International Journal of Pharmaceutics, 53 (1989) 145–155
Elsevier

IJP 01798

The effect of food on gastrointestinal transit and drug absorption of a multiparticular sustained-release verapamil formulation

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(Received 3 November 1988)
(Modified version received 2 January 1989)
(Accepted 13 January 1989)

Key words: Gastrointestinal transit; Drug absorption; Effect of food; Multiparticular formulation; Verapamil

Summary

The effect of a heavy meal on the gastrointestinal transit of ethylcellulose-coated verapamil pellets in a hard gelatin capsule was studied in 6 healthy volunteers utilizing a radiological procedure. Serum drug concentrations were also determined. Food affected not only the gastrointestinal transit of the pellets but also the absorption rate of verapamil. With food the absorption began earlier and more strongly than under fasting conditions due to longer retention of the pellets in the upper gastrointestinal tract, which favours drug absorption. It is important that in the development of modified-release formulations, whether single- or multiple-unit, bioavailability studies should be carried out in both fasting and non-fasting conditions.

Introduction

Clearly too little attention has been paid to the effect of food on drug absorption from sustained-release formulations. It is still very common for absorption studies in the drug development stage to be carried out in fasted subjects, even though in clinical practice non-fasting conditions are far more usual. For instance, some formulations such as sustained-release theophylline have been reported to cause serious side-effects when combined with food (Hendeles et al., 1985), these adverse effects correlating with high peak drug concentrations in the blood. Both single-unit (Lagas and Jonkman, 1983) and multiple-unit (Hendeles et al., 1985) theophylline formulations have been implicated, although in some investigations food had no effect on theophylline blood concentrations when multiple-unit formulations were used (Osman et al., 1983; Sips et al., 1984; Delhotal-Landes et al., 1988). In some cases food has caused a delay or decrease in theophylline absorption from a multiple-unit product (Leeds et al., 1982; Pedersen and Moller-Pedersen, 1984).

It is well documented that food has a clear effect on the gastrointestinal transit of single-unit controlled-release products (Cortot and Colombel, 1984; Davies et al., 1986a). Even small amounts cause substantial prolongation of the gastric residence time. In contrast, the commonest claim

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concerning multiple-unit formulations (pellets, granules, etc.) is that food does not affect their gastric emptying rate if the diameter of the subunits is less than 2 mm (Davies et al., 1986a; O'Reilly et al., 1987).

In our previous study the gastrointestinal transit and concomitant verapamil absorption from a single-unit film-coated sustained-release tablets was studied in healthy volunteers (Marvola et al., 1987). The position of the tablet in the alimentary tract at each blood sampling was detected radiographically. The results showed that food affected not only the gastrointestinal transit of the tablet but also the absorption rate of verapamil. With food, drug absorption was more rapid than under fasting conditions (t_{max} values 8 h and 12 h, respectively) since the tablet was retained longer in the upper parts of the gastrointestinal tract, which favours drug absorption.

The aim of the present study was to repeat the experiments of the previous study using a multiple-unit verapamil formulation instead of the single-unit one. The in vitro dissolution pattern of both formulations is approximately equal, thus allowing their biopharmaceutical properties to be compared.

Materials and Methods

Drug product

The product used was a hard gelatin capsule, size 0 (Posilok, Elanco), containing coated verapamil hydrochloride pellets (corresponding to 100 mg of verapamil hydrochloride) and coated barium sulphate pellets.

The verapamil pellets contained equal parts of verapamil hydrochloride (Fermion) and lactose (Ph.Eur.) plus 4% of gelatin binder. They were coated using a fluidized bed technique (Aeromatic Strea 1, Aeromatic AG). The coat consisted of ethyl cellulose (Ethocel N-50, Hercules) and 20% dibutyl sebacinate (E. Merck) as a plasticizer. The calculated amount of coating in the pellets was 10%. The density of the verapamil pellets was 1.13. The in vitro dissolution pattern was determined according to the USP paddle method; 50% of the drug was dissolved after 4.2 h.

Barium sulphate pellets were prepared using the same procedure. The ratio of barium sulphate (Barisulf-HD, Leiras) to lactose was 3 : 5 and the density of the barium sulphate pellets 1.35. The 0.7–1.7 mm (mean 1.2 mm) fraction was used from both coated pellets. The volumetric ratio of verapamil pellets to barium sulphate pellets in the final formulation was 1 : 2.

Absorption test

Six healthy male volunteers aged 21–30 years and weighing 65–85 kg were informed about the possible risks and side-effects of the study and their written consent was obtained. Routine clinical tests showed all subjects to have values within the normal ranges. The Ethical Committee of the Helsinki Deaconess Institute Hospital approved the experimental protocol.

The cross-over study was carried out in two parts. In the first part the subjects were fasted overnight and at 08.00 h took one capsule with 100 ml of tap water. Food was subsequently withheld for 3 h, following which a standard lunch was served. Blood was sampled (10 ml) just before and 2, 4, 8, 12, 24 and 32 h after dosage. Immediately following each blood sample (except at 0 and 32 h) an X-ray was taken to determine the position of the pellets in the gastrointestinal tract. The X-rays were taken in the supine position, the sites of the alimentary canal were numbered (see Table 1).

One week later the test was repeated under non-fasting conditions. Just before drug administration a standard heavy breakfast was served

TABLE 1

Number codes for different parts of the gastrointestinal tract

Number	Anatomical part
1	Stomach
2	Duodenum
3	Jejunum
4	Ileum
5	Terminal ileum
6	Ascendent colon
7	Transverse colon
8	Descendent colon
9	Sigmoid colon
10	Rectum

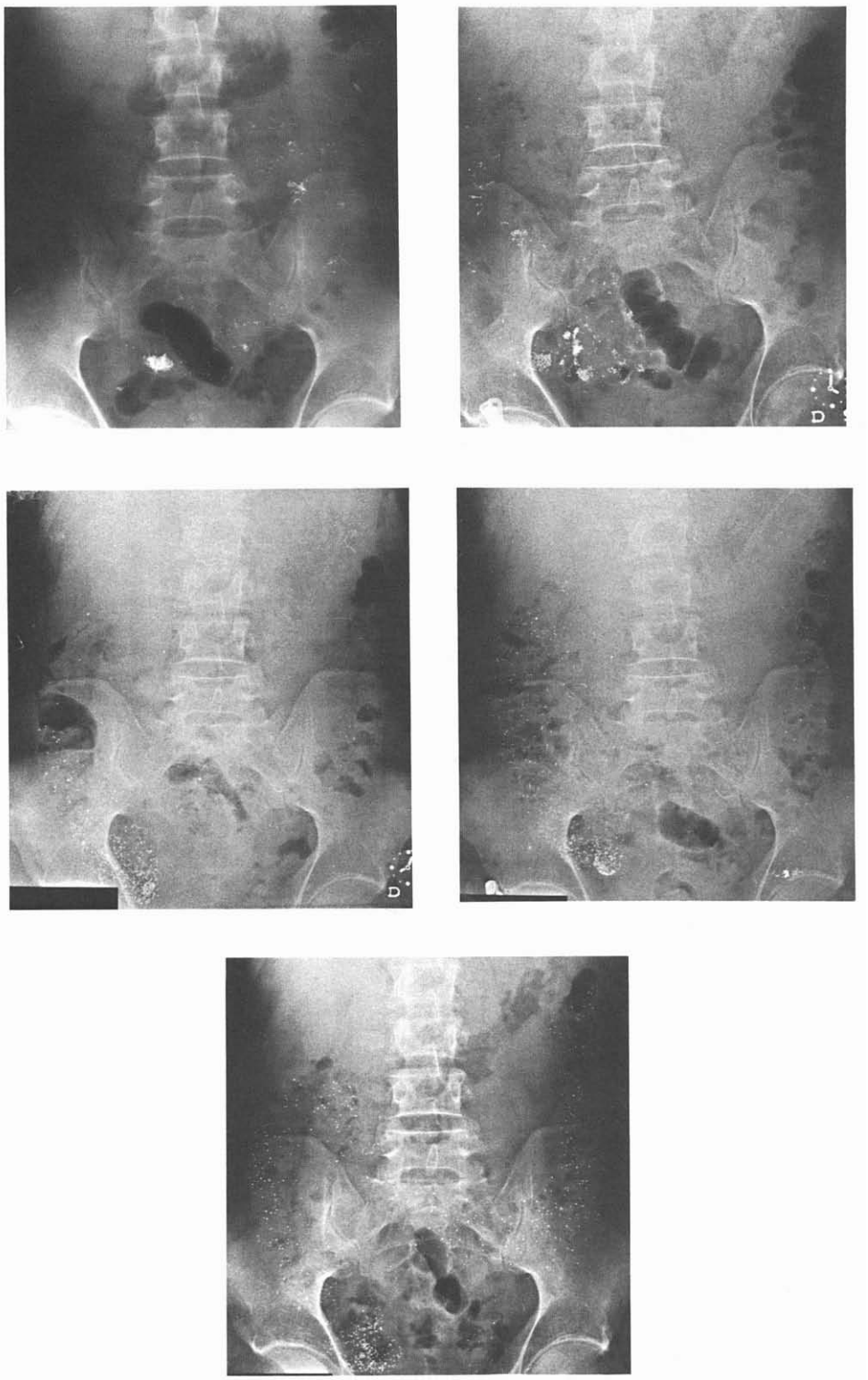

Fig. 1. Gastrointestinal transit of ethylcellulose-coated pellets in *fasting* conditions (volunteer M.T.). Timing of X-rays: 2, 4, 8, 12 and 24 h.

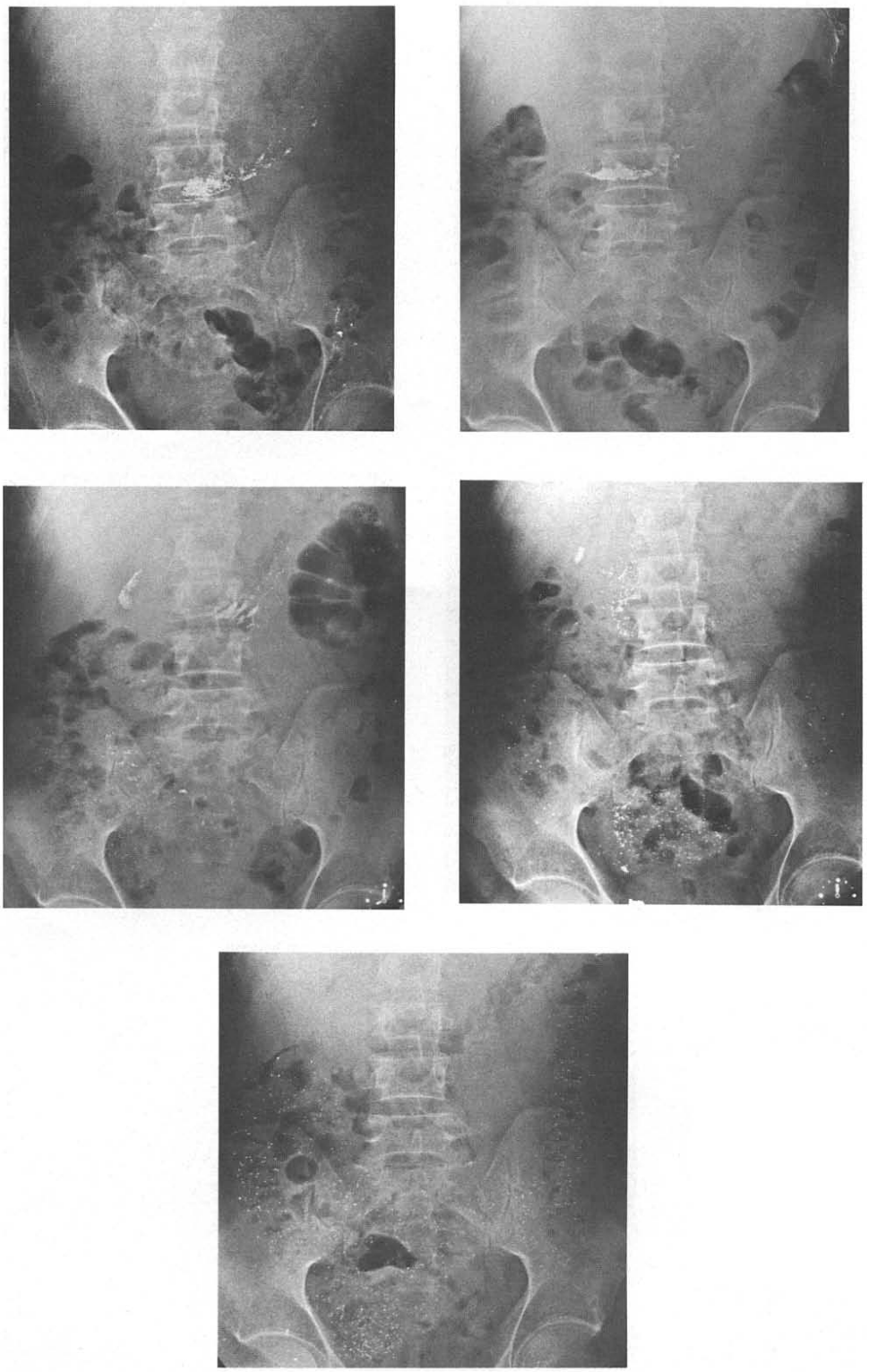

Fig. 2. Gastrointestinal transit of ethylcellulose-coated pellets in *non-fasting* conditions (volunteer M.T.). Timing of X-rays: 2, 4, 8, 12 and 24 h.

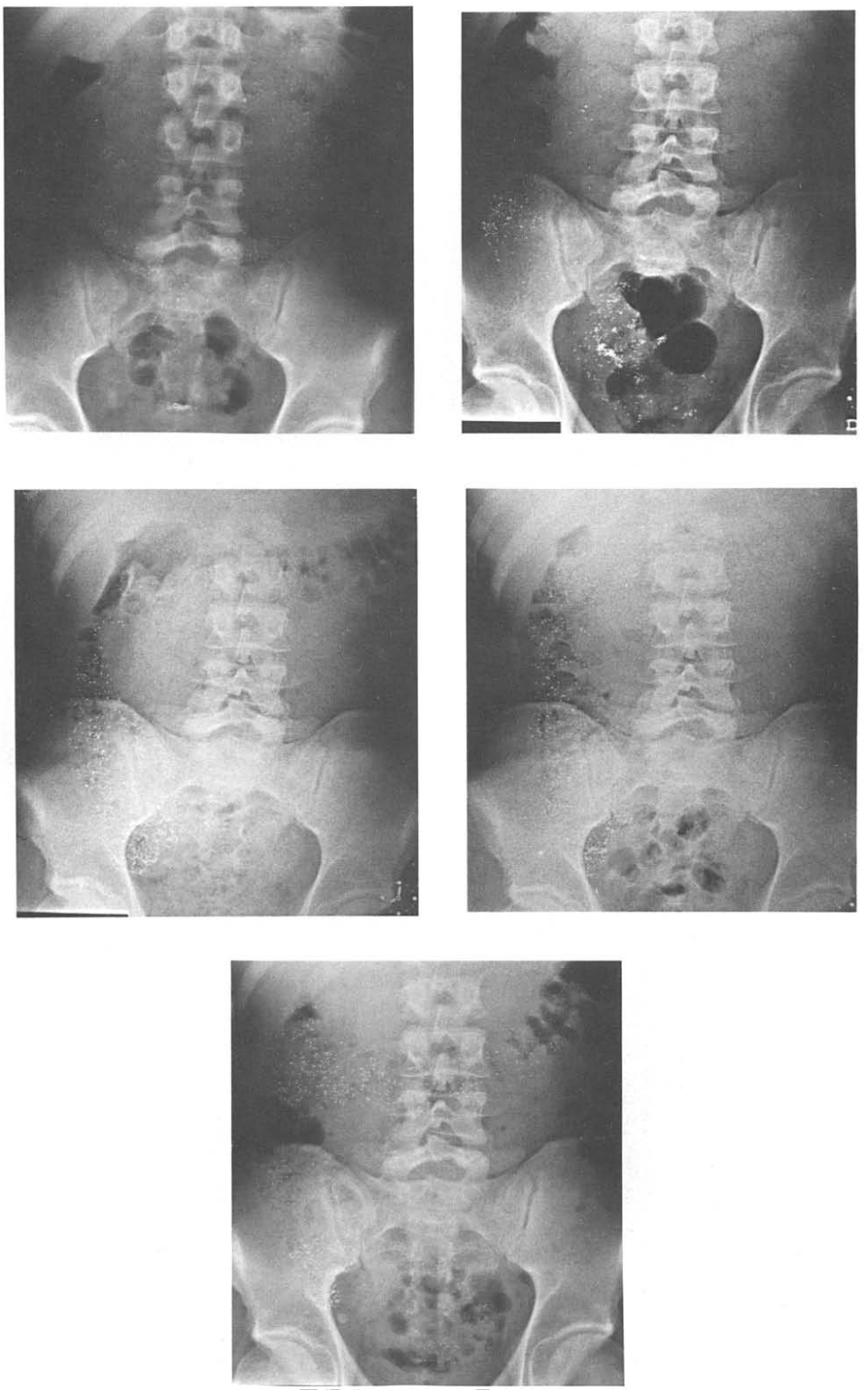

Fig. 3. Gastrointestinal transit of ethylcellulose-coated pellets in *fasting* conditions (volunteer M.H.). Timing of X-rays: 2, 4, 8, 12 and 24 h.

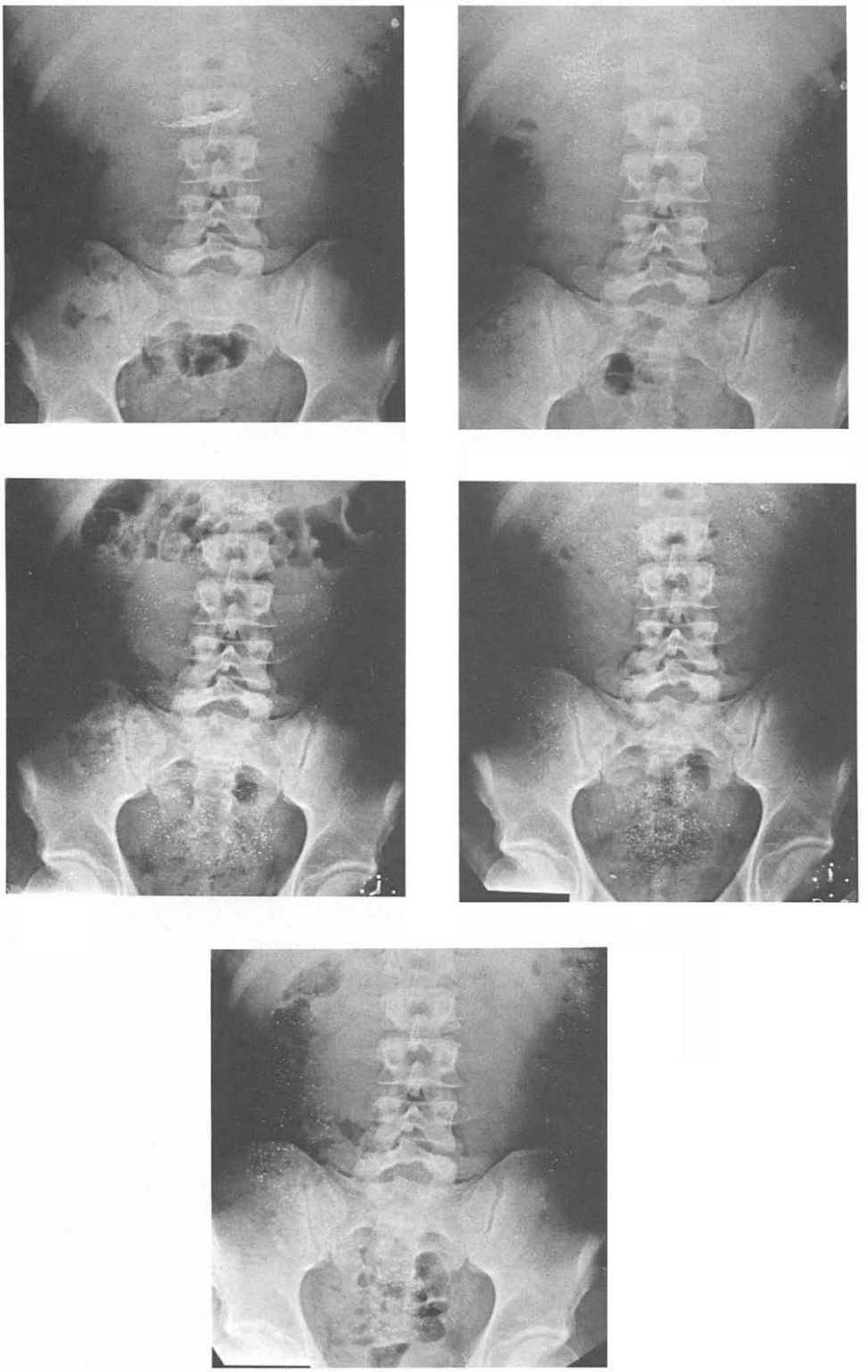

Fig. 4. Gastrointestinal transit of ethylcellulose-coated pellets in *non-fasting* conditions (volunteer M.H.). Timing of X-rays: 2, 4, 8, 12 and 24 h.

TABLE 2

Radiological evaluation of the time during which the majority of pellets were retained in the stomach

Experimental conditions	Volunteer					
	J.A.	M.H.	P.J.	K.M.	J.O.	M.T.
Fasting	2	< 2	< 2	2	2	< 2
Non-fasting	8	4	8	4	12	8

TABLE 3

Radiological evaluation of the time at which the majority of the pellets had entered the colon

Experimental conditions	Volunteer					
	J.A.	M.H.	P.J.	K.M.	J.O.	M.T.
Fasting	12	8	4	4	8	12
Non-fasting	24	12	12	12	> 24	24

consisting of oatmeal porridge (400 g), milk (200 ml), one egg, two wheat rolls, butter (10 g), cheese (40 g), orange juice (100 ml) and coffee or tea (200 ml). A standard lunch was served 3 h later.

Verapamil and its active metabolite norverapamil were assayed from serum (frozen at −18°C) using a gas chromatographic/mass spectrometric method (Marvola et al., 1985). The detection limit of the method was 1 ng/ml. The areas under the concentration–time curves (AUC 0–32 h) were calculated by the trapezoidal method. Statistical evaluation was carried out using the paired Wilcoxon test and paired Student's *t*-test.

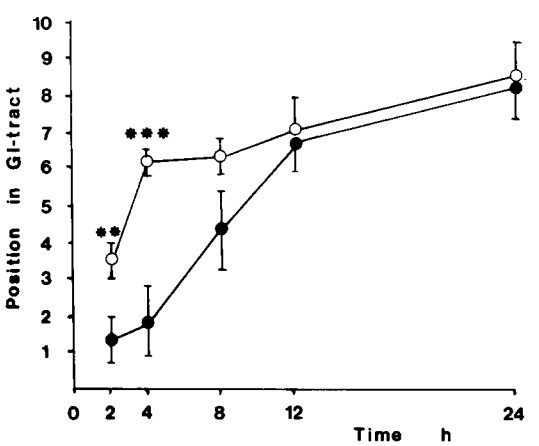

Fig. 5. Passage of ethylcellulose-coated pellets through the gastrointestinal tract in 6 healthy volunteers. The position of the foremost part of the dose has been numbered according to Table 1. Each point represents the mean ± S.D. ** $P < 0.01$; *** $P < 0.001$. ○ = fasting, ● = non-fasting.

Results

Figs. 1–4 show the X-rays from two of the 6 volunteers. Figs. 1 and 2 (volunteer M.T.) show the most prominent effect of food on gastrointestinal transit, whereas Figs. 3 and 4 show the smallest effect (volunteer M.H.). A summary of the gastrointestinal transit in all 6 volunteers is given in Fig. 5. The position of the pellets farthest down

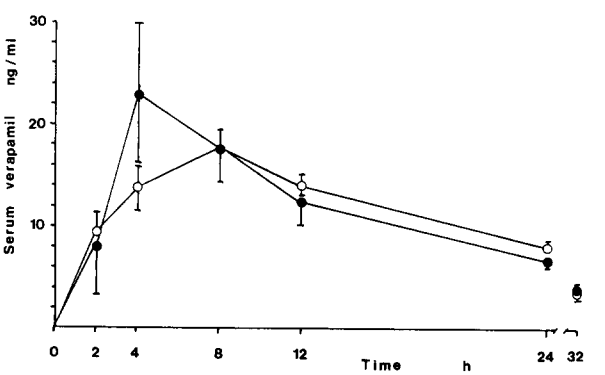

Fig. 6. Effect of food on the absorption of verapamil from a multiparticular sustained-release capsule formulation (100 mg). ○ = fasting, ● = non-fasting (means ± S.E.M., $n = 6$).

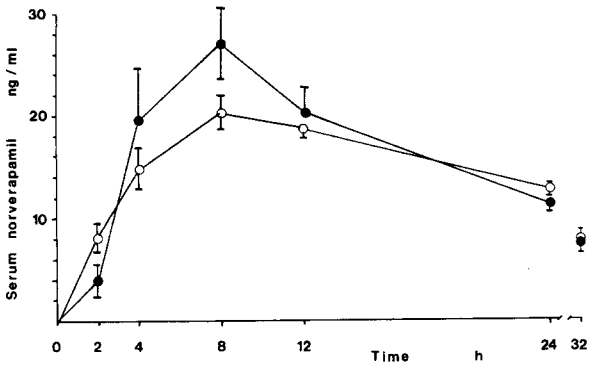

Fig. 7. Effect of food on serum norverapamil concentrations after administration of verapamil hydrochloride (100 mg) in a multiparticular sustained-release capsule formulation. ○, Fasting, ●, non-fasting conditions (means ± S.E.M., $n = 6$).

in the gastrointestinal tract was numbered according to Table 1. Fig. 5 shows that food taken just before drug administration clearly delayed gastric emptying of the pellets up to 8 h. The differences were statistically significant at 2 and 4 h ($P < 0.01$).

Examining the results on the basis of the position of the majority of pellets (Table 2) shows that food increased the gastric residence time in each volunteer by 2–10 h. The entry of most pellets into the colon was usually delayed 4–12 h, but in one case (J.O.) for more than 18 h (Table 3).

The effect of food on serum verapamil and norverapamil concentrations is shown in Figs. 6 and 7. Verapamil showed a tendency toward higher and earlier peak concentrations, but the only statistically significant ($P < 0.05$) difference was found in t_{max} values, which were 8.7 ± 1.6 h (mean ± S.D.) in fasting and 4.8 ± 2.7 h in non-fasting conditions. The $AUC_{0-32\,h}$ values for verapamil were 340 ± 52 ng/ml · h (mean ± S.D.) in fasting conditions and 338 ± 145 ng/ml · h in non-fasting conditions. The respective values for norverapamil were 453 ± 61 ng/ml · h and 480 ± 139 ng/ml · h. There were no statistically significant differences in the AUC values.

Fig. 8 shows the serum verapamil levels of each volunteer both in the fasted and fed states, and the position of the majority of pellets at each blood sampling. Especially large differences in time–concentration curves were noted if in the fasted state the majority of pellets had already entered the intestine at 2 h but in the fed state remained in the stomach for more than 4 h (volunteers K.M. and T.M.).

Discussion

An important finding in the present study was that food, in the amount given, had a very clear effect on the gastric transit time of multiparticular sustained-release verapamil capsules. The literature claims that food does not affect the gastric emptying of pellets with a diameter of less than 2 mm (Sips et al., 1984; Davis et al., 1986a; Delhotal-Landes et al., 1988), but in earlier studies the amounts of food given with the drugs were quite small, consisting mostly of a light breakfast (roughly 1000–2000 kJ) or at the most a heavy breakfast (3000–4000 kJ). In practice drugs are administered also with lunch or dinner with a calorigenic content of roughly 4000–5000 kJ. Thus the meal given in the present study contained approximately 5000 kJ. Closer examination of the report by Davis et al. (1986a) reveals that already a light breakfast has a slight retarding effect on the gastric emptying of pellets and that a heavy breakfast strengthens this effect. As early as 1965, Horton et al. demonstrated that the gastric emptying time of enteric-coated barium sulphate pellets (diameter 0.5–3 mm, density 1.85) ranged from 4 to 8 h if the pellets were administered with a heavy meal.

The present results are consistent with those of the study by Heinämäki et al. (1988) in which the gastric emptying rate of similar enteric-coated barium sulphate pellets was studied in non-fasted dogs. Although small portions of the pellets passed through the canine pylorus immediately after administration, the great majority remained in the stomach for up to 6–8 h before being swept into the duodenum by the "housekeeper" wave in the interdigestive mode of the gastrointestinal tract.

One might think that barium sulphate pellets do not accurately reflect the transit of verapamil pellets due to the difference in density, but the difference is in fact very small. Recent studies have also shown that the density of the pellets has

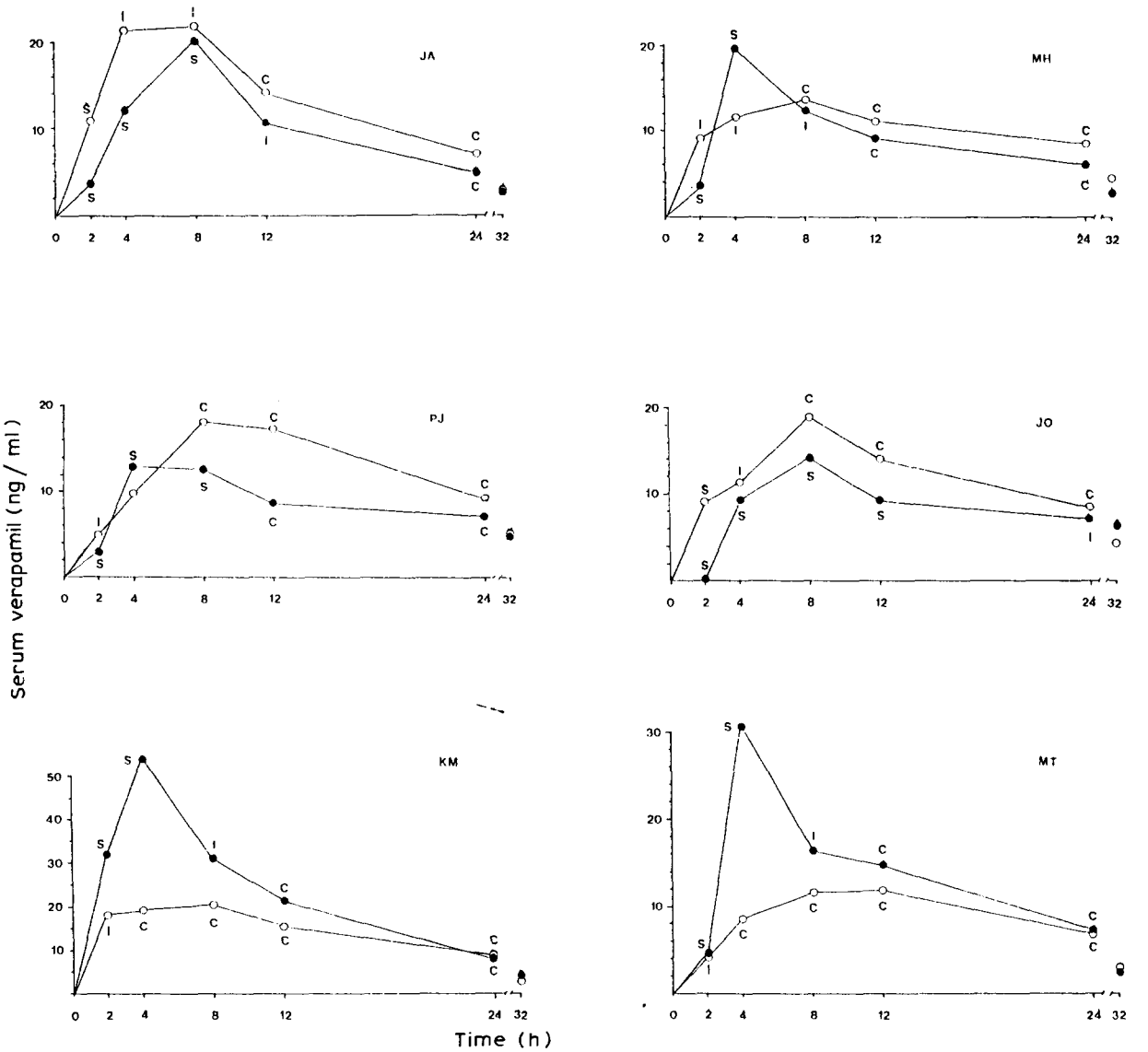

Fig. 8. Absorption of verapamil after a single dose of a sustained-release pellet formulation in 6 healthy volunteers. The position of the majority of pellets at each blood sampling was detected by X-ray. S, stomach; I, intestine; C, colon. ○, fasting, ●, non-fasting conditions.

no significant effect on gastrointestinal transit (Bechgaard et al., 1985; Davies et al., 1986b).

In our study, in one fasted subject (M.T., Fig. 1) the majority of the pellets emptied from the stomach as a bolus and were seen after 2 h in the ileum. In all other cases (fasting or non-fasting) the contents of the capsule had dispersed throughout the gastrointestinal contents before the first X-ray at 2 h. This agrees with the finding that in the dog stomach capsules containing identical ethyl cellulose-coated pellets disintegrated roughly in 10 min and that the pellets dispersed into the gastric contents (Marvola et al., 1988).

If the present bioavailability data are compared with those of the single-unit verapamil tablet with similar in vitro dissolution characteristics, it can

be concluded that the dosage form did not significantly affect the AUC values of verapamil or of its main metabolite norverapamil. However, the absorption rate of verapamil was higher from the multiple-unit formulation, t_{max} in fasting conditions being 12 h from the single-unit and 8 h from the multiple-unit formulation. The respective values in non-fasting conditions were 8 h and 4 h. The drug concentration at 2 h was also significantly higher when the multiparticular formulation was given. Thus, similar in vitro dissolution rates of different dosage forms do not necessarily imply similar absorption rates.

The phenomenon that food can retain controlled-release formulations, both single-unit and multiple-unit, for a long time in the upper part of the alimentary tract may explain the enhanced bioavailability of theophylline on postprandial administration, both with matrix tablets (Lagas and Jonkman, 1983) and with multiparticular formulations (Hendeles et al., 1985). The postprandial peak concentrations of verapamil in our studies have not been very much higher than those in fasted subjects, but this may be due to the adequate absorption of verapamil also from the colon (Marvola et al., 1987). However, if drug absorption from the colon is negligible there may be marked changes in the concentration–time curves of a sustained-release formulation depending on whether food is present or not.

Conclusion

We conclude that food, and especially a heavy meal, markedly enhances the gastric residence time of pellets administered in a hard gelatin capsule. Clearly most of the pellets were only swept out of the stomach by the migrating motor complex ("housekeeper wave"). This delay in gastric emptying can cause a higher and earlier peak in blood drug concentration, leading to some side-effects. Thus it is important that in the development of modified-release formulations, both single-unit and multiple-unit, bioavailability studies should be carried out under both fasting and non-fasting conditions. Testing a light breakfast only may be misleading. According to the results of absorption studies, patients must also be informed on the proper timing of drug administration in relation to meals.

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