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Gastrointestinal transit of small tablets in patients with ulcerative colitis

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Summary

The gastrointestinal transit of 5 small tablets has been monitored in each of 6 patients with ulcerative colitis. The mean gastric emptying time of 1.6 h and small intestinal transit time of 3.4 h were the same as found previously for healthy subjects. The tablets were retained within the proximal colon for at least 6 hours. Only one patient excreted any of the tablets within 24 h. These findings indicate that small tablets could be used as controlled-release drug delivery systems in ulcerative colitis.

Introduction

The gastrointestinal transit of pharmaceutical dosage forms has been studied extensively in healthy subjects (Davis et al., 1986), but little information is available concerning transit in patients with conditions such as ulcerative colitis. This condition is usually treated with topically acting preparations and the efficacy of such treatments will be influenced by the residence time of the drug product within the colon.

In a previous study enteric-coated mesalazine tablets exhibited normal gastric emptying and transit through the small intestine in a group of patients with inflammatory bowel disease (Hardy et al., 1987). Colonic transit, however, is highly variable even in healthy subjects (Metcalf et al., 1987). Indeed, it is well established that capsules pass through the colon more rapidly than solutions and small particles (Hardy et al., 1985, 1986). Capsule size and density, over the range normally encountered in pharmaceutical preparations, appear to have little influence on colonic transit (Parker et al., 1988).

The present study investigates the potential of small tablets as drug delivery systems for use in the treatment of ulcerative colitis. Such a system should have the advantage of providing a spreading of the delivered drug to the target region.

Materials and Methods

Patients

Six patients, 5 male and one female, aged 29–80 years, participated. Their clinical details are summarised in Table 1. Two had active disease, and in 4 the disease was quiescent. None of the patients

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TABLE 1

Patients with ulcerative colitis

Subject	Age (years)	Sex	Time since diagnosis (years)	Current disease		Current treatment
				Extent	Activity	
1	29	M	11	whole colon	active	mesalazine, loperamide, prednisolone
2	72	M	4	L colon	active	mesalazine, loperamide
3	50	F	6	L colon	inactive	sulphasalazine
4	54	M	10	mid-transverse and R colon	inactive	mesalazine, loperamide, prednisolone
5	59	M	12	whole colon	inactive	prednisolone
6	80	M	7	L colon	inactive	sulphasalazine

had been treated surgically. All were taking medication at the time of the study.

The study was approved by the Hospital Ethical Committee and each patient gave written informed consent before taking part.

Procedure

Non-disintegrating tablets, 4 mm diameter and 4 mm thick, were prepared from ethyl cellulose and coated with cellulose acetate. Each tablet contained 0.6 mg cation exchange resin powder (Amberlite CG120) radiolabelled with 0.2 MBq indium-111, referenced to the time of dosing.

Each patient consumed a normal diet and took no alcohol on the two days immediately prior to the study. On the study day, after an overnight fast, each subject was provided with a breakfast of fruit juice, toast with butter and marmalade, and a cup of tea, at 08.30 h. At about 09.10 h each patient swallowed 5 tablets with 100 ml water. The water was radiolabelled with 4 MBq $^{99}Tc^{m}$-labelled diethylenetriaminepenta-acetic acid to outline the anatomy of the stomach and intestine.

Immediately after dosing, an anterior image of the abdomen of 60 s duration was recorded using a gamma camera. The camera had a 40 cm diameter field of view and was fitted with a medium-energy (300 keV maximum) parallel-hole collimator. The camera was tuned to detect simultaneously the 245 keV radiation of indium-111 and the 140 keV radiation of technetium-99m, and the two images were recorded separately by computer. The subjects were imaged at intervals over a 12 h period: approximately every 15 min during the initial 4 h, at 30-min intervals until 18.00 h, and subsequently every 40 min. The images were recorded with the subjects standing, but they were seated for most of the study period. The subjects returned for imaging the following morning.

During the 12 h after dosing each subject consumed: lunch at 13.00 h comprising grilled steak, chips and peas followed by a cup of coffee; and an evening meal at 18.00 h of ham, salad, bread and butter, a cold sweet and a cup of tea. They had coffee at 11.15 h, 15.30 h and 19.45 h and were free to choose their own breakfasts on the second day.

The gamma camera images were viewed on a television monitor. The technetium distribution outlined the stomach and the colon, facilitating localisation of the tablets (Fig. 1).

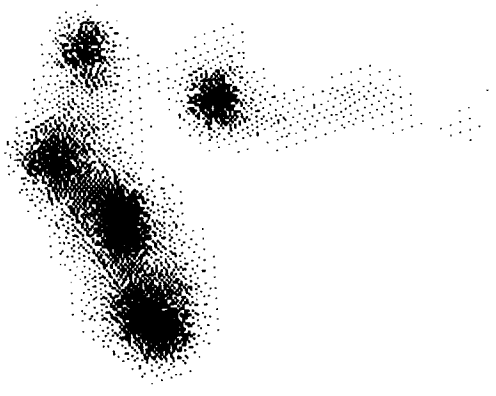

Fig. 1. Combined ^{111}In-tablet and $^{99}Tc^{m}$-solution image recorded 8 h after dosing, showing 5 tablets in the colon of Subject 2.

Results

The mean gastric emptying and small intestinal transit times for each subject are listed in Table 2. All the tablets had left the stomach within 3.6 h. Small intestinal transit times for individual tablets ranged from 1.8 h in Subject 6 to 5.4 h in Subject 5.

The residence times in the ascending colon ranged from less than 1 h to over 20 h. The values for each tablet are given in Table 3. The tablets remained in the ascending and transverse colon region for at least the times listed in Table 4, and were all in this region 12 h after dosing. In Subjects 3–6, 4 or 5 of the tablets were still present in the proximal colon at 24 h.

Subject 1 voided all 5 tablets within 24 h. This patient defaecated 5 times during the study period, at 11.15 h, 18.30 h, 06.15 h, 07.30 h and 08.45 h. Since at 21.20 h, 4 tablets were in the ascending colon and one in the transverse colon, excretion must have occurred between 21 and 24 h after dosing. None of the other patients had diarrhoea, nor did they excrete any of the tablets within 24 h, although 4 defaecated between 06.30 h and the time of recording the final images.

TABLE 2

Gastric emptying and small intestinal transit times

Subject	Gastric residence (h) mean (±1 S.D.)	Small intestinal transit (h) mean (±1 S.D.)
1	1.7 (0.97)	3.7 (0.74)
2	3.1 (1.00)	2.3 (0.78)
3	1.3 (0.76)	2.7 (0.74)
4	1.4 (0.33)	2.4 (0.29)
5	1.6 (0.40)	4.9 (0.42)
6	0.46 (0.22)	3.9 (0.25)
Overall	1.6 (1.0)	3.4 (1.1)

TABLE 3

Residence times in the ascending colon

Subject	Tablet residence (h)				
1	< 1.1	> 6.3	> 6.6	> 6.6	> 6.6
2	0.9	1.1	3.6	3.6	3.6
3	0.8	0.8	1.3	1.3	4.1
4	7.9	> 7.9	> 8.6	> 8.6	> 20
5	1.6	1.6	> 5.9	> 5.9	> 5.9
6	> 20	> 20	> 20	> 20	> 20

TABLE 4

Combined residence times in the ascending and transverse colon

Subject	Minimum tablet residence (h)				
1	6.6	6.6	6.6	6.6	7.9
2	6.7	6.7	6.7	6.7	7.2
3	8.2	20	20	20	20
4	7.9	20	20	20	20
5	17	17	17	17	17
6	20	20	20	20	20

Discussion

The mean gastric emptying time of 1.6 h for tablets taken after a light meal, and the mean small intestinal transit time of 3.4 h are the same as for healthy subjects (Davis et al., 1986). These findings are in agreement with the transit rates for enteric-coated mesalazine tablets in patients with ulcerative colitis (Hardy et al., 1987).

Capsule transit times through the proximal colon in healthy subjects are highly variable. In a study in males aged 19–22 years, 50% of capsules reached the splenic flexure within 7 h of entering the colon (Parker et al., 1988). In a similar group (Hardy et al., 1985) the median capsule residence in the ascending and transverse colon was 21 h. Metcalf et al. (1987) estimated an average caecum to splenic flexure transit time of 14 h for subjects drawn from a wider population.

In a group of patients with quiescent inflammatory bowel disease, a dispersed mesalazine preparation was retained in the colon of most subjects 23 h after dosing (Hardy et al., 1987). In the present study colonic transit was fastest in the two patients with active disease. Even in the patient with diarrhoea, however, the tablets were retained in the proximal colon for more than 6 h and in the large bowel for at least 18 h.

Tablet transit was not abnormally fast in the group of patients with ulcerative colitis in the present study. The results indicate that small tablets could form the basis of spreading con-

trolled-release drug delivery systems for the treatment of this condition. Since colonic transit rates were highly variable, it would seem appropriate that drug release in the colon from such units should be limited to about 10 h. This would allow most of the drug to be delivered to the site of action in patients with relatively rapid transit, whilst avoiding an unacceptable accumulation of drug in those in whom transit is slow.

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