Moderation of lactulose-induced diarrhea by psyllium: effects on motility and fermentation1,2

Neena Washington, Margaret Harris, Amanda Musselwhite, and Robin C Spiller

ABSTRACT Psyllium has been reported to inhibit lactulose-induced colonic mass movements and to benefit patients with irritable bowel syndrome, improving both constipation and diarrhea. Our aim was to define how psyllium modified the whole-gut transit of a radiolabeled lactulose-containing test meal by using gamma scintigraphy. Eight subjects participated in a randomized crossover study comparing gastric emptying and small bowel and colonic transit after consumption of 20 mL lactulose three times daily with or without 3.5 g psyllium three times daily. Psyllium significantly delayed gastric emptying: the time to 50% emptying increased from a control value of 69 ± 9 to 87 ± 11 min (\(x±SEM\); \(P<0.05, n=8\)). Small bowel transit was unaltered. However, progression through the colon was delayed with an increase in the percentage of the dose at 24 h in the ascending (control group: 2 ± 3%, psyllium group: 11 ± 8%; \(P<0.02\)) and transverse colon (control group: 5 ± 12%, psyllium group: 21 ± 14%) with correspondingly less in the descending colon. Although the time for 50% of the isotope to reach the colon was not significantly different with psyllium, psyllium significantly delayed the rise in breath-hydrogen concentrations, which reached 50% of their peak at 217 ± 34 min compared with control values of 155 ± 27 min (\(P<0.05\)). Psyllium delays gastric emptying, probably by increasing meal viscosity, and reduces the acceleration of colon transit, possibly by delaying the production of gaseous fermentation products. Am J Clin Nutr 1998;67:317–21.

KEY WORDS Gastric emptying, colon transit, lactulose, psyllium, diarrhea, constipation, irritable bowel syndrome, gamma scintigraphy, small bowel

INTRODUCTION Although various plant-based fibers are widely recognized as laxatives, the different mechanisms of action of these substances, which have different physicochemical properties, are poorly understood. Viscosity is an important determinant of gastric emptying (1–3) and small bowel transit (4) and many forms of vegetable fiber produce viscous chyme that alters the small bowel transit of other meal components, which may alter the colonic fermentation of poorly absorbable carbohydrates such as lactulose (5).

Psyllium is the husk from the seeds of Plantago ovata and has a high concentration of mucilage polysaccharides that gel over a wide range of concentrations. It is composed of a highly branched acidic arabinoxylan. Psyllium has been shown to have the paradoxical property of both improving constipation by increasing stool weight (6) and ameliorating chronic diarrhea (7). Being a structural component of the plant, psyllium forms a matrix that resists hydrolysis so that absorption of free arabinose during passage through the stomach and small intestine amounts to <5%. Similarly, psyllium also resists colonic bacterial degradation (8).

Lactulose by contrast is a water-soluble, semisynthetic disaccharide that resists enzymatic hydrolysis in the human small intestine and acts as an osmotic laxative, trapping fluid in the small bowel, accelerating transit (9), and increasing flow through the ileocecal valve (10). Once in the colon, lactulose is rapidly fermented to short-chain fatty acids, hydrogen, carbon dioxide, and methane, lowering cecal pH within 1–2 h (11). The combination of gas, bacterial growth, and acidification accelerates colonic transit and increases stool weight.

Previous studies in Nottingham, United Kingdom, showed that 20 mL lactulose given three times daily provides a useful model of chronic diarrhea characterized by an acceleration of transit through the ascending colon with a pattern of bolus movements suggestive of mass movements (12). These same studies indicated that psyllium inhibited these movements and slowed transit. Possible mechanisms for this effect included delayed mouth-cecum transit of lactulose or alteration in the colonic fermentation of lactulose. The aim of this study was to address these issues by assessing the effect of psyllium on gastric emptying and small bowel transit of a lactulose solution. We also hoped to gain insight into the effect on colonic fermentation by assessing the pattern of breath-hydrogen production over the 16-h study period.

SUBJECTS AND METHODS

Study population Eight healthy volunteers aged 19–23 y participated in the study. All were screened for suitability by use of a medical ques-

1 From the Division of Gastroenterology and Department of Surgery, Queen’s Medical Centre, Nottingham, United Kingdom.
2 Address reprint requests to N Washington, Department of Surgery, E Floor, West Block, Queen’s Medical Centre, Nottingham, NG7 2UH. E-mail: neena.washington@nottingham.ac.uk.
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tionnaire. All female volunteers had a urine pregnancy test on each study day before radioisotope administration. The study was approved by the Nottingham Medical School Ethical Committee and an Administration of Radioactive Substances Advisory Committee license required for the administration of radioisotopes to healthy subjects was obtained from the Department of Health. The trial was carried out in accordance with the Declaration of Helsinki (Hong Kong amendment).

Protocol

The eight subjects were studied with use of a randomized, two-way crossover format. Each study leg consisted of a period of 5 d separated by a washout period of 1 wk. Throughout the whole study volunteers were asked to adhere to a standard 20-g fiber diet and to abstain from eating cathartic foods such as curries or drinking > 40 g alcohol/d.

Before the trial the subjects were asked to provide a fresh stool sample to determine a control pH value. On days 1–3 of each study period, each subject consumed 20 mL lactulose solution (containing 13.4 g lactulose) three times per day before meals. The evening dose was omitted on day 3 to minimize basal breath hydrogen, which was measured during the study. During the psyllium treatment subjects also took 3.5 g psyllium (Fybogel; Reckitt and Colman Products, Kingston-upon-Hull, United Kingdom) in 100 mL water before meals with the lactulose dose.

Subjects fasted from 2000 the evening before study day 4. Subjects cleaned their teeth to reduce the bacterial population in their mouth before control and expiratory breath samples were taken for breath-hydrogen measurements. Breath-hydrogen concentrations were measured with an exhaled hydrogen monitor (GMI Ltd, Renfrew, United Kingdom).

Anatomical radiolabeled markers consisting of < 0.1 MBq 99mTc (a metastable form of the isotope) contained in waterproof tape were taped to the abdomen of each subject. These were used as reference points for the accurate alignment of sequential images. The subjects were then given a test meal containing 200 mL of an isotonic feed (Clinifeed-ISO; Roussel Laboratories, Uxbridge, United Kingdom) containing 1575 kJ energy, 10.5 g protein, 49 g carbohydrate, and 15.4 g fat and radiolabeled with 1 MBq 111In diethylenetriaminepentaacetic acid (DTPA) and 3 MBq 99mTc DTPA, together with 20 mL lactulose with or without 7 g psyllium.

Anterior and posterior images of each subject of 30-s duration were taken immediately after dosing with an IGE Maxicamera II (IGE Ltd, Herts, United Kingdom) fitted with a medium-energy, parallel hole collimator. The subjects cleaned their teeth for a second time and rinsed their mouths with a bactericidal mouthwash (Corsodyl; SmithKline Beecham, Weybridge, United Kingdom) before further breath-hydrogen measurements were made. Scintigraphic images and samples for breath-hydrogen analysis were taken every 15 min until the isotope had reached the colon, after which measurements were made hourly.

Fluid intake was restricted until lunchtime, but thereafter water or decaffeinated tea and coffee with semiskim milk were provided. Lunch consisting of sandwiches, crisps (potato chips), and a choice of fruit (2520 mJ) was provided at 1400. Dinner was provided at 1800 and consisted of prawn cocktail, steak, chips (French fries), vegetables, and a cold sweet (4200 mJ). A midvening snack of biscuits (cookies) was allowed at 2000. Subjects were given 20 mL lactulose with or without 3.5 g psyllium before their evening meal. All subjects were given 20 mL lactulose at 2200 when imaging was finished. On day 5, the subjects took lactulose, and psyllium if appropriate, before both breakfast and lunch and two further scintigraphic images were taken at 0900 and at 1700.

Subjects were asked to note all changes in bowel habit and any adverse effects of the treatment during the trial. The pH of the stool samples produced during the study was measured.

Data analysis

99mTc activity was used to measure gastric emptying, but because of this isotope’s rapid decay (half-life of 6 h), indium was used to measure colon transit. Images were analyzed by creating a region of interest around the stomach and the ascending, transverse, and descending colon (obtained by bisecting the splenic and hepatic flexures). The counts and areas for each region were recorded and the data were then corrected for background radiation and radioactive decay. The geometric mean of the anterior and posterior data was calculated to correct for attenuation and effect of depth. Data were then normalized by calculating the percentage of isotope in each region of interest. All calculations were carried out on a spreadsheet (Microsoft EXCEL; Microsoft, Seattle). The time for 50% of the activity to leave the stomach and the area under the gastric emptying curves were calculated. Measurement of mean transit time through the ascending colon was calculated from the difference between the time when 50% of the activity was counted in or beyond the ascending colon and the time that 50% of the activity was counted beyond the hepatic flexure, the junction between the ascending and transverse colon. The small intestinal transit time was defined as the difference between the time for 50% of the dose to leave the stomach and the time for 50% of the dose to reach the colon. Comparisons were made between treatment groups by a paired *t* test.

Breath-hydrogen concentration was plotted against time after dose for each subject and the time to peak concentration noted. The area under the breath hydrogen versus time curve for the first 8 h after lactulose administration was also calculated.

RESULTS

The study was completed by all eight volunteers and no serious side effects were reported. Most subjects experienced increased flatulence with both lactulose and lactulose plus psyllium. As expected from previous studies, subjects tended to suffer from more frequent and looser bowel movements with lactulose treatment, with the main effect occurring during the first 2 d of dosing (12). Addition of the psyllium to the diet resulted in slight constipation in two subjects. All subjects except one had normal bowel habits on the study day, possibly as a result of adaptation to the lactulose and psyllium, although five subjects reported diarrhea overnight when the evening dose of lactulose was not followed by a meal. Stomach cramps were reported by one subject who was taking lactulose alone and one subject who was taking lactulose and psyllium.

Gamma scintigraphy

Psyllium significantly slowed gastric emptying: the time for 50% of the test meal to empty from the stomach was 87 ± 11 min (x ±
SEM) in subjects treated with lactulose and psyllium compared with 69 ± 7 min in subjects treated with lactulose alone (P = 0.031) (Figure 1). Small intestinal transit time was unchanged by the psyllium (control group: 107 ± 35 min, psyllium group: 97 ± 35 min).

The time for 50% of the isotope to reach the ascending colon was also not significantly altered by the psyllium (control group: 177 ± 36 min, psyllium group: 184 ± 29 min; Figure 1). However, transit through the ascending and transverse sections of the colon was significantly slowed by the psyllium, as shown by the increased percentage of radioisotope in these sections at 24 h (Figure 2, Table 1). The decreased transit rate through the ascending and transverse colon led to a corresponding decrease in the amount of isotope reaching the descending colon by 24 h. There was no significant difference in the total amount of isotope in the whole colon at 24 h with or without the psyllium because the isotope had not reached the rectum by this time.

It was possible to detect mass movements of the ascending colonic contents in image sequences from individual subjects, and the number of movements were counted for each subject. The occurrence of mass movement was recognized when > 20% of the contents of the ascending colon were propelled distally within 1 h. The mean (± SEM) number of such movements was 3.75 ± 0.5 in the control group and 2.5 ± 0.5 in the psyllium-treated group, a significant reduction (P = 0.001).

**Stool pH**

The average stool pH before entry into the study was 6.7 ± 0.7. pH was unchanged over the course of the study by lactulose treatment (6.4 ± 0.2, P = 0.17) or treatment with lactulose and psyllium (6.5 ± 0.6, P = 0.23).

**Breath hydrogen**

The time for 50% of the maximum value for breath hydrogen to be achieved was 155 ± 27 min with lactulose and 217 ± 34 min with psyllium and lactulose and the delay was significant (P = 0.041). Although the peak in mean breath hydrogen occurred 30 min later when psyllium was added to the diet, the area under the breath-hydrogen curve did not change (mass fraction of lactulose only: 223 ± 98 ppm · h; mass fraction of lactulose and psyllium: 217 ± 69 ppm · h; where ppm is parts per million), indicating no overall change in the amount of bacterial fermentation occurring in the colon.

**Discussion**

These studies confirm that there are important interactions between different forms of poorly absorbable carbohydrate. Thus, we showed that the gelling agent psyllium slows the gastric emptying of a lactulose-containing, mixed-nutrient meal and also reduces the effect of lactulose on accelerating transit through the colon.

Gastric emptying is known to be powerfully influenced by meal viscosity, with more viscous meals allowing less deep (13, 14) and hence less effective antral contractions, associated with delayed gastric emptying (15–17). The effect on gastric emptying is greater with liquid meals whose initial viscosity is lowest and hence altered most by the addition of gelling agents (18). Although viscosity is reduced rapidly by dilution by gastric juices (19) and other studies did not show such a marked effect, we observed a significant delay in emptying, particularly in the late phase (20). The difference may be due to the exact meal composition, affecting the manner in which the psyllium acts. The meal used in the current study had a very low viscosity that would be significantly altered by the addition of psyllium. The meal used by MacIntyre et al (19) had a high viscosity and hence the effect of the psyllium would be less. The mechanism by which the psyllium affects gastric emptying is uncertain but may be due to psyllium inducing a degree of malabsorption, particularly of fat, both by reducing convective diffusion (21) and hence absorption (22) and also by inhibiting lipase activity (23). Malabsorbed nutrients that reach the distal small bowel 1–2 h after meal ingestion excite the inhibitory ileal brake mechanism (24, 25) and thus delay the late phase of gastric emptying. A similar effect was noted when amylase inhibitors were added to starch.
meals (26). Alternatively, psyllium may have a greater influence on emptying when the stomach is less full because as the stomach empties, gastric folds form that trap the viscous chyme.

Overall transit through the small bowel was not altered in the present study but subsequent movement through the ascending colon was delayed by psyllium. This agrees with our earlier studies in which psyllium delayed ascending colon transit, possibly by inhibiting the occurrence of mass movements (12). Note that in these previous studies the readily fermentable guar accentuated rather than inhibited the laxative effect of lactulose, suggesting that bacterial fermentation products are the key to these differing effects of poorly absorbed carbohydrates. Anaerobic bacterial fermentation of guar causes a rapid fall in viscosity, with acidification and production of gas, whereas psyllium is more slowly fermented and maintains its viscosity longer (27). Previous authors showed a good correlation between scintigraphic and breath-hydrogen methods for assessing cecal arrival of lactulose (28). The time to 50% of the peak breath-hydrogen concentration indicates the arrival of 50% of the meal into the colon. Comparison of these values with the transit measurements made by use of isotopes (in which 50% arrival time was also used to assess transit) makes it clear that in the presence of psyllium, fermentation lags considerably behind arrival, whereas in the control studies they are comparable. Hence, the change in the rate of breath hydrogen is due to a change in the rate of fermentation and not to a change in arrival time. It is likely that this is because the smaller lactulose molecule becomes trapped and hence protected from fermentation within the complex three-dimensional matrix of psyllium. If the laxative effect of lactulose depends on it stimulating colonic mass movements, then delay of breath hydrogen is due to a change in the rate of fermentation and not to an arrival time. It is likely that this is because the smaller lactulose molecule becomes trapped and hence protected from fermentation within the complex three-dimensional matrix of psyllium. If the laxative effect of lactulose depends on it stimulating colonic mass movements, then delaying its fermentation and production of irritant metabolites would be expected to inhibit this effect. Mass movements may be a nonspecific reaction to either colonic acidification or more likely gaseous distention as a result of rapid fermentation. Alternative ways of preventing fermentation, such as giving broad-spectrum antibiotics, have also been shown to inhibit the laxative effects of lactulose (29).

Our model is probably representative of patients with diarrhea, which may explain the difference between our findings and those of Ashraf et al (30), who showed no change in overall transit in constipated patients with use of psyllium. Another difference from our study and those of others (8) who did not show an accelerating effect on colonic transit is that we measured proximal colon transit, which is likely to be more sensitive to changes in ileal input than is overall transit, which is influenced by many other factors.

These studies suggest that psyllium may modify the response to rapidly fermentable, poorly absorbed dietary carbohydrates such as lactose, fructose, and sorbitol, which have been implicated in some studies of irritable bowel syndrome (31–33). The well-recognized benefit of psyllium in irritable bowel syndrome (6, 34, 35) is partly due to its treatment of constipation (6), but psyllium also benefits those with diarrhea and pain (7, 34). The possibility that psyllium benefits those with occult carbohydrate intolerance is worthy of further study. These effects of psyllium should not be taken as a recommendation to include psyllium as part of a normal diet. Similar gelling agents are found more economically in fresh fruit and vegetables.

### REFERENCES