The Effect of Meal Composition on the Gastrocolonic Response: Implications for Drug Delivery to the Colon

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The response of the colon to eating, the gastrocolonic response (GCR), may have important implications for the design of drug dosage forms for selective delivery to the colon. Therefore, the effect of meal composition on the GCR and its relation to the transit of nondisintegrating tablets has been investigated. Eight healthy male volunteers each received 5 × 6-mm radiolabeled nondisintegrating tablets, and the transit was followed using a gamma camera. When the tablets reached the ileocolonic region, each volunteer received a test meal (1000 kcal) containing 70% carbohydrate, 15% fat, and 15% protein. The subsequent movement of the tablets was then monitored. The study was repeated using a 70% fat meal and a 70% protein meal, so that the effects of a high-carbohydrate, a high-fat, and a high-protein meal on the GCR could be compared. The incidence of GCRs was similar after all meals. Thus, there appeared to be no effect of meal composition on the movement of the tablets into the colon. This implies that the ingestion of food may not necessarily stimulate the passage of material across the ileocecal junction and that other factors may also be involved.

KEY WORDS: gastrocolonic response; gamma scintigraphy; drug delivery to the colon; tablets.

INTRODUCTION

Site-Specific Delivery

The specific delivery of drugs to the colon is becoming increasingly important for the local treatment of disorders of the large bowel, for example, inflammatory bowel disease. Such direct delivery of a drug to its site of action can lead to improved efficacy and a reduction in systemic side effects (1). In addition, the colon has been suggested to be the optimal site for the absorption of orally administered peptides, since digestion by gastric and pancreatic enzymes could be avoided (2). Consequently, there has been considerable research into the design of colonic delivery systems for both peptides and antiinflammatory agents. These have included selectively degradable hydrogels (2,3), polymeric coatings (4), and prodrugs (5). However, to achieve the maximum performance from such systems, it is essential to have a good understanding of the behaviour of solid oral dosage forms within the gastrointestinal (GI) tract, in particular, their movement through the ileocecal junction (ICJ) and their transit in the colon.

The factors that control movement of dosage forms from the ileum, across the ICJ, into the colon remain poorly understood (6). This is due partly to the inaccessible nature of this region of the human GI tract. Indeed, if the mechanisms associated with ileocolonic transit were known, it might be possible to develop improved colon-selective delivery systems.

The Gastrocolonic Response

The ingestion of a meal is known to stimulate colonic activity. This is termed the gastrocolonic response (GCR) (7). Both calorific load and the dietary components of a meal are believed to play important roles in the GCR (7,8). For example, fat appears to be the major stimulant, while carbohydrates and whole protein have no stimulatory effects (8). However, the role of meal composition on the transit of pharmaceutical dosage forms through the colon is not known. We have found recently that the ingestion of food can lead to a GCR that is associated with the transit of tablets (9). However, the composition of the meals in terms of fat, carbohydrate, and protein content was not controlled.

Little is known about the effect of food ingestion on the colonic transit of pharmaceutical dosage forms and, in particular, ileocolonic transit. The flow of material into the colon has been shown to be rapid after feeding (10), which implies that food ingestion may stimulate ileocolonic transit of dosage forms. This may have important implications in the design of delivery systems for colonic drug targeting. Thus, the aim of this study was to compare the effect of meal composition on the GCR, by measuring the transit of nondisintegrating tablets.

MATERIALS AND METHODS

Preparation of Formulations

Nondisintegrating tablets (6-mm diameter, 140-mg weight) were prepared from ethylcellulose (BDH, Poole, Dorset), containing a small quantity of Amberlite IRP-69 resin. The resin was radiolabeled with indium-111, a radionuclide that has a half-life of 67 hr, which is ideal for measuring the transit of dosage forms for periods of time longer than 24 hr. The powder blend was directly compressed using a Manesty F3 single-punch tablet machine to produce tablets with an activity of 0.2 MBq/tablet at the time of administration. The tablets were coated with ethylcellulose and then cellulose acetate in order to prevent their disintegration and leaching of the radiolabel *in vivo* (11).

Subjects

The study was undertaken in two groups of four healthy male volunteers (age 20–25 years). All the volunteers were nonsmokers and none were on any medication at the time of the study. Each provided written informed consent for participating in the study.

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The study was approved by the Ethics Committee of the University of Nottingham and was conducted in accordance with the Guidelines of the Declaration of Helsinki for Ethics in Research. Approval to administer the radiolabelled formulations was obtained from the Department of Health, London.

Diets

The food intake of the subjects was carefully controlled for 6 days before the start of the study, in order to allow the GI tract to become accustomed to the new diet (12). Nutritionally balanced diets were designed to contain 18 g nonstarch polysaccharides (NSP), the currently accepted way of defining dietary fiber. This figure represents the recommended daily intake of fiber in the United Kingdom (13). The diets used on each of the study days also contained 18 g NSP. The subjects recorded details of their bowel habits throughout the study period.

Study-Day Dosing and Imaging Procedure

On each of the study days, the subjects received five 6-mm ^{111}In radiolabeled tablets and 200 mL of water. The latter was radiolabeled with $^{99}Tm^{m}$ diethylenetriaminepentaacetic acid (DTPA), to outline the anatomy of the stomach and colon (14). Anterior images, each of 45-sec duration, were taken every 5–10 min over a period of 11 hr, using a gamma camera (General Electric) having a medium energy (300-keV) parallel-hole collimator. The images were recorded on computer and stored on magnetic tape for later analysis (15).

When the tablets were observed by scintigraphy to reach the ileocolonic region, a test meal containing 70% carbohydrate, 15% protein, and 15% fat was given (1000 kcal), and the subsequent transit of the tablets scintigraphically monitored. The frequency of imaging was unaltered during the feeding periods but the subjects stopped eating momentarily in order to allow an image to be taken. In addition, an evening meal was provided for the volunteers before the end of the study day. The study was repeated using a 70% fat meal and a 70% protein meal, so that the effects of ingesting a high-carbohydrate meal, a high-fat meal, and a high-protein meal could be compared. The composition of the study-day meals is shown in Table I. The whole study protocol was repeated in a further group of four volunteers.

Data Analysis

The recorded images were analyzed by constructing anatomical outlines of the stomach and large bowel. Images of the latter were divided into seven regions of interest: cecum, ascending, transverse, descending, and sigmoid colon, and hepatic and splenic flexures (16). On examination of the images, it was possible to locate the position of the tablets within the GI tract at any particular time point. Histograms depicting the passage of the tablets through each region of the gut were then constructed.

The time taken for at least three tablets to empty from the stomach (T50% GE) and the corresponding small intestinal transit times (T50% SITT) were estimated as previously described (15). The effect of test meal composition on GCR was investigated by measuring the incidence of a positive response. We have defined this as being the movement of at least two tablets from one region of the GI tract to the next within 20 min of onset of meal ingestion (9).

Table I. Study-Day Test Meal Compositions

	Fat	Carbohydrate	Protein
"Carbohydrate" test meal			
kcal	152	700	150
kJ	634	2928	628
%	15.1	69.9	15.0
"Fat" test meal			
kcal	700	152	149
kJ	2924	634	622
%	69.9	15.2	14.9
"Protein" test meal			
kcal	149	150	700
kJ	623	626	2926
%	14.9	15.0	70.1

RESULTS AND DISCUSSION

Gastric Emptying and Small Intestinal Transit

The mean T50% GE time was found to be 33 ± 28 min, and the mean T50% SITT was found to be 150 ± 51 min. These results are in good accord with those reported in previous studies (11,14,15,17).

The Ileocecal Junction

In the majority of subjects, the tablets reached the ICJ as a bolus and did not spread until they had progressed to the more distal regions of the colon.

Originally, the ICJ was believed to act as a valve (18), however, it has now been suggested that it possesses more the characteristics of a sphincter (19). The functions of this region include the separation of the flora of the large intestine from the ileum (20), the regulation of the flow of material from the ileum to the colon (6), and the prevention of retrograde flow from the colon into the small bowel (6). Thus, it determines how intestinal contents move between the small and the large bowel and may contribute to gut homeostasis (21). Evidence is also emerging which suggests that the regulation of the transit of material across the ICJ is a function of the whole ileocolonic region and is not confined to a short sphincteric zone (6).

Meal Ingestion and the Gastrocolonic Response

Seven of the eight volunteers completed all their study meals; volunteer 1 ate only 80% of the protein meal. However, all subjects expressed a feeling of fullness after ingesting the high-protein meal. This is because the volume of this test meal was much greater than that of the other test meals, since protein has a lower calorific density than either fat or carbohydrate. The only means by which this volume difference could have been overcome would have been to feed the volunteers with liquid meals or broths. However, the aim of the study was to characterize the transit of tablets under conditions which mimicked normal everyday conditions.

Table II. Position of 5 × 6-mm ^{111}In-Labeled Nondisintegrating Tablets After Ingesting a High-Fat, a High-Carbohydrate, and a High-Protein Test Meal (1000 kcal)[a]

	Fat test meal		Carbohydrate test meal		Protein test meal	
Volunteer	Before	After	Before	After	Before	After
1	5SI	5ICJ	2ICJ, 3Ca	5Ca	3ICJ, 2Ca	5Ca
2	5SI	5ICJ	5Ca	5Ca	5Ca	5AC
3	5Ca	5AC	5Ca	5Ca	3Ca, 2AC	3Ca, 1AC, 1SF
4	5SI	5ICJ	5Ca	3Ca, 2AC	2Ca, 3AC	2Ca, 3AC
5	5Ca	4AC, 1HF	1ICJ, 4AC	1Ca, 4AC	5Ca	5AC
6	3SI, 2Ca	3Ca, 2AC	3ICJ, 2Ca	2Ca, 3AC	5ICJ	5AC
7	1SI, 4AC	5AC	3Ca, 2AC	4AC, 1HF	5Ca	5AC
8	5Ca	2Ca, 3AC	5Ca	5AC	5Ca	5Ca

[a] SI, small intestine; ICJ, ileocecal junction region; Ca, cecum; AC, ascending colon; HF, hepatic flexure; SF, splenic flexure. The ICJ is shown as a distinct region in this table in order to illustrate that the tablets were observed to be in the proximity of the cecum. However, this region was classified as being in the small intestine region of interest when measuring the incidence of GCR, since the tablets were not considered to have entered the colon.

Therefore, the subjects were given conventional meals. The differences in meal volumes were reflected in the mean times taken to eat the study meals, which were as follows: fat meal, 12 ± 4 min; carbohydrate meal, 15 ± 5 min; and protein meal, 47 ± 15 min.

Gastric distension has been found to lead to an increase in motility in the rectosigmoid region (22). Wiley *et al.* observed that increasing the volume of balloon distension in the stomach, leads to corresponding increases in the motility index (MI). However, significant changes in MI were observed with distension volumes of as little as 100 mL. It is therefore believed that the volume differences between the test meals would not influence the results, since all the meal volumes were much greater than 100 mL.

In those subjects where a GCR was elicited, the mean times after the onset of eating at which the GCR was observed were 10 ± 4 min after the fat meal, 13 ± 6 min after the carbohydrate meal, and 10 ± 7 min after the protein meal. Therefore, the prolonged eating time of the protein meal did not appear to affect the appearance of a GCR. It may therefore be concluded that the volume differences between the test meals did not have a significant effect upon the outcome of the study.

The position of the tablets within the GI tract before and after the consumption of each of the test meals is shown in Table II, and the incidence of GCR is detailed in Table III. Examples of transit histograms illustrating the movement of the tablets after ingestion of each of the test meals (volunteer 6) are shown in Figs. 1–3.

It should be noted that when the incidence of GCR was

Table III. Incidence of GCR[a] After Ingesting a High-Fat, a High-Carbohydrate, and a High-Protein Test Meal (1000 kcal)[b]

	Test meal		
Volunteer	Fat	Carbohydrate	Protein
1	−	+[c]	+[c]
2	−	−	+
3	+	−	−
4	−	+	−
5	+	−	+
6	+[c]	+[c]	+[c]
7	−	+	+
8	+	+	−

[a] Defined as being the movement of at least two tablets from one region of the GI tract to the next within 20 min of onset of meal ingestion.

[b] (+) A GCR observed.

[c] Denotes movement of tablets from the small intestine into the colon.

	Time (mins)	Stomach	SI	ICJ	Caecum	AC	HF	TC
Dosed	1	·····						
	18	···	··					
	23		·····					
	141		····	·				
	150			····	·			
Eat 198 - 214	197			···	··			
	202			···	··			
	207				·····			
	212				···	··		
	216				··	···		
	253				·	····		

· = carbohydrate study day tablet

Fig. 1. Gastrointestinal transit of 5 × 6-mm ^{111}In-labeled nondisintegrating tablets after the carbohydrate test meal, volunteer 6. SI, small intestine; ICJ, ileocecal junction; AC, ascending colon; HF, hepatic flexure; TC, transverse colon.

	Time (mins)	Stomach	SI	ICJ	Caecum	AC	HF	TC
Dosed	0	|||||						
	29	|||	||					
	33		|||||					
	138		|||||					
	271		|||||					
	277			|||||				
	307			|||	||			
Eat 312-320	311			|||	||			
	318				|||||			
	328				|||	||		
	443				|||	|	|	

| = fat study day tablet

Fig. 2. Gastrointestinal transit of 5 × 6-mm ^{111}In-labeled nondisintegrating tablets after the fat test meal, volunteer 6. SI, small intestine; ICJ, ileocecal junction; AC, ascending colon; HF, hepatic flexure; TC, transverse colon.

	Time (mins)	Stomach	SI	ICJ	Caecum	AC	HF	TC
Dosed	2	ΔΔΔΔΔ						
	20		ΔΔΔΔΔ					
	173		ΔΔΔΔΔ					
	178			ΔΔΔΔΔ				
Eat 192 - 267	191			ΔΔΔΔΔ				
	197				ΔΔΔΔΔ			
	204				ΔΔΔ	ΔΔ		
	209					ΔΔΔΔΔ		
	342					ΔΔΔ	Δ	Δ

Δ = protein study day tablet

Fig. 3. Gastrointestinal transit of 5 × 6-mm ^{111}In-labeled nondisintegrating tablets after the protein test meal, volunteer 6. SI, small intestine; ICJ, ileocecal junction; AC, ascending colon; HF, hepatic flexure; TC, transverse colon.

measured, the ICJ was not classified as being a distinct region of interest. When the tablets were observed to be located in this area of the GI tract, they were recorded as being in the small intestine, since they were not considered to have entered the colon. The ICJ has been included in Table II and Figs. 1–3, to indicate the times at which the tablets were in close proximity to the cecum.

Volunteer 1 defecated 35 min after commencement of the high-fat meal, however, there was no corresponding movement of the tablets at this time point. This implies that propulsion of material could have occurred in the distal colon but not in the ileocolonic region.

Snape and others have shown that, in man, the ingestion of a meal stimulates an increase in colonic activity, the GCR (7,8). This is believed to be mediated via gastric mechanoreceptors using a cholinergic pathway and intestinal opiate receptors (22–24). Thus the GCR is controlled by both neural and humoral inputs.

Previous studies by Snape *et al.* have shown that when electrical spike activity (ESA) and MI in the rectosigmoid were measured, a greater response was elicited from a 1000-kcal mixed meal than a 350-kcal meal (7). In addition, the dietary components of a meal appear to have different effects upon colonic motility (8). Fat has been suggested as being the major stimulant, while carbohydrates and whole protein have little or no stimulatory effects upon the colon. Interestingly, the addition of amino acids to fat has been found to abolish the entire response (8). Bassotti *et al.* also measured MI in the ascending, transverse, and descending colon. After a 1000-kcal meal, they found MI to increase in all portions of the colon. However, the colon was cleansed prior to the start of the investigation, and so the study was not conducted under normal physiological conditions (25). In our previous studies the ingestion of food has also been shown to lead to a GCR, and this was associated with the transit of tablets from the ileum to the cecum or from the cecum to the ascending colon (9). However, the exact composition of the meals was not controlled.

The motility of the ileocolonic region has been shown by Spiller *et al.* to increase transiently after feeding (10). In the same study, inflow of a ^{99}Tc^{m} marker into the colon was found to be rapid after a meal, however, the MI did not correlate with the rates of colonic inflow. Others have also observed an increase in both MI and ESA in the vicinity of the ICJ after food (20,21). This implies that the ingestion of food could influence the transit of dosage forms across the ICJ.

The present results suggest that meal composition does not appear to affect the response of the colon to eating, in terms of the transit of labeled tablets (Table III). Previous studies have concentrated upon MI and ESA within the distal regions of the colon and not the transit of tablets through the ICJ and in the proximal colon. As stated above, food increases the motility of the ileocolonic region (10), however, an increase in motility does not necessarily lead to the aboral propulsion of material. It can often lead to an increase in segmental contractile activity, which aids the mixing of luminal contents and facilitates absorption (26).

The detailed analysis of the scintigraphic results for subjects 1, 2, and 4 showed that the high-fat meal had actually been consumed when the tablets were probably located in the distal ileum, rather than in the ileocolonic region. However, within 6, 7, and 13 min, respectively, after the com-

mencement of eating, all five tablets were observed to move rapidly to the ICJ region. The flow of chyme through the small intestine has been found to increase promptly after the ingestion of a liquid meal (27). However, this increase was found not to be significant in the terminal ileum when compared to the jejunum. It should be noted that the terms "flow" and "transit" are not interchangeable. Therefore, although no defined GCRs were noted in these subjects, it is possible that the high-fat meal may have had a greater effect upon transit than the other two meals.

In conclusion, the response of the colon to eating, in terms of tablet transit, does not appear to be directly affected by specific dietary components. Also, the sensitivity of the colon to the ingestion of food appears to differ between individuals, which implies that other factors may be involved. Since the food intake of the subjects during the study was identical, it is believed that these "other factors" may be unrelated to diet. Further work needs to be carried out to characterize the role of the ICJ, in order to facilitate and optimize the design of colon-selective drug delivery systems.

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