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Psyllium is superior to docusate sodium for treatment of chronic constipation

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SUMMARY

Background: Stool softening is a physician's first step in the management of chronic constipation.
Aim: To compare stool softening (stool water content) and laxative efficacy of psyllium hydrophilic mucilloid vs. docusate sodium.
Methods: The multi-site, randomized, double-blind, parallel-design study of 170 subjects with chronic idiopathic constipation involved a 2-week baseline (placebo) phase followed by 2 weeks of treatment. The treatment phase compared psyllium (5.1 g b.d.) plus docusate placebo to docusate sodium (100 mg b.d.) plus psyllium placebo. Stools were collected and assessed.
Results: Compared to baseline, psyllium increased stool water content vs. docusate (psyllium 2.33% vs. docusate 0.01%, $P = 0.007$). Psyllium also increased stool water weight (psyllium 84.0 g/BM; docusate 71.4 g/BM; $P = 0.04$), total stool output (psyllium 359.9 g/week; docusate 271.9 g/week; $P = 0.005$), and O'Brien rank-type score combining objective measures of constipation (psyllium 475.1; docusate 403.9; $P = 0.002$). Bowel movement (BM) frequency was significantly greater for psyllium (3.5 BM/week) vs. docusate (2.9 BM/week) in treatment week 2 ($P = 0.02$), with no significant difference ($P > 0.05$) between treatment groups in treatment week 1 (3.3 vs. 3.1 BM/week).
Conclusion: Psyllium is superior to docusate sodium for softening stools by increasing stool water content, and has greater overall laxative efficacy in subjects with chronic idiopathic constipation.

INTRODUCTION

Chronic idiopathic constipation is common in the general population, especially in women and the elderly.[1] Constipation is the most common gastrointestinal complaint in the US, resulting in 2.5 million physician visits every year, and hard stool is a complaint often associated with constipation.[2] This suggests that a significant stool softening effect would provide a major benefit in the treatment of chronic idiopathic constipation. The present study was conducted to compare the stool softening (stool water content) and laxative efficacy of psyllium vs. docusate sodium in subjects with chronic idiopathic constipation using objective and subjective measures associated with constipation.

Psyllium husk (psyllium) consists of the ground husk of the psyllium seed (*Plantago ovata*), a mixture of polysaccharides comprised of pentoses, hexoses and uronic acids. Psyllium is a predominantly soluble fibre in the same class of materials as other natural seed gums and plant exudates used in foods and pharmaceutical products, and is marketed as a bulk fibre laxative. Numerous clinical studies have evaluated the effect of psyllium on laxation in subjects with constipation.[3–12]

Dioctyl sodium sulphosuccinate (docusate sodium) is a synthetic anionic detergent that is marketed as a stool softener laxative.[13] Its mechanism of action is attributed to a decrease in surface tension, allowing penetration of water and fat into the faeces. Literature documenting controlled clinical trials of docusate sodium is

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limited.[14–17] These studies show that, compared to placebo, docusate sodium and docusate calcium had no significant effect on: stool weight, stool frequency, stool water content or mean transit time. The present study tested the hypothesis, derived from the published literature, that psyllium is more effective than docusate sodium as a stool softener laxative.

METHODS

This was a multi-site, double-blind, parallel-design study of 170 subjects with chronic idiopathic constipation. A 2-week baseline placebo phase preceded a 2-week treatment phase. Subjects were randomized into one of two treatment groups: psyllium (5.1 g b.d. + docusate placebo; 88 subjects), and docusate sodium (100 mg b.d. + psyllium placebo; 82 subjects). The primary inclusion criterion was a bowel movement (BM) frequency of < 3/week during the baseline week just prior to treatment. Subjects with more frequent small, hard stools were also included in the study by a designation of 'non-productive' vs. 'productive' stools. Clinical site study personnel evaluated stool samples for size and number as compared to a glass marble (2 cm in diameter) model. Bowel movements containing ≤ 4 stool pieces, each piece being less than or equal to the size of the marble model were designated 'non-productive' BMs. Only 'productive' BMs were counted for the ≤ 3 BMs per week for inclusion in this study. Subjects with obstructive or metabolic aetiology for constipation, and subjects with a history of regular stimulant laxative use (>1 dose/week) or laxative abuse (greater than daily dosage recommended on the label for any laxative) were not admitted to the study.

Psyllium (Smooth Texture Sugar-Free Orange-Flavored Metamucil, The Procter & Gamble Co.) and docusate sodium (Colace, Apothecon) were dosed at their maximum recommended daily doses according to their product labels. The docusate sodium was overcapped for blinding purposes in '00' Red hard gelatin capsules and backfilled using maltodextrin. The placebo for the 2-week baseline phase of the study consisted of both psyllium-free excipients of Smooth Texture Sugar-Free Citrus-Flavored Metamucil and maltodextrin-filled capsules. The placebos for the treatment phase consisted of both psyllium-free excipients of Smooth Texture Sugar-Free Orange-Flavored Metamucil and maltodextrin-filled capsules.

Objective measures included BM frequency, stool weight, total stool output, dry stool weight, stool water weight, percentage water, and a rank variable for objective measures. Subjective measures included patient ratings (7-point scales) of stool consistency (very soft to very hard), straining during BM (none to extreme), pain during BM (none to extreme), completeness of evacuation (complete to incomplete), and overall feeling of constipation. Additionally, a rank variable score including the first three subjective measures, and a rank variable score including all subjective measures were calculated. Safety evaluations included a physical examination on admission to the study and a brief physical examination at completion of the study. Since docusate is systemically absorbed and its safety in pregnancy has not been established,[18, 19] a urine pregnancy test for all females of childbearing potential was performed on admission to the study, and pregnant or nursing females were excluded. Women of childbearing potential were required to use effective birth control during the study. Subjects were counselled at the initial visit not to change their usual diet and physical activity throughout the course of the study.

This study was double-blind with precautions taken to minimize bias on the part of the subjects, analysts, study personnel and investigators regarding test articles, packaging and breaking the blind. The test articles used during the treatment phase were formulated to be as similar in taste, appearance and texture as possible. The psyllium, docusate sodium and placebos were supplied in kits containing 18 individual packets of psyllium or placebo and one bottle containing 18 capsules of docusate sodium or placebo. Subjects were instructed to take the contents of one packet stirred in 8 oz of cool water, and one capsule twice a day immediately prior to breakfast and dinner. Subjects were also instructed to take the capsule from the study medication bottle while drinking the packet contents. The first dose of test article for each visit was taken in the presence of site personnel. Subjects non-compliant with test article administration during baseline or treatment phases as evidenced by taking < 75% of either of the test articles during a 1-week period throughout the course of the study were excluded from the evaluable patient data analysis.

Stools were collected for the latter 3 weeks of the study. Stools were frozen in the supplied container filled with dry ice, then returned to the investigator within 48 h during weekdays and within 72 h on weekends and holidays. The stool diary, which was filled out and returned with the stool samples, was used to provide a stool accounting system and to obtain subjective

measures of efficacy. For each BM, evaluations were made for stool weight and dry stool weight (following freeze-drying; Hill Top Research, Inc., West Palm Beach, FL). The study was approved by Institutional Review Boards, and was conducted in accordance with Good Clinical Practices. All subjects signed an informed consent approved by Institutional Review Boards.

An analysis of covariance (ANCOVA) was performed on each of the efficacy variables. The responses were computed as the averages of the weekly measurements for treatment weeks 1 and 2, except for the variables 'BM frequency' and 'total stool output', which were calculated as weekly totals. The covariates were defined as the averages of the baseline measurements during the placebo week, except for the variables 'BM frequency' and 'total stool output', which were calculated as weekly totals. The O'Brien rank variable[20] of the objective measures was calculated as the sum of the ranks associated with BM frequency, stool weight, dry stool weight, stool water weight and percentage water (Rank 1). There were two O'Brien rank variables performed on the subjective measures. One was based on all subjective efficacy measures (Rank 2), and the other was based on consistency of stool, straining during BM, and pain during BM (Rank 3). The statistical tests were one-sided (psyllium superior to docusate sodium) and were performed with a Type I error rate of 5%. To allow for bowel transit of both treatments, stools collected on days 1 and 2 of the treatment period were not included in the analysis. The remaining 12 days were divided equally into two 6-day periods and designated treatment weeks 1 and 2. Treatment least square means were adjusted for baseline (covariate).

RESULTS

Study population

Out of 381 subjects enrolled in the study, 187 subjects were randomized to treatment and were included in the intention-to-treat population. The remaining 194 subjects did not meet entry criteria (e.g. > 3 BMs during baseline) and were dropped from the study. Of those randomized, 170 subjects (91%) were determined evaluable. The subjects ranged in age from 20 to 74 years with a mean (± S.E.M.) of 37.2 ± 0.83 years. Females accounted for 156 (91.8%), while males accounted for 14 (8.2%) of the 170 subjects. Caucasians accounted for 109 (64.1%) of the subjects, while 38 (22.4%) were Black, 15 (8.8%) were Hispanic, and the remaining 8 (4.7%) subjects were Asian, Indian or Other. There was one serious adverse event, a motor vehicle accident, which occurred prior to randomization while the subject was taking placebo.

Table 1. Comparison of stool weight and stool water content for 'productive' vs. 'non-productive' stools

	Stool weight (g)	Stool water content (%)
Productive BM	113.6	71.41
Non-productive BM	30.0	69.85

Twenty-seven per cent of the subjects (24/88 psyllium; 22/82 docusate) were included in the study by the 'non-productive bowel movement' definition. Subjective evaluation of stool size by the study staff, using a 2 cm diameter marble as a model, resulted in an objective difference in mean stool weight and water content of productive vs. non-productive stools (Table 1).

The objective and subjective measures for treatment weeks 1 and 2 are reported in Tables 2 to 5 as least square means (± standard error of the mean). Table 2 shows the objective measures for baseline and treatment week 1 for both treatment groups. Note that, although there was no significant difference for BM frequency between treatment groups at week 1, BM frequency increased compared to baseline for the psyllium treatment group (3.08 vs. 3.26) and decreased compared to baseline for the docusate treatment group. Psyllium was significantly greater compared to docusate for total stool weight (g/week), stool water weight (g/BM), stool water content (%), and the O'Brien rank-order score, a statistical method for combining objective measures.

Table 3 shows values for subjective measures for baseline and treatment week 1. There was no significant difference between treatment groups at week 1 for any of the subjective measures. Stool consistency, straining with BM, pain with BM and evacuation completeness showed directional improvement of symptoms for both treatment groups. Constipation, O'Brien Rank 2 and O'Brien Rank 3 showed directional improvement of symptoms for the psyllium treatment group only.

Table 4 shows the objective measures for baseline and treatment week 2 for both treatment groups. The psyllium treatment group was significantly greater compared to the docusate treatment group for BM frequency (BM/week), stool water content (%), and

Table 2. Objective measures for treatment week 1

Measurement	Psyllium baseline	Psyllium treatment	Docusate sodium baseline	Docusate sodium treatment	One-sided *P*-value
BM frequency (BM/week)	3.08 (± 0.18)	3.26 (± 0.19)	3.44 (± 0.20)	3.07 (± 0.20)	0.247
Stool weight (g/BM)	95.26 (± 7.02)	112.37 (± 6.12)	95.81 (± 7.79)	99.48 (± 7.03)	0.085
Dry stool weight (g/BM)	26.44 (± 1.64)	28.76 (± 1.53)	26.52 (± 1.82)	27.95 (± 1.81)	0.366
Total stool weight (g/week)	260.94 (± 19.28)	359.89 (± 22.88)	282.9 (± 21.41)	271.91 (± 24.50)	0.005
Stool water weight (g/BM)	68.82 (± 5.56)	84.02 (± 4.78)	69.29 (± 6.17)	71.43 (± 5.39)	0.041
Stool water content (%)	70.68 (± 0.66)	73.01 (± 0.52)	71.05 (± 0.73)	71.06 (± 0.60)	0.007
O'Brien Rank 1	442.22 (± 18.50)	475.13 (± 15.92)	473.85 (± 20.54)	403.87 (± 18.22)	0.002

Values for the treatment phase represent least squared means (± S.E.M.). *P*-values are for comparison of treatment values at week 1. Each bowel movement was collected and analysed for objective measures. Stool weight represents a wet-weight. Dry stool weight represents the dry matter remaining after lyophilization. Stool water content is the difference of stool weight minus dry stool weight. The O'Brien rank variable[12] of the objective measures was calculated as the sum of the ranks associated with BM frequency, stool weight, dry stool weight, stool water weight and percentage water (Rank 1).

Table 3. Subjective measures for treatment week 1

Measurement	Psyllium baseline	Psyllium treatment	Docusate sodium baseline	Docusate sodium treatment	One-sided *P*-value
Stool consistency	3.57 (± 0.15)	3.38 (± 0.13)	3.52 (± 0.17)	3.27 (± 0.15)	0.722
Straining with BM	3.51 (± 0.16)	3.00 (± 0.14)	3.30 (± 0.18)	3.24 (± 0.17)	0.147
Pain with BM	2.50 (± 0.15)	2.28 (± 0.12)	2.24 (± 0.17)	2.22 (± 0.15)	0.618
Evacuation completeness	3.43 (± 0.17)	3.03 (± 0.15)	3.32 (± 0.19)	3.14 (± 0.17)	0.319
Constipation	4.06 (± 0.16)	3.78 (± 0.11)	3.96 (± 0.17)	3.99 (± 0.12)	0.106
O'Brien Rank 2	479.91 (± 23.73)	449.08 (± 18.51)	446.2 (± 26.46)	461.48 (± 21.91)	0.333
O'Brien Rank 3	289.98 (± 15.36)	268.65 (± 12.82)	266.46 (± 17.14)	270.68 (± 15.07)	0.459

Subjects completed a diary with subjective scores (7-point scale: 1 = normal/no symptoms; 7 = constipated/extreme symptoms) for each bowel movement. O'Brien Rank 2 is the sum of all five ranked subjective measurements. O'Brien Rank 3 is the sum of ranked measurements: consistency, straining with BM and pain with BM.

O'Brien Rank 1, a statistical method for combining objective measures.

Table 5 shows values for subjective measures for baseline and treatment week 2. Psyllium showed a significant improvement of evacuation completeness compared to docusate, and directional improvement of all other subjective measures compared to docusate.

Figure 1 shows a plot of the daily mean moisture content for each treatment group. Stools were collected from 00.01 hours to 24.00 hours of each calendar day, but dosing for day 1 did not begin until 7–18 h into day 1. Treatment effects were therefore not observed until day 2. Psyllium exhibited a trend towards higher water content in the first days of treatment, showing a

Table 4. Objective measures for treatment week 2

Measurement	Psyllium	Docusate sodium	One-sided *P*-value
BM frequency (BM/week)	3.51 ± 0.22	2.87 ± 0.22	0.021
Stool weight (g/BM)	109.24 ± 6.30	110.44 ± 6.95	0.551
Dry stool weight (g/BM)	26.98 ± 1.74	29.49 ± 1.98	0.828
Total stool weight (g/week)	354.34 ± 24.86	312.44 ± 24.93	0.118
Stool water weight (g/BM)	82.15 ± 4.79	80.61 ± 5.18	0.414
Stool water content (%)	73.89 ± 0.58	71.58 ± 0.62	0.004
O'Brien Rank 1	448.84 ± 15.59	391.19 ± 17.11	0.007

Values represent least squared means ± S.E.M.. Each bowel movement was collected and analysed for objective measures. Stool weight represents a wet-weight. Dry stool weight represents the dry matter remaining after lyophilization. Stool water content is the difference of stool weight minus dry stool weight. The O'Brien rank variable of the objective measures was calculated as the sum of the ranks associated with BM frequency, stool weight, dry stool weight, stool water weight, and percentage water (Rank 1).

Table 5. Subjective measures for treatment week 2

Measurement	Psyllium	Docusate sodium	One-sided *P*-value
Stool consistency	3.08 ± 0.14	3.20 ± 0.15	0.289
Straining with BM	2.82 ± 0.15	3.05 ± 0.16	0.153
Pain with BM	2.04 ± 0.13	2.27 ± 0.14	0.116
Evacuation completeness	2.85 ± 0.15	3.23 ± 0.17	0.041
Constipation	3.53 ± 0.11	3.74 ± 0.13	0.109
O'Brien Rank 2	420.18 ± 19.38	456.31 ± 21.61	0.108
O'Brien Rank 3	251.99 ± 13.15	265.49 ± 14.53	0.246

Subjects completed a diary with subjective scores (7-point scale: 1 = normal/no symptoms; 7 = constipated/extreme symptoms) for each bowel movement. O'Brien Rank 2 is the sum of all five ranked subjective measurements. O'Brien Rank 3 is the sum of ranked measurements: consistency, straining with BM and pain with BM.

more rapid onset of stool softening, vs. docusate sodium. The data, however, were not appropriate for statistical analysis on a day-by-day basis because a majority of the subjects did not supply a stool sample on a daily basis.

When viewed as a plot of the least squared means for stool water content over 2 weeks (Figure 2), the psyllium treatment group exhibited an increase in stool water content (stool softening) for both weeks 1 and 2 compared to baseline. When expressed as a linear regression of a 2-week treatment trend, the slope for psyllium is 3.34 times greater than the slope for docusate ($P = 0.008$).

DISCUSSION

The objective of this study was to compare the stool softening and laxative efficacy of psyllium vs. docusate sodium in subjects with chronic idiopathic constipation. The double-blind, randomized, parallel-design study comprised a 1-week washout period, where subjects were not allowed any laxative treatment, and a 1-week baseline followed by a 2-week treatment period where all stools were collected and analysed. The primary focus of a stool softening study is stool water content, which is proportional to stool consistency.[21] The psyllium treatment group showed a significant increase in stool water content in treatment weeks 1 and 2 compared to the docusate treatment group. While this increase in water content may seem relatively small, a pre-clinical study comparing stool water content to mechanical softening of intestinal contents in pigs[21] showed that a 2% increase in water content (71% to 73%) resulted in a 30% reduction in peak force for extrusion, which is proportional to viscosity. Such a

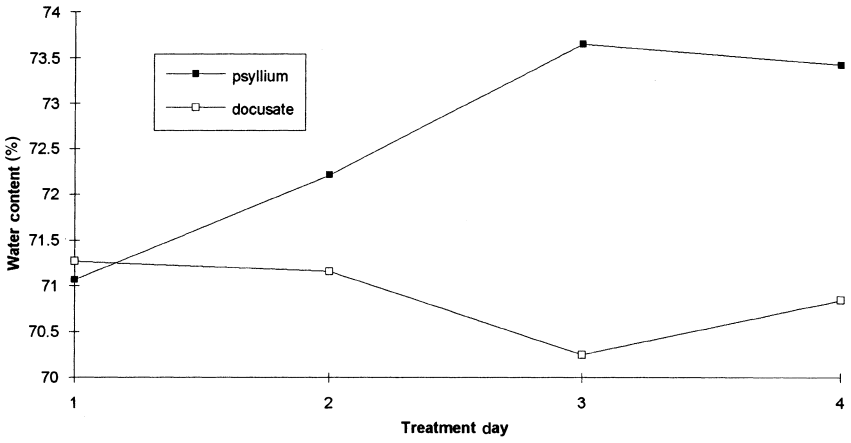

Figure 1. Plot of the daily mean stool water content for psyllium and docusate treatment groups for treatment days 1–4. Day 1 stool collection began at 00.01 hours, while dosing did not begin until 7–18.4 h later (07.00–18.25 hours). The psyllium treatment group produced moister (softer) stools on days 2–4.

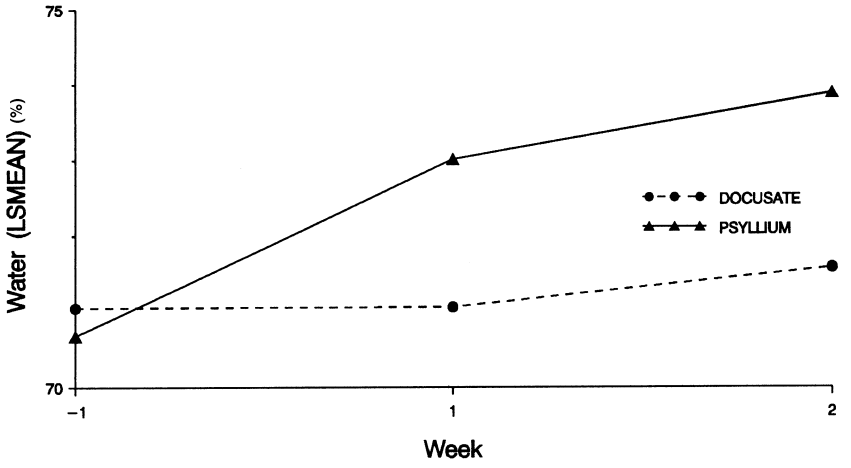

Figure 2. Plot of the least squared means of the stool water content for psyllium and docusate treatment groups for baseline (– 1), and treatment weeks 1 and 2. The psyllium treatment group produced moister (softer) stools throughout the treatment period.

change in water content thus represents a significant stool softening effect, and corroborates data showing that psyllium is superior at softening stool compared to docusate. In contrast to the widely held perception that stool softeners work faster than bulk laxatives, this study showed that psyllium treatment resulted in softer stools for the 3 days after initiation of treatment. Furthermore, the superior stool softening effect of psyllium increased over the 2-week treatment period, suggesting that the effect may increase with continued use.

Clinical investigators and physicians often define constipation as less than 3 stools/week.[22] A more complete definition of constipation includes two or more of the following complaints (in the absence of laxatives) for at least 12 months: straining on >25% of BMs, feeling of incomplete evacuation after >25% of BMs, hard or pellety stools on >25% of BMs, fewer than 3 stools/week, or stools less frequent than 2/week with or without other symptoms of constipation.[22] This study included subjects who experience BMs with few 'hard pellets' in excess of three episodes per week by instructing study personnel to evaluate stool samples for size and number of pellets as compared to a glass marble model. Twenty-seven per cent of subjects in this study were included by the 'non-productive bowel movement' definition. The observed differences in both stool weight and stool water content support the use of a subjective measure of stool size to predict a measurable difference in stool weight and water content.

The O'Brien Rank score[20] is a statistical method of combining all of the objective measures in a single, comprehensive measure of constipation. Using this method, the psyllium treatment group was superior to the docusate treatment group for overall treatment of the objective measures of constipation. It should be noted that docusate is approved for one indication, softening stools. This study demonstrates that psyllium is superior to docusate for stool softening, as measured by percentage water content, as well as the other

objective measures of constipation, suggesting that psyllium is a more comprehensive treatment for the objective measures associated with constipation. The use of a non-systemic bulk fibre may also be preferable from a safety perspective, particularly for women of childbearing potential.

There were no significant differences in subjective measures of constipation between treatment groups in the first week of treatment. Stool consistency, straining with BM, pain with BM and evacuation completeness showed directional improvement of symptoms for both treatment groups. Constipation, O'Brien Rank 2 and O'Brien Rank 3 showed directional improvement of symptoms for the psyllium treatment group only. In the second week of treatment, the psyllium treatment group was significantly better than the docusate treatment group for 'completeness of evacuation' ($P = 0.041$) and directionally better in all subjective scores. While the objective data clearly show that psyllium is superior to docusate for softening stool in the first and second week of treatment, the subjective data suggest that the measures used may not be sensitive enough to detect these significant objective changes.

This study has shown that psyllium is superior to docusate sodium for increasing stool water content in subjects with a history of chronic idiopathic constipation. Psyllium was also superior to docusate for overall improvement of the objective measures of constipation, suggesting that psyllium is a more comprehensive treatment for constipation. This study shows that the superior stool softening effect of psyllium increases over a 2-week treatment period, suggesting that the stool softening effect may be greater with continued use.

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