Fiber-supplemented enteral formula slows intestinal transit by intensifying inhibitory feedback from the distal gut

Henry C Lin, Xiao-Tuan Zhao, Alex W Chu, Yea Ping Lin, and Lijie Wang

ABSTRACT  Because an increase in flow rate accelerates intestinal transit, a reduction in the flow rate of formula delivery is recommended frequently for treatment of diarrhea that develops during enteral feeding. Because intestinal transit is slowed by nutrient-triggered inhibitory feedback, the rate of intestinal transit during enteral feeding may depend on a balance between the accelerating effect of flow and the inhibiting effect of the nutrient load. The addition of fiber to a formula may alter this balance. By delaying absorption of nutrients, fiber may extend the length of small intestine exposed to nutrients and thereby trigger more intense inhibitory feedback. To determine whether the addition of fiber favors nutrient-triggered inhibition over flow-driven acceleration, we studied intestinal transit after perfusion of a low-residue enteral formula compared with a fiber-supplemented formula at two perfusion rates (50 or 100 mL/h for 2 h) into the duodenum of dogs each with both a duodenal and midgut fistula. With the low-residue formula, intestinal transit accelerated when the flow rate increased from 50 to 100 mL/h ($P < 0.05$). With the fiber-supplemented formula, however, intestinal transit was inhibited regardless of the flow rate. To determine whether the fiber-supplemented formula inhibited intestinal transit by displacing nutrients distally, we compared intestinal transit when the two formulas, delivered at 100 mL/h, were diverted completely at the midgut fistula. Intestinal transit of the fiber-supplemented formula increased by 400%, eliminating the difference in intestinal transit speed between the two formulas. We concluded that the fiber-supplemented formula slowed intestinal transit by intensifying inhibitory feedback from the distal gut.  


KEY WORDS  Gastrointestinal motility, small intestine, dietary fiber, fiber-supplemented formula, diarrhea, enteral feeding, intestinal transit, inhibitory feedback, dogs

INTRODUCTION  

A treatment recommended frequently for diarrhea related to enteral feeding is reduction in the rate of formula delivery (1, 2). This recommendation is based on the idea that increased flow accelerates intestinal transit (3, 4). Intestinal transit is slowed when inhibitory sensors along the small intestine are exposed to nutrients (5, 6). This inhibition is load-dependent because the magnitude of the inhibitory feedback is determined by the length of the small intestine exposed to nutrients (7) and by whether nutrients spill into the distal small intestine to trigger the potent ileal brake (5, 8, 9). Therefore, because intestinal transit is dependent on the opposing forces of flow (accelerating) and nutrient load (inhibiting), reducing the rate of delivery of a formula may decrease not only the accelerating effect of high flow but also the inhibiting effect of an increased nutrient load.

The balance between flow and nutrient load may not be uniform for all enteral formulas. On the basis of their fiber content, these products are characterized as either low-residue or fiber-supplemented formulas. Because fiber delays absorption of nutrients from the lumen of the small intestine (10-12), it may intensify the inhibitory effect of the nutrient load by spreading nutrients more distally along the gut.

We tested the hypothesis that a fiber-supplemented formula may shift the balance between the opposing effects of flow and nutrient load in favor of nutrient-triggered inhibition by comparing intestinal transit in a fistulated (duodenum and midgut) dog model during perfusion of a low-residue or a fiber-supplemented enteral formula at either 50 or 100 mL/h. To test whether the hypothesis that the inhibitory effect of the fiber-supplemented formula on intestinal transit depended on the spread of nutrients into the distal intestine, we also compared intestinal transit when the two formulas were excluded from the distal one-half of the gut.

MATERIALS AND METHODS  

General design  

Intestinal transit was compared in nine dogs with duodenal and midgut fistulas. In six dogs the effect of exposing the whole gut to the formulas was tested by delivering a low-residue or fiber-supplemented formula into the duodenum at 50 or 100 mL/h while the temporarily diverted output of the midgut fistula was returned to the distal gut. In four dogs (one of which was also in the whole-gut experiments) the effect of eliminating inhibitory feedback from the distal one-half of the gut was also tested.

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gut was tested by diverting the output of the midgut fistula completely. The order in which the experiments were conducted followed a randomized schedule.

Animal preparations

The procedures used in this study were approved by the Institutional Animal Care and Use Committee at Cedars-Sinai Medical Center, Los Angeles. Nine mongrel dogs weighing \( \approx 25 \) kg were each surgically prepared with a chronic duodenal fistula located 10 cm from the pylorus and a midgut fistula located 160 cm from the pylorus (13). Each fistula was fitted with a modified Thomas cannula (custom made by the University of California Los Angeles machine shop). Just distal to the fistula, Tygon tubing (Cole-Palmer Inc, Chicago) with a diameter of 2 mm was looped around the intestine to create a stent and was fixed by suture through the visceral peritoneum to the intestinal wall. The length of tubing was individualized to be as short as possible without producing a tightening effect on the lumen. The cannula was brought out through the abdominal wall and fixed to prevent rotation. A postoperative recovery period of 4 wk was provided and dogs underwent testing only after normal feeding behaviors were reestablished. This procedure resulted in excellent survival; all nine dogs remained healthy with stable body weights for \( > 1 \) y of observation.

Perfusion formulas

A low-residue formula (Osmolite; Ross Products Division, Abbott Laboratories, Columbus, OH) and a fiber-supplemented formula (Jevity; Ross Products Division, Abbott Laboratories) were tested. Both formulas were polymeric and isotonic and provided 4435 kJ (1060 kcal)/L. Except for fiber content, the two formulas had a similar composition (Table 1). The fiber-supplemented formula contained 14.4 g dietary fiber/L in the form of soy polysaccharide (14). The viscosity of the low-residue and fiber-supplemented formulas was 4.4 \( \pm 0.3 \) and 20.9 \( \pm 0.2 \) mPa \( \cdot \) s, respectively, which was measured at 60 rotations/min with a digital viscometer (model LVTD; Brookfield Engineering, Stoughton, MA).

Experimental preparations

Dogs were deprived of food but not water for 18 h before the experiment. Thirty minutes before each experiment began, the cannulas were uncorked to allow the fistulas to drain freely by gravity and a Foley catheter (CR Bard, Inc, Covington, GA) to be placed into the distal limb of the midgut fistula. A watertight seal was created by inflating the balloon of the catheter with 8–10 mL water and pulling the balloon up against the stent (13). To begin the experiment, the test solution was perfused through a blunted needle inserted through a cork placed back in the duodenal cannula. This method allowed the perfusate to be mixed with endogenous biliary and pancreatic secretions.

Access to the whole gut

In six dogs the test formulas were perfused at 50 or 100 mL/h [\( \approx 209 \) or 418 (50 or 100 kcal)/h] for 2 h, which allowed access to the whole gut. The output of the midgut fistula was returned to the gut through the Foley catheter in the distal limb of the fistula with use of a dual-headed pump (heads with different pumping capacities, Masterflex; Cole-Palmer, Inc) that was controlled by the outflow of the fistula (13). The output was returned to the distal limb of the midgut fistula by the large pump head so that most of the chyme traversed the bowel as it would have done normally. The small pump head pumped a fraction of the total flow (7%) into a collecting tube for sampling.

Access limited to the proximal one-half of gut

In four dogs the test formulas were perfused at 100 mL/h for 2 h and excluded from the distal one-half of the gut. The output of the midgut fistula was diverted completely and substituted with saline (13). A dual-headed pump with identically sized heads was used; one head pumped the output of the fistula into a beaker whereas the other pumped synchronously an equal volume of saline through the Foley catheter in the distal limb of the fistula (13).

Viscosity measurement

The output from the midgut fistula in the experiments in which access was limited to the proximal one-half of the gut was pooled at the end of each experiment for measurement of viscosity at room temperature (60 rotations/min). Viscosity of the original perfusates was measured concurrently.

Measurement of intestinal transit

The recovery of \(^{99m}\text{Tc}\) chelated to diethyleneetriamine pentaacetic acid \((^{99m}\text{Tc-DTPA})\) was used to track the rate of intestinal transit (15). Because this marker is not absorbed, intestinal transit can be tracked at the same time nutrients, water, and electrolytes are being absorbed by the small intestine. Sixty minutes after the start of perfusion, \( \approx 740 \) kBq of the marker was delivered into the duodenum as a bolus through a blunted needle while a matched amount of the marker was set aside for later counting to determine the dose of \(^{99m}\text{Tc}\) given to the dog. This value represented 100% recovery. Every 5 min for 60 min, 0.5 mL of the output from the midgut fistula was collected and then counted in a well counter. All counts were corrected for radioactive decay to time zero. The cumulative percentage of \(^{99m}\text{Tc-DTPA}\) recovered was used to represent the rate of intestinal transit.

Data analysis

To normalize the distribution and stabilize variance, the data were analyzed by taking the square root of the area under the curve (\( \sqrt{AUC} \)) (16) represented by the cumulative percentage recovery of \(^{99m}\text{Tc}\) during the 60-min measuring period. We ran a two-factor (formula \( \times \) rate) repeated-measures analysis of

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>Composition of the fiber-supplemented and low-residue formulas</td>
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<tr>
<td>ORAL FORMULA</td>
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<tr>
<td>Energy (kJ/L)</td>
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<tr>
<td>(kcal/L)</td>
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<tr>
<td>Protein (g/L)</td>
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<td>Fat (g/L)</td>
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<td>Carbohydrate (g/L)</td>
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<tr>
<td>Water (mL)</td>
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<td>Dietary fiber (g/L)</td>
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\( ^{1} \) Percentage of energy in brackets.
variance (ANOVA) using BMDP (version 2; SPSS Inc., Chicago) (17). The √AUC values (unitless) ranged from 0 (no recovery by 60 min) to 74.2 (instantaneous recovery at time 0); thus, a higher value represented faster intestinal transit. Paired t tests were used for additional comparisons.

RESULTS

Intestinal transit represented by the cumulative percentage recovery of 99mTc-DTPA is shown in Figure 1 for dogs in which the enteral formulas had access to the whole gut and in Figure 2 for dogs in which access was limited to the proximal one-half of the gut.

Access to the whole gut

The √AUC values corresponding to the rate of intestinal transit are shown in Table 2. Intestinal transit depended on both the formula tested (P < 0.005, ANOVA; Figure 1) and the rate of perfusion (P < 0.05, ANOVA). For the low-residue formula, the cumulative marker recovery increased from a mean (± SE) of 23.6 ± 12.5% to 72 ± 10.6% when the flow rate was increased from 50 to 100 mL/h. The corresponding mean √AUC values also rose; thus, the speed of transit increased about twofold when the flow rate was doubled.

In contrast with the results for the low-residue formula, the cumulative marker recovery for the fiber-supplemented formula was low regardless of whether the flow rate was 50 (13.9 ± 10.1%) or 100 (3.5 ± 2.0%) mL/h. Correspondingly, the √AUC values for the formulas were not significantly different. Because there was a significant interaction between type of formula and flow (P < 0.05, ANOVA), formula-dependent intestinal transit was determined by the flow rate.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Intestinal transit in dogs in which low-residue (low-fiber) and fiber-supplemented (high-fiber) enteral formulas had access to the whole gut, represented by the mean cumulative amount of 99mTc recovered from output of the midgut fistula during the last 60 min of a 120-min perfusion of the formulas at flow rates of 50 and 100 mL/h. Overall, intestinal transit was significantly greater with the low-residue formula (P < 0.005, ANOVA) and the higher perfusion rate (P < 0.05, ANOVA).

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Intestinal transit in dogs in which low-residue (low-fiber) and fiber-supplemented (high-fiber) enteral formulas had access only to the proximal one-half of the gut, represented by the mean cumulative amount of 99mTc recovered from output of the midgut fistula during the last 60 min of a 120-min perfusion of the formulas at a flow rate of 100 mL/h. There were no significant differences between the formulas.

Access limited to the proximal one-half of gut

When fistula output was diverted completely at the midgut fistula, there was no longer a significant difference in intestinal transit between the low-residue formula and the fiber-supplemented formula delivered at 100 mL/h. (Table 2 and Figure 2). The cumulative recovery was 70.9 ± 5.3% (√AUC: 35.6 ± 5.3) and 57.2 ± 17.4% (√AUC: 30.6 ± 10.2) for the low-residue and fiber-supplemented formulas, respectively. The viscosity of the output from the midgut fistula was 1.1 ± 0.2 mPa·s for the low-residue formula and 10.6 ± 2.8 mPa·s for the fiber-supplemented formula.

DISCUSSION

In a fistulated canine model, we found that the effect on intestinal transit of changing the rate of formula delivery was different for low-residue compared with fiber-supplemented formulas. Although intestinal transit of the low-residue formula

<table>
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<tr>
<th>Exposure and formula</th>
<th>50 mL/h</th>
<th>100 mL/h</th>
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<tbody>
<tr>
<td>Whole gut</td>
<td></td>
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<tr>
<td>Low residue</td>
<td>18.7 ± 5.7</td>
<td>41.1 ± 6.0&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fiber supplemented</td>
<td>7.5 ± 4.6&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4.3 ± 2.1&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Proximal one-half of gut</td>
<td></td>
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<tr>
<td>Low residue</td>
<td>—</td>
<td>35.6 ± 5.3</td>
</tr>
<tr>
<td>Fiber supplemented</td>
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<td>30.6 ± 10.3</td>
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<sup>1</sup> ± SE. √AUC, square root of the area under the curve of the cumulative percentage recovery of 99mTc where 0 = no recovery by 60 min and 74.2 = theoretical, instantaneous recovery at time 0 (rapid transit).

<sup>2</sup> Significantly different from 50 mL/h, P < 0.05 (t test).

<sup>1</sup> Significantly different from low-residue formula, P < 0.05 (ANOVA).
FIBER-SUPPLEMENTED FORMULA SLOWS TRANSIT

was accelerated by a higher flow rate, there was no such flow-dependent accelerating effect with the fiber-supplemented formula. Instead, intestinal transit of the fiber-supplemented formula was markedly inhibited compared with that of the low-residue formula at both flow rates tested.

We tested the idea that the rate of intestinal transit during enteral feeding depends on a balance between the accelerating effect of flow (3, 4) and the inhibiting effect of nutrient load (5–8). Because intestinal transit of the low-residue formula accelerated when flow rate was increased from 50 to 100 mL/h, the accelerating effect of the higher flow must have exceeded the inhibitory effect of the greater nutrient load to determine the intestinal transit response to the formula. Conversely, because intestinal transit with the fiber-supplemented formula was slow regardless of whether the rate of delivery was 50 or 100 mL/h, the inhibitory effect of the greater nutrient load must have exceeded the accelerating effect of the higher flow in the presence of fiber. These observations suggest that decreasing the rate of formula delivery (1), the usual treatment for enteral feeding–related diarrhea, may slow intestinal transit of low-residue formulas but not that of fiber-supplemented formulas.

The striking difference in intestinal transit between the two formulas was likely related to the difference in fiber content because the two formulas are equienergetic and similar in nutrient composition (Table 1). The presence of soy polysaccharides in the fiber-supplemented formula was responsible for about a fivefold difference in the viscosity of the two formulas at the start of the experiments (4.4 compared with 20.9 mPa·s). Although chyme from the midgut fistula remained more viscous during perfusion with the fiber-supplemented formula, the difference in viscosity between chyme with the two perfusates (10.6 compared with 1.1 mPa·s) could not alone explain the potent inhibition of intestinal transit by the fiber-supplemented formula.

Because there was no longer a difference in intestinal transit between the two formulas when they were diverted completely at the midgut fistula and excluded from the distal one-half of the gut (Figure 2), the potent inhibitory effect of the fiber-supplemented formula during exposure to the whole gut must have depended on the spread of nutrients to the distal gut and the triggering of the ileal brake. This change in the intestinal transit pattern of both formulas after complete diversion at the midgut fistula must have resulted primarily from the 400% increase in the speed of transit of the fiber-supplemented formula (access to the whole gut as compared with the proximal one-half only) (the √AUC value increased from 7.4 to 30.5) because diverting the low-residue formula had no significant effect on intestinal transit (√AUC: 41.1 when access was limited to the whole gut and 37.8 when access was limited to the proximal one-half gut).

Although the idea that a higher flow rate increases intestinal transit speed is well accepted (3, 4) the concept that transit is slowed by a greater nutrient load is relatively new. Similar to what occurs in regulation of gastric emptying (13), intestinal transit is slowed when inhibitory sensors along the small intestine are exposed to nutrients (5–7). Because the magnitude of this inhibition is determined by the total inhibitory feedback generated by these sensors (7, 13), inhibition is greater when nutrients gain access to a longer length of gut. Inhibitory feedback also depends on the region of gut exposed to nutrients. Intestinal transit is inhibited by fat confined to the proximal one-half of the gut as the jejunal brake (18). When nutrients such as fat (5, 7, 8), carbohydrate (5), and protein (5) spread to the distal small intestine, intestinal transit may be further inhibited by triggering of the ileal brake. Because the ileal brake is more potent than the jejunal brake (9), when the distal gut comes into contact with nutrients during enteral feeding, the magnitude of the inhibitory feedback on intestinal transit may be intensified.

The addition of dietary fiber delays absorption of nutrients from the lumen of the small intestine (10–12, 19). Dietary fiber slows the digestion and absorption of fat by binding bile salts (20) and by slowing diffusion of the nutrient (21). Fiber also impairs lipase activity, thereby slowing digestion by delaying hydrolysis of triacylglycerols (22). These effects on digestion and absorption also occur with other nutrients. Dietary fiber delays absorption of carbohydrate by increasing the viscosity of the lumen (23) and the thickness of the unstirred layer (19). Similarly, dietary fiber delays absorption of protein by increasing luminal viscosity (24). In this study, the ability of fiber to delay digestion and absorption of nutrients may explain the loss of potent inhibition when the fiber-supplemented formula was excluded from the distal one-half of the gut. Because fiber delays the removal of nutrients from the lumen, it may slow intestinal transit by increasing the length of the small intestine exposed to nutrients (25) and by displacing nutrients into the distal small intestine to trigger the ileal brake.

Our observations extend those of Meyer et al (25), who found that the presence of fiber in the small intestine but not in the stomach slowed gastric emptying of a glucose meal. Thus, they concluded that inhibition of gastric emptying by fiber resulted from an increase in nutrient-driven intestinal feedback. Slowing of intestinal transit by fiber has been reported. Bueno et al (26) found that adding fiber to a solid meal slowed intestinal transit of the test meals in dogs. This effect was also observed in humans (27) and rats (28). The motility response involved in the slowing of intestinal transit by fiber-supplemented formula is not known but may depend on a shift in the temporospatial pattern of motor activity of the small intestine (6) toward braking, nonpropagated contractions. Because nutrients are the primary trigger responsible for shifting the pattern of contractions from a propagated to a braking, nonpropagated pattern (29), fiber may achieve its slowing effect on intestinal transit by enhancing the nonpropagated motility response to nutrients. This idea is supported by the observation that guar gum prolongs the fed-motility state (26).

Because intestinal transit is determined by the balance between the accelerating effect of flow and the inhibiting effect of the nutrient load, the relation between the rate of intestinal transit and the rate of formula flow depends on the fiber content. Although flow rate is the primary determinant of the rate of intestinal transit of a low-residue formula, nutrient-triggered inhibitory feedback is the most important determinant of the intestinal transit rate of a fiber-supplemented formula. This difference is explained by the ability of fiber to intensify nutrient-triggered inhibitory feedback by spreading nutrients to the distal gut.

REFERENCES


