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The transit rate of different-sized model dosage forms through the human colon and the effects of a lactulose-induced catharsis

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Summary

Gamma scintigraphy has been used to compare the colonic transit rate of different sizes of radiolabelled model dosage forms in healthy human subjects. Studies simultaneously compared the ascending colon residence time of ^{111}In-labelled 0.2 mm ion-exchange resin particles and ^{99m}Tc-labelled 5 or 8.4 mm non-disintegrating tablets. Under normal conditions, no difference was observed between the rate of transit through the ascending colon of 0.2 mm particles vs 5 mm tablets ($n = 11$) or 0.2 mm particles vs 8.4 mm tablets ($n = 10$). The mean period of residence of 50% of the administered 0.2 mm particles in the ascending colon was 11.0 ± 4.0 h ($n = 21$). Coadministration of the laxative, lactulose, to subjects receiving the 0.2 and 5 mm particles significantly accelerated colonic transit. Under these conditions, the ascending colon residence of the 0.2 mm resin was significantly shorter than for the 5 mm tablets, although the magnitude of the effect was small.

Introduction

The colon is currently receiving considerable attention as a site for drug absorption and targeted drug release. Until recently, this portion of the gastrointestinal tract was largely neglected when considering oral drug delivery and interest in the area was confined to rectally administered dosage forms, i.e., enemas and suppositories. There are primarily three reasons for the current interest in colon drug delivery.

Firstly, gamma scintigraphy has revealed that the small intestinal transit time is relatively short (Davis et al., 1986) and as a result, sustained-release oral dosage forms could arrive at the colon within as little as 4 h of administration. Consequently, such dosage forms could be spending a considerable period of their drug-releasing lifetime in the colon (Davis et al., 1988; Wilson et al., 1989). If the drug is only poorly absorbed from the colon, this could severely compromise the efficacy of the dosage form.

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The second major stimulus for an interest in the colon is as a site for local treatment of disease, e.g., inflammatory bowel disease (IBD). Much of the research effort has been directed toward oral site-specific delivery of the topical anti-inflammatory agent, 5-aminosalicylic acid (5-ASA), using colon-targetable prodrugs (Jarnerot, 1989) and polymers (Dew et al., 1983).

Finally, a proliferation of molecules arising from biotechnology is injecting impetus into the feasibility of peptide/protein delivery by the oral route. The colon is of particular interest in this respect since the lumenal pH and low levels of brush border enzymes are considered to be more favourable to peptide/protein stability than the rest of the GI tract (Saffran et al., 1986; Ikesue et al., 1991). However, the low permeability of the intestine to such large molecules and the presence of degradative enzymes produced by colonic bacteria are major obstacles (Friend, 1991).

This paper describes work carried out as part of a project investigating the development of novel microsphere-based dosage forms for drug delivery into colon, and in particular the ascending colon (Watts et al., 1991). The ascending colon is of interest for two reasons. Firstly, for the treatment of IBD it is only accessible by the oral route since the spread of rectally administered dosage forms is generally confined to the descending colon (Hardy et al., 1986). Secondly, it is probably the most suitable site for drug absorption within the colon, since the increase in viscosity of the colon contents at more distal sites may hinder drug diffusion and absorption; this has been demonstrated for the antibiotic, ciprofloxacin (Staib et al., 1989).

There is evidence to suggest that the rate of passage of materials through the ascending colon increases with particle size. Using gamma scintigraphy, large (25 mm × 9 mm) single units were shown to move ahead of 0.5–1.8 mm pellets in the ascending colon (Hardy et al., 1985). In another study, a statistically significant difference has been reported between the transit rate of 6 mm radiopaque and 0.5–1.8 mm radiolabelled pellets (9.9 ± 3.8 h for 6 mm vs 11.9 ± 2.0 h for 0.5–1.8 mm) (Proano et al., 1990). On the other hand, no difference was seen between the rate of emptying of 0.5–1.8 mm pellets and a radiolabelled solution (Proano et al., 1991) from the ascending colon, suggesting that there may be a critical size below which separation of materials does not occur. If ascending colon retention could be enhanced by virtue of dosage form size, this could be of considerable benefit, especially for the local treatment of disease conditions where transit is increased, e.g., inflammatory bowel disease.

To examine this phenomenon further, we have investigated the simultaneous colonic passage of 0.2 mm particulates vs 5 mm tablets and 0.2 mm particulates vs 8.4 mm tablets in healthy human subjects to establish whether any differences in transit rate exist between the two sizes. In addition, the transit of the 0.2 mm particles and 5 mm tablets has been measured during coadministration of the laxative, lactulose, to establish how particle transit patterns are altered in a hypermotile colon.

Materials and Methods

Materials

Ethylcellulose (Sigma, Poole, U.K.), Amberlite IRA410 ion-exchange resin (BDH, Poole, U.K.), Amberlite IR120 ion-exchange resin (BDH), acetone (Analar grade) (Rhône-Poulenc, Dagenham, U.K.), indium chloride solution (Amersham International, Amersham, U.K.), sodium pertechnetate solution (radiopharmacy, Queen's Medical Centre, Nottingham), 000 size hard gelatin capsules (Farillon, Romford, U.K.) and lactulose solution (Duphar, Southampton, U.K.) were obtained from the indicated sources.

Methods

Dosage form preparation

5 and 8.4 mm tablets were compressed from a blend of ethylcellulose and finely ground Amberlite IRA410 resin. The Amberlite resin had been radiolabelled with technetium (^{99m}Tc) by mixing with sodium pertechnetate solution followed by drying. Tablets were coated with a solution of

ethylcellulose in acetone to ensure integrity was maintained in vivo.

0.2 mm particles were prepared by grinding Amberlite IR120 resin and collecting a 0.18–0.25 mm sieve fraction. The particles were radiolabelled with indium (^{111}In) by mixing with indium chloride solution followed by drying.

Into each of three 000-sized hard gelatin capsules were placed two of the tablets and 100 mg of the 0.2 mm particles. The capsules were coated with a polymer to resist disintegration until reaching the colon. This was to ensure that the tablets and particulates arrived simultaneously at the colon, avoiding problems in data interpretation if they became separated during gastric emptying.

At the time of dosing the radioactivity administered was 0.67 MBq/tablet and 0.33 MBq/100 mg of 0.2 mm particles.

Study design

Two separate studies were undertaken. The studies met the prior approval of the Nottingham University Medical School ethical committee and were conducted in accordance with the Declaration of Helsinki Guidelines for Ethics in Research. Subjects gave written consent and were at all stages free to withdraw.

Volunteers were recruited from the Nottingham University student population and had to meet the following criteria: (a) absence of gastrointestinal disease; (b) non-vegetarian diet; (c) free from medication likely to alter GI motility; (d) non or light smoker; (e) alcohol intake within accepted limits; (f) female volunteers not pregnant (required to take pregnancy test on day prior to study).

During the 4 days prior to the investigation each volunteer was requested to follow dietary guidelines in order to provide approx. 20 g of dietary fibre/day. The guidelines excluded certain high fibre foods and cathartics, e.g., spicy foods, and were used to provide a degree of standardisation to the group.

Study 1. The study was carried out in two parts, A and B, separated by a period of 2 weeks. 12 healthy human volunteers (7 male and 5 female, age 20–22) were recruited and undertook both parts of the study.

Part A: On the morning of the study day volunteers arrived having fasted from 10 p.m. the previous evening. Radioactive markers containing ^{99m}Tc were attached to each subject anterior and posterior over the right lobe of the liver to assist in alignment during scintigraphic imaging. At approx. 08:30 each subject swallowed, with 150 ml of water, the three capsules containing the 0.2 mm particles and 5 mm tablets. Immediately after swallowing the capsules, each subject stood in front of the gamma camera for dual isotope scintigraphic imaging. An anterior and posterior image of 30 s duration was recorded. Imaging was continued at 30–60 min intervals throughout the day for a period of 12–14 h and again at 24 h post-dose. Images were recorded using an IGE Maxicamera II gamma camera (IGE, U.K.) fitted with a medium-energy parallel collimator (300 keV). Data was stored and processed using a Nuclear Diagnostics computer system (Nuclear Diagnostics, Gravesend, U.K.).

Once the three capsules were seen to have left the stomach, subjects received breakfast (10–11 a.m.) and thereafter lunch (1 p.m.), coffee/tea and biscuits (4 p.m./9–10 p.m.) and dinner (6 p.m.).

Part B: The study design was identical to part A, but in addition the subjects also ingested 10–20 ml of lactulose solution, three times daily for 4 days prior to the study, and on the study day itself. The dose was adjusted by the subjects in order to approximately double their stool frequency.

Study 2. 12 healthy student volunteers were recruited (8 male and 4 female, age 18–24). The protocol was identical to study 1A, except that each of the three capsules contained two 8.4 mm tablets and 100 mg of 0.2 mm particles.

Data analysis

The position of capsule break-up and the rate and extent of spread of the radioactivity were assessed by computer analysis of the stored scintigraphic images.

From their set of images, an outline picture of the colon was constructed for each subject. Using a variable region of interest programme, the colon images were divided into four regions and the

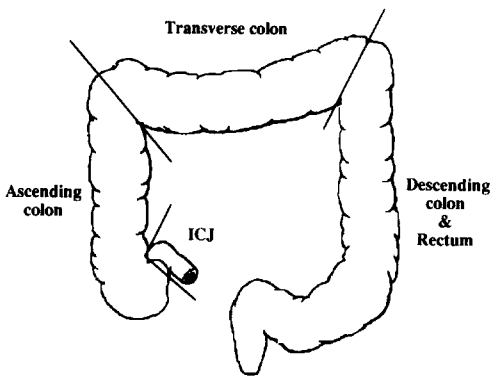

Fig. 1. Divisions of colon used for scintigraphic analysis.

number of counts in each recorded. The activity in each region could then be expressed as a percentage of the total counts administered, making corrections for tissue attenuation (Hardy and Perkins, 1985) and background radiation. The four regions were the ileo-caecal junction (ICJ) (I), the ascending colon (II), the transverse colon (III), and the descending colon/rectum (IV) (Fig. 1). Distribution of the tablets could be determined visually by simply counting the number in each region.

From the activity-time data, the mean residence time of 50% of the administered tablets and 0.2 mm particles in the ascending colon was calculated. On the same graph, the percentage of the administered dose in the whole colon (regions II, III, and IV) and the regions beyond the ascending colon (III and IV) vs time were plotted. The difference between the two curves at the 50% activity level represented the residence time of 50% of the administered activity in the ascending colon and we defined this as the mean residence time (MRT) (Fig. 2). In addition, the percentage of activity from the 0.2 mm particles remaining in the whole colon and ascending colon after 24 h was estimated. As a result of the short-half life of the ^{99m}Tc label (6 h), it was not possible to accurately assess the distribution of tablets at 24 h.

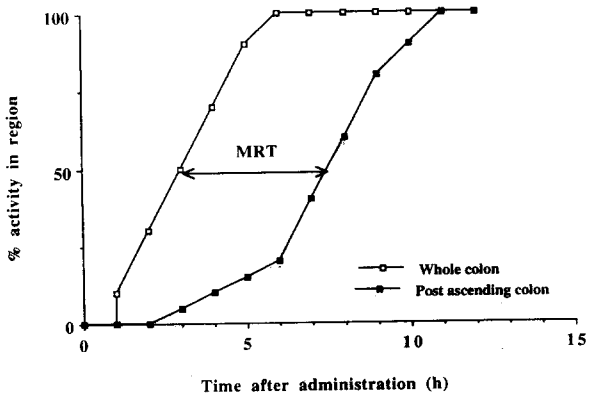

Fig. 2. Graph to define the ascending colon mean residence time (MRT).

Wilcoxon signed rank sum tests were used to test for statistical significance.

Results and Discussion

Study 1

The results for 11 subjects are presented in Table 1 since the data from one subject had to be excluded due to abnormally rapid colon transit.

Part A. The coated capsules arrived at the ICJ intact and together, from where they proceeded to disintegrate. Mean ICJ arrival time was 2.2 ± 1.3 h, with the principal source of variation being the time for gastric emptying. Small intesti-

TABLE 1

Colon transit data for study 1A (0.2 mm particles vs 5 mm tablets, without lactulose coadministration)

Subject	Ascending colon MRT (h)		% of administered 0.2 mm particles remaining after 24 h	
	5 mm tablets	0.2 mm particles	Ascending colon	Whole colon
1	7.50	10.75	18.6	31.2
2	23.50	23.25	56.0	94.7
3	18.75	13.25	9.6	85.4
4	15.75	13.50	28.0	90.2
5	14.75	10.50	15.2	75.9
6	11.25	10.25	14.9	85.6
7	14.75	13.00	28.2	100
8	16.25	14.25	26.0	89.5
9	11.25	11.00	26.9	86.2
10	7.50	9.75	20.2	80.8
11	13.75	12.25	10.6	68.0

TABLE 2

Colon transit data for study 1B (0.2 mm particles vs 5 mm tablets, with lactulose coadministration)

Subject	Ascending colon MRT (h)		% of administered 0.2 mm particles remaining after 24 h	
	5 mm tablets	0.2 mm particles	Ascending colon	Whole colon
1	9.00	7.50	3.5	51.8
2	8.25	9.25	4.0	100
3	7.25	7.25	11.2	49.9
4	9.50	9.25	22.7	97.6
5	8.75	4.50	7.5	83.5
6	6.75	4.25	4.5	79.8
7	6.25	3.75	2.4	51.4
8	16.00	8.50	5.6	62.7
9	13.00	10.75	18.2	80.4
10	3.00	3.50	6.3	94.2
11	7.50	8.25	42.7	87.0

nal transit was invariably rapid and, although it was not measured precisely, in most instances it was less than 90 min.

The mean MRT for 50% of the 5 mm tablets in the ascending colon was 13.7 ± 5.5 h and for the 0.2 mm resin, 12.9 ± 3.7 h. A wide variation was seen in the MRT values. For example, the shortest tablet MRT was 7.5 h and the longest was 23.5 h (Table 1).

There was no significant difference between the mean MRT of the 0.2 mm resin particles and the 5 mm tablets ($p = 0.07$).

After 24 h, the majority of the administered dose of 0.2 mm particles ($80.7 \pm 18.6\%$) still resided in the colon. The percentage of the administered particles resident in the ascending colon at 24 h was $23.1 \pm 12.8\%$ (Table 1).

Part B. With lactulose administration, the mean time of capsule arrival at the ICJ was 2.1 ± 1.0 h.

The increase in colon motility resulting from lactulose administration was reflected in the transit data (Table 2). For both the tablets and particles a marked reduction in MRT was seen. The mean MRT for the 5 mm tablets was 8.7 ± 3.4 h and for the 0.2 mm particles 7.0 ± 2.5 h. These values represented, respectively, a 37 and 46% reduction in residence time compared to part A, and were statistically significant ($p = 0.012$ and 0.002, respectively).

Although the mean MRT of the 5 mm tablets was significantly longer than for the 0.2 mm particles ($p = 0.03$), from the individual patient data there was no clear trend, since in five of the 11 subjects, the 0.2 mm MRT was either greater than the 5 mm MRT or about the same (Table 2).

Lactulose administration did not significantly reduce the activity residing in the whole colon after 24 h ($76.2 \pm 19.1\%$), although the amount of activity remaining in the ascending colon was reduced by almost 50% from 23.1 ± 12.8 to $11.7 \pm 12.2\%$ ($p = 0.025$).

Study 2

Data from the study investigating the differential transit of 0.2 mm particles and 8.4 mm tablets are for 10 subjects, since in two subjects one of the three capsules was resident, intact, in the stomach for the whole of the study day.

Again, all of the capsules arrived intact at the ICJ. The mean arrival time was 3.7 ± 0.9 h.

The mean MRT was 8.9 ± 3.2 h for the 0.2 mm particles and 8.6 ± 3.7 h for the 8.4 mm tablets (Table 3). The MRT values for both sizes of particles were markedly reduced compared to

TABLE 3

Colon transit data for study 2 (0.2 mm particles vs 8.4 mm tablets)

Subject	Ascending colon MRT (h)		% of administered of 0.2 mm particles remaining after 24 h	
	8.4 mm tablets	0.2 mm particles	Ascending colon	Whole colon
1	8.75	11.00	12.1	69.3
2	14.00	9.75	10.3	81.3
3	15.75	15.75	29.8	87.6
4	6.75	10.00	16.5	82.6
5	6.00	7.50	2.5	65.3
6	7.50	8.25	9.1	83.1
7	9.75	5.75	2.6	73.3
8	6.25	9.25	20.5	86.2
9	3.50	3.75	16.2	97.9
10	7.75	8.00	6.6	66.9

study 1A, although this may simply reflect the small number of subjects used and the inherently large intersubject variation in colon residence. Presumably, with lactulose administration the residence times of the subjects in study 2 would have been reduced still further.

Again, as for study 1A, there was no significant difference between the mean MRT of the tablets and particles.

At 24 h, $79.3 \pm 10.4\%$ of the administered activity resided in the whole colon and $12.6 \pm 8.5\%$ in the ascending colon (Table 3).

Conclusions

Combining the 0.2 mm MRT values from studies 1A and 2, a mean ascending colon MRT of 11.0 ± 4.0 h is obtained ($n = 21$). This value is in good agreement with other studies which have reported transit times through the ascending colon of 10–12 h (Proano et al., 1990) and 8–11 h (Metcalf et al., 1987). This slow rate of transit supports the premise that the ascending colon may represent a good site to achieve sustained local action or absorption of drug from dosage forms resident there.

Lactulose caused a marked acceleration in transit (study 1B) and may provide a useful model in healthy subjects of disease states where hypermotility is a feature.

As discussed in the introduction, other studies have suggested that the rate of transit through the ascending colon is size-related, with large particles moving more rapidly than small. In the work presented here, under normal conditions there would appear to be no obvious difference in the rate of transit of materials in the size range 0.2–8.4 mm through the ascending colon. Although lactulose administration appeared to cause a separation of the two sizes, the effect was far from universal. A general problem when interpreting the results of colon studies is the inherent inter- and intrasubject variability in transit, which may be large (Price et al., 1991). Consequently, a definitive relationship between particle size and colon transit may only become clear when many more similar studies have been undertaken.

Although there may be no difference in the rate of transit between different sizes of particles, a multiparticulate dosage form may offer benefits over a single unit for sustained drug release in the colon. For example, the wide dispersion of multiparticulates in the colon would be useful for the treatment of widespread colonic disease. In addition, for dosage forms carrying drugs for systemic action, the wide dispersion might enhance drug absorption, especially in distal regions of the colon where close contact between delivery system and mucosa is desirable because of probable poor diffusion through the viscous faecal contents.

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