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Gastrointestinal transit of a controlled release naproxen tablet formulation

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Summary

The gastrointestinal transit of a controlled release naproxen tablet formulation has been measured in healthy young and old subjects using the technique of gamma scintigraphy. Gastric emptying of the tablet was affected by food (mean emptying times for fasted subjects were 0.64 h (young) and 0.86 h (old) increased to 3.0 h (young) and 3.3 h (old) following a light breakfast). The small intestinal transit times for both fed and fasted states was about 3.2 h. There were no significant differences that could be attributed to subject age for gastric emptying and small intestinal transit.

Introduction

The rate of gastric emptying and intestinal transit of tablets can be an important determinant of the pharmacokinetic profiles and measured bioavailability of absorbed drugs (Koch-Weser and Schechter, 1981). A variety of factors is known to affect gastric emptying of tablets, which include diet, disease states and co-administered drugs (Minami and McCallum, 1984). However, little information has been reported on the variables affecting the transit of tablets through the small intestine. Recent studies suggest that transit of food as well as dosage forms from stomach to ileocaecal junction is remarkably independent of physiological or pharmaceutical factors (Davis et al., 1984a and b).

In previous studies we have described the use of gamma scintigraphy to follow the gastrointestinal transit of various dosage forms including controlled release tablets and pellet systems (Davis et al., 1984a and b; Christensen et al., 1985). The present study describes an investigation of the effect of food on the gastrointestinal transit of a controlled release naproxen tablet in healthy young and old subjects.

Materials and Methods

Subjects

Studies were carried out on 6 young males aged between 20 and 23 years (mean 21 years) of weight range 56–88 kg (mean 72 kg) and 6 elderly females aged between 63 and 76 years (mean 67 years) of

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weight range 62–82 kg (mean 67 kg). Each subject gave informed consent for the study to be performed and the experimental protocol was approved by the Ethical Committee of the University of Nottingham. The young male volunteers refrained from taking medication for 2 weeks prior to the study; the elderly volunteers did not take any medication known to interfere with the results of the study, including anticholinergics, laxatives or other drugs expected to affect gastrointestinal motility.

Tablets

Controlled release matrix tablets containing 1 g naproxen 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 indium-111. These tablets, of dimension 17 × 4 mm, had been designed to erode slowly such that the naproxen delivery rate would provide once daily dosing.

Procedure

After an overnight fast the groups of young and elderly subjects were each subdivided into two equal groups and were given either a breakfast at 08.30 h of fruit juice, poached egg on toast and tea or coffee (total energy intake about 1600 kJ) or were maintained in the fasted condition, according to a cross-over design. The labelled tablet was administered at 09.00 h together with 200 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 standing the subjects in front of a gamma camera at intervals over a 12 h period, as described previously (Davis et al., 1984a and b). The [^{99m}Tc]DTPA solution outlined the anatomy of the stomach and intestines, and facilitated identification of the location of the tablets. The subjects remained upright during the course of the investigation, usually in a seated position. A drink of coffee or tea was permitted after 2 h following administration of the dosage form and a lunch of roast chicken, roast potatoes, peas and carrots, blackcurrant crumble and custard followed by coffee (approximately 4000 kJ) was taken at about 13.00 h. An evening meal at 18.00 h consisted of ham and Scotch egg, mixed salad, coleslaw and gateau. On a subsequent occasion one week later the subjects repeated the study, having breakfast or no breakfast as appropriate.

Results

Gastric emptying

The times for emptying of the tablets from the stomach of the subjects are given in Table 1 and Fig. 1. The presence of food delayed gastric emptying in all cases except one. The mean emptying times for old and young fasted were 0.86 ± 0.22 h (mean ± S.E.M.) and 0.64 ± 0.12 h, respectively, and for the same subjects fed were 3.3 ± 0.83 h and 3.0 ± 1.2 h, respectively. Statistical analyses

TABLE 1

GASTRIC EMPTYING TIMES (h)

Old			Young		
Subject	Fasted (G1)	Fed (G2)	Subject	Fasted (G3)	Fed (G4)
1	0.4	2.8	7	0.7	9.0
2	1.5	0.8	8	0.5	1.8
3	0.6	4.6	9	1.2	2.1
4	1.6	3.6	10	0.4	2.1
5	0.7	6.6	11	0.4	1.4
6	0.4	1.7	12	0.7	3.3
Mean	0.86	3.3		0.64	3.0
S.E.M.	0.22	0.83		0.12	1.2
Median	0.65	3.2		0.57	2.1

STATISTICAL ANALYSIS

	G1 G2	G1 G3	G3 G4	G2 G4
Paired t-test				
t	2.83	0.84	2.24	0.46
P	0.036	0.43	0.075	0.96
	sig	ns	sig	ns
Mann-Whitney				
P	< 0.01	> 0.05	< 0.01	> 0.05
	sig	ns	sig	ns

sig = significant
ns = not significant

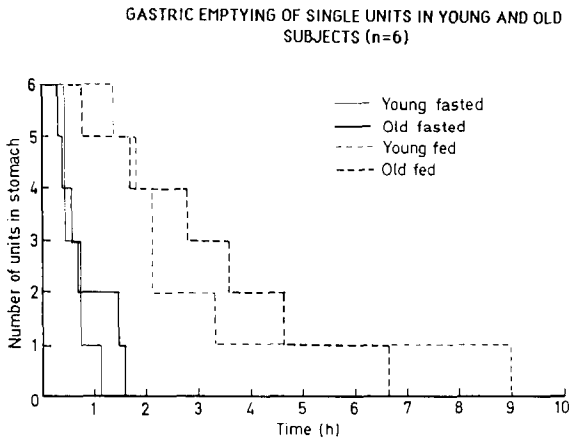


Fig. 1. Gastric emptying profiles.

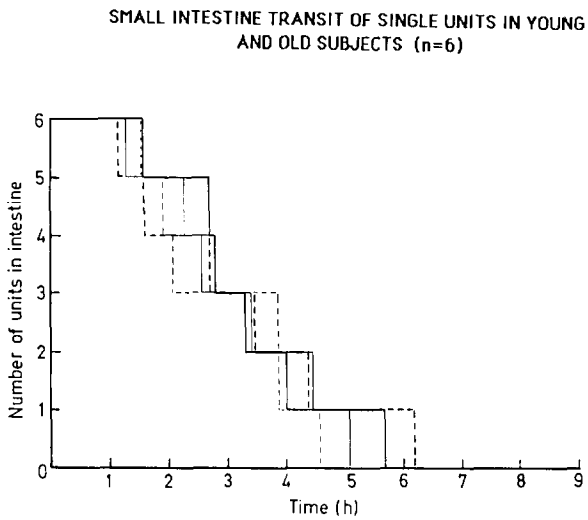


Fig. 2. Small intestinal transit profiles.

(paired *t*-test, Mann-Whitney test) showed that such differences in emptying due to food were highly significant. There were no statistically significant differences between the gastric emptying behaviour of the old and young subjects in either the fasted or fed conditions.

Small intestine transit

Table 2 and Fig. 2 provide the data for the transit times of the tablets from stomach to ileocaecal junction. In this case the mean transit times were independent of whether the subjects were dosed fasted or fed and there was no significant difference between the groups of old and young subjects. Indeed the mean transit time of the tablets through the small intestine was remarkably constant being of the order of 3.2 ± 0.6 h.

TABLE 2

SMALL INTESTINAL TRANSIT TIMES (h)

Subject Old			Subject Young		
	Fasted (I1)	Fed (I2)		Fasted (I3)	Fed (I4)
1	1.6	2.7	7	2.1	2.3
2	3.5	5.7	8	4.6	4.4
3	4.4	3.4	9	3.9	5.1
4	1.2	1.6	10	1.9	2.6
5	2.7	4.0	11	3.9	3.3
6	6.2	2.8	12	1.6	1.3
Mean	3.3	3.4		3.0	3.2
S.E.M.	0.74	0.56		0.50	0.56
Median	3.1	3.1		3.0	3.0

Statistical analyses

	I1,I2	I3,I4
Mann-Whitney	> 0.05 ns	> 0.05 ns

Discussion

Gastric emptying

The emptying of solid non-digestible materials such as tablets, from the stomach will follow patterns that depend upon the other stomach contents (Minami and McCallum, 1984). In the digestive phase liquids (and small particles) are able to empty through the pylorus. In contrast, digestible solids are retained in the stomach and are only able to empty when these have been reduced to relatively small particles (Kelly, 1980; Minami and McCallum, 1984). Contractions of the distal stomach have the effect of mixing and grinding solid foods and large particles, retained by the antropyloric closure, and retropelled and triturated in this so-called 'antral mill' (Minami and McCallum, 1984). The result of this grinding action and the presence of digestive enzymes reduces administered solid food to a liquid-like con-

sistency (the chyme) which can then be emptied. An indigestible solid will be retained in the stomach during the digestive phase to await clearance by another mechanism, the migrating myoelectric complex (MMC) (Code and Marlett, 1975).

This complex has four phases that correspond to different levels of motor activity. The third phase consists of an interdigestive contraction which is able to sweep undigested solids from the stomach through the pylorus and into the terminal ileum. The period of one entire cycle of the MMC is about 2 h in man (Kelly, 1981). Thus it can be predicted that a single unit dosage form administered with or shortly after a meal will be retained in the stomach until the end of the digestive phase. The period of retention is dependent on the size and composition of the meal. In contrast, if an indigestible solid (tablet) is given to a fasted individual it should be cleared relatively rapidly, the time of clearance depending on the arrival of the third phase of the MMC. A tablet could be administered just before the Phase III wave and therefore empty within a few minutes; equally it could be administered just afterwards and then retained until the next Phase III wave (Park et al., 1984).

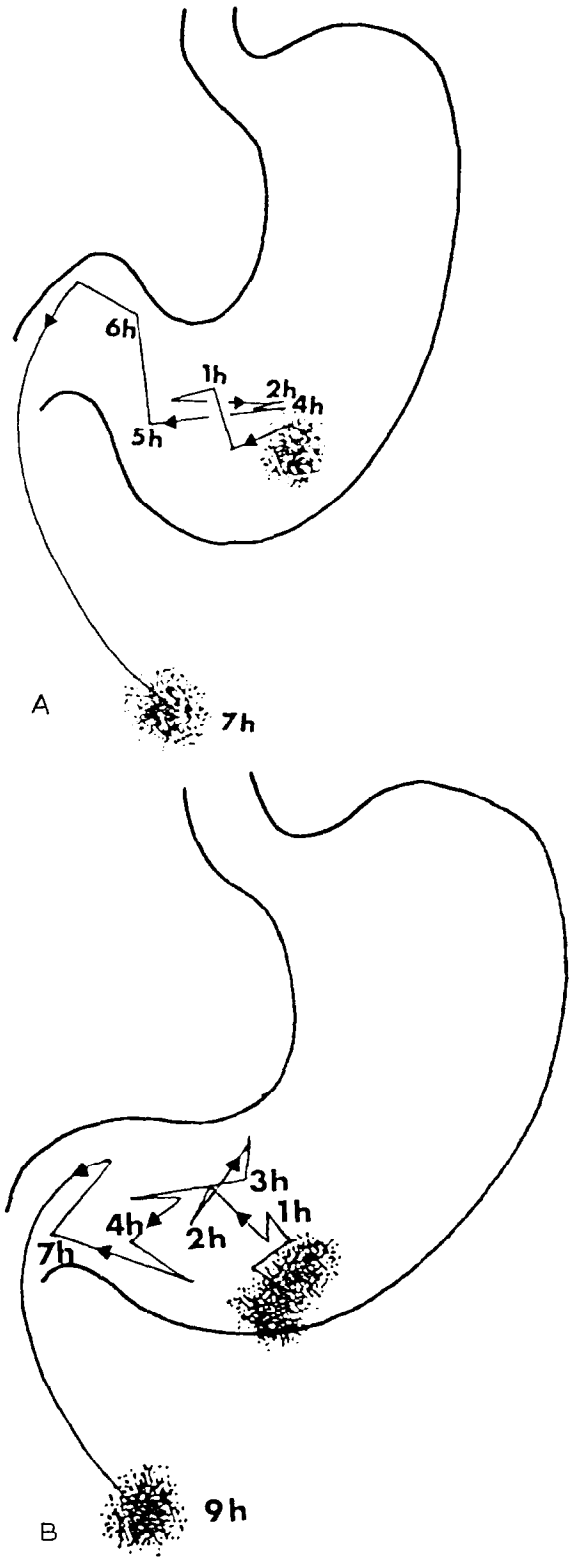
The data in Table 1 reflect these physiological processes extremely well. It would be expected that a heavier meal would delay gastric emptying of a single unit even longer. Previously it has been shown that osmotic modules of similar size to the matrix tablets in the present study were all retained in the stomach in 6 subjects for 9 h or longer following a heavy breakfast (Davis et al., 1984b).

Park et al. (1984) administered tablets of various sizes and shapes to fasted subjects, the largest unit being 17.6×9.5 mm in size. They concluded that the physical properties of the tablets had no effect upon gastric emptying and 80% of all dosage forms had emptied by 2 h. Feldman et al. (1984) have described the gastric emptying of 10 units of size 10×2 mm in 30 subjects who received a meal of similar size to that in the present study (about 1600 kJ). Few markers (15%) had emptied in 2 h, most emptied in the fourth postprandial hour and all 10 had emptied by 6 h in 45 out of 40 experiments. It will be noted from Table 1 that in two instances the tablets were retained in the fed stomach for periods in excess of 6 h. There is no evidence to suggest that the dosage form was localized in any one region of the stomach; sequential gamma camera images have been superimposed in Fig. 3 to indicate the movement of the tablet during this time for two subjects with long gastric residence times.

In the present study the age of the subject had no significant effect upon gastric emptying of the tablets. Recent studies on the emptying of meals have shown that there were no significant differences in the gastric emptying times of solid food for young and elderly subjects. However, the liquid components of a meal appeared to empty more slowly in elderly patients (Moore et al., 1983; Evans et al., 1981). In contrast Kupfer et al. (1985) have shown that the initial rate (derived from the first 5 min of study) of emptying was significantly higher in elderly subjects (mean age 79 years) when compared with young controls, but that the gastric emptying patterns in the two groups after 5 minutes were not significantly different.

Small intestine transit

The constancy of small intestine transit in the two groups under conditions of feeding and fasting is well demonstrated in Table 2. Davis et al. (1986) have reported similar findings for solutions, pellets and single units. The mean transit time of just over 3 h represents the movement of the dosage form through the small intestine by the peristaltic waves initiated by the Phase III activity of the MMC. Recent studies by Malagelada et al. (1984) on non-digestible solid particles consisting of ^{131}I-labelled fibre have shown a similar mean transit time of 2.7 ± 0.33 h. Statements in the pharmaceutical literature suggesting that the average small intestine transit time can be of the order of 8 h (Houston and Wood, 1980) are not correct for single unit tablet formulations in moderately active healthy subjects. The longest intestinal transit time recorded in the present study was 6.2 h and the shortest 1.3 h; without effects that can be attributed to age. This finding is in agreement with the very limited data in the literature on the



effect of age on the intestinal transit of liquids (Kupfer et al., 1985).

Implications for oral delivery of drugs

The data on gastric emptying in Table 1 indicate clearly the importance of food intake in determining gastric residence time. If a single unit dosage form is given to a fasted individual, the unit may empty from the stomach within a period of a few minutes and arrive at the ileocaecal region after about a further 3 hours. After a light meal gastric emptying is delayed significantly and residence times greater than 6 h can occur if the stomach is maintained in a digestive mode. For slow release formulations that are intended to release the drug over a period of 12 (or even 24) h, such data could explain variabilities in observed bioavailability if the administered drug was poorly or erratically absorbed from the large intestines. However, in the present study, excellent bioavailability, comparable to unlabelled tablets, was observed (Kent, 1985).

The administration of controlled release oral systems before meals is not to be recommended unless rapid delivery of the system to the large intestines is intended. Similarly, the use of fasted subjects in bioavailability tests on controlled release formulations can be questioned without comparable studies under fed conditions.

The age of the subject does not appear to have a marked effect on gastrointestinal transit. Therefore, data obtained in healthy young subjects should also be relevant to healthy old subjects. Furthermore, the constancy of the transit of tablets in the small intestine offers a means of delivering a drug to the colon by means of an enteric coated system that incorporates a lag phase before the subsequent delivery of an active pharmacological agent (Hardy et al., 1985).

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Fig. 3. Superimposed scintiscans to show the relative movement of a slow release tablet in the stomach of two healthy young subjects.

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References

Christensen, F.N., Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G., The use of gamma scintigraphy to follow the gastrointestinal transit of pharmaceutical formulations. J. Pharm. Pharmacol., 37 (1985) 91–95.

Code, C.F. and Marlett, J.A., The interdigestive myo-electric complex of the stomach and small bowel of dogs. J. Physiol. (London), 246 (1975) 289–309.

Davis, S.S., Hardy, J.G. and Fara, J.W., Transit of pharmaceutical dosage forms through the small intestine. Gut, (1986) in press.

Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G., A comparative study of the gastrointestinal transit of a pellet and tablet formulation. Int. J. Pharm., 21 (1984a) 167–177.

Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G., The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). Int. J. Pharm., 21 (1984b) 331–340.

Evans, M.A., Triggs, E.J. Cheung, M., Broe, G.A. and Creasey, H., Gastric emptying rate in the elderly: implications for drug therapy. J. Am. Geriatr. Soc., 29 (1981) 201–205.

Feldman, M., Smith, H.J. and Simon, T.R., Gastric emptying of solid radiopaque markers: studies in healthy subjects and diabetic patients. Gastroenterology, 87 (1984) 895–902.

Hardy, J.G., Wilson, C.G. and Wood, E., Drug delivery to the proximal colon. J. Pharm. Pharmacol., 37 (1985) 874–877.

Houston, J.B. and Wood, S.G., Gastrointestinal absorption of drugs and other xenobiotics. In J.W. Bridges and L.F. Chausseaud (Eds.), Drug Metabolism, Vol. 4, Wiley, Chichester, 1980, pp. 57–125.

Kelly, K.A., Gastric emptying of liquids and solids: roles of proximal and distal stomach. Am. J. Physiol., 239 (1980) G71–G76.

Kelly, K.A., Motility of the stomach and gastroduodenal junction. In L.R. Johnson (Ed.), Physiology of the Gastrointestinal Tract, Vol. 1, Raven Press, New York, 1981, pp. 393–410.

Kent, J.B., personal communication, 1985.

Koch-Weser, J. and Schechter, P.J., Slow release preparations in clinical perspective. In L.F. Prescott and W.S. Nimmo (Eds.), Drug Absorption, MTP Press, Lancaster, 1981, pp. 217–27.

Kupfer, R.M., Heppell, M., Haggith, J.W. and Bateman, D.N., Gastric emptying and small bowel transit rate in the elderly. J. Am. Geriatr. Soc., 33 (1985) 340–343.

Malagelada, J.-R., Robertson, J.S., Brown, M.L., Remington, M., Duenes, J.A., Thomforde, G.M. and Carryer, P.W., Intestinal transit of solid and liquid components of a meal in health. Gastroenterology, 87 (1984) 1255–1263.

Minami, H. and McCallum, R.W., The physiology and pathophysiology of gastric emptying in humans. Gastroenterology, 86 (1984) 1592–1610.

Moore, J.G., Tweedy, C., Christian, P.E. and Datz, F.L., Effect of age on gastric emptying of liquid solid meals in man. Dig. Dis. Sci., 28 (1983) 340–344.

Park, H.M., Chernish, S.M., Rosenek, B.D., Brunelle, R.L., Hargrove, B. and Wellman, H.N., Gastric emptying of enteric-coated tablets. Dig. Dis. Sci., 29 (1984) 207–212.