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Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food

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Summary

The gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid has been studied in human subjects. The pellets were labelled with a gamma-emitting radionuclide and their gastric emptying and colon arrival profiles monitored using a gamma camera after two different feeding conditions; light breakfast and heavy breakfast. It is clearly demonstrated that feeding has an important effect upon the gastrointestinal transit profiles. The presence of the heavy breakfast causes a lengthened gastrointestinal time and also a greater spreading of the pellets within the small intestine. As has been found previously, the transit time of the pellets (expressed as time for 50%) to move from pyloric sphincter to ileocaecal sphincter was of the order of 3 h and was independent of the nature of the meal provided.

Introduction

Tiaprofenic acid (Surgam) is a well-tolerated non-steroidal anti-inflammatory drug with a serum half-life of approximately 2 hours (Singh et al., 1986). Clinical benefit could arise if the drug were to be administered as a controlled release dosage form.

Pellets manufactured by a process of extrusion and subsequent spheronisation are widely used in current medical practice to provide the convenience of twice-a-day (and in some cases even once per day) administration (Bechgaard, 1982). Pellets smaller than about 2–4 mm in size can be emptied

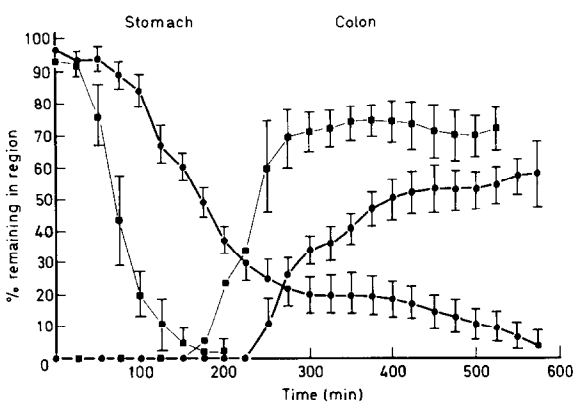

Fig. 1. Gastrointestinal transit of labelled pellets containing tiaprofenic acid (mean data ($n = 6$) ± S.D.). ■, gastric emptying — light breakfast; ●, gastric emptying — heavy breakfast; ■, colon arrival — light breakfast; ●, colon arrival — heavy breakfast.

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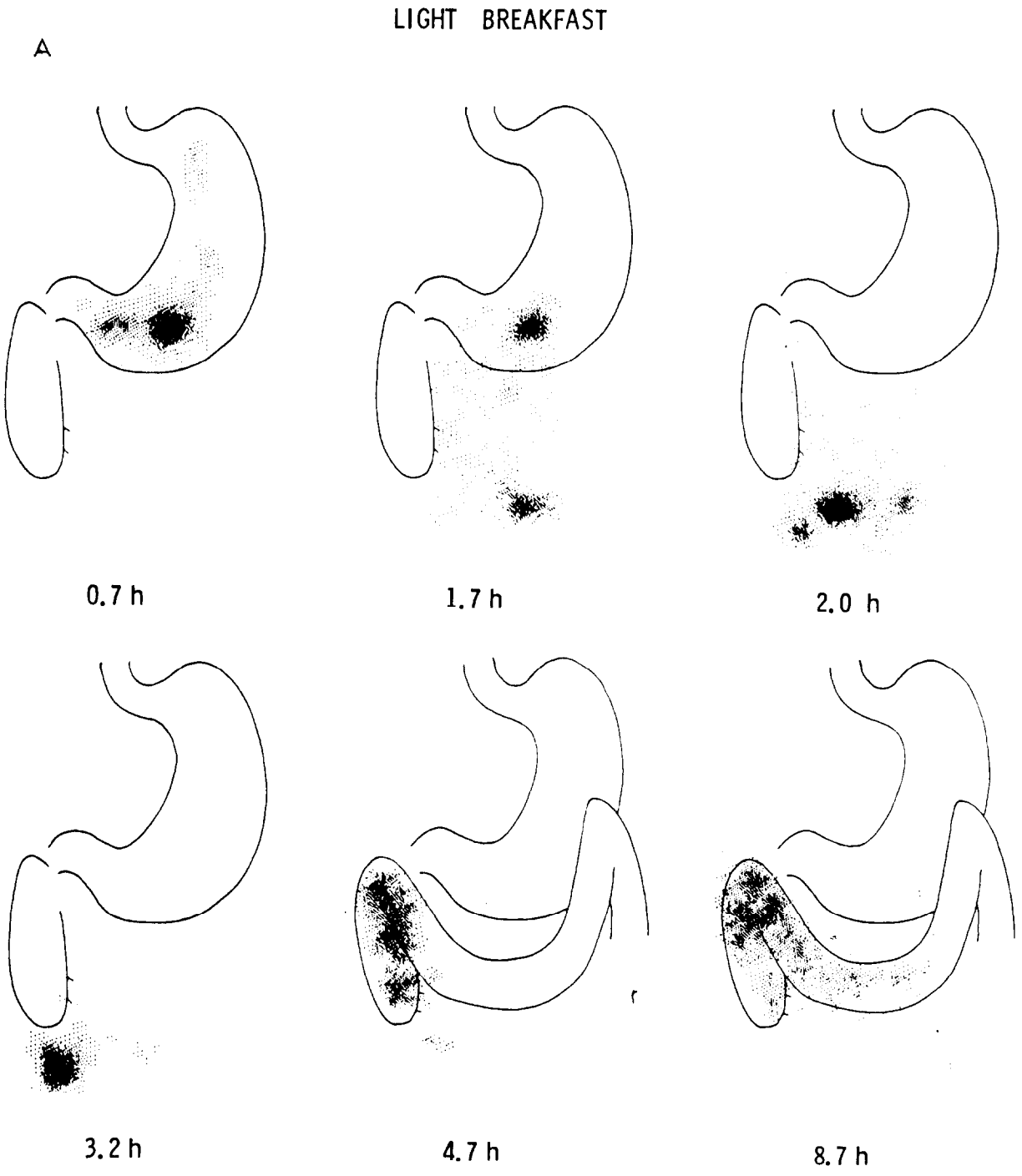

Fig. 2. Representative scintiscans showing transit of pellets after: (A) light breakfast; and (B) heavy breakfast.

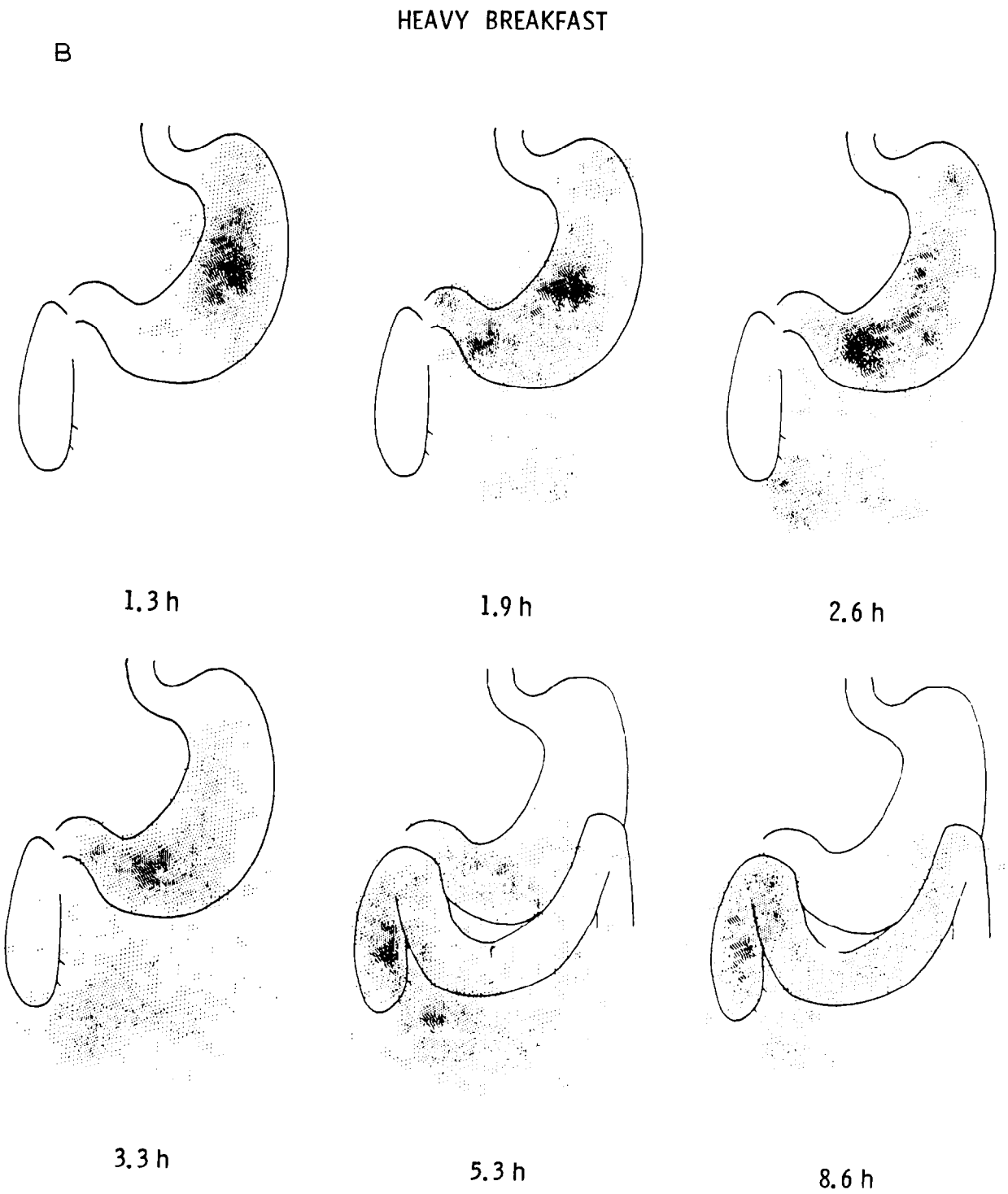

Fig. 2 continued.

from the stomach even when it is in the digestive mode. Previous studies conducted with small-labelled ion exchange beads have indicated that the rate of gastric emptying and thereby the spreading of the dosage form in the small intestines can be influenced by the quantity of food ingested immediately prior to dosing. The present study had the objectives of monitoring the transit of a controlled-release pellet formulation of tiaprofenic acid through the gastrointestinal tract and to investigate the effect of food on gastric emptying and intestinal transit.

Design of study

An open, single dose, randomized cross-over evaluation of the gastrointestinal transit of a controlled-release tiaprofenic acid pellet formulation was conducted in healthy young male subjects, after meals of different size. All the subjects were examined by a physician before the study, and had blood and urine samples taken for standard haematological and biochemical analyses. The subjects had a mean age of 22 years (range 22–23), mean weight 78 kg (range 65–120) and mean height 1.77 m (range 1.70–1.85).

Each volunteer was provided with a written and oral explanation of the study and signed an informed consent agreement. The protocol was approved by the University of Nottingham Ethical Committee. Approval was obtained from the DHSS, London, for the administration of radioactive substances. The study was conducted in accordance with the Declaration of Helsinki Guidelines for Ethics and Research, and the ABPI Code of Practice on Volunteer Studies.

The pellets of tiaprofenic acid were labelled by firstly incorporating a small amount of finely powdered Amberlite IR410 resin (BDH) into the mass prior to extrusion. A level of 10 mg resin per dose was chosen. Preliminary studies indicated that this very low level of additional material did not alter the drug release properties of the pellets.

Following coating of the pellets they were labelled with technetium-99m by a sorption method. The pellets (20 g) were placed in a flask containing 0.1 N HCl (50 ml) and [^{99m}Tc]-sodium pertechnetate solution (300–400 MBq) obtained from a generator (Amersham International). The mixture was stirred at room temperature for 2 h. The labelled pellets were collected and dried in an oven at 40 °C. The extent and rate of sorption had been evaluated previously by a similar process conducted over 5 h using a 2 g batch. Here, 1 ml samples were withdrawn at regular intervals over a period of 5 h. The samples were counted in a gamma well counter (Intertechnique CG400). This procedure was repeated using pellets (2 g) which contained no resin.

After 5 h, 60% of the available activity was taken up by the pellets containing resin. Pellets containing no added resin took up a maximum of 7% of the available activity over the same time period.

The stability of the technetium-99m label was assessed by placing approximately 1 g of the labelled pellets, of known activity, into flasks containing 0.1 N HCl (100 ml) and phosphate buffer pH 7.2 (100 ml), respectively. Each mixture was stirred and 1 ml samples were taken at regular intervals over a period of 5 h and counted as before to determine the released activity. About 10% of the label was lost from the labelled pellets after 5 h in both acid and phosphate buffer media.

The radiolabelled pellet formulation was contained within a hard gelatin capsule and administered to each subject together with 100 ml of water. Each subject was given two capsules, each containing a dose of 300 mg of tiaprofenic acid. The position of the pellets within the gastrointestinal tract was monitored using gamma scintigraphy as described by Daly et al. (1982) and Davis et al. (1984a, b and c). The study was repeated in each subject after an overnight fast and following either a light (1 500 kJ) and heavy (3 600 kJ) breakfast.

Results and Discussion

The gastrointestinal transit of the pellets in the different regions of the gastrointestinal tract is shown in Fig. 1 (grouped data for 6 subjects) and summarized in Table I. Fig. 2 is a composite showing a typical sequence of scintiscans for the transit of the pellets in the different regions of the

TABLE 1

Gastrointestinal transit of pellets

Subject	Gastric emptying ($T_{50\%}$) (min)	Colon arrival ($T_{50\%}$) (min)	Small intestinal ($T_{50\%}$) (min)
Light breakfast			
RE	90	250	160
TN	99	250	151
NW	60	240	180
AB	98	280	182
NA	65	200	135
NW	55	300	245
Mean ± S.E.M.	77.8 ± 8.2	253 ± 14.1	176 ± 15.7
Heavy breakfast			
RE	198	360	162
TN	150	520	370
NW	170	390	220
AB	130	> 520	390
NA	180	350	170
JW	190	380	190
Mean ± S.E.M.	170 ± 10.5	420 ± 32.1	250 ± 41.9

gastrointestinal tract in one subject. The dispersion of the pellets at longer time periods and the effect of fed state is apparent.

The half-time for the gastric emptying of pellets (Table 1) was influenced by the size of the administered meal; the mean time was 78 ± 8 min (S.E.M.) after the light breakfast and 170 ± 10 min (S.E.M.) for the same subjects for the heavy breakfast. Statistical analysis (paired *t*-test) shows that such differences in emptying due to food are highly significant.

The presence of food in the stomach is known to have an effect on the gastric emptying of pharmaceutical dosage forms (Kelly, 1981). In the fed state contractions in the antrum of the stomach mix and grind digestible material. Periodically waves of activity move suspended solid material to the distal antrum. The pylorus is contracted but a small quantity of liquid chyle containing particles of suspended (food) material of a size less than about 5 mm is allowed to pass through the pylorus into the duodenum. Material of a large size is returned to the body of the stomach for further digestion. This process of grinding followed by sieving by the pyloric region continues until the stomach is empty of digestible material. Non-digestible material is cleared by a separate process termed the interdigestive migrating myoelectric complex (MMC) (Szurszewski, 1969). The fasted stomach undergoes a series of rapid contractions about every 2 h (phase 3 of the MMC) which cause undigested material to be swept from the stomach into the duodenum and down to the ileum. Thus, in the fed condition the gastric emptying of a non-disintegrating tablet cannot normally occur until the stomach has emptied of food and the remaining undigested material is cleared by action of the MMC. In contrast, small pellets (less than 2–5 mm in size) are able to empty from a fed stomach. Previously, the half time for emptying and the spreading of the pellet mass in the small intestine has been well correlated with the calorific value of the administered meal (Davis et al., 1984a). The data shown in Table 1 and in Fig. 2 are consistent with these previous suggestions.

Table 1 also provides data for the transit of the pellets from stomach through the small intestines to colon. Here it is found that the mean transit times were independent of the feeding state. The calculated mean value of about 3–4 h for small intestine transit (50%) has been found previously for pellets (3.2 ± 0.2, $n = 37$) and single unit systems (3.2 ± 0.2, $n = 27$) under various conditions of feeding (fasted, large meal, small meal, etc.). These observations are also in agreement with data on the transit of meals of different types (Read et al., 1982; Davis et al., 1986).

Conclusion

The emptying of controlled-release pellets of tiaprofenic acid from the stomach is influenced by the presence of food. In the lightly fed state the pellets are emptied more rapidly than for the heavily fed state. The transit of the pellets through the small intestine is unaffected by food and on average the pellets reach the ileocaecal junction about 3–4 h after leaving the stomach.

Acknowledgements

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