J. Pharm. Pharmacol. 1988, 40: 376–377
Communicated November 23, 1987

© 1988 J. Pharm. Pharmacol.

The effect of capsule size and density on transit through the proximal colon

G. PARKER, C. G. WILSON, J. G. HARDY, *Department of Medical Physics and Department of Physiology and Pharmacology, Queen's Medical Centre, Nottingham, NG7 2UH, UK*

Abstract—Colonic transit of radiolabelled capsules has been monitored in 18 healthy subjects using gamma scintigraphy. The capsules ranged in volume from 0·3–1·8 cm^3 and in density from 0·7–1·5 gcm^{-3}. The capsules were administered after an overnight fast and entered the colon, on average, 5 h after dosing. Transit rates through the proximal colon were independent of capsule density. Any effect due to capsule volume was small when compared with intersubject variations in transit rates. Within 10 h of entering the colon 80% of the units had reached the splenic flexure. These findings have implications in the design of non-disintegrating, sustained release dosage forms.

The rate of transit of pharmaceutical preparations through the colon can have a major influence on the bioavailability of drugs, such as oxprenolol, which are absorbed throughout the intestines (Davis & Hardy 1988). Additionally, transit rates through the intestines determine the sites of drug release from enteric-coated preparations, which is particularly important for topically acting compounds (Hardy et al 1987).

The gastric emptying and small intestinal transit of pharmaceutical preparations has been studied extensively (Davis et al 1986). The presence of food in the stomach delays the gastric emptying of tablets and capsules, whilst transit through the small intestine is independent of the physical characteristics of the dosage forms. Within the colon, transit is characterized by short bursts of propulsion separated by periods of stasis. Solutions and small particles pass through the proximal colon more slowly than large units (Hardy et al 1985). Little information is available, however, concerning the relationship between colonic transit and the physical properties of pharmaceutical preparations. The present study investigates the influence of capsule size and density on transit through the proximal colon.

Methods

Materials. Units were prepared comprising hard gelatin capsules filled with ion exchange resin and glass beads and enclosed in tight fitting rubber sheaths secured with suture thread. In-vitro studies demonstrated that such units would remain intact in a water bath for over 20 h. Five types of unit were prepared: three of density 1·1 gcm^{-3} with volumes 0·3, 0·8 and 1·8 cm^3, plus two of volume 0·8 cm^3 with densities 0·7 and 1·5 gcm^{-3}.

The ion exchange resins were Amberlite IRA 410 labelled with technetium-99m and Amberlite IR 120 labelled with indium-111. At the time of dosing each capsule contained either 1 MBq technetium-99m or 0·3 MBq indium-111.

Subjects. Eighteen healthy male volunteers aged 19–22 years participated. None was taking any medication nor on a special diet, and all abstained from alcohol for at least 24 h before dosing. The study was approved by the Medical School Ethical Committee and each subject gave written informed consent.

Correspondence to: J. G. Hardy, Department of Medical Physics, Queen's Medical Centre, Nottingham, NG7 2UH, UK.

Procedure. The study was undertaken in two parts: one an investigation of the effect of capsule size, and the other of capsule density. Nine subjects participated in each part.

Each subject was dosed on two occasions one week apart. On each occasion he swallowed three identical technetium-labelled units of a specific size and density and three identical indium-labelled units of a different type. Dosing was randomized, such that each combination of units was monitored in six subjects.

After an overnight fast, at 0700 h each subject swallowed six units along with 100 mL water radiolabelled with 1·5 MBq ^{99m}Tc-labelled diethylenetriaminepentaacetic acid. A small ^{111}In-labelled anatomical reference marker was taped to the skin to the right of the stomach. The distributions of the radioactivity were monitored using a 40 cm diameter field of view gamma camera fitted with a medium energy (300 keV maximum) parallel hole collimator. The gamma camera was tuned to detect separately the 245 keV radiation of indium-111 and the 140 keV radiation of technetium-99m. Anterior images of 60 s duration were recorded at regular intervals over a period of 17 h. The subjects were moderately active during the monitoring period and were imaged standing.

During each experiment the subjects were provided with lunch at 1300 h comprising, orange juice, steak, chips and peas followed by gateau (4500 kJ); and dinner at 1830 h of orange juice, scampi, chips and salad followed by cheesecake (5300 kJ). Additionally each subject consumed 100 mL orange juice at 1030 h, a cup of coffee at 1600 h and coffee and biscuits at 2030 h.

The locations of the units were determined by viewing the full sequence of images on a television monitor. The distribution of the radiolabelled water facilitated localization of the stomach and colon relative to the anatomical reference marker. For each time of imaging, from the pair of technetium and indium images the number of units in the stomach, small intestine and in each section of the colon could be established.

Results

The median times for gastric emptying and small intestinal transit are listed in Table 1. Similar times were obtained from both groups of subjects and for all the preparations.

Previous studies have demonstrated increasing separation of large capsules and small particles during transit through the ascending and transverse colon (Hardy et al 1985, 1986a). Distal to the splenic flexure the preparations tend to come together before defaecation. In the present study, therefore, caecum to splenic flexure transit times were measured. The proportions of

Table 1. Median transit times.

Subject group	Capsule volume (cm^3)	Capsule density (gcm^{-3})	Gastric emptying (h)	Small intestinal transit (h)
A	0·8	0·7	0·8	4·0
	0·8	1·1	0·9	4·7
	0·8	1·5	0·7	4·8
B	0·3	1·1	0·9	4·3
	0·8	1·1	0·5	4·7
	1·8	1·1	1·0	4·5

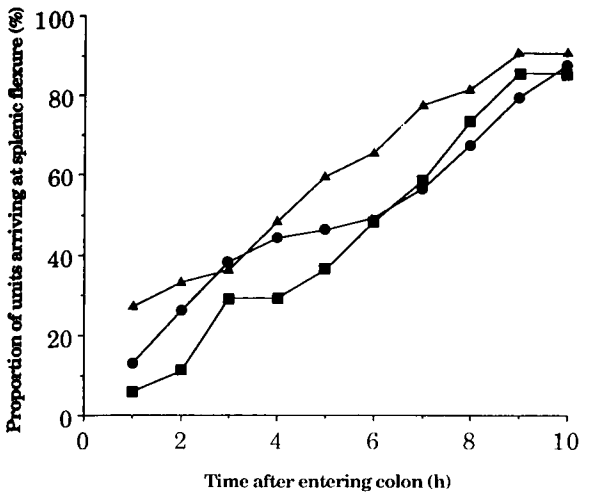

FIG. 1. Effect of capsule density on colonic transit in the subjects of group A. The capsules had a volume of 0·8 cm^3 and densities of 0·7 (●), 1·1 (▲) and 1·5 gcm^{-3} (■).

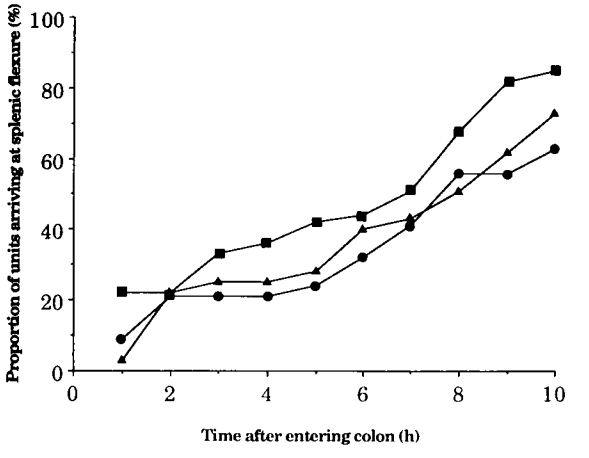

FIG. 2. Effect of capsule size on colonic transit in the subjects of group B. The capsules had a density of 1·1 gcm^{-3} and volumes of 0·3 (●), 0·8 (▲) and 1·8 cm^3 (■).

the units reaching the splenic flexure as a function of time after entering the colon are shown in Figs 1, 2.

From Fig. 1 it is apparent that capsule transit through the proximal colon is not dependent on density. For capsules of the same density, there was a tendency for the transit rates to increase with unit size (Fig. 2). Over the range of volumes investigated, however, the differences were small and were masked by the differences between the transit rates of the same capsule type in the two groups of subjects. Overall 80% of the units had reached the splenic flexure within 10 h of entering the colon.

Discussion

It is well established that propulsion of colonic contents occurs as a series of mass movements. Such propulsion has been related to increases in colonic motility resulting, for example, from eating (Holdstock et al 1970) or chemical stimulation (Spiller et al 1986). In resting subjects, however, consumption of a meal results in increases in segmental pressure activity but has little effect on propulsion (Holdstock et al 1970; Hardy et al 1986b). Transit times through the colon are subject to wide intersubject variations, even in healthy individuals.

Small particles and solutions pass through the proximal colon more slowly than large units (Hardy et al 1985). Residence of topically acting drugs in the proximal colon can be maximized, therefore, by dosing with enteric-coated preparations designed to disintegrate about 5 h after leaving the stomach (Hardy et al 1987). Additionally, it has been shown that the solution from an osmotic pump sustained release dosage form is retained in the ascending and transverse colon for a longer period than the device (Davis et al 1984). It is not clear from previous studies whether the small particles are dealt with in the colon in a similar manner to liquids, or whether there is a systematic separation of solids based on size or density.

In the present study, dosing after an overnight fast minimized retention of the units in the stomach. The average gastric emptying times of 0·5–1·0 h for all the sizes and densities are in agreement with previous findings (Davis et al 1986). The median small intestinal transit times were about 4·5 h for all the preparations. Thus the units entered the large intestine about 5 h after dosing.

The results of the present study show that for large units such as capsules, transit through the proximal colon is little affected by size or density. On average, 50% of the units reached the splenic flexure within 7 h of entering the colon. These findings are particularly relevant to the design of non-disintegrating, sustained release dosage forms. There was a tendency for the larger units to arrive earlier at the splenic flexure. When, however, the data from the two groups of subjects were compared it was evident that, even in healthy individuals, any effect of unit size was masked by intersubject variability. When subjects are drawn from wider populations even greater variations in transit times are likely to occur due, for example, to differences in diet or pathology. Thus, in the study by Metcalf et al (1987) the estimated average caecum to splenic flexure transit time was 14 h with, in general, faster transit in men than women. Allowance must be made for such variability when designing pharmaceutical products.

The authors wish to thank Smith and Nephew Research Limited for financial assistance with this study.

References

Davis, S. S., Hardy, J. G. (1988) Drug delivery in the gastrointestinal tract. In: Kumar, D., Gustavsson, S. (eds) Illustrated Guide to Gastrointestinal Motility, John Wiley, Chichester, in press.

Davis, S. S., Hardy, J. G., Taylor, M. J., Stockwell, A., Whalley D. R., Wilson, C. G. (1984) The in-vivo evaluation of an osmotic device (Osmet) using gamma scintigraphy. J. Pharm. Pharmacol. 36: 740–742

Davis, S. S., Hardy, J. G., Fara, J. W. (1986) Transit of pharmaceutical dosage forms through the small intestine. Gut 27: 886–892

Hardy, J. G., Wilson, C. G., Wood, E. (1985) Drug delivery to the proximal colon. J. Pharm. Pharmacol. 37: 874–877

Hardy, J. G., Wood, E., Clark, A. G., Reynolds, J. R. (1986a) Whole-bowel transit in patients with the irritable bowel syndrome. Eur. J. Nucl. Med. 11: 393–396

Hardy, J. G., Wood, E., Clark, A. G., Reynolds, J. R. (1986b) Colonic motility and enema spreading. Ibid. 12: 176–178

Hardy, J. G., Healey, J. N. C., Lee, S. W., Reynolds, J. R. (1987) Gastrointestinal transit of an enteric-coated delayed-release 5-aminosalicylic acid tablet. Aliment. Pharmacol. Ther. 1: 209–216

Holdstock, D. J., Misiewicz, J. J., Smith, T., Rowlands, E. N. (1970) Propulsion (mass movements) in the human colon and its relationship to meals and somatic activity. Gut 11: 91–99

Metcalf, A. M., Phillips, S. F., Zinsmeister, A. R., MacCarty, R. L., Beart, R. W., Wolff, B. G. (1987) Simplified assessment of segmental colonic transit. Gastroenterology 92: 40–47

Spiller, R. C., Brown, M. L., Phillips, S. F. (1986) Decreased fluid tolerance, accelerated transit, and abnormal motility of the human colon induced by oleic acid. Ibid. 91: 100–107