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The gastrointestinal transit of a controlled release formulation of indomethacin

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Summary

The gastrointestinal transit of a controlled release indomethacin tablet has been evaluated in vivo in a group of six fasted and fed subjects using the technique of gamma-scintigraphy. The product was similar in its gastrointestinal transit behaviour to other pharmaceutical dosage forms; emptying of the tablet from the stomach was slowed by the presence of food but transit through the small intestine was not affected by feeding conditions. In vivo the tablet underwent a process of gradual dissolution and diffusion followed by complete dispersion. The bioavailability of indomethacin from this preparation was not affected by the presence of food.

Introduction

Indomethacin is a well-known non-steroidal anti-inflammatory drug that has been used clinically for many years in the treatment of osteo and rheumatoid arthritis. The drug has a half-life ranging from 2.6 to 11.2 h (Alvan et al., 1975) and the normal dosage is 75–150 mg daily in divided doses. Advantages in therapy and avoidance of gastro-intestinal tract intolerance and CNS side effects can be obtained if the drug is made available in an oral controlled release form. A variety of sustained release pellet formulations is available.

The present report describes the evaluation of a patented controlled release tablet system from Napp Laboratories incorporating indomethacin (Leslie, 1986). This product was designed using the principles of dissolution and diffusion in such a way that the indomethacin delivery rate should provide once daily dosing. The gastrointestinal transit of the indomethacin controlled release tablet (FLEXIN CONTINUS tablets 75 mg) has been studied in healthy subjects using the technique of gamma scintigraphy. Plasma level determinations of indomethacin were also undertaken following administration of the preparation. One tablet was administered on two separate occasions; once fasting and once after food to ascertain whether the presence of food affected bioavailability.

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Materials and Methods

Subjects

Studies were carried out on 6 young males aged between 20 and 22 years (mean 21 years) of weight range 73–86 kg (mean 78 kg). Each subject gave written informed consent for the study to be performed and the experimental protocol was ap-

proved by the Ethical Committee of the University of Nottingham. The volunteers refrained from taking medication for 2 weeks prior to the study. Smokers were excluded from the investigation and consumption of alcohol was not permitted during the study or for 24 h prior to dosing. The study was performed under medical supervision.

Tablets

The controlled release matrix tablets (Leslie, 1986) containing 75 mg of indomethacin were labelled by the incorporation of a small quantity of ion-exchange resin powder (Amberlite IR-120 (H), BDH Chemicals, Poole) radiolabelled with 1 MBq of ^{111}In. The in vitro release rate of the drug was monitored utilising USP dissolution test equipment (paddle).

Procedure

After an overnight fast the subjects were divided into two equal groups, one of which was given a light breakfast at 08.30 h (total energy intake of 1600 kJ), while the other was maintained in the fasted condition according to an open, two-part cross-over design. The radiolabelled tablet was administered at 0.900 h together with 100 ml of water radiolabelled with 2 MBq ^{99m}Tc-labelled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA). The gastric emptying of the tablet and its subsequent passage through the small intestine to the ileocaecal junction was followed by gamma scintigraphy at intervals over a 24 h period, as previously described (Davis et al., 1984a,b). The ^{99m}Tc-DTPA solution outlined the anatomy of the stomach and intestines and facilitated identification of the location of the tablet. The subjects remained upright during the course of the investigation. A drink of coffee or tea was permitted after 2 h following administration of the dosage form and lunch (approx. 4000 kJ) was taken at about 13.00 h. An evening meal was taken at about 18.00 h (approx. 5000 kJ).

A blood sample was obtained for each subject prior to dosing and thereafter blood samples were taken at hourly intervals up until 6 h and then at the 8, 10, 12 and 24 h periods. The concentration of indomethacin in the plasma was measured by a validated HPLC method with UV detection.

Pharmacokinetic parameters

The areas under the plasma concentration vs time curves between zero and the final data point (AUCn) were calculated using the combination regular and logarithmic trapezoidal method (Chiou, 1978). The systemic availability of indomethacin in the fed state relative to the fasted state (F_{rel}) was determined from the ratio of AUCn values. The maximum observed plasma concentrations (C_{max}) and the times to these values (t_{max}) were taken directly from the reported data.

The t_{max} values were compared using the Wilcoxon matched-pair signed rank test. All other parameters were compared using a paired t-test, the AUCn values being log-transformed prior to analysis. Statistical significance was accorded if the calculated p value was less than or equal to 0.05.

Results and Discussion

Gastrointestinal transit times

On each occasion that the subjects were imaged, the position of the tablet in the gastrointestinal tract and its integrity were recorded (Table 1). Individual values for gastric emptying and arrival at the colon (the difference being a measure of the small intestine transit time) are given in Table 2. The recorded values represent the time when the dosage form was first seen to have left or to have arrived at a designated region. It should be noted that these are approximate values dependent upon the frequency of imaging.

The effect of food on gastric emptying is clearly demonstrated. The mean time for the fasted state was 0.53 h (SE = 0.14) and for the fed state was 2.42 h (SE = 0.3). Statistical analyses (paired t-test, Mann-Whitney) shows that such differences in emptying time due to food are highly significant. The coefficient of variation for the fasted state is greater than that for the fed state.

It is well known that the gastric emptying of a controlled release pharmaceutical dosage form will be dependent on two main factors; food and the nature of the controlled release pharmaceutical dosage form. In the fasted state, a single unit as well as multiparticulate systems are cleared by the action of a physiological process known as the

TABLE 1

Position and integrity of FLEXIN CONTINUS tablets 75 mg in the gastrointestinal tract of subjects

St, stomach; Si, small intestine; ICJ, ileocaecal junction; AC, ascending colon; TC, transverse colon; DC, descending colon; SC, sigmoid colon; R, rectum.

Time (h)	Subject											
	1		2		3		4		5		6	
	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed
0	St	St	St	St	St	St	St	St	St	St	St	St
0.5	St	St	Si	St	Si	St	Si	St	St	St	St	St
1.0	Si	St	Si	St	Si	St	Si	St	Si	St	Si	St
1.5	Si	St	Si	St	Si	Si	Si	St	Si	St	Si	St
2.0	Si	St	Si	Si	Si	Si	Si	St	Si	St	Si	St
2.5	Si	St	Si	ICJ	Si	ICJ	ICJ	Si	Si	St	Si	St [a]
3.0	ICJ [a]	Si	ICJ	AC	ICJ	ICJ	AC	Si [a]	Si	St	ICJ	Si
3.5	ICJ	Si	ICJ	AC	ICJ	ICJ	AC	ICJ	ICJ	Si	ICJ	Si
4.0	AC	Si	AC [a]	AC/TC [a]	ICJ	ICJ	AC/TC [a,b]	AC	AC	Si	AC	ICJ
4.5	AC	Si	AC	AC/TC	ICJ	AC	AC/TC [b]	AC	AC [a]	Si	AC [a]	AC
5.0	AC	Si [a]	AC	AC/TC	AC	AC [a]	AC/TC [b]	AC	AC	ICJ	AC	AC
6.0	AC	ICJ	AC	AC/TC	AC [a]	AC	TC/DC	AC	AC	AC [a]	AC	AC
7.0	AC	AC	AC/TC [b]	AC/TC	AC	AC	TC/DC	AC/TC [b]	AC	AC	AC	AC
8.0	AC	AC	AC/TC [b]	AC/TC	AC	AC/TC	TC/DC	TC	AC	AC	AC	AC
10.0	AC	AC	AC/TC [b]	AC/TC	AC	AC/TC	TC/DC	TC	AC/TC	AC	AC	AC/TC [b]
12.0	AC	AC	AC/TC [b]	AC/TC	AC	AC/TC	TC/DC	TC	AC/TC	AC	AC	AC/TC [b]
24	TC/DC	SC	DC/R	TC	TC/DC	TC/DC	DC/R	TC/DC	TC/DC	TC/DC	AC/TC	TC

[a] Tablet begins to disintegrate.

[b] Bulk of material mainly at hepatic flexure.

migrating myoelectric complex (MMC) (Code and Martlett, 1975). This has four phases of activity that range from quiescence to strong contractions. It is the strong contractions in the third phase of the MMC that 'clear' non-food material from the stomach and into the small intestines. Because of their 'clearing' effect, these contractive waves have been termed 'house-keeper' waves. They last for about 10–15 min and occur every 90–120 min. Thus, any dosage form given to a fasted subject, with a relatively small quantity of water, will be cleared before 120 min. The actual gastric emptying time is quite variable since it is dependent upon the time of arrival of the next phase 3 event. Other reports have shown that the average gastric emptying time for single unit systems from the fasted stomach is of the order of 0.5 h (Park et al., 1984).

The administration of food immediately inhibits the MMC. Normally, a tablet greater than 10 mm in size has to await the end of the digestive phase before it can be cleared from the stomach into the small intestine (Khosla et al., 1989). Also, the greater the size of the meal, the greater the delay in gastric emptying. Since all the subjects received the same breakfast at the same time, the subsequent emptying of the tablet is expected to demonstrate less variability (synchronization of phase 3).

The transit time of the tablet in the small intestine is not influenced by the presence of food. The mean values for the fed state is 1.8 h as compared with 2.6 h for the fasted state; the difference is not significant. This finding that small intestine transit is not affected by food is not surprising, especially if it is assumed that the movement through the small bowel following administration to fed or fasted subjects is controlled by the action of the MMC. The results are in accordance with the findings of Davis et al. (1986) who studied data obtained from 84 subjects who had received a variety of dosage forms under variable feeding conditions. They reported a mean value of 3.2 h (S.D. = 1.0 h). In the present study, the calculated values for small intestine transit time range from 0.7 to 3.25 h, with a mean of 2.2 h and S.E. = 0.22 ($n = 12$). The mean gastric emptying and small intestine transit data obtained in the present study are similar to values reported elsewhere for placebo formulations (Davis et al., 1986). It can be concluded that indomethacin has little or no effect on gastrointestinal transit. This is in line with the limited data available from studies in rats (Ruwart et al., 1979) and monkeys (Nompleggi et al., 1980).

Dosage form integrity

The observed scintigraphic images indicate that the tablets remain generally intact within the stomach and disintegration commences at later time periods (Tables 1 and 2). Scintiphotos demonstrating this phenomenon are given in Fig. 1. In

TABLE 2

The gastrointestinal transit of FLEXIN CONTINUS tablets 75 mg

Subject	Gastric emptying time (h)		Colon arrival time (h)		Small intestine transit time (h)		Observed disintegration time of dosage form (h)	
	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed
1	0.6	3.0	3.0	6.1	2.5	3.1	2.8	2.7
2	0.3	2.0	2.5	2.7	2.2	0.7	7.1	2.7
3	0.2	1.4	3.5	3.0	3.3	1.6	5.6	5.0
4	0.5	2.3	2.8	4.1	2.3	1.8	4.0	3.0
5	1.0	3.4	4.2	5.6	3.2	2.1	4.2	6.0
6	0.6	2.5	3.1	4.0	2.5	1.5	4.2	2.2
Mean	0.5	2.4	3.2	4.2	2.6	1.8		
±SE	±0.1	±0.3	±0.2	±0.6	±0.2	±0.3		
Statistics								
Fasted vs fed t	−9.9		−2.1		2.4			
Paired t-test p	$p < 0.001$		$0.1 > p < 0.05$ ns		$0.1 > p < 0.05$ ns			

ns, not significant.

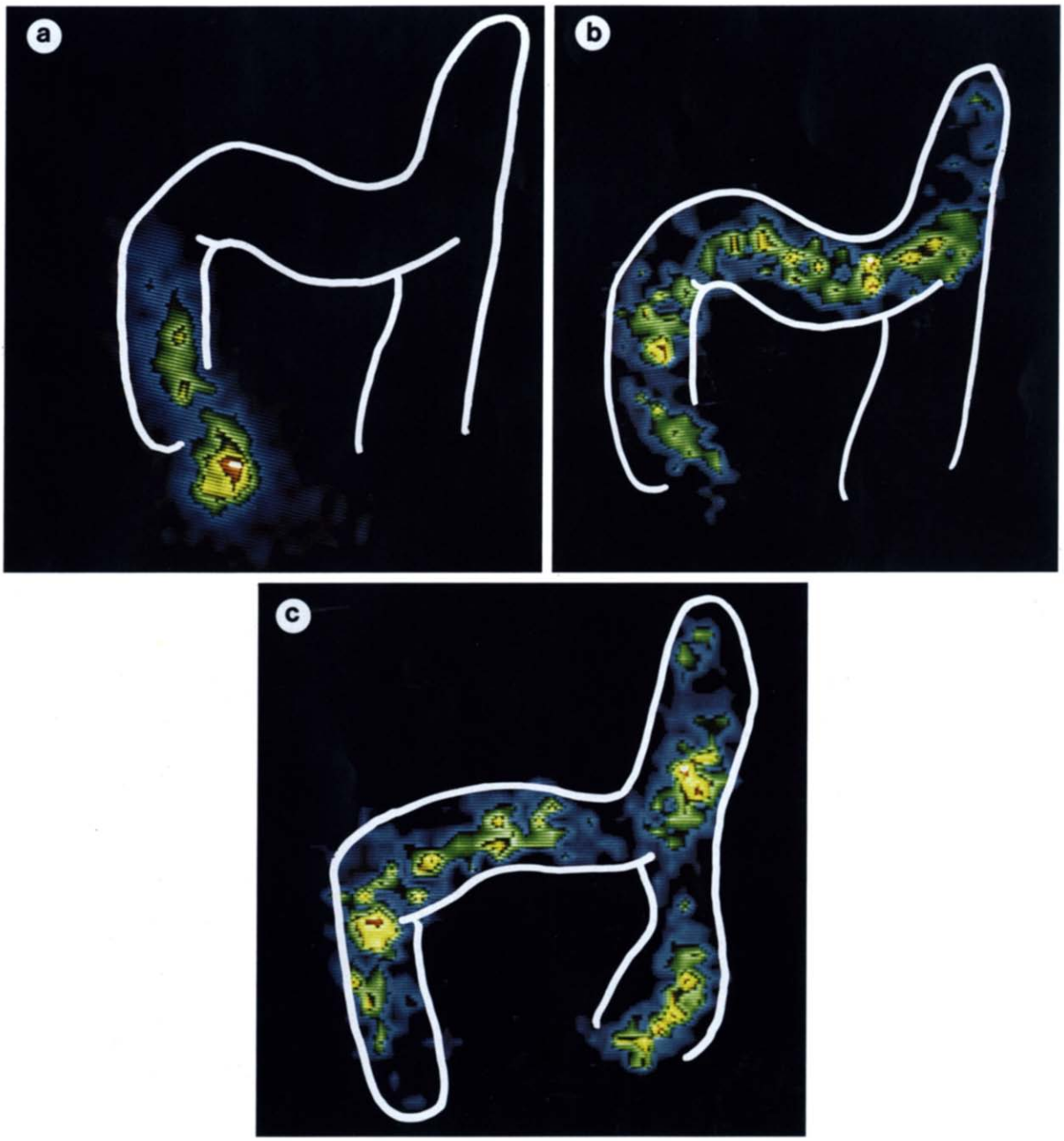

Fig. 1. Scintiphotos for subject 2 at (a) 4.0 h, (b) 11.5 and (c) 24.0 h after dosing to fasted stomach.

TABLE 3

Pharmacokinetic parameters of indomethacin after the administration of FLEXIN CONTINUS tablets 75 mg in the fed and fasted states

	Fed	Fasted
AUC_n (ng h ml^{-1}) [a]	7.4 (1.13)	7.8 (1.24)
F_{rel} (%) [b]	94.2 (74.9–118.5)	
C_{max} (μg ml^{-1}) [c]	2.03 (0.55)	1.45 (0.28)
t_{max} (h) [d]	3.0 (2.0–5.0)	4.0 (2.0–5.0)

[a] Logarithmic mean (standard deviation ratio).
[b] Logarithmic mean (95% confidence interval).
[c] Mean (standard deviation).
[d] Median (range).

particular, it should be noted that some hours after ingestion the activity is well spread in the colon, thereby minimizing the possibility of local high concentrations of drug. Furthermore, with controlled release matrix systems operating by a dissolution/diffusion release mechanism, there is little danger of the system becoming entrapped in a diverticulum as might have been the case with a single unit system based upon an osmotic pump mechanism (Osmosin [R], MSD).

Pharmacokinetics

Data on the pharmacokinetics of indomethacin are listed in Table 3. There is no significant difference in the areas under the indomethacin plasma level vs time curves between zero and the final data point for the fed/fasted states. This is reflected in the relative systemic availability of 94.2% with a 95% confidence interval of 74.9–118.5%. Thus food, in the form of a light breakfast, has no effect on the bioavailability of indomethacin from the controlled release tablets of 75 mg.

The t_{max} values are not significantly different, however, the C_{max} values are slightly higher in the fed state. Although the latter difference achieves statistical significance, it should have no effect on the therapeutic result.

It is interesting to note that satisfactory blood levels of indomethacin were maintained when the product was present in the different regions of the colon.

Conclusion

It may be concluded from this scintigraphic study that the controlled release matrix dosage form of indomethacin (FLEXIN CONTINUS tablets 75 mg) is similar in its gastrointestinal transit behaviour to other pharmaceutical dosage forms. Emptying from a fasted stomach was rapid whereas that from a fed stomach was slower. The transit through the small intestine was not affected by feeding conditions. The tablet underwent a process of gradual dissolution and diffusion followed by complete dispersion.

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