J. Pharm. Pharmacol. 1985, 37: 874–877
Received April 4, 1985

Drug delivery to the proximal colon

JOHN G. HARDY*, CLIVE G. WILSON, ELIZABETH WOOD

*Department of Medical Physics and Department of Physiology and Pharmacology, Queen's Medical Centre, Nottingham NG7 2UH, UK

The transits of a capsule and a multiparticulate pellet system have been monitored through the gastrointestinal tract in six healthy volunteers. Both preparations moved together through the stomach and small intestine, reaching the colon, on average, 4 h after dosing. Within the colon the pellets dispersed and moved at a slower rate than the capsule. There was considerable intersubject variability in the large bowel transit times. The findings are discussed in terms of drug delivery to the colon.

Inflammation of the colon is commonly treated topically by enema administration. For example, prednisolone solutions have been shown to be effective in the management of ulcerative colitis, particularly for disease affecting the distal colon (Matts 1961; McIntyre et al 1983). The spreading of enema solutions within the large intestine is highly variable, even in healthy subjects (Wood et al 1985). The preparations often fail to reach even the transverse colon (Hay 1982; Wood et al 1985). Oral dosing, therefore, may be a more appropriate route for drug delivery to the proximal colon.

The use of controlled release systems, such as osmotic devices and coated multiparticulate preparations, may facilitate drug delivery to the colon. Such systems could be designed to protect the active compound from the acidic environment of the stomach, and minimize systemic absorption from the small intestine (Dew et al 1982).

The factors affecting the transit of pharmaceutical preparations through the stomach and small intestine have been investigated extensively (Bennett et al 1984; Christensen et al 1985; Davis et al 1984a; Kaus et al 1984). The presence of food in the stomach can greatly delay the gastric emptying of large units such as tablets and capsules (Davis et al 1984a, b). Solutions and small particles tend to empty along with the meal. Having left the stomach, however, tablets, capsules, pellets and solutions all travel through the small intestine together (Christensen et al 1985; Davis et al 1984a; Kaus et al 1984). In normal subjects, transit times through the small intestine are typically 3–4 h (Hardy et al 1984). Within the colon multiple units tend to become widely dispersed (Halls 1965; Hardy & Perkins 1985), although the rates of spreading and transit vary considerably.

The present study compares the transit through the colon of a non-disintegrating capsule and a multiparticulate pellet system. Both preparations were administered simultaneously to normal subjects. The implications of the findings are considered in relation to drug delivery to the colon.

* Correspondence.

MATERIALS AND METHODS

Materials

Two radiolabelled preparations were administered; a non-distintegrating capsule and a multiparticulate system. The non-disintegrating capsule was a pressure sensitive radiotelemetry device, 25 mm long by 9 mm diameter and weighing 3·3 g. The device, along with 5 MBq ^{99m}Tc-labelled diethylenetriaminepentaacetic acid absorbed into filter paper, was contained within a close fitting rubber sheath. The multiparticulate system comprised 0·2 g cation exchange resin pellets 0·5–1·8 mm diameter (Amberlite IR 120 (H), BDH Chemicals, Poole) on to which was adsorbed 1 MBq indium-111. Each dose was contained within a hard gelatine capsule.

Methods

Six healthy male subjects aged 19–22 years participated in the study. None was taking medication and all were non-smokers. All the subjects were regular in their bowel habits and usually defaecated once or twice a day. The study was approved by the local ethical committee and each subject gave written informed consent before taking part.

The volunteers fasted for at least 9 h before the study and had abstained from taking alcoholic drinks for over 30 h. Small anatomical reference markers radiolabelled with indium-111 were taped to the skin anteriorly and posteriorly over the right lobe of the liver. At approximately 0900h each volunteer swallowed the two preparations along with 200 ml water.

Imaging was carried out using a gamma camera

having a 40 cm diameter field of view and fitted with a medium energy (300 keV maximum) parallel hole collimator. The gamma camera was tuned to detect, simultaneously but separately, the 140 keV radiation of technetium-99m and the 245 keV radiation of indium-111. Immediately after dosing, anterior and posterior images, each of 60 s duration, were recorded with the subjects standing. The data were stored by computer for subsequent analysis. Imaging was repeated at approximately 20 min intervals during the first 2 h, at 40 min intervals for the next 3 h and then hourly until midnight. During the night images were recorded at 0200h and 0430h, and hourly imaging was resumed at 0730h. Additional imaging was undertaken immediately before and immediately after eating and defaecation. Except during the night when sleeping, the subjects remained in upright postures, walking, sitting or standing. During the study period each subject consumed: a cup of coffee at 1·5, 5·2, 9·5, 13, 24 and 30 h after dosing; a glass of orange juice at 7·5 h; dinner (energy content 6000 kJ) of prawn cocktail, grilled steak, chips and peas, and fruit salad at 9 h; a breakfast (energy content 1800 kJ) of fruit juice, toast with butter and marmalade, and coffee at 23·5 h. On the first day, lunch (energy content 3200 kJ) comprising one ham and one cheese and tomato roll, and a small carton of fruit yoghurt was eaten by subjects 3 and 4 at 3 h and by subjects 5 and 6 at 5 h; subjects 1 and 2 remained fasting. On the second day the subjects were free to choose their own lunches.

The full sequence of images from each subject was viewed on a television monitor. Dispersion of the pellets allowed clear definition of the stomach and large intestine and the anatomical positions were related to the sites of the reference markers. The location of the non-disintegrating capsule could be readily identified even in the presence of the pellets. The proportion of the pellet dose in each anatomical region was determined by defining regions of interest in the images, as described by Hardy & Perkins (1985). The count rates from each region were corrected for background count rates determined from a region of interest away from the abdomen, and for radioactive decay. The geometric means of the count rates from corresponding regions of interest in pairs of anterior and posterior images were calculated. The radioactivity in each region was expressed as a proportion of the administered dose.

The intraluminal intestinal pressure measurements recorded during this study will be the subject of a separate communication.

RESULTS

At the time of recording the first pair of images from each subject, both preparations were in the stomach. The pellets were released from the gelatine capsule within a few minutes after dosing.

The pellets and the radiotelemetry capsule emptied from the stomach at about the same rates (Table 1). For each subject the difference between the times for 50% of the pellets to empty from the stomach and 50% to enter the large intestine was taken as the small intestinal transit time. The time of the movement of a capsule from one anatomical region to the next was taken to be the mid-time between the successive images about the transition. The median times for gastric emptying, colonic arrival and transit through the small intestine were similar for both preparations (Table 1). In each subject the capsule was observed to move through the small intestine along with the bulk of the pellets.

Table 1. Transit time through the small intestine.

	Time (h)					
	Gastric emptying		Colonic arrival		Small intestinal transit	
Subject	Pellets	Capsule	Pellets	Capsule	Pellets	Capsule
1	1·1	0·8	4·3	3·9	3·2	3·1
2	0·4	0·7	2·5	3·9	2·1	3·2
3	1·2	1·2	3·4	3·6	2·2	2·4
4	1·2	0·2	4·7	3·1	3·5	2·9
5	4·4	3·9	9·2	8·8	4·8	4·9
6	0·6	0·6	4·7	4·8	4·1	4·2
Median	1·2	0·8	4·5	3·9	3·4	3·2
Standard deviation	1·3	1·2	2·1	1·9	1·0	0·8

Both preparations entered the large intestine together. Transit of the tracers within the colon was characterized by occasional aboral movements separated by prolonged periods of stasis. The pellets became dispersed within the ascending and transverse colon (Fig. 1). The duration of residence of the capsules within the proximal colon was highly

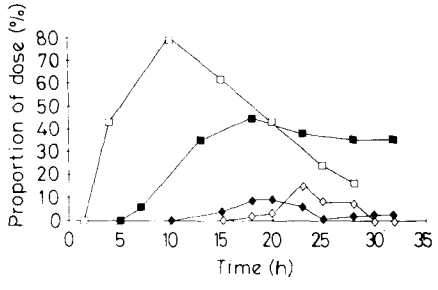

FIG. 1. Distribution of the pellets within the large intestine (mean values n = 6): □ ascending colon, ■ transverse colon, ◆ descending colon, ◇ sigmoid colon.

variable (Table 2), however, they moved through the colon at a faster rate than the pellets. Although both preparations entered the large intestine together (Fig. 2), on average the capsule reached the transverse colon before 86% of the pellets (Table 3). Of the three capsules excreted during the period of imaging, the capsule that travelled fastest through the large bowel was excreted with the smallest proportion of pellets (Table 4). Since the amounts of pellets excreted were estimated from the imaging data, values were not obtained for the other three subjects.

Table 2. Capsule residence in the proximal colon.

Subject	Time (h) Ascending colon	Transverse colon
1	7·5	12
2	3·4	>25
3	5·9	>22
4	5·6	17
5	1·5	11
6	0·7	10

Table 3. Relative transits of the preparations through the proximal colon.

Subject	Proportion of pellets along with or ahead of capsule (%) Terminal ileum	Ascending colon	Transverse colon
1	100	43	9
2	100	65	33
3	100	70	16
4	96	34	8
5	98	34	17
6	100	34	0

Table 4. Excretion of the tracers.

Subject	Capsule transit (h) Mouth to anus	Large bowel	(%) pellets excreted with capsule
1	25	21	78
2	72	68	
3	35	31	
4	37	33	
5	23	14	33
6	17	13	8

The eating of lunch had no apparent effect on the transit of the tracers. By 1800h all the capsules and most of the pellets were in the colon. Imaging immediately before and immediately following din-

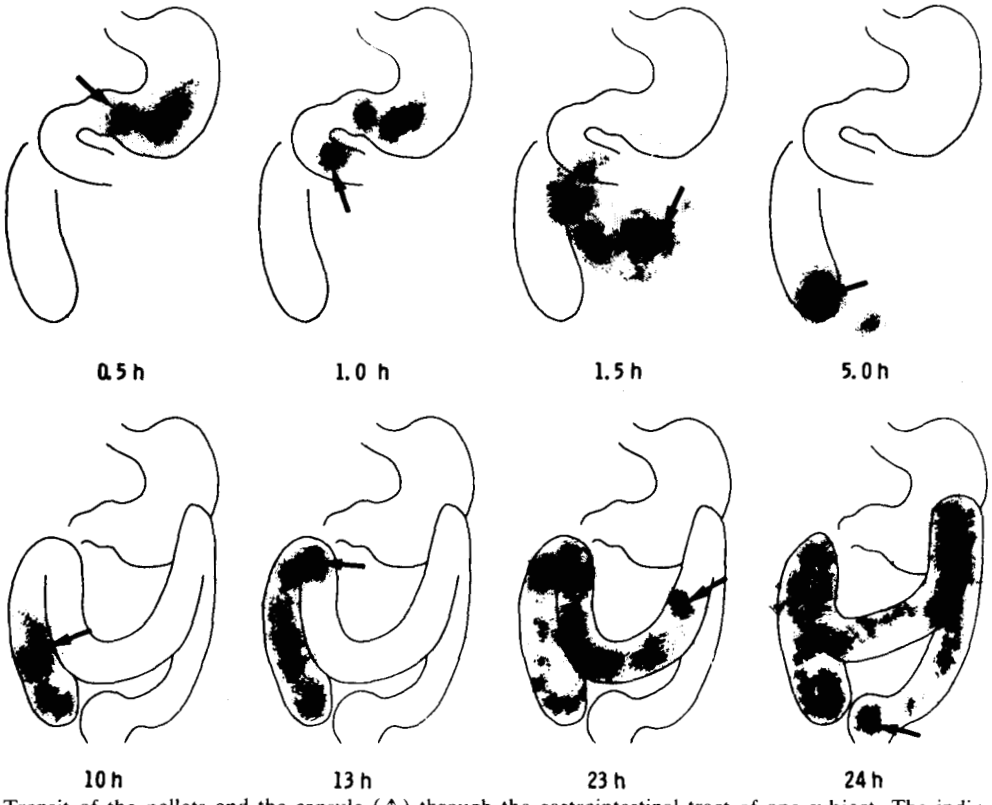

FIG. 2. Transit of the pellets and the capsule (↑) through the gastrointestinal tract of one subject. The indium and technetium images have been superimposed.

ner showed the location of the capsule to be unchanged in three subjects, to have moved from the ascending colon to the hepatic flexure in one subject, and from the hepatic flexure into the transverse colon in the remaining two. Thus eating does not seem to be an important stimulus of intestinal transit.

DISCUSSION

Ideally a system for the delivery of a drug to the proximal colon would avoid release of the active compound whilst in the stomach and small intestine, but allow dispersion on reaching the caecum. Following dosing of moderately active normal subjects on an empty stomach, preparations usually reach the colon within about 5 h. This applies to both multiparticulate and single unit systems. The caecum arrival time, however, can be influenced greatly by the gastric emptying rate, as observed with subject 5 (Table 1). In agreement with previous reports (Christensen et al 1985; Davis et al 1984a), the transit times through the small intestine were similar for the two different preparations.

Within the colon, dispersive systems such as pellets, become widely distributed (Hardy & Perkins 1985). Both the pellets and the capsules remained in the proximal colon for many hours. The large radiotelemetry capsule passed through the colon more rapidly than the much smaller pellets. Such movement has been observed previously (Davis et al 1984a, c). This phenomenon may explain the mixing of markers within the colon reported by Halls (1965). In that study subjects were dosed with markers of increasing sizes along with successive meals. Within the large intestine the batches of markers became interdispersed, which would be in accord with the largest particles moving fastest.

Myoelectrical and intraluminal pressure measurements demonstrate increased colonic motility following a large meal (Snape et al 1978). It has been found both in the present study and previously (Holdstock & Misiewicz 1970; Holdstock et al 1970; Jian et al 1984) that this increased motility does not, in general, result in aboral propulsion of the colonic contents. Anterograde movement of materials through the colon is not a continuous process. It is the result of periods of rapid transit often separated by several hours of little progression. There was considerable intersubject variation in transit times through each section of the colon, and this was unrelated to the gastric emptying rates or the transit times through the small intestine. This independence of transit rates through stomach, and small and large intestines was also observed by Read et al (1980). Intersubject mouth-to-anus transit times show considerable variability (Hinton et al 1969; Read et al 1980). We found the capsule transit times to range from 17 to 72 h; subjects were dosed when fasted and normally defaecated at least once a day.

The present study provides data upon which to base the design of systems for the delivery of drugs to the proximal colon. The drug should be retained within the preparation for approximately the first 5 h after administration to a fasted patient, to allow time for gastric emptying and transit through the small intestine. If drug were released from a dispersive preparation over the next 10 h it would tend to distribute throughout the ascending and transverse colon. Drug levels would be difficult to control if the active compound were released over longer periods, due to the variability in excretion patterns.

REFERENCES

Bennett, C. E., Hardy, J. G., Wilson, C. G. (1984) Int. J. Pharm. 21: 341–347

Christensen, F. N., Davis, S. S., Hardy, J. G., Taylor, M. J., Whalley, D. R., Wilson, C. G. (1985) J. Pharm. Pharmacol. 37: 91–95

Davis, S. S., Hardy, J. G., Taylor, M. J., Whalley, D. R., Wilson, C. G. (1984a) Int. J. Pharm. 21: 167–177

Davis, S. S., Hardy, J. G., Taylor, M. J., Whalley, D. R., Wilson, C. G. (1984b) Ibid. 21: 331–340

Davis, S. S., Hardy, J. G., Taylor, M. J., Stockwell, A., Whalley, D. R., Wilson, C. G. (1984c) J. Pharm. Pharmacol. 36: 740–742

Dew, M. J., Hughes, P. J., Lee, M. G., Evans, B. K., Rhodes, J. (1982) Br. J. Clin. Pharmacol. 14: 405–408

Halls, J. (1965) Proc. R. Soc. Med. 58: 859–860

Hardy, J. G., Perkins, A. C. (1985) Nucl. Med. Commun. 6: 217–224.

Hardy, J. G., Davis, S. S., Wilson, C. G. (1984) J. Nucl. Med. 25: P59

Hay, D. J. (1982) in: Wilson, C. G., Hardy, J. G., Frier, M., Davis, S. S. (eds) Radionuclide Imaging in Drug Research. Croom Helm, London, pp 171–180

Hinton, J. M., Lennard-Jones, J. E., Young, A. C. (1969) Gut 10: 842–847

Holdstock, D. J., Misiewicz, J. J. (1970) Ibid. 11: 100–110

Holdstock, D. J., Misiewicz, J. J., Smith, T., Rowlands, E. N. (1970) Ibid. 11: 91–99

Jian, R., Najean, Y., Bernier, J. J. (1984) Ibid. 25: 728–731

Kaus, L. C., Fell, J. T., Sharma, H., Taylor, D. C. (1984) Int. J. Pharm. 20: 315–323

Matts, S. G. F. (1961) Br. Med. J. 1: 165–168

McIntyre, P. B., Macrae, F. A., Berghouse, L., English, J., Lennard-Jones, J. E. (1983) Gut 24: A998–A999

Read, N. W., Miles, C. A., Fisher, D., Holgate, A. M., Kime, N. D., Mitchell, M. A., Reeve, A. M., Roche, T. B., Walker, M. (1980) Gastroenterology 79: 1276–1282

Snape, W. J., Matarazzo, S. A., Cohen, S. (1978) Ibid. 75: 373–378

Wood, E., Wilson, C. G., Hardy, J. G. (1985) Int. J. Pharm. 25: 191–197.