not synergetic.

The full text of this article is available in english, free of charge, on the web on: www.e2medcom/gcb.

RÉSUMÉ

Effets isolés et combinés d'un laxatif de lest et d'un laxatif par voie rectale dans le traitement de la constipation

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(Gastroenterol Clin Biol 2004;28:438-443)

Objectifs — Le but de cette étude était de rechercher si un laxatif de lest (psyllium) et un médicament favorisant l'exonération (Eductyl®) avaient une action synergique dans le traitement de la constipation.

Méthodes — Vingt sujets témoins et 20 malades souffrant de constipation chronique ont été inclus dans une étude randomisée, contrôlée, en cross-over. L'étude s'est déroulée en 4 périodes successives de 2 semaines chacune : pré-inclusion, puis traitement par les 3 traitements suivants : psyllium, Eductyl®, et Eductyl®-psyllium. Une mesure du temps de transit colique était réalisée en fin de chaque période thérapeutique. Durant chacune des 4 périodes du test, un auto-questionnaire était rempli quotidiennement pour évaluer la variation des paramètres utilisés pour le diagnostic de constipation.

Résultats — Sous traitement par Eductyl® ou Eductyl®-psyllium, une amélioration clinique évaluée par l'augmentation de la fréquence des selles, la diminution du pourcentage de selles dures, de la sensation d'évacuation incomplète et de la nécessité de pousser fortement lors de l'exonération était observée chez les malades constipés. Cette amélioration était associée à une diminution du temps de transit colique total et segmentaire. Le psyllium ne modifiait pas significativement ces paramètres. L'effet des 2 produits n'était pas synergique.

Conclusions — Le traitement par Eductyl® est plus efficace que le traitement par psyllium seul. Il n'y a pas d'effet synergique des 2 produits.

First-line treatment for patients complaining of chronic constipation may involve the use of osmotic laxatives, lubricating agents, dietary fiber, bulk-forming agents or rectal evacuants. The choice depends on whether the clinical context is suggestive of slow transit [1-3] or evacuation disorders [4, 5].

Psyllium is one of the most widely used bulking agents world wide [6]. This drug increases the frequency and weight of stools, softens hard stools, and reduces pain at defecation [7]. A recent study demonstrated its superior effect compared with sodium docusate [8].

Laxatives administered as rectal suppositories trigger the evacuation reflex by contact irritation (bile, glycerol, etc.) or by releasing gas (sodium bicarbonate in Eductyl®). Eductyl®, which has been used in France since 1951, has an original mode of action: in a moist medium the suppository releases carbonic gas into the rectal ampulla stimulating the evacuation reflex by increasing intra-rectal pressure. Used in combination with other types of laxatives, this drug can be proposed for patients with clinical symptoms suggestive of slow transit or evacuation disorders.

The purpose of this work was to evaluate the efficacy of a bulking agent (psyllium) and a rectal evacuant (Eductyl®), administered alone or in combination, for the treatment of chronic constipation. Treatment effect was assessed on the basis of clinical improvement and colonic transit time.

Material and methods

Patients

This study included 20 healthy volunteers (14 men, 6 women, mean age 31 ± 8.6 years, range 20-52) recruited by advertisement and 20
patients (4 men, 16 women, mean age 50.7 ± 14.9 years, range 19-65) consulting for constipation (Centre Hospitalier Necker Enfants Malades, Paris, France). The study protocol was approved by the local ethics committee (CCPRPB Saint Germain-en-Laye, France).

The healthy volunteers were disease free. History taking during the pre-inclusion period disclosed normal stool frequency: < 3 stools per day and > 3 stools per week [9]. Use of any medication during the study, except for oral contraceptives, was an exclusion criterion.

The patients were referred to the Laennec Hospital Gastrointestinal Physiology Laboratory for management of chronic constipation as defined by the Rome II criteria [10]. In accordance with these criteria, all patients presented, during the pre-inclusion period, at least two of the following signs for a period of at least three months during the preceding year: decreased stool frequency (less than 3 stools per week), hard or very hard stools at least 25% of the time, sensation of anorectal blockage at least 25% of the time, sensation of anorectal blockage at least 25% of the time, use of digital maneuvers to facilitate evacuation at least 25% of the time.

Prior to inclusion, anorectal manometry was performed to rule out Hirschsprung disease (presence of rectoanal reflex) and colonic transit time was measured in all patients.

**Study design**

This was a direct-patient-benefit randomized comparative open crossover study conducted in a single center. The study included four 14-day periods: a pre-inclusion period and three treatment periods (Figure 1). Each patient was given three different treatment regimens, assigned at random, one for each of the three treatment periods. The three regimens were commercial products (Techpharma, Monaco): psyllium (3.6 g t.i.d.), Eductyl® (1 suppository in the morning), and psyllium (3.6 g t.i.d.) plus Eductyl® (1 suppository in the morning). Patients were instructed to make no changes in their ordinary diet during the eight weeks of the study and to keep a diary card, presented as a self-administered questionnaire with items to record compliance with treatment and stool habits.

Colonic transit time was measured at the end of each period of treatment.

**Study parameters**

Compliance with treatment was assessed from the data recorded in the diary. Stool habits and total and segmentary colonic transit time were the assessment variables.

**STOOL HABITS**

Stool habits were assessed from data recorded in daily diary cards. The questionnaire items were: number of stools, stool consistency (very hard, hard, normal, soft, liquid, scored 1 to 5 respectively), straining (minimal, normal, severe, scored 1 to 3 respectively), sensation of incomplete evacuation (yes or no, scored 1 and 2, respectively).

**Fig. 1 - Study design**

The study was divided into four 2-week periods. During each period, the subject, control or constipated patient, filled in a self-administered questionnaire to evaluate constipation. At the end of each treatment period, colonic transit time was measured. Représentation synthétique du protocole utilisé. L’étude a été divisée en 4 phases de 2 semaines chacune au cours desquelles le sujet, témoin ou constipé, remplissait un auto questionnaire d’évaluation de la constipation. A la fin de chaque période de traitement, une mesure du temps de transit colique était réalisée. ASP : radiographie sans préparation de l’abdomen.

**Results**

**Data collected at inclusion**

The control subjects (healthy volunteers) were younger (P < 0.001) and predominantly male (P < 0.001) compared with the constipated patients. Control subjects weighed more than the patients (72.5 ± 16.1 kg vs 58.9 ± 1.3 kg, P = 0.004) however neither height (171.9 ± 9.3 cm vs 169.3 ± 6.8 cm) nor heart rate were significantly different between the two groups (71.8 ± 0.9 ± 70.4 ± 2.9 bpm).

Manometric data recorded at inclusion for the patients are presented in Table I. Total colonic transit time was 104 ± 23 hr. Segmentary transit times were 36 ± 11, 45 ± 15, and 23 ± 14 hr for the ascending, descending and terminal colon respectively. Among the 20 patients, total transit time was less than 65 hours in two; transit time was predominantly long in the ascending colon in seven patients, in the descending colon in eight and in the terminal small bowel in three.

The main results for controls and patients are given in Tables II and III respectively.

At inclusion, constipated patients reported significantly fewer stools (P < 0.01), harder stools (P < 0.01), and more straining (P < 0.01) compared with the controls as well as more frequent sensation of incomplete evacuation (P < 0.01) (Tables II and III).

**Tolerance**

All patients complied perfectly with the three treatments. There were no side effects.
Table I. – Results of manometric exploration in patients with constipation at inclusion.

Résultats des exploration manométrique des malades constipés à l’inclusion.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± standard deviation; 3 patients with anismus.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal anal pressure (mm Hg)</td>
<td>42 ± 6</td>
</tr>
<tr>
<td>Marginal pressure (mm Hg)</td>
<td>52 ± 9</td>
</tr>
<tr>
<td>Maximal pressure at contraction (mm Hg)</td>
<td>70 ± 12</td>
</tr>
<tr>
<td>Threshold volume for sensation (mL)</td>
<td>62 ± 10</td>
</tr>
<tr>
<td>Volume of persistent sensation (mL)</td>
<td>92 ± 12</td>
</tr>
<tr>
<td>Maximal tolerable volume (mL)</td>
<td>129 ± 14</td>
</tr>
</tbody>
</table>

Changes in clinical symptoms (tables II and III)

CONSTIPATED PATIENTS VERSUS CONTROLS

Treatments were tolerated better by constipated patients than controls as assessed by the subjects themselves (F = 13.24, P < 0.01) and the physician (F = 4.04, P < 0.05).

TREATMENT EFFECT

The three treatments were tolerated similarly as assessed by the subjects themselves (F = 0.36, P < 0.68) and the physician (F = 0.13, P = 0.88).

Table II. – Treatment results in control subjects.

Résultats des traitements dans le groupe témoin.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Eductyl®</th>
<th>Psyllium</th>
<th>Eductyl®-Psyllium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic transit time, hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending colon</td>
<td>8.4 ± 5.7</td>
<td>9.7 ± 8.4</td>
<td>11.2 ± 10.0</td>
<td></td>
</tr>
<tr>
<td>Descending colon</td>
<td>8.3 ± 12.6</td>
<td>6.1 ± 5.7</td>
<td>8.9 ± 11.1</td>
<td></td>
</tr>
<tr>
<td>Rectosigmoid</td>
<td>6.4 ± 8.6</td>
<td>7.6 ± 8.5</td>
<td>8.8 ± 12.0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23.1 ± 14.9</td>
<td>22.9 ± 14.5</td>
<td>28.9 ± 22.8</td>
<td></td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of stools per week</td>
<td>6.3 ± 1.0</td>
<td>6.7 ± 0.7</td>
<td>6.7 ± 0.8</td>
<td>6.7 ± 0.8</td>
</tr>
<tr>
<td>Hard stools %</td>
<td>13.1 ± 10.4</td>
<td>5.8 ± 12.4</td>
<td>8.9 ± 10.7</td>
<td>6.0 ± 11.7</td>
</tr>
<tr>
<td>Sensation of incomplete evacuation %</td>
<td>20.2 ± 25.6</td>
<td>27.1 ± 34.2</td>
<td>27.4 ± 27.8</td>
<td>26.8 ± 30.0</td>
</tr>
<tr>
<td>Straining during defecation %</td>
<td>9.7 ± 8.4</td>
<td>5.3 ± 8.6</td>
<td>13.5 ± 23.6</td>
<td>4.7 ± 11.1</td>
</tr>
<tr>
<td>Efficacy assessed by</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>3.5 ± 0.5</td>
<td>3.5 ± 0.6</td>
<td>3.2 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Subject</td>
<td>3.5 ± 0.6</td>
<td>2.8 ± 0.9</td>
<td>2.9 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Tolerance assessed by</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>3.5 ± 0.5</td>
<td>3.5 ± 0.5</td>
<td>3.3 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Subject</td>
<td>3.3 ± 0.6</td>
<td>3.5 ± 0.5</td>
<td>3.2 ± 0.6</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± standard deviation.
Table III — Treatment results in patients with constipation.

Résultats dans le groupe des malades avec constipation.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Eductyl®</th>
<th>Psyllium</th>
<th>Eductyl®-Psyllium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic transit time, hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending colon</td>
<td>36.1 ± 11.1</td>
<td>24.9 ± 21.8</td>
<td>26.6 ± 18.7</td>
<td>21.5 ± 19.5</td>
</tr>
<tr>
<td>Descending colon</td>
<td>44.9 ± 14.9</td>
<td>25 ± 20.3</td>
<td>33 ± 20.6</td>
<td>29.5 ± 22.5</td>
</tr>
<tr>
<td>Rectosigmoid</td>
<td>23.2 ± 13.9</td>
<td>9.5 ± 14.3</td>
<td>12.4 ± 10.6</td>
<td>10.9 ± 11.9</td>
</tr>
<tr>
<td>Total</td>
<td>104.2 ± 23.0</td>
<td>59.4 ± 39.5</td>
<td>72 ± 33.1</td>
<td>61.8 ± 40.6</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of stools per week</td>
<td>2.7 ± 1.6</td>
<td>4.1 ± 2.0</td>
<td>3.3 ± 1.9</td>
<td>4.1 ± 2.4</td>
</tr>
<tr>
<td>Hard stools %</td>
<td>87.2 ± 18.7</td>
<td>52.5 ± 40.8</td>
<td>68.9 ± 36.7</td>
<td>46.9 ± 42.5</td>
</tr>
<tr>
<td>Sensation of incomplete evacuation %</td>
<td>91.8 ± 20.1</td>
<td>48.2 ± 38.5</td>
<td>80.5 ± 31.2</td>
<td>47.7 ± 34.6</td>
</tr>
<tr>
<td>Straining during defecation %</td>
<td>75.7 ± 31.9</td>
<td>48.2 ± 42.1</td>
<td>64.0 ± 39.6</td>
<td>46.4 ± 38.9</td>
</tr>
</tbody>
</table>

Tolerance assessed by

<table>
<thead>
<tr>
<th>Physician</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7 ± 0.9</td>
<td>2.4 ± 0.9</td>
</tr>
<tr>
<td>2.6 ± 0.9</td>
<td>2.4 ± 0.8</td>
</tr>
<tr>
<td>3.7 ± 0.5</td>
<td>3.7 ± 0.5</td>
</tr>
</tbody>
</table>

Mean ± standard deviation.

Segmentary colonic transit time decreased in the ascending colon during treatment with Eductyl® alone (t = -2.04, P < 0.05) and with Eductyl®-psyllium (t = -2.91, P < 0.01) but not with psyllium (t = -1.95).

**CONSTIPATED PATIENTS VERSUS CONTROLS**

Total transit time and segmentary transit time in the ascending colon and in the descending colon were longer in constipated patients than in controls (F = 52.77, P < 0.01; F = 49.27, P < 0.01; F = 26.93, P < 0.01, respectively) but no difference between groups was found for the rectosigmoid colon (F = 2.60, P = 0.11).

**TREATMENT EFFECT**

Treatment effect was not significant for total transit time (F = 0.47, P = 0.62) or segmentary transit times (F = 0.17, P = 0.85; F = 0.37, P = 0.69; F = 0.38, P < 0.68 for the ascending, descending, and terminal colons, respectively).

**Patient and physician subjective assessment of treatment efficacy**

**CONSTIPATED PATIENTS VERSUS CONTROLS**

When assessed by patients and control subjects, treatment efficacy was pronounced for the patient group (3.03 vs 2.60; F = 9.01, P = 0.01). The same finding was recorded by the physician (3.37 vs 2.57; F = 36.24, P = 0.01).

**TREATMENT EFFECT**

When assessed by patients and control subjects, efficacy was different for the three treatments (F = 3.29, P = 0.04); psyllium alone was considered to be less effective than Eductyl® alone (2.58 ± 0.87 vs 3.03 ± 0.86, P = 0.02) or the Eductyl®-psyllium combination (2.85 ± 0.74 vs 3.03 ± 0.86, P = NS). The physician considered the three treatments to have similar efficacy (F = 0.68, P = 0.51).

**Discussion**

This study has demonstrated that: 1) clinical symptoms of constipation improved (more frequent stools, fewer hard stools, less sensation of incomplete evacuation and less straining during defecation) and total colonic transit time shortened in constipated patients given Eductyl®; 2) Eductyl® alone was more effective than psyllium alone, increasing weekly stool frequency and reducing sensation of incomplete evacuation; 3) the Eductyl®-psyllium combination was not more effective than Eductyl® alone; and 4) psyllium alone did not lead to any significant improvement in clinical symptoms of constipation.

Psyllium grain particles (Plantago Ovata Forsk) are food fibers containing a highly hydrophilic mucilage which has the property of forming a viscid gel. This property favors normal intestinal function (bulking effect) leading to increased stool volume [7, 8, 12] and water content [13-16]. In addition, it has a cholesterol lowering effect [17] and reduces post-prandial hyperglycemia [18-20]. As demonstrated in earlier studies, psyllium increases stool frequency and weight and decreases stool consistency in constipated patients [7, 21-23]. These effects are not associated with significant changes in colorectal motility [7]. The clinical parameters studied here were not found to be significantly affected by treatment with psyllium although there was a significant decrease in transit time.

Eductyl® is a drug administered in suppository form which triggers the evacuation reflex. After rectal administration of the suppository, the constituents (sodium bicarbonate and potassium tartrate) release approximately 100 mL carbonic gas. The induced distension of the rectal ampulla reproduces the physiological mechanism triggering the defecation reflex: inhibition of the smooth sphincter and contraction of the rectal ampulla to evacuate the stool.

The control population exhibited some differences compared with the study population which included more women and was older. This type of recruitment bias can be important in pathophysiology studies due to the prevalence of static pelvic...
disorders in older women [24]. In our study however, each subject was his/her own control. The study protocol was designed without a washout period. With our method for measuring transit time, even after the correction we used to take into account the time frame considered [25], potential retention of the markers two weeks after ingestion can be ruled out. This methodological limitation is nevertheless of importance when comparing to other studies [26].

The Rome II criteria are designed, in our opinion, to distinguish “painful constipation”, also called “irritable bowel syndrome with predominant constipation”, from functional constipation [10] and pelvic dysynergism [27]. This clinical classification does not however have any objective or pathophysiologically basis. In the present study, the clinical inclusion criterion was functional constipation as defined by the Rome II criteria, a definition which clearly includes potentially different pathogenic mechanisms. The objective of our work was to compare the efficiency of three regimens for the treatment of functional constipation with predominant constipation. In this context, the Eductyl®-psyllium combination is a reasonable choice. Furthermore, psyllium stimulates colonic motility by increasing the volume of the fecal bolus, colonic stimulation resulting from distension of the colon [28, 29]. Eductyl® facilitates evacuation of the distal bowel by triggering the defecation reflex. The results of our study demonstrate that these two drugs do not have a synergetic effect but rather that terminal evacuation is the main factor related to symptom improvement in constipated patients.

Classically progression constipation due to slow transit (slow-transit constipation) is distinguished from constipation due to evacuation difficulties. The efficacy of Eductyl® is logical for patients with evacuation abnormalities. Its effect on colonic transit could be related to elimination of fecal stasis. The physiological mechanism underlying the efficacy of Eductyl® in the treatment of so-called slow-transit constipation remains however a subject of debate. Since the entire gut exhibits defective functional motility in patients with slow-transit constipation [30, 31], the efficacy of Eductyl® might be explained by better evacuation of the distal colon. Furthermore, the difference in the efficacy of the three treatments tested was more pronounced in terms of symptom relief than in terms of colonic transit time. This improvement demonstrates the importance of rectal mechanisms both for motor-related and sensory-related constipation [32]. This result is in line with the work published by the group from St Mark’s Hospital [33] who demonstrated the efficacy of biofeedback, irrespective of the type of constipation, i.e. slower transit time or by perineal dysynergism.

Our findings also confirm earlier physiological work [34]: continence involves both colonic function and evacuation function. Our data demonstrate the discordance between clinical symptoms (clear improvement with Eductyl®) and measurements of colonic transit time. This discordance has already been underlined in an effort to explain the limitations of transit time measurements for studying constipation [12]. In this study, the discordance could however be explained by the short duration of evaluation; extension of investigations to a a longer study (6 months to 1 year) would be useful for confirmation.

From a therapeutic point of view, the observed action of Eductyl® alone on segmentary transit times is noteworthy suggesting further evaluation of this type of treatment in patients with either slow-transit or distal constipation would be useful.

**Conclusion**

This single-center study conducted to assess the effect of psyllium, Eductyl® and the psyllium-Eductyl® combination in constipation demonstrates that in the populations of healthy volunteers and constipated patients studied, treatment with Eductyl® alone is more effective than treatment with psyllium alone and that the Eductyl®-psyllium combination is not more effective than Eductyl® alone. Finally, for clinical practice, it can be concluded that addition of a bulking agent is not useful in patients treated with Eductyl®.

**REFERENCES**


