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The use of gamma scintigraphy to follow the gastrointestinal transit of pharmaceutical formulations

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The technique of gamma scintigraphy has been used to follow the transit of a solution and a pellet formulation in the gastrointestinal tract of healthy volunteers. The emptying of the formulations from the stomach and their arrival at the caecum could be quantified, thereby allowing calculation of transit times for the small intestine. Gastric emptying was affected by the nature of the formulation, i.e. liquid or solid. However, transit through the small intestine was independent of the nature of the administered material.

Controlled release dosage forms normally comprise two distinct types; single unit dosage forms such as matrix tablets, osmotic devices etc., and multi-unit dosage forms, such as coated tablets and coated crystals. Each particular system has its own advantage or disadvantage in terms of pharmaceutical processing and release profiles. It has also been claimed that multiple unit dosage forms are more reliable in-vivo, in that they empty from the stomach in a randomized way, and also that they can spread out in the intestines, thereby giving a more predictable and reliable release of the drug contained therein (Bechgaard & Christensen 1982). Liquids and very small particles (less than 3 mm diameter) have been shown to be emptied from the stomach more rapidly than larger particles (Dozois et al 1971). The rate of emptying of a solution can be normally described by an exponential function and typical half-times for emptying range from 10–60 min (Bechgaard 1982). Larger particles are retained in the stomach for longer periods and for single unit dosage forms, gastric emptying has been characterized by an essentially random process with a large intra- and inter-subject variation (Rosswick et al 1967).

Pellet dosage forms of sizes of 1 mm and less are said to be small enough to pass through the pylorus when closed, and it has even been suggested that they can behave more as a solution than a solid when administered (Kelly 1981). Similar arguments have been applied to transit in the intestine, particularly where spreading of the dosage form is concerned (Beckett 1981).

Early studies employed X-ray techniques to monitor the gastrointestinal transit of radiopaque dosage forms (Wagner et al 1960; Galeone et al 1981). These preparations usually contained barium sulphate, and this almost certainly modified the characteristics of the dosage forms. Other disadvantages of radiographic studies are the relatively high radiation doses to which the subjects are exposed, and the difficulty of quantification of the transit of dispersable systems. For definition of gastrointestinal anatomy, however, X-ray examinations such as barium meals and enemas remain the methods of choice.

In recent times the technique of gamma scintigraphy has been used to monitor physiological processes such as the gastric emptying of pharmaceutical dosage forms (Alpsten et al 1976; Hunter et al 1980, 1981, 1982; Daly et al 1982; Digenis 1982). Similarly, the use of gamma-emitting radiolabelled foodstuffs or pellets to follow gastric emptying in clinical practice is now well established (Christian et al 1980; Theodorakis et al 1980, 1982) and recently the use of gamma scintigraphy for following small bowel transit times has been described (Read et al 1982a). The correlations between data obtained by radionuclide imaging and the use of chemical markers has been good (Caride et al 1982).

In contrast, there have been a few studies that have investigated gastrointestinal transit (mouth to caecum) of dosage forms in normal volunteers. The data of Bogentoft et al (1982) obtained using a profile scanning technique indicate that pellets have

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transit times through the small intestine of about 2–5 h. New preparations designed to release drugs in the human colon have been investigated by Dew et al (1982) who, in a radiographic study, found that for 36 capsules and 6 subjects, 50% of the controlled release capsules reached the colon in 5 h, 72% in 8 h and 89% in 12 h.

In our own studies we have used the gamma camera and gamma emitting radionuclides as a means of following the gastrointestinal transit of a variety of non-disintegrating sustained release dosage forms, and the release of labelled compounds (Daly et al 1982; Davis et al 1983; Wilson et al 1984). The present paper extends this work and describes studies of the transit of liquid and pellet systems from the stomach through the small intestines to the colon. Using scintigraphic imaging it has been possible to identify the ileocaecal junction and thereby allow determination of stomach to caecum transit times of these dosage forms.

MATERIALS AND METHODS

Radiopharmaceuticals

The liquid preparation was an aqueous solution of ^{99m}Tc-labelled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA). The technetium-99m was obtained as sodium pertechnetate solution by elution of a generator (CIS (UK) Limited, London), and the ^{99m}Tc-DTPA prepared using a kit containing 9·1 mg calcium trisodium diethylenetriaminepentaacetate and 0·45 mg stannous chloride dihydrate (CIS (UK) Ltd, London). Each dose contained 2 MBq ^{99m}Tc-DTPA in 100 ml water.

The pellets were prepared as described by Christensen (1984). These were non-toxic, had a density of 1·81 Mg m^{-3} (sieve fraction 0·71–1·4 mm) and were radiolabelled by soaking in ^{99m}Tc-sodium pertechnetate solution. Each dose contained approximately 500 pellets (0·8 g) radiolabelled 2 MBq technetium-99m.

In-vivo studies

A group of 10 healthy male volunteers, 19–32 years, height 1·76–1·85 m, 64–93 kg, participated with informed consent. Each was allowed to have, if desired, a light breakfast comprising cereal, coffee or tea, toast, butter, marmalade, at least 1 h before the commencement of the study. Each volunteer swallowed 100 ml of a labelled preparation. (Two volunteers received only the solution while five received only the pellet. Three volunteers received both solution and pellet formulations on separate occasions.) The pellets were dosed in the form of a mixture consisting of 100 g Complan in 300 ml of water. No additional food was allowed until 2 h after dosing. After this time the subjects ate and drank normally, although throughout the study smoking was not allowed.

Imaging was undertaken with the subjects standing using a gamma camera having a 40 cm field of view fitted with a low energy parallel hole collimator. External anatomical reference markers comprising adhesive patches labelled with a small quantity of technetium-99m were positioned anteriorly and posteriorly over the right lobe of the liver. Anterior and posterior images each of 60 s duration were taken at suitable (e.g. 20–30 min) intervals over a period of 10 h, and the data recorded on a computer for analysis. Subsequently regions of interest were defined around the stomach and colon regions of the images and the activity in these areas quantified. Corrections were applied for background activity and for radioactive decay. The attenuation of the radiation by overlying tissues can give rise to incorrect estimates of the amounts of radioactivity in the regions of interest when unidirectional images only are recorded (Tothill et al 1978). However, the use of the geometric mean of the anterior and posterior counts gives a result that is relatively independent of the depth of the source (Tothill et al 1978) and this procedure was adopted in the present study.

RESULTS

Representative images are shown in Fig. 1 for different regions of the gastrointestinal tract. The stomach and colon images were characteristic and easily permitted the identification of a region of interest for subsequent quantification of the radioactivity. The transit of activity through the small

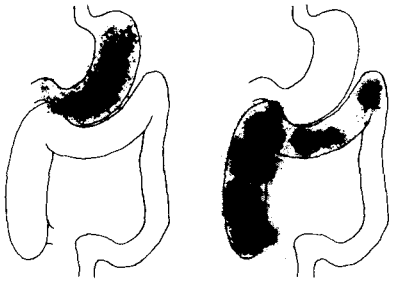

FIG. 1. Scintiscans showing different regions of GIT following administration of solution and pellet formulations.

intestine could be followed within a given individual and regions such as the duodenum, jejunum and ileum identified. However, the looping of intestinal segments and the overlying of different regions of activity precluded quantification.

The transit of solution and pellets in the small intestine was also characterized by a change in the position of the activity at each imaging time. In contrast, once the labelled material reached the colon the transit was relatively slow. The rate of gastric emptying was the main factor affecting the spreading of the pellets in the small intestine and once the material had left the stomach there was little, if any, additional spreading. In one subject, after the administration of the labelled pellets, a fraction of the material is seen to have left the stomach as a discrete bolus. This bolus of activity is discernible in the small intestine with no evidence of spreading (Fig. 2).

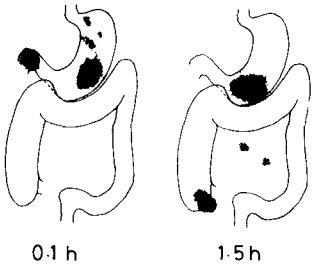

FIG. 2. Scintiscans showing the bolus emptying of part of a pellet formulation from the stomach.

Table 1. Gastrointestinal transit of solution and pellet formulations. V = volunteer, GE = gastric emptying, CA = colonic arrival, T = transit through small intestine.

	Solution t50% (min)			Pellets t50% (min)		
V	GE	CA	T	GE	CA	T
1	25	230	205	—	—	
2	10	190	180	—	—	
3	30	270	240	95	220	125
4	10	270	260	116	198	82
5	15	360	345	120	290	170
6	—	—	—	124	362	238
7	—	—	—	95	407	312
8	—	—	—	93	285	192
9	—	—	—	81	266	175
10	—	—	—	61	400	339
Mean	18	264	246	99	304	204
s.e.m.	4	28	28	7	28	31
n = 5				n = 8		

Table 1 gives values for the time for 50% activity to leave or reach the given region of interest. The activity-time profiles for gastric emptying and colonic arrival are shown in Fig. 3 for the pellet formulations in the form of pooled data for the 8 subjects. The emptying from the stomach and the arrival in the colon are seen to be linearly related to time. A measure of the degree of spreading of the pellets can be obtained from the gradient of the curve for gastric emptying.

DISCUSSION

The results of the present study show that it is possible to measure both the gastric emptying of

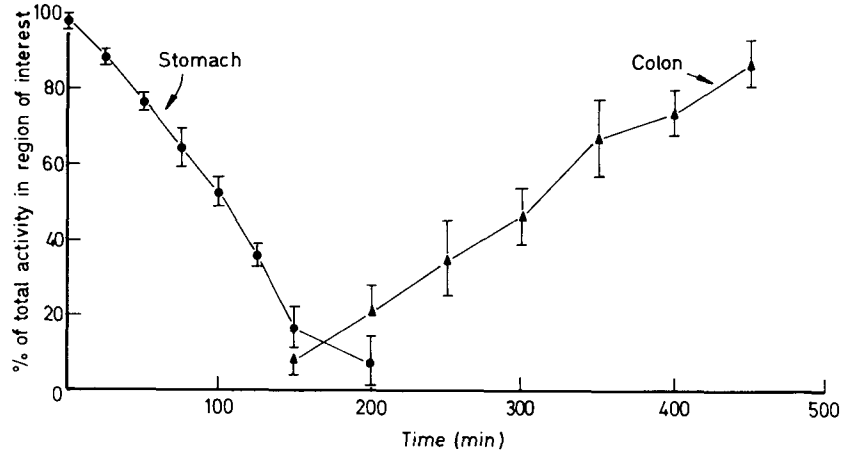

FIG. 3. Gastrointestinal transit of radiolabelled pellets (Mean ± s.e.m., n = 8).

formulations and their arrival at the caecum, thereby permitting the calculation of the transit times for the passage through the small intestine. The results for gastric emptying are in agreement with the known behaviour of solids (Heading et al 1971). The mean time for half emptying for the liquid (10–30 min) is within the range 12–50 min as observed in previous investigations (Bechgaard & Christensen 1982). Similarly the gastric emptying of the pellets (t50% = 99 ± 7 min) agrees well with literature values for light solid meals (77 ± 5 min for a 300 g meal) (Christian et al 1980) and the limited data for multiple unit dosage forms (t50% 90–180 min depending upon fasting or non-fasting state) (Bechgaard & Christensen 1982).

Gastrointestinal transit data for lactulose solutions labelled with ^{99m}Tc-DTPA solutions administered in a replicate study to 7 fasted subjects reported by Caride et al (1982) were t50% 72·7 ± 7 min with a range of 47–139 min (n = 14). The values obtained in the present study, however, are much longer, but the subjects were not in a fasted state and the preparation did not contain lactulose which has been shown to accelerate small intestinal transit (Read et al 1982a). Indeed, in a recent abstract, Prokop et al (1984) have reported a small intestinal transit time in man (n = 4) for water of 248 ± 58 min, 240 ± 47 min and 232 ± 54 min on three seperate occasions using a scintigraphic method. Our value of 246 ± 28 min fits extremely well. Data for the transit through the small intestine of multiple units have been reported by Bogentoft et al (1982) as being between t50% = 132 and 282 min depending on fasting or non-fasting state with a range 30–465 min (n = 6). Our mean value of 204 ± 31 min for pellets agrees well. Our results also show that, although there was a significant difference between the gastric emptying of solution and pellet formulations, there was no significant difference in their transit through the small intestine. That is, the different times at which solutions and pellets arrived at the caecum were determined solely by differences in gastric emptying and not transit through the small intestine. Similarly Read et al (1982b) have failed to show any correlation between gastric emptying and small bowel transit time in a large number of normal subjects after they had eaten the same test meal. The rate of gastric emptying could influence the transit of food along the first 70 cm of the small intestine, but had little or no influence on the rate of transit through the whole of the small intestine. Read et al (1982b) suggested that the ileum may act as a kind of buffer zone delaying and concentrating solid material. Passage through the ileum would then tend to normalize mouth to caecum transit, provided that the bulk of material entering the ileum was not excessive, nor the rate of entry into the ileum too rapid.

Gastrointestinal transit can be greatly influenced by factors such as diet and emotional state, which may account for the inter- and intra-subject variations in transit times in the present study. As a consequence, it is suggested that the best way to compare formulations using small groups of subjects would be to use two formulations administered concurrently, each being labelled with a different radionucide emitting radiation of different gamma ray energies. In this way a cross-over investigation could be carried out on the one occasion.

The technique of gamma scintigraphy can be used to follow the gastric emptying and intestinal transit of solution and multiple unit (pellet) formations. The results suggest that the dispersion of liquid and pellet pharmaceutical formulations is controlled by the rate and pattern of gastric emptying. Within the small intestine the materials tend to move as boluses and spreading is not as great as we might have expected. The transit times for 50% of the labelled material to reach the caecum from the stomach are not statistically different for the liquid and pellet systems. The results also show that gamma scintigraphy is a powerful technique for studying formulation variables (e.g. particle size or density) as well as for the comparison of different formulation types (multiple versus single unit systems).

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