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Research Paper

Meal-Induced Acceleration of Tablet Transit Through the Human Small Intestine

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Purpose. The transit of dosage forms through the small intestine is considered to be constant at around 3 h, and unaffected by the presence of food. Here we address this assumption and examine how the timing of tablet and food administration can influence small intestine transit time.
Methods. A non-disintegrating, radiolabelled tablet was given to ten healthy volunteers in a three-way crossover study using three different feeding regimens (1) fasted (tablet administered on an empty stomach and food withheld for four hours) (2) fed (tablet administered after food) and (3) pre-feed (tablet administered 45 min before food). Tablet transit through the gastrointestinal tract was followed using gamma scintigraphy.
Results. The small intestinal transit times of tablets after fasted and fed dosing regimens were similar, median 204 and 210 min respectively. With the pre-feed dose, small intestinal transit time was significantly shorter than in the fasted or fed state at 141 min. With this dosing regimen, in six of the volunteers tablets were in the upper small intestine when food arrived and these had a median small intestinal transit time of 100 min.
Conclusions. The timing of food ingestion has a clear effect on small intestinal transit of single-unit formulations and this has implications for drug bioavailability.

KEY WORDS: gamma scintigraphy; gastrointestinal transit; intestinal flow; migrating myoelectric complex; modified release; motility.

INTRODUCTION

The small intestine is considered the major site for drug absorption and as such, its importance in bioavailability is understood. The rate and extent of absorption from the small intestine can be influenced by the residence time of the drug or dosage form. A meta-analysis by Davis *et al.* (1) using data pooled from 201 dosage form administrations puts the average residence time in the small intestine at 3 h irrespective of dosage form type (tablets, liquids or pellets), and similar average values have been reported by more recent studies (2–4). The ability of drugs (5–7) or excipients (8–13) to modulate intestinal transit is known, but the presence of food is thought to be negligible (1). However, the Davis meta-analysis and the majority of other studies only consider two feeding regimens: (1) *fasted* in which the dosage form is given on an empty stomach with food withheld for a number of hours or (2) *fed* in which the formulation is taken after food. These feeding regimens are endorsed by regulatory authorities, but they do not necessarily represent how people take their medicines outside a clinical trial unit. In this study, we consider the scenario in which people take their medicines before food. Might the arrival of food in the stomach trigger physiological mechanisms in the small intestine which alter the transit of the dosage form? A limited number of previous studies have considered alternative feeding regimens with modified release dosage forms and have reported conflicting effects on transit (14–16). Here, a study was designed specifically to investigate the timing of food administration on small intestinal transit. The transit of a non-disintegrating single-unit dosage form (tablet) was followed in man by gamma scintigraphy using the typical "fasted" and "fed" dosage regimens, in addition to a "pre-feed" dose. In this latter regimen, the tablet was administered to the volunteers 45 min before food, to give this dosage form the opportunity to empty into the small intestine before the arrival of the meal.

MATERIALS AND METHODS

Preparation of Non-Disintegrating Tablets

Model placebo tablet cores were produced and coated with a non-digestible insoluble polymer coating to ensure they would pass through the gastrointestinal tract intact. The tablet formulation was prepared by wet granulation as described previously (17) and the granules compressed using a single punch tableting machine (Manesty, Speke, UK) to

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produce 5 mm diameter tablets. These were coated with the water insoluble ethylcellulose dispersion Surelease™ EA-7100 (Colorcon Inc.). A Strea-1 bottom spray fluidized bed coater (Aeromatic AG, Bubendorf, Switzerland) was used for coating at an inlet temperature of 50°C, an outlet temperature of 40°C, an atomizing pressure of 0.2 bar and a spray rate of 1 g/min. The tablets were coated to a 5% weight gain and dried in an oven at 60°C for one hour. The coated tablets were radiolabelled with Indium-111 (^{111}In) complexed to diethylenetriaminepentaacetic acid, as described by Ibekwe *et al*. (18). Briefly, lactose was dissolved in the radioactive complex and oven dried. A 1 mm diameter hole was drilled into the coated tablet surface though to the core and the radiolabelled lactose used to fill the hole, to an activity of 1 MBq and the hole sealed with bone cement (AquaCem, DENSPLY DeTrey Gmbh, Germany).

Study Protocol

The study protocol and radioactivity administration was approved by the Joint UCL/UCLH Committees on the Ethics of Human Research and the Administration of Radioactive Substances Advisory Committee (Department of Health). The study followed the tenets of the Declaration of Helsinki (1964). Ten healthy adult male volunteers, aged 22–46 years, took part in the study, with treatment order randomised and 7 day washout periods observed. The volunteers were administered a radiolabelled ethylcellulose coated tablet after an overnight fast, with 150 ml of water, in one of the following dosing regimens.

(a) Fasted
Tablet administered on an empty stomach.
(b) Fed
Tablet administered immediately *after* a standard breakfast (30 g cornflakes, 100 ml semi-skimmed milk, two slices of toasted brown bread, 5 g margarine, one banana and 150 ml orange juice [513 kcal])
(c) Pre-Feed
Tablet administered 45 min *before* the standard breakfast (513 kcal)

A standard lunch (cheese sandwiches [two pieces], packet of crisps and 250 ml orange juice [600 kcal]) was provided at 4 h post-dose, after which water and other non-alcoholic drinks were freely available.

Gamma Scintigraphy

A sealed point source of 0.1 MBq ^{111}In was taped to the most lateral part of the lower costal margin to be used for correction of posture between imaging and as an anatomical reference marker. Images were acquired using a double-headed gamma camera (Maxxus, General Electric Medical Systems, Milwaukee, WI, USA) fitted with two opposed detectors, each having a 508×368 mm useful field of view and capable of simultaneous data acquisition. Each detector was fitted with a medium energy parallel hole collimator suitable for ^{111}In imaging. Images were acquired over a one minute period, at approximately 5 min intervals for up to 8 h. The acquired images were digitally recorded for each volunteer using an integrated computer system (Starcam 3200i, General Electric Medical Systems, Milwaukee, WI, USA) and archived onto optical disk for subsequent analysis. Analysis of the images and derivation of the gastric emptying, small intestinal transit and caecal arrival times were performed. Since the images were not continuous, the time of the various events were taken as the mean of the two time points either side of the event. The transit times were considered to be Bernoulli random events and the median and interquartile ranges were calculated according to this principle as described by Podczeck *et al.* (19).

Statistical Analysis

The gastric emptying, small intestinal transit and caecal arrival times were analysed for differences between fasted, fed and pre-feed doses using one-way ANOVA followed by post-hoc analysis using Tukey's test. Analysis was carried out using SPSS for Windows *vs.* 15.0.

RESULTS

The transit times of the non-disintegrating tablet administered with the fasted and fed regimens are shown in Tables I and II. The gastric emptying time was rapid in the fasted state but administration of the tablet after food significantly increased this time (median 37 and 149 min respectively; $p=0.00$). The small intestinal transit times were found to be similar for the fasted and fed states (204 and 210 min respectively; $p=1$). There was no relationship between the gastric emptying time and small intestinal transit time in either the fasted or fed state.

The pre-feed dose transit times are reported in Table III. The gastric emptying time had a median of 39 min. The small intestinal transit time was found to be significantly shorter with the pre-feed regimen (median 141 min range) than in either the fasted ($p=0.006$) or fed state ($p=0.004$). These results were further subdivided into those with a gastric emptying time <45 min or a gastric emptying time of >45 min and are shown in Tables IV and V. Food was administered at 45 min post-dose; six tablets emptied before this time (median gastric emptying

Table I. Gastrointestinal Transit Times of Tablets Administered with the Fasted Regimen

Subject number	Transit times (min)		
	Gastric emptying time	Small intestinal transit time	Caecal arrival time
1	33	214	247
2	19	241	260
3	43	167	210
4	18	252	270
5	108	260	368
6	41	164	205
7	31	168	199
8	92	251	343
9	15	193	208
10	68	167	235
Median	37	204	241
Interquartile range	19–74	167–251	207–288

Table II. Gastrointestinal Transit Times of Tablets Administered with the Fed Regimen

Subject number	Transit times (min)		
	Gastric emptying time	Small intestinal transit time	Caecal arrival time
1	80	220	290
2	65	196	261
3	202	213	415
4	170	206	376
5	145	270	415
6	132	214	346
7	162	202	364
8	175	198	373
9	153	243	396
10	134	166	300
Median	149	210	369
Interquartile range	119–171	198–226	298–398

time of 19 min) and were observed to be in the proximal small intestine when food arrived. Four tablets emptied after 45 min (median gastric emptying time of 167 min).

The relationship between gastric emptying time and small intestinal transit time with the pre-feed regimen is shown in Fig. 1. The median small intestinal transit time of those tablets that emptied before the food arrived was 100 min (Table IV) which is significantly different to that seen in the fasted and fed states ($p=0.002$). Those that remained in the stomach until food arrived had a median transit time of 185 min (Table V) which was similar to that seen in the fasted and fed states ($p=0.9$).

DISCUSSION

The rapid gastric emptying in the fasted state is as expected; non-disintegrating tablets will empty under the influence of the phase III contractions of the migrating myoelectric complex (MMC). The MMC cycle (90–120 min) has four phases, of which phase III has the most intense continuous contractions (20). The ability of food to interrupt the MMC is well known (21); the postprandial motor activity of the stomach comprises steady, low amplitude contractions (four to five per min) (21). The lower motility in the fed state helps explain the longer gastric emptying time in the fed state; tablets rely on 'fortuitous emptying' from the fed stomach as the pyloric sphincter is contracted. Failure to empty by this means in the fed state results in the tablet waiting for the return of the fasted MMC and phase III contractions.

The small intestinal transit times for the tablet administered without food (fasted) and after food (fed) are statistically similar; this is what has been described previously (1, 22). The pre-feed dose, which was administered 45 min before food, shows differences in small intestinal transit. The time period of 45 min was chosen in order to maximise the chance of the tablet emptying from the stomach and being present in the proximal small intestine before food arrived. This happened in six volunteers. In those other four volunteers in whom the tablet was still in the stomach at 45 min, the arrival of food interrupted the MMC and delayed the gastric emptying. In this case, the dosage form may be effectively experiencing the fed state, and thus behaves accordingly.

Table III. Gastrointestinal Transit Times of Tablets Administered with the Pre-feed Regimen

Subject number	Transit times (min)		
	Gastric emptying time	Small intestinal transit time	Caecal arrival time
1	40	72	112
2	12	122	134
3	92	164	256
4	31	134	165
5	198	255	453
6	37	91	128
7	28	120	148
8	163	192	355
9	186	184	370
10	15	148	163
Median	39	141	162
Interquartile range	25–169	115–188	134–360

Table IV. Gastrointestinal Transit Times of Tablets Administered with the Pre-Feed Regimen in Which the Tablets had Emptied from the Stomach Before Food Arrived at 45 min

Subject number	Transit times (min)		
	Gastric emptying time	Small intestinal transit time	Caecal arrival time
1	40	72	112
2	12	122	134
4	31	134	165
6	37	91	128
7	28	120	148
10	15	148	163
Median	19	100	130
Interquartile range	14–34	84–124	122–152

Table V. Gastrointestinal Transit Times of Tablets Administered with the Pre-feed Regimen in Which the Tablets were Still in the Stomach when Food Arrived at 45 min

Subject number	Transit times (min)		
	Gastric emptying time	Small intestinal transit time	Caecal arrival time
3	92	164	256
5	198	255	453
8	163	192	355
9	186	184	370
Median	167	185	358
Interquartile range	99–189	166–211	266–395

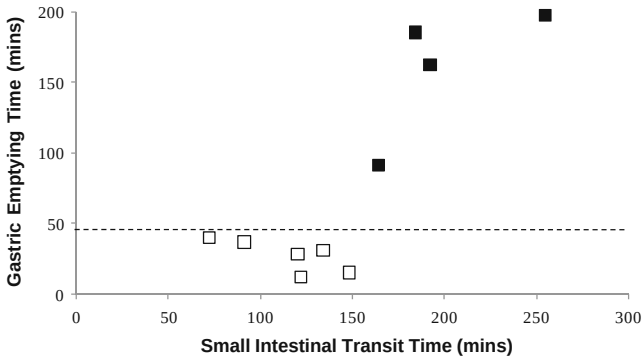

Fig. 1. Relationship between gastric emptying time (min) and small intestinal transit time (min) of tablets with the pre-feed regimen (*open symbols* are those which emptied into the small intestine before food arrived at 45 min, *closed symbols* are those which were still in the stomach when food arrived).

For those six tablets that had emptied from the stomach and moved to the upper small intestine before food arrived at 45 min, an accelerated transit through the small intestine is seen (Fig. 1, Table IV). This is significantly faster than the small intestinal transit in the fasted or fed state, or for those tablets which remained in the stomach from the pre-feed dose (Fig. 1, Table V). It should be noted that there is still considerable inter-subject variability as expected from such measurements. In a previous paper by our group a similar transit trend was noted; the upper small intestine transit of an enteric coated tablet appeared faster with a pre-feed dose (30 min before food) than that taken after food or on an empty stomach but this was inconclusive since the dosage form was designed to disintegrate in the distal intestine and therefore no relationship could be drawn between the arrival of food and the total small intestinal transit time of the tablet (15). Stronger evidence of a food effect on intestinal transit was noted by Digenis *et al.* (14) who administered enteric coated erythromycin pellets 30 min before food and measured a 50% decrease in bioavailability with this dosing regimen; this was attributed to a more rapid small intestinal transit of the dosage form. This study, however, was complicated by the fact that erythromycin is a prokinetic drug which stimulates gastric and duodenal motility (23). In another study in which a pre-feed dose of radiolabelled particles was given 90 min before food, no transit effects were seen (16). In light of the results reported here, timing of dosing and location of the tablet upon food ingestion may be more important than has been generally assumed. Nevertheless, the effect of dosage form size, type (multi-unit vs. single unit) dosage timing and calorific loading of meals may play a role in this transit phenomenon and therefore require further investigation.

In the fasted state the MMC plays a role in intestinal motility. The MMC, which originates not only in the stomach, but in the small intestine (24) has a reported velocity down the intestine of 4.7 cm/min (25). This is a mean value and true motility is intermittent and includes short periods of increased velocity (12–120 cm/min) (26). Work in the 1980s showed that the speed of a non-disintegrating capsule through the small intestine was between 4.2 and 5.6 cm/min (27) which corresponds to the velocity of the MMC. In a different study transit of dosage forms was also demonstrated to be intermittent, with periods of stasis and retropropulsion (28). The intestinal MMC accounts for the transit observed in our fasted study. However, under fed conditions, motility is altered. Upon the arrival of food in the stomach MMC controlled motility ceases (29) and at this point, alternative transit mechanisms come into play.

Peristaltic activity in the small intestine intensifies after a meal and cholecystokinin release in the small intestine increases the transit of fluids (30). Propagating contractile clusters sweep digesta along the length of the small intestine. This propelling and spreading mechanism (gastro-enteric response) serves to maximise the exposure of the surface area of the intestine to nutrients (31, 32) which activate the receptors that feedback on the stomach and small intestine. The intestinal flow rates also increase in response to the arrival of food in stomach. In the fasted state the mean intestinal flow rates for all phases of the MMC are 0.73 ml/min in the jejunum and 0.33 ml/min in the ileum. Postprandially, these flow rates were significantly increased to 3.0 and 2.35 ml/min respectively, for the first hour (25). Tablets still in the stomach will not be subject to these flow and motility changes. However, the location of the six pre-feed dose tablets in the proximal small intestine upon food ingestion means that they will be immediately subject to these flow changes, and the tablet is accelerated through the small intestine. It seems feasible that a combination of the increased intestinal flow and the gastroenteric response to clear food from the small intestine to make room for newly arrived food from the stomach, may contribute to the rapid small intestinal transit seen with the pre-feed dose.

The design of this study has allowed the effect of these physiological mechanisms on dosage forms to be elucidated. Ingestion of food at 45 min, when the tablet could be located in the upper small intestine, subjects the tablet to these increases in small intestinal motility and flow. Clearly, the timing of food and dosage form administration is important, and this is something that is not routinely considered in bioavailability studies which typically comprise fasted and fed treatments. Introduction of a pre-feed dosing regimen may show important differences in bioavailability, reflective of the faster small intestinal transit.

CONCLUSIONS

This study demonstrated a clear effect on food administration and timing on small intestinal transit of a tablet. Administration of tablets 45 min before food resulted in an increased small intestinal transit time over fasted and fed doses. The effect was especially pronounced for those tablets which had moved into the proximal small intestine before the food was ingested at 45 min. With these tablets rapid propulsion through the small intestine was observed. For drugs with a narrow small intestinal absorption window and modified release systems, the timing of food administration after dosing could be critical.

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