International Journal of Pharmaceutics, 68 (1991) 199–204

ADONIS 037851739100089A

IJP 02305

Gastrointestinal transit of a multiparticulate tablet formulation in patients with active ulcerative colitis

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(Received 14 September 1990)
(Accepted 1 October 1990)

Key words: Ulcerative colitis; Gastrointestinal transit; Dosage form; Gamma scintigraphy

Summary

The gastrointestinal transit of a multiparticulate formulation has been measured in a group of patients with active colitis, using the technique of gamma scintigraphy. Small tablets of 5 mm diameter were dosed in the morning and in the evening. The transit behaviour for morning dosing was similar to that observed previously for patients with the non-active form of the disease and for healthy volunteers. For evening dosing, there was an indication that movement through the small intestine was slower than for morning dosing. Acute ulcerative colitis did not lead to an accelerated transit in the colonic regions, although retrograde movement was observed quite frequently.

Introduction

Our group has made extensive studies in healthy volunteers on the gastrointestinal transit of various dosage forms, to include multiple and single unit systems (Davis, 1983, 1985, 1986; Davis et al., 1984a,b,c, 1986; Davis and Hardy, 1988). Gastric emptying can be determined by a combination of dosage form size and the calorific content of the meal (if any) taken prior to dosing. Small intestinal transit is apparently little affected by either dosage form size or the prior feeding status of the volunteer and an average small intestine transit time of 3 h has now been widely accepted (Davis et al., 1986). Transit through the different regions of the colon can be much more variable but for most subjects is well in excess of 12 h and can be considerably longer depending on food intake, bowel habits and the size of the dosage form (Parker et al., 1988). Large single unit systems that do not disintegrate can move more rapidly in the colon than can small pellets or drug solutions; a phenomenon known as 'streaming' (Eastwood, 1975).

We have conducted far fewer studies in patient groups but it is to be expected that the transit behaviour of dosage forms will be little different in patients to that observed in healthy subjects, unless the gastrointestinal tract is involved in the pathological condition. We, and others, have found little difference in transit behaviours between

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young and old subjects, and little effect of factors such as exercise, body position and bed-rest (Davis and Hardy, 1988). This is because normally, dietary intake has an overwhelming effect on these more subtle variables.

Certain important clinical conditions involve pathologies of the gastrointestinal tract and opportunities exist for well designed (drug) delivery systems. In ulcerative colitis, benefit can be gained by the 'positioned' release of an active therapeutic agent in the colon and single unit systems with this capability have been investigated (Hardy et al., 1988). A multiple unit system that spreads in the colon and is little influenced by the streaming effect would be an advantage. Previously we have studied such a system in six patients with ulcerative colitis (Hardy et al., 1988). The delivery system comprised five non-disintegrating tablets, 4 mm thick and 4 mm in diameter. The mean gastric emptying time after dosing following a light breakfast was 1.6 h and the small intestine transit time 3.4 h (these values are similar to those found previously in healthy subjects). The tablets were retained in the proximal colon for at least 6 h and only one patient voided any of the tablets within 24 h of dosing. These results indicated that the multiple tablet dosage form could be used as a controlled release delivery system in ulcerative colitis. It was recognised, however, that of the six patients only two presented with the active form of the disease. While there is no evidence to suggest that the phase of the disease greatly affects transit behaviour (Rao et al., 1987), it was considered appropriate to repeat our previous investigations with patients who were all in an active phase of the disease. The effect of dosing time, either morning or evening was also evaluated. It should be noted that such a study is not easy to arrange since patients can change from an inactive to active phase (and vice versa) in a short period of time. Furthermore, when the disease is in its active form there can be an understandable unwillingness to be involved in a clinical investigation. A review of the literature on the treatment of ulcerative colitis reveals a surprisingly small number of studies where transit behaviour has been studied in patients during the active phase of ulcerative colitis (Rao et al., 1987; Rao and Read, 1990).

Materials and Methods

Subjects

13 patients, six male and seven female, aged 40–77 years participated. The time since diagnosis ranged from 1 to 19 years. Three were diagnosed with Crohn's disease and ten with ulcerative colitis. In nine subjects the left colon was involved; in the remainder the whole colon was involved. Current treatments included steroid enemas, salazopyrine or mesalazine. All were diagnosed to be in an active phase of the disease. None of the patients had been treated surgically and all were taking medication at the time of the study. Patients were required to stop anti-diarrhoeal medication 2 days prior to the dosing day. The study was approved by the University Hospital (Nottingham) Ethics Committee and each patient gave written informed consent before taking part.

Procedure

Non-disintegrating tablets, 5 mm in diameter were prepared as previously (Hardy et al., 1988) from ethylcellulose using normal curvature punches with a Manesty F3 machine. Each tablet contained 1% Amberlite CG120 resin (160 μm size fraction) radiolabelled with ^{111}In to give a total dose of radioactivity of about 1 MBq for the five administered tablets at the time of dosing. The tablets were coated with two coatings, one of ethylcellulose and one of cellulose acetate. Each patient consumed a normal diet and took no alcohol on the 2 days prior to the study. The patients were then dosed either in the morning or the evening in order to obtain a total of 20 completions (with if possible an equal number for morning and evening dosing). Some patients took part in both morning and evening dosage studies while others participated in only one part of the study. A period of at least 1 week was allowed before a patient was redosed. Each patient kept a diary for the 2 days prior to the study day which provided information on all meals (time and content) and bowel emptying times, together with details of the times and nature of all medication.

For morning dosing, the patients fasted overnight and were given a standard breakfast at about 8.00 a.m. This consisted of a glass of orange juice,

two slices of toast, with butter and marmalade, tea or coffee. 30 min later, the subjects were given the ^{111}In-labelled tablets contained in a hard gelatin capsule together with 100 ml of water. The water contained 3 MBq of ^{99m}Tc-diethylenetriamine-pentaacetic acid to provide an outline of the anatomy of the stomach and intestine. Immediately after dosing, anterior images of 30 s duration were recorded at 15 min intervals, using a gamma camera until the tablets were seen to have left the stomach (approximately at 3.5 h). Afterwards, images were taken at 30 min intervals. The ^{99m}Tc images were recorded simultaneously but stored separately on computer. The camera had a 40 cm diameter field of view and was fitted with a medium energy collimator.

For evening dosing, the patients were given a standard evening meal of steak, chipped potatoes and vegetables, tea or coffee at 8.00 p.m. and were then dosed immediately with the labelled tablets. They were allowed to return home and on the following morning at 8.00 a.m., 30 min before breakfast, were given 100 ml of water labelled as described above with a ^{99m}Tc marker. After the standard breakfast had been consumed, imaging was carried out at 30 min intervals for a period of 10 h.

The data were analysed by recording the position of the individual tablets and displaying these as histogram versus time plots to provide information on position and spreading. The times for 50% to empty from the stomach, arrive in the colon, and by difference the small intestinal transit times were estimated (Table 1). The time of arrival of 50% of the tablets in the transverse colon and total transit was also estimated. For those dosed in the

TABLE 1

Estimated time for 50%, emptying or arrival in designated region (min)

Subject	Gastric emptying	Colon arrival	Small intestine transit	Arrival in transverse colon	Total transit
Morning dosing ($n = 9$)					
CW (1)	61	150	89	615	$704 < x < 1414$
KN (2)	100	225	125	630	> 1412
RJ (3)	85	206	121	$748 < x < 1443$	> 1443
IN (4)	45	137	92	380	> 1433
RB (5)	130	435	305	> 1445	> 1445
JBr (6)	128	206	78	$655 < x < 1446$	> 1446
JBy (7)	50	175	125	$735 < x < 1412$	> 1412
AD (8)	45	200	155	580	> 1412
WH (9)	75	170	95	350	> 1410
(Mean) (S.E.)	80 (11)	211 (29)	131 (23)		
Evening dosing ($n = 11$)					
CW (1)	$0 < x < 792$	< 792	–	> 1368	> 1368
IN (4)	$0 < x < 805$	< 805	–	900	> 1347
AM (10)	$0 < x < 797$	< 797	–	> 1372	> 1372
LO (11)	$0 < x < 794$	< 794	–	1125	> 1379
GJK (12)	$0 < x < 789$	< 789	–	810	1100
WH (9)	$0 < x < 806$	< 806	–	1230	> 1281
RJ (3)	$0 < x < 843$	< 843	–	1180	> 1365
JBr (6)	$0 < x < 807$	< 807	–	930	> 1326
JBy (7)	$0 < x < 795$	< 795	–	840	> 1357
AD (8)	$0 < x < 800$	885	–	1250	> 1351
JG (13)	$0 < x < 790$	830	–	1130	> 1367

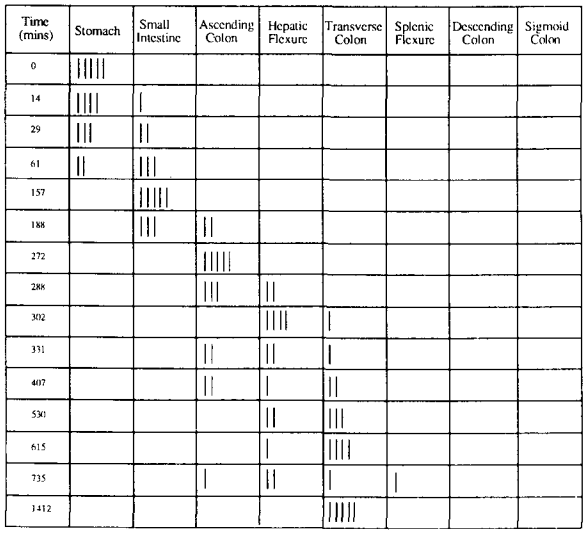

Fig. 1. Gastrointestinal transit of a mini-tablet formulation in ulcerative colitis patients. Subject initials: AD. Morning dosing.

evening, the study design did not permit collection of gastric emptying (and in most cases) colon arrival data.

Results and Discussion

Visualisation of transit behaviour

Figs 1–4 show some representative transit versus time histograms for the morning and evening dosing schedules. The positioning of the tablets

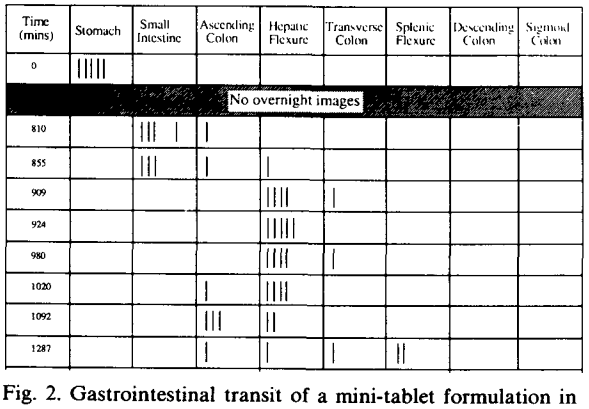

Fig. 2. Gastrointestinal transit of a mini-tablet formulation in ulcerative colitis patients. Subject initials: AD. Evening dosing.

and their spreading can be seen. Of special note in this study was the observation of frequent retrograde movement of the tablets. This is rarely observed when similar studies are conducted in healthy individuals.

Quantification of transit behaviour

The gastrointestinal transit data for the morning and evening legs of the study are listed in Table 1. For morning dosing, tablets were found to empty from the stomach within 2.5 h. Small intestinal transit times ranged from 1.3 h to 6 h. The mean value of 2.2 h was shorter than that normally seen for healthy young volunteers and for the patients with ulcerative colitis studied in the previous investigation (3.4 h). However, the values observed are well within the normal range and are not considered to be related to the fact that the patients displayed an active phase of the disease. The data for arrival in the colon and total transit are generally in line with data for patients in a non-active form of the disease. However, one subject voided all the tablets between 11.7 and 23.6 h. This is a shorter total transit than that usually seen for a multiple unit system such as small pellets. Total transit times of less than 12 h have been recorded by our group but for large single units undergoing 'streaming' in the colon (Eastwood, 1975). The critical size above which

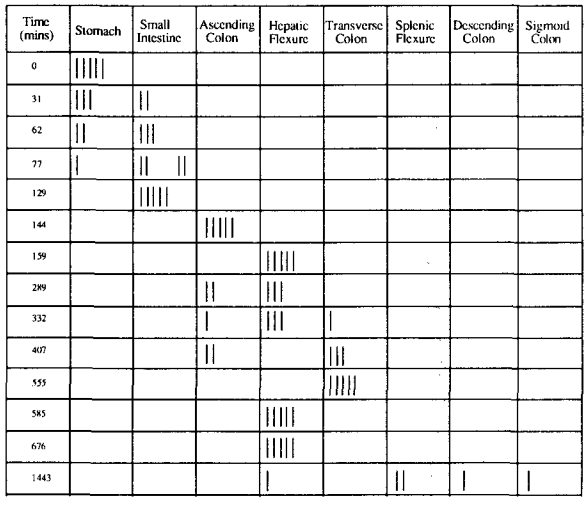

Fig. 3. Gastrointestinal transit of a mini-tablet formulation in ulcerative colitis patients. Subject initials: IN. Morning dosing.

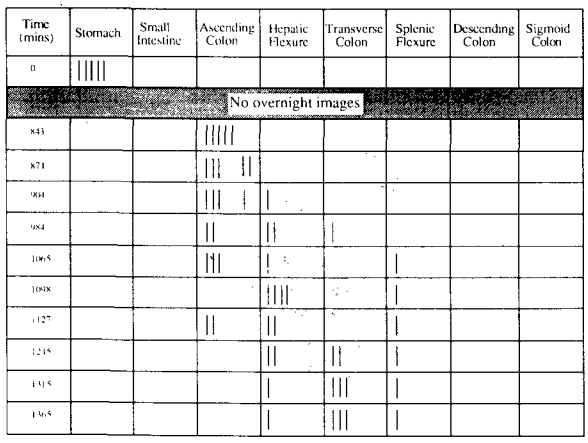

Fig. 4. Gastrointestinal transit of a mini-tablet formulation in ulcerative colitis patients. Subject initials: RJ. Evening dosing.

the streaming effect can occur has not yet been ascertained.

Diurnal effects

For evening dosing, the data for gastric emptying were not available. In eight individuals all the tablets had all reached the colon before the first image had been recorded on the morning following dosing. However, with three subjects, some (and in one case all) of the tablets were still in the small intestine at this time. Subsequently, all tablets reached the colon within the next 100 min. These data suggest that the transit of the tablets could have been affected by the fact that they were dosed at night rather than in the morning. From our previous experience we would have expected that the evening meal of moderate calorific value would have delayed gastric emptying of the tablets, to give a time for 50% emptying of between 3 and 4 h (Khosla et al., 1989). To this we can add the average small intestinal transit time of 3 h (Davis et al., 1986). On this basis, 50% of the tablets should have arrived in the colon by about 7 h. It is therefore noteworthy that for two of the subjects, the colon arrival time is at least twice this value. The reason for this apparent delay in transit is not established but it is known that the motility of the gastro-intestinal tract changes at night when subjects are asleep and the phenomenon known as the migrating myoelectric complex (MMC) (responsible for phases of motility) runs more slowly when subjects are asleep (Evans et al., 1982; Kumar and Wingate, 1985). It is our intention to investigate this possible effect of sleep in more detail using in the first instance, volunteers dosed prior to bed-time and then ascertaining transit during the sleeping period.

Transit in the colon

The times for dosage forms to arrive in the transverse colon and the total transit times (generally greater than 11 h), are similar for both morning and evening dosing and are in line with data for normals or those in an inactive phase of the disease. The one patient that demonstrated a more rapid total transit than the others had acute diarrhoea. Rao et al. (1987) and Rao and Read (1990) have reported studies on the mechanism of bowel disturbance in ulcerative colitis. The transit of a radiolabelled meal through the gastrointestinal tract and stool output were measured in 62 patients and 20 matched normal subjects. Mouth to caecum transit was slower than normal in all patient groups but whole gut transit was not accelerated. Interestingly, in active colitis, patients had proximal colonic stasis, whereas transit through the rectosigmoid region was rapid, i.e. diarrhoea in ulcerative colitis is associated with rectosigmoid irritability rather than rapid transit per se. The paradoxical slowing of transit in the small intestine and proximal colon were consistent with the constipation often prominent in patients with active disease.

Conclusion

Our results show that active ulcerative colitis does not lead to an accelerated gastrointestinal transit of non-disintegrating tablets of 5 mm diameter. Such small tablets (that could contain medication for the treatment of the disease) will remain in the ascending and transverse colon for extended periods of time. The retrograde movement of tablets seen in these patients is worthy of note but this apparent increased motility of the large bowel in the acute phase of the disease does not lead to an acceleration of transit.

Acknowledgement

The authors wish to thank Dr Neena Washington for technical assistance.

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