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GASTROINTESTINAL TRANSIT AND CONCOMITANT ABSORPTION OF VERAPAMIL FROM A SINGLE-UNIT SUSTAINED-RELEASE TABLET

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ABSTRACT

A radiographic procedure is described for determining the position of a single-unit sustained-release tablet and the concomitant drug serum level. The results confirmed that, under fasting conditions, an essential part of the absorption of the model drug, verapamil, takes place in the colon. Food affected not only the gastrointestinal transit of the tablet but also the absorption rate of verapamil. With food the commencement of absorption was clearly more rapid than under fasting conditions. This is because the tablet is retained for a longer time by the food in the upper parts of the gastrointestinal tract, which favour drug absorption. It is concluded that absorption of verapamil from the colon is also effective and can be utilized in sustained-

release formulations. The ratio of AUC values of verapamil to those of norverapamil was markedly higher under fasting conditions, indicating enhanced bioavailability of verapamil from formulations which release most of the drug into the colon.

INTRODUCTION

In the development of sustained-release formulations it is important to evaluate the gastrointestinal transit of the drug product and the efficacy of drug absorption in various regions of the G.I. tract. Our previous study with a sustained-release tablet formulation of verapamil hydrochloride (90 mg) showed substantially prolonged drug absorption (1). After a single dose in healthy volunteers the mean verapamil serum levels between 4 and 24 h ranged from 11 to 16 $ng \cdot ml^{-1}$. It has been claimed that drug released more than 8 to 12 h after oral administration cannot be utilized (2-3). However, pharmacokinetic calculations based on our results showed that absorption must also have occurred 8 and even 12 h after dosing. If this were not the case the drug concentrations in the plasma at 12 and 24 h would have been much lower since the elimination half-life of verapamil is only 5 to 6 h. However, with the procedure used in our previous study it was not possible to determine from which part of the G.I. tract absorption had occurred.

The transit of drug preparations in the G.I. tract has usually been studied by two different methods. The first involves inclusion of a radio-opaque material into the product, enabling it to be visualized on radiographs. The second method is to include a gamma-emitting radionuclide in the formulation, allowing external observation with a gamma

camera or scintiscanner. These two methods are reviewed by Fell and Digenis (4). Both methods are usually applied to experimental formulations containing a model substance (e.g. barium sulphate or ^{99m}Tc-labelled diethylenetriaminepenta-acetic acid), not a drug substance. Thus simultaneous determinations of the position of a drug preparation and the absorption characteristics of the drug substance from it has not been possible. Rare exceptions are drug absorption from a sustained-release acetylsalicylic acid tablet monitored using a scintigraphic method (5) and a new technique based on topical burst-release of drugs from conventional formulations (6).

The aim of the present study was to develop a procedure for determining radiographically the position of a single-unit sustained-release product in the G.I. tract at each blood sampling. The effect of food on drug absorption and on gastrointestinal transit time was also studied.

MATERIALS AND METHODS

Drug product

The composition and structure of the tablet used are shown in Fig. 1. The tablet was analogous to that used in our previous study, but contained a hollow stainless steel ball in the core. The ball was added during manual tableting once half the granules had been weighed in the die. The stainless steel ball did not significantly change the in-vitro release pattern of verapamil hydrochloride determined according to the USP paddle method ($t_{50\%}$ value 4.3 h). More detailed information about the manufacture and technical properties of the tablet is given elsewhere (7).

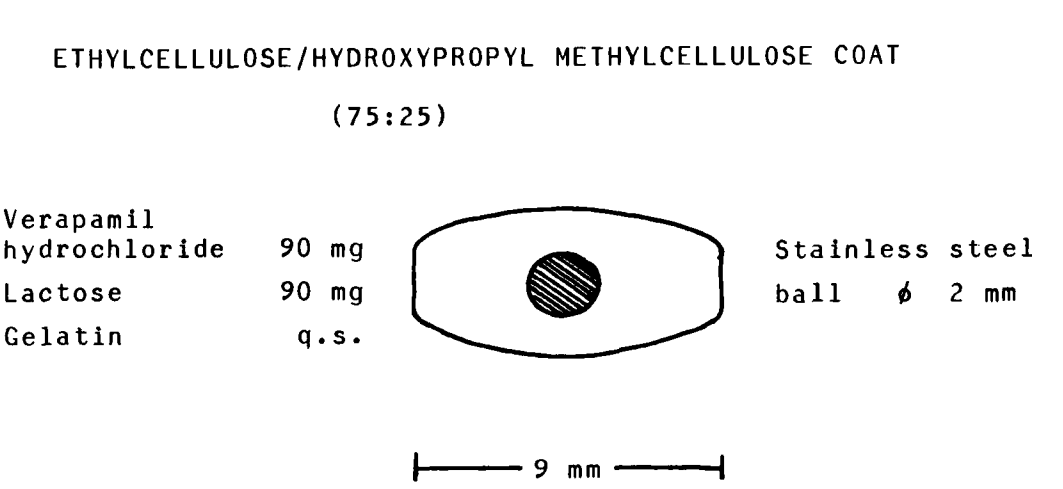

FIGURE 1
Film-coated sustained-release verapamil tablet containing a stainless steel ball for radiographic visualization.

Absorption test

Seven healthy male volunteers, aged 20 to 44 y (mean 26 y), weighing 65 to 80 kg (mean 73 kg) were informed about the possible risks and side effects of the study and their written consent was obtained. Routine clinical tests showed that all subjects had values within normal ranges. The Ethical Committee of the Hospital of Helsinki Deaconess Institute approved the experimental protocol.

Initially, a pilot test was carried out on one volunteer using drug administration at 0 and 6 h. Subsequently the main cross-over study was carried out on six volunteers. In the first part fasting conditions (overnight fast) were used. In the morning at 8 a.m. each subject took one tablet 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

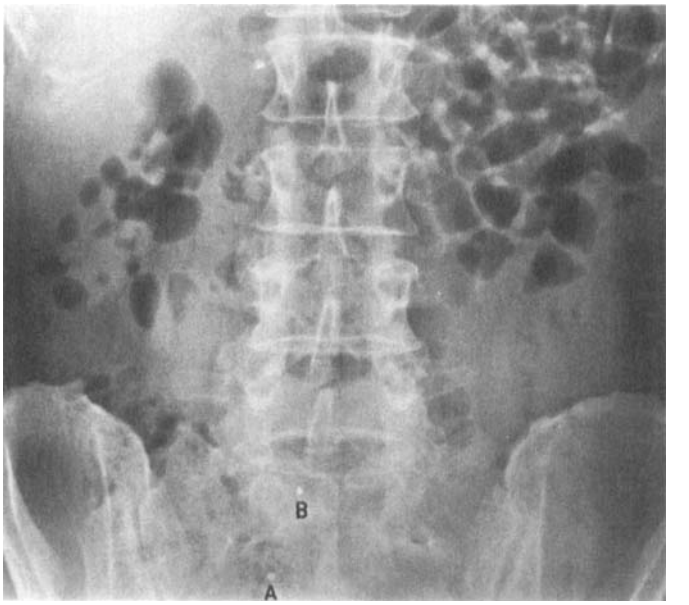

FIGURE 2
Positions of two sustained-release film-coated tablets administered (A) 8 h and (B) 2 h before X-ray (fasting conditions).

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 tablet in the G.I. tract.

One week later the test was repeated using non-fasting conditions. Just prior to drug administration a standard heavy breakfast was served consisting of oat 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.

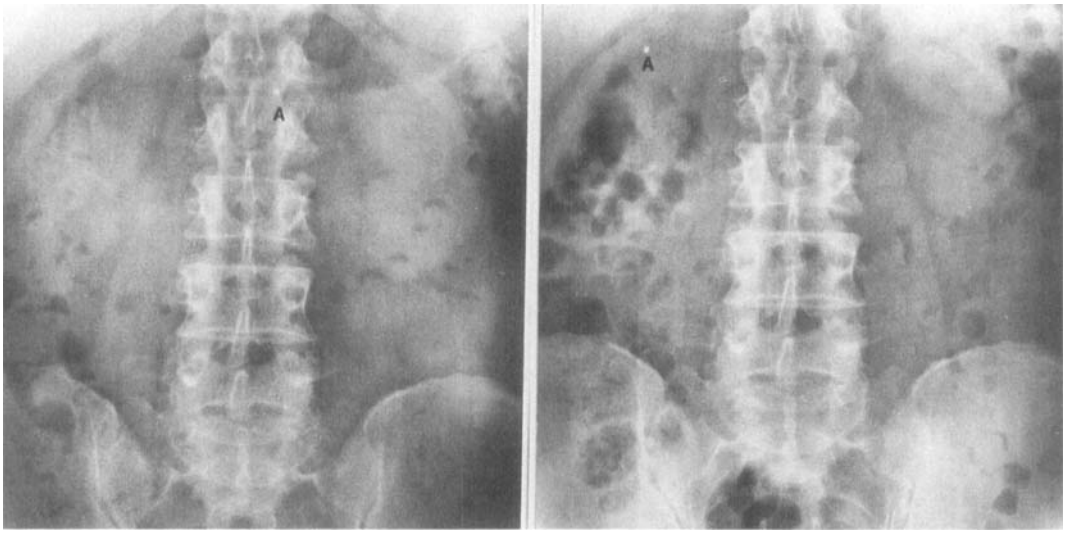

FIGURE 3
Gastrointestinal transit of two sustained-release film-coated tablets under non-fasting conditions. Drug dosing (A) at 8 a.m. and (B) at 2 p.m. Timing of the X-rays: 2,4 ,8, 12 and 24 h after ingestion of Tablet A.

Verapamil and its active metabolite norverapamil were assayed from serum (frozen at -18 ^{o}C) using a gas chromatographic/mass spectrometric methos (1). The detection limit of the method was 0.1 $ng \cdot ml^{-1}$. The areas under the concentration-time curves (AUC_{0-32h}) were calculated by the trapezoidal method. Statistical evaluations were carried out using the paired Wilcoxon test and paired Student t-test.

RESULTS

Tests were carried out in one volunteer to determine weather transit of the formulation could be follow-

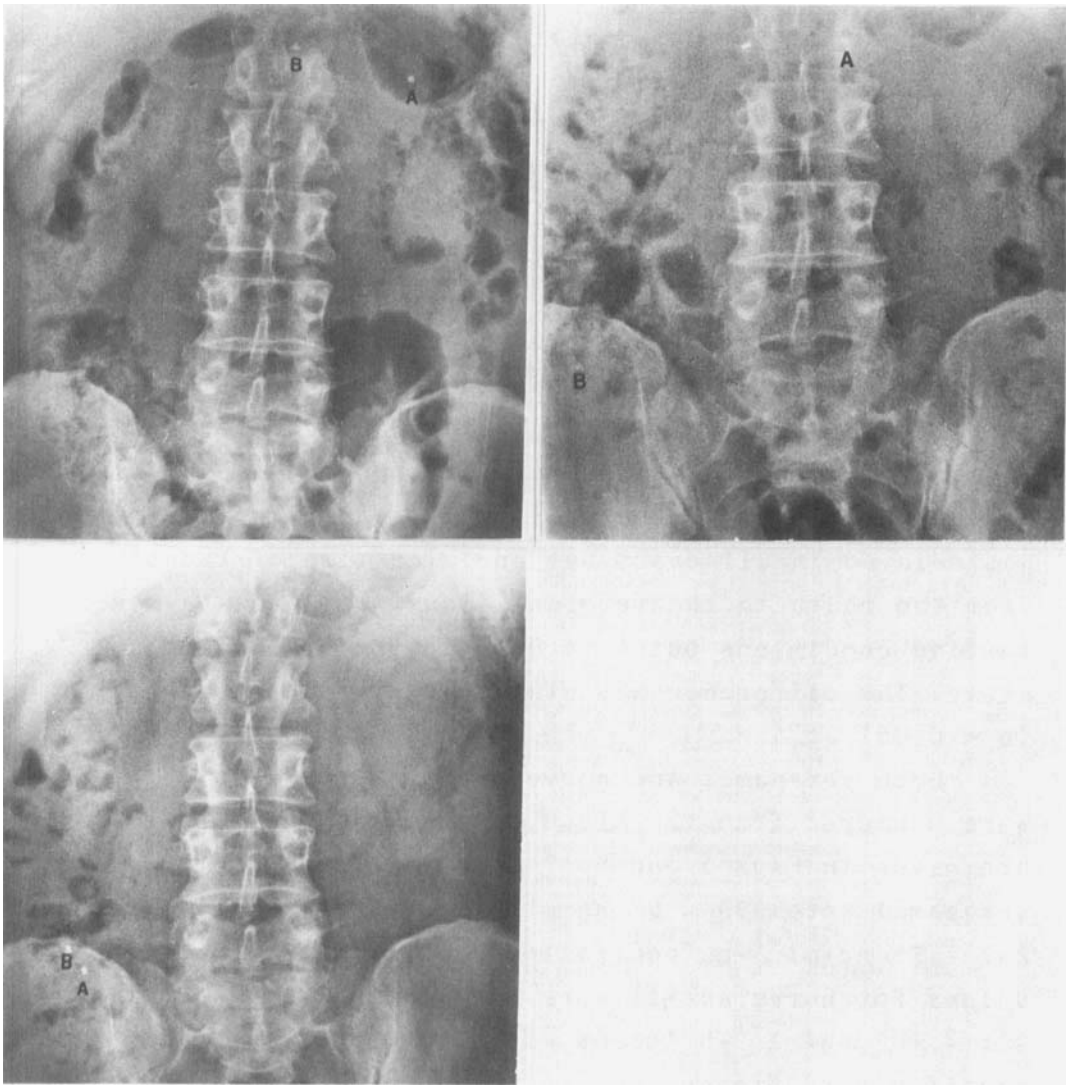

FIGURE 3 CONTINUED

ed radiographically for up to 24 h. The first test was carried out under fasting conditions. The drug was administered at 8 a.m. and 2 p.m. The X-ray taken at 4 p.m. showed both tablets to be situated in the terminal ileum (Fig. 2). The second test was performed with the

same volunteer under non-fasting conditions and using the ordinary procedure containing all five X-rays (Fig. 3). Tablet A was given at 8 a.m. and Tablet B (having a small notch for identification) at 2 p.m. Tablet A remained in the stomach for at least 12 h, Tablet B only for about 4 h. The radiologist in our group had no difficulty locating the tablets on the X-rays.

The main part of the study was carried out as a cross-over test under both fasting and non-fasting conditions. Positions of the tablets on each X-ray are summarized in Fig. 4. Food delayed transit, especially in the upper part of the G.I. tract; gastric emptying was delayed in all cases but one. The time of transit from the mouth to the terminal ileum was 2 to 4 h under fasting conditions but 4 to 24 h in the non-fasted state. The difference was statistically significant ($p < 0.05$) at 4 h.

Both verapamil and norverapamil serum levels were measured from the blood samples and the results are given in Figs 5 and 6. The AUC_{0-32h} values for verapamil were 333 ± 92 ng·ml^{-1}·h (fasted state) and 287 ± 78 ng·ml^{-1}·h (non-fasted state). The respective values for norverapamil were 349 ± 81 ng·ml^{-1}·h and 421 ± 102 ng·ml^{-1}·h (means ± S.D.). No statistically significant differences were noted between the non-fasted and fasted groups. However, the ratio of the AUC_{0-32h} value of verapamil to that of norverapamil was 0.95 ± 0.15 under fasting conditions and 0.68 ± 0.09 under non-fasting conditions. This difference is statistically significant ($p < 0.01$).

Figs. 7 and 8 show verapamil levels at blood sampling and the concomitant positions of the tablets in each volunteer.

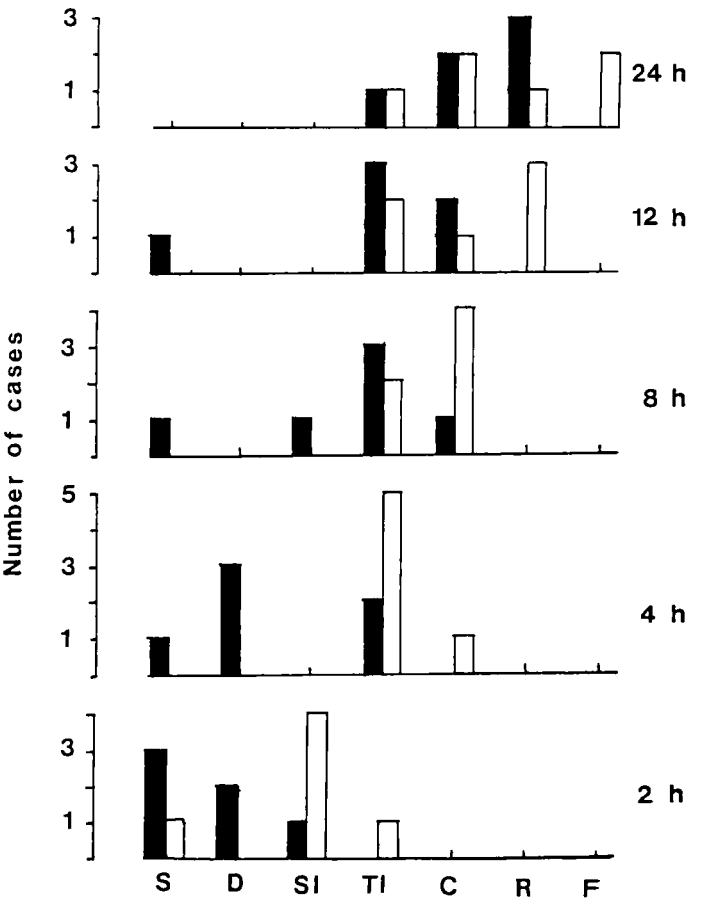

FIGURE 4
Gastrointestinal transit of sustained-release verapamil tablets detected by X-rays. ■ = non-fasting and □ = fasting conditions. Positions: S = stomach, D = duodenum, SI = small intestine, TI = terminal ileum, C = colon, R = rectum and F = defaecated.

DISCUSSION

The method described here is suitable for studying the gastrointestinal transit of a single-unit non-disintegrating sustained-release formulation.

It was possible to determine simultaneously the position of the tablet resulting drug serum level right

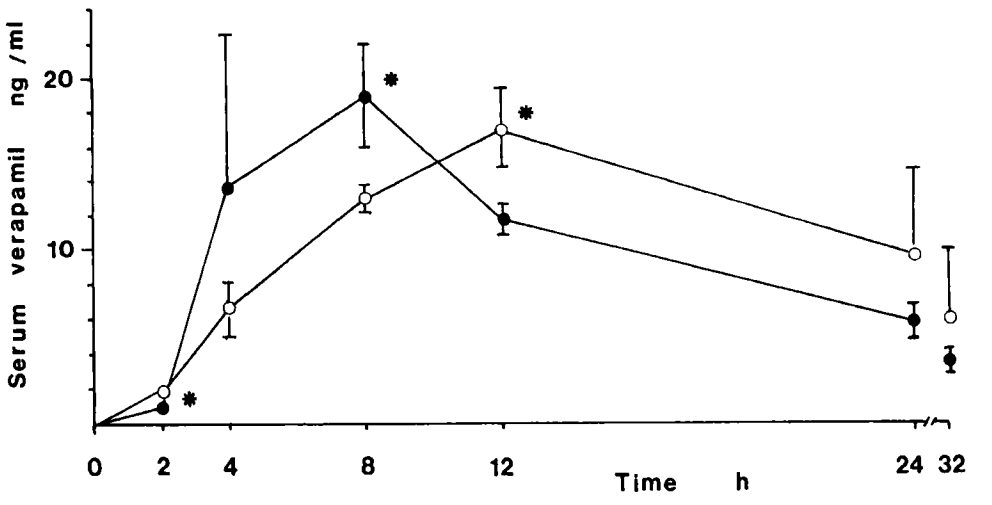

FIGURE 5
Effect of food on the absorption of verapamil from film-coated sustained-release tablets (90 mg). ○ = fasting, ● = non-fasting (means ± S.E.M., n = 6). ✱ = $p < 0.05$.

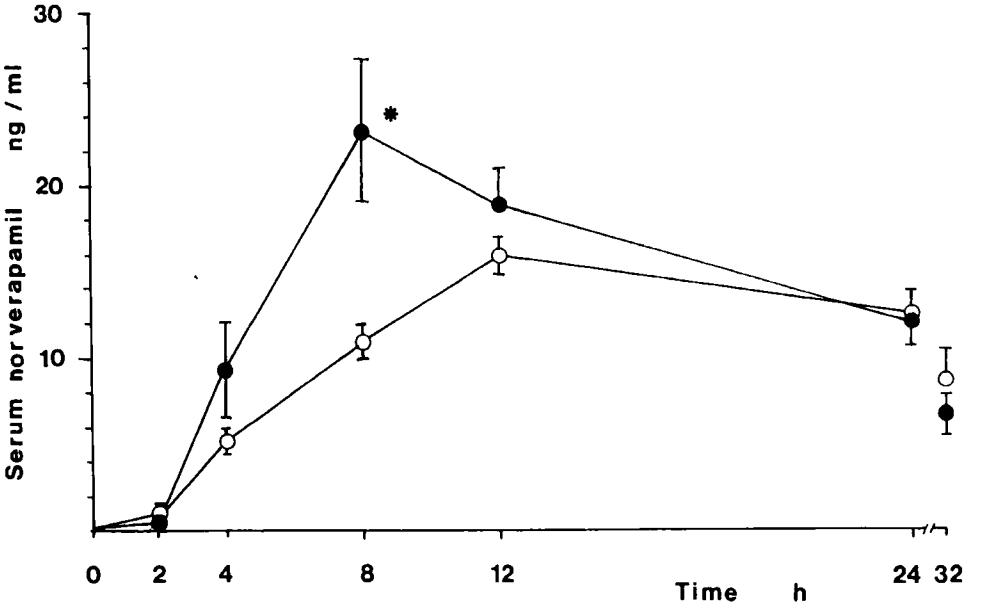

FIGURE 6
Effect of food on serum norverapamil levels after administration of verapamil hydrochloride (90 mg) in sustained-release tablets. ○ =fasting, ● = non-fasting conditions (means ± S.E.M., n = 6). ✱ = $p < 0.05$.

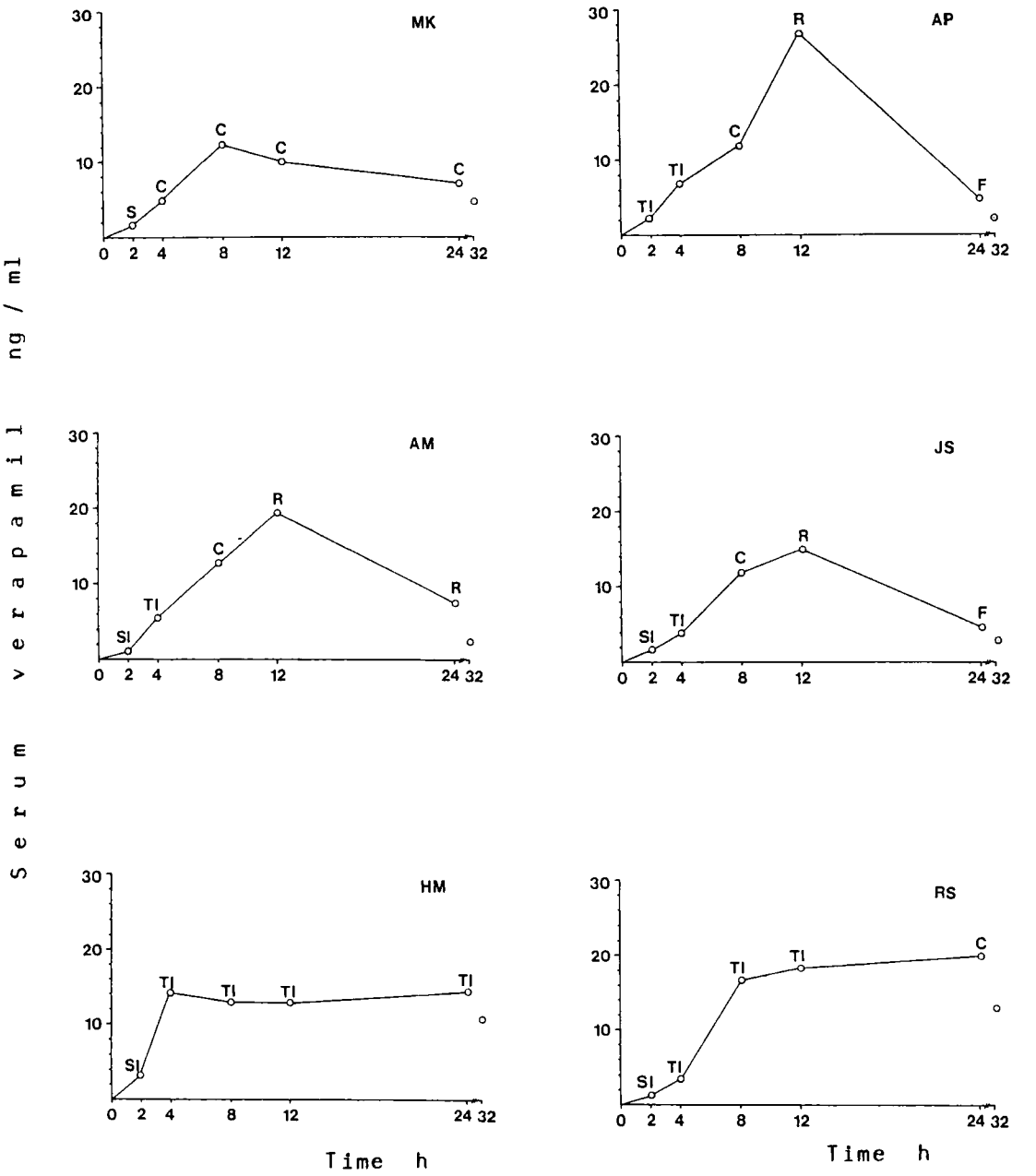

FIGURE 7
Absorption of verapamil after a single dose of a sustained-release tablet in six healthy volunteers under fasting conditions. The position of the tablet at each blood sampling was detected by X-rays. S = stomach, D = duodenum, SI = small intestine, TI = terminal ileum, C = colon, R = rectum and F = defaecated.

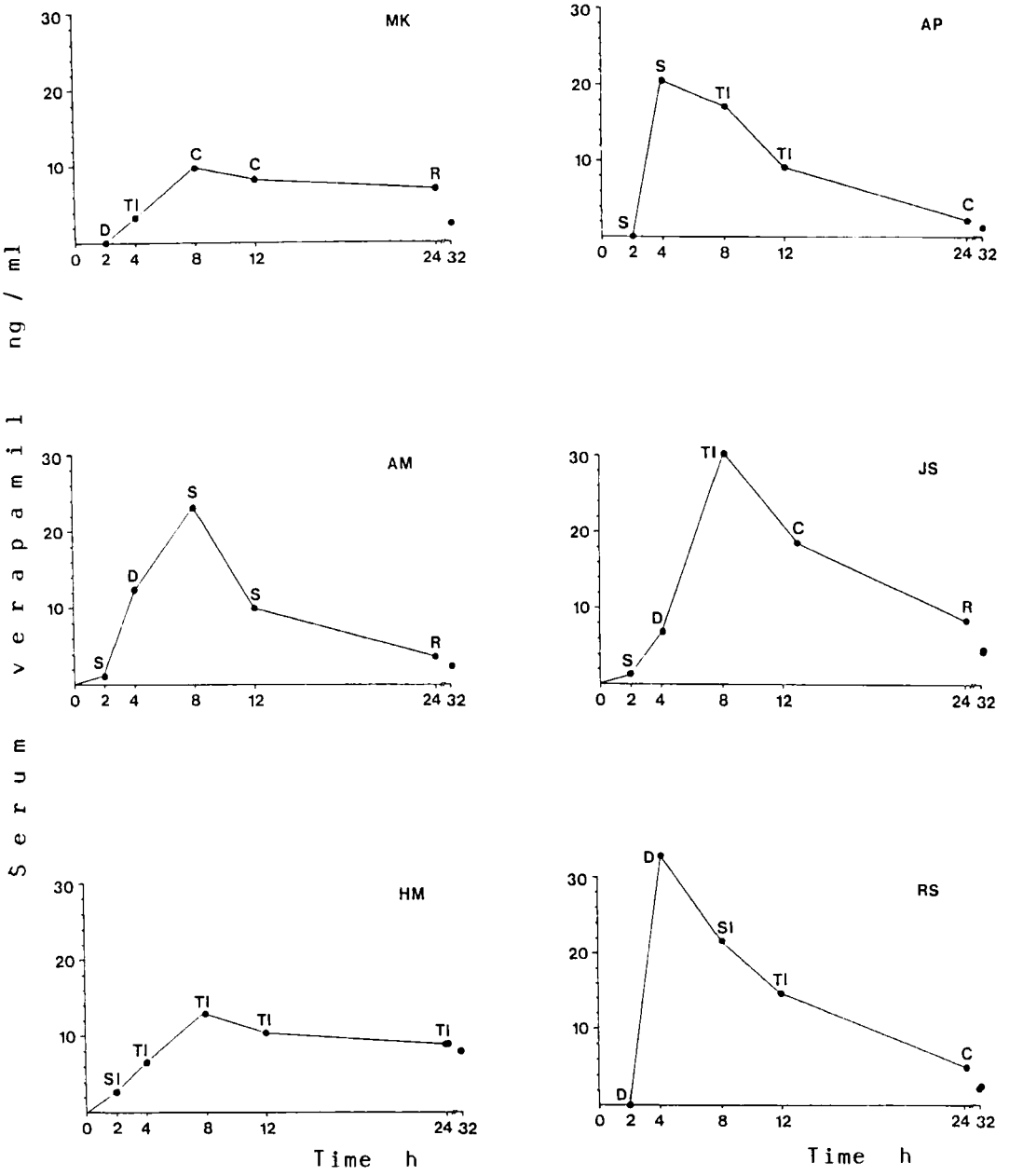

FIGURE 8
Absorption of verapamil after a single dose of a sustained-release tablet in six healthy volunteers under non-fasting conditions. The position of the tablet at each blood sampling was detected by X-rays. S = stomach, D = duodenum, SI = small intestine, TI = terminal ileum, C = colon, R = rectum and F = defaecated.

through to defaecation of the preparation. In this respect the present procedure differs from most of the previous studies, in which only the position of the preparation has been localized, usually only for up to 12 h because insufficient isotope tracer remained associated with the device to ascertain the exact position of the unit (5, 8-9).

Gastric emptying under fasting conditions took place within 2 h in five of the six volunteers (Fig. 4). This is in accordance with previous results with similar formulations. The gastric emptying time for matrix tablets in young fasted men has been reported to be 0.64 $\pm$ 0.12 h (mean $\pm$ S.E.M.) (9) and that of a non-disintegrating capsule 0.25 to 3.5 h (10). In the present study transit through the small intestine was rapid under fasting conditions. At 4 h all tablets were in the terminal ileum, except for one which was already in the colon. Davis et al. (9) have found the small intestinal transit time to be 3.2 $\pm$ 0.6 h (mean $\pm$ S.E.M.) for matrix tablets.

The present results confirm previous studies in which food intake has clearly prolonged the gastric residence time. The finding that in two non-fasted volunteers (one in the main study and the volunteer used for testing the method, Figs. 3 and 4) the tablet remained in the stomach for at least 12 h is similar to earlier findings that food occasionally causes greatly prolonged gastric retention (8, 11-13). It has been shown that the sizes of non-disintegrating particles must be less than 2 mm if they are to enter the duodenum during the digestive mode of the gastrointestinal canal (14-15).

In five cases of the twelve in the present study a delay or stop in tablet transit was noted in the terminal ileum (Fig. 7: HM, AP and RS and Fig. 8: HM

and AP). Also in Fig 2. both tablets, although administered at a six hour interval, are situated in the terminal ileum, indicating a delay in the transit of Tablet A. Thus the ileo-caecal valve may also function as a regulator for drug transit in the G.I. tract. This possibility has been discussed by Wilson and Washington (16).

The present results confirm that under fasting conditions an essential part of the verapamil absorption takes place in the colon (Fig. 7). It has been believed for far too long that absorption takes place in the duodenum or small intestine and not in the colon. It is obvious that relatively few drug substances have so-called absorption window (17). If absorption is carefully examined, several drugs (e.g. 5-aminosalicylic acid, metoprolol and oxprenolol) also show marked absorption from the colon (18-20).

Food affects both the gastrointestinal transit of the tablet and the absorption rate of verapamil. The commencement of absorption was delayed, as shown by the values at 2 h (Fig. 5), while subsequently absorption was clearly faster than under fasting conditions. The reason for the shorter t_{max} value is that food retained the tablet for longer in the upper parts of the G.I. tract where conditions are more favourable for drug absorption. If the site of the tablet at 2 or 4 h was in the duodenum, high peak concentrations at 4 or 8 h were obtained (Fig. 8: AM, JS and RS). This phenomenon could also explain the enhanced bioavailability of theophylline on postprandial administration of sustained-release matrix tablets found by Lagas and Jonkman (21).

Food and the concomitant change in the main absorption site markedly ($p < 0.01$) altered the ratio of verapamil to its metabolite, norverapamil (Figs. 5-6).

The higher relative amount of the metabolite after food ingestion may be due to the release of the drug in the upper parts of the G.I. tract, where metabolic activities may be higher. A change in the ratio of verapamil to norverapamil has also be been observed when verapamil solution and a sustained-release product have been studied in the same subjects (22). Thus, enhanced bioavailability of verapamil, the unchanged drug, can be obtained if sustained-release formulations are used which release most of the drug into the colon.

CONCLUSIONS

It is concluded that verapamil is effectively absorbed from the colon and that it can be utilized in sustained-release formulations, although absorption from the duodenum is still better. It is important that, in the development of modified-release formulations, bioavailability studies are carried out under conditions as close as possible to those existing in the therapeutic situation. The use of fasting conditions only is inadequate. Many patients take their medicine with a meal to avoid gastric irritation or just to remember when they took the drug. As shown in this and many other studies food may considerably change the absorption profile of a drug. 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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