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Gastric emptying of OROS tablets in man

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Summary

Twenty normal fasted subjects received, simultaneously, 3 OROS tablets containing stainless steel pellets. The gastric emptying of the tablets was monitored by X-ray. In 10 of the subjects, breakfast was followed by the gastric emptying of all 3 tablets. In 7 others, the emptying was slower or incomplete, and in the last 3, the tablets were still all in the stomach after 5 h, i.e. after breakfast and lunch.

Introduction

OROS (oral osmotic system) is a new sustained-release dosage form (Theeuwes, 1975) in which the active ingredient is enclosed within an insoluble, semipermeable membrane. In the gastrointestinal (GI) tract, the active ingredient passes into solution and, under the osmotic pressure generated, is slowly expelled, at a constant rate, through a hole in the membrane. The tablets do not disintegrate and retain their shape for several hours, so that it was important to determine their sojourn in the human stomach under normal conditions.

The OROS tablets administered in the present study each contained a small stainless-steel pellet, and their gastric emptying was monitored by serial radiography. To reproduce the usual conditions of tablet ingestion, the investigation extended over the space of a whole morning, from breakfast until after lunch.

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Materials and Methods

Subjects

Twenty healthy male volunteers participated in the study. They had no history of any digestive or haematological disorders, and had not been exposed to X-rays during the previous 6 months. All gave their informed consent.

Tablets

The OROS tablets (diameter 8.8 mm, thickness 4.25 mm, weight 310 mg) corresponding to those of Trasicor-OROS 17/170 [1] but without active ingredient, each contained a stainless-steel pellet (diameter 2.38 mm).

Meals

Breakfast consisted of coffee (2 teaspoonfuls of instant coffee in 150 ml of hot water) with sugar (20 g), white bread (60 g) and butter (20 g). The total calorific value was 381 calories, of which 5% was made up by proteins, 40% by lipids, and 55% by carbohydrates.

Lunch consisted of one boiled egg, a beefsteak (100 g), mashed potatoes (250 g), cheese (30 g), one banana and 200 ml water. Its calorific value was 606 calories, made up of 26% proteins, 35% lipids, and 39% carbohydrates.

Procedure

The experimental conditions were as close as possible to the actual therapeutic situation in which the tablets would be used. Each fasted volunteer swallowed 3 OROS tablets at once with 50 ml of water. Forty-five minutes later, the subject ate breakfast within 15 min. Lunch was eaten between 3.5 and 4 h after the intake of the tablets. X-Rays were taken 15 min after ingestion of the tablets and then every hour for the next 5 h.

The X-Ray pictures were inspected by two different observers in a blind manner. Divergencies in the location of one or more tablets in the GI tract were not frequent and could be estimated at less than 10% of the total number of X-rays taken (i.e. 12 out of 120). The contested X-rays were examined again by the two observers together, and the final location of the tablets was decided.

Results

The results are given in Table 1 and displayed graphically for each individual subject in Fig. 1. In the majority of the volunteers, the tablets left the stomach during the first hour after intake, i.e. during or shortly after breakfast. By the end of the first hour, 9 of the 20 subjects had no tablets left in the stomach whereas only 5 had retained all 3 tablets (Table 1). The influence of lunch was less marked: the number of volunteers with no tablets in the stomach increased from 9 to 13 after

[1] Ciba-Geigy.

lunch, but there were still 3 subjects with all 3 tablets remaining in their stomachs 5 h after intake and 1 h after the end of lunch (Table 1).

On the basis of the 20 individual graphs (Fig. 1), the subjects can be classified into four groups:

TABLE 1

Time after tablet intake	Number of subjects whose stomach still contained:			
	3 tablets	2 tablets	1 tablet	no tablets
15 min	17	2	1	0
1 h	5	3	3	9
2 h	4	3	3	10
3 h	4	3	2	11
4 h	4	1	2	13
5 h	3	1	3	13

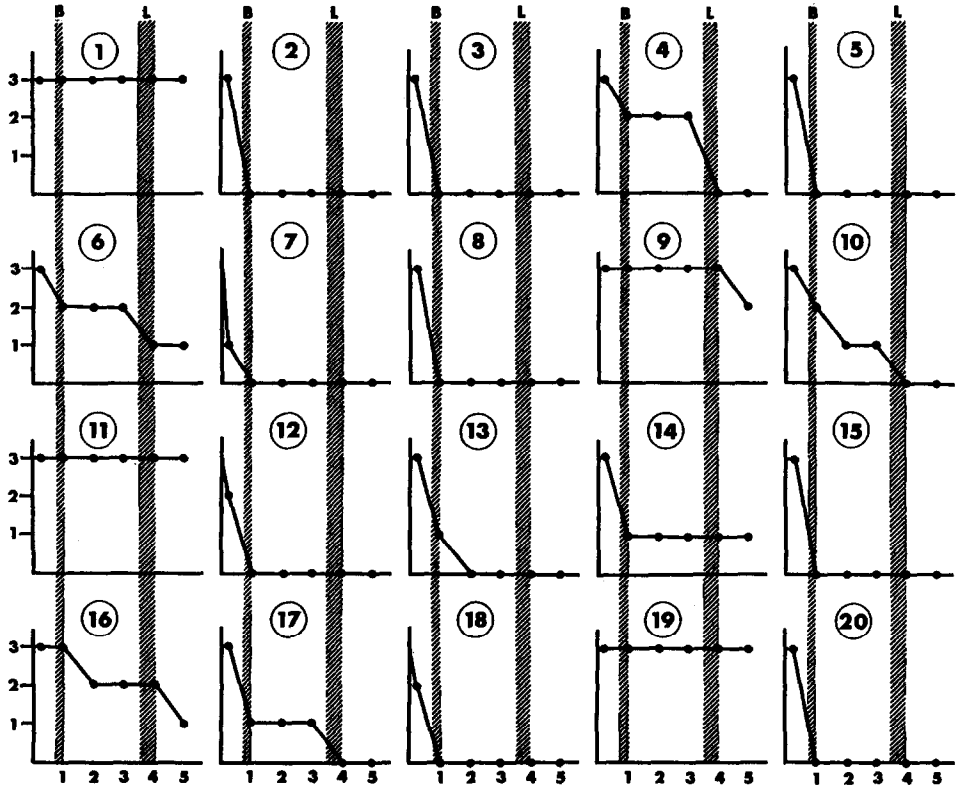

Fig. 1. Gastric emptying profile in the 20 volunteers. Abscissa: time after tablet intake (h). Ordinate: number of tablets in the stomach. B = breakfast; L = lunch.

Group I (Subjects 1, 11, 19)—all 3 tablets still remained in the stomach after 5 hours;
Group II (Subjects 2, 3, 5, 7, 8, 12, 13, 15, 18, 20)—breakfast was followed by complete gastric emptying of the 3 tablets;
Group III (Subjects 4, 10, 17)—breakfast *and* lunch were followed by gastric emptying of the 3 tablets;
Group IV (Subjects 6, 9, 14, 16)—*incomplete* gastric emptying occurred after breakfast (14), lunch (9), or both (6, 16).

Ten of the 20 subjects fall into category II, but it is interesting to note that in 3 of them (7, 12, 18) partial gastric emptying had already occurred within 15 minutes of intake, i.e. before breakfast.

Discussion

There is relatively little information available on the gastric empying of non-digestible solids, like OROS tablets. In 1938, Crane and Wruble (1938), in a series of 1000 X-ray examinations in 116 young adults who took enteric-coated tablets, found that the mean residence time in the stomach was 3.6 h in 80% of the cases, and about 10 h in 15%. According to Blythe (1958), the time taken by an enteric-coated tablet to pass the pylorus varies from a few minutes to 12 h, with an average of 1.5 h.

In a recent study (Dew et al., 1982), 6 capsules (length 22 mm, diameter 7.5 mm) containing barium sulfate and coated with an insoluble resin were taken at once by 6 convalescent patients after breakfast. Five hours later, there were no capsules still detectable by X-ray in the stomachs of any of the patients. In another experiment (Galeone et al., 1982), two fasting healthy volunteers received two capsule-shaped tablets containing barium sulfate with 100 ml water. Thirty minutes later, all the tablets had disappeared from the stomach.

Four healthy volunteers each swallowed one tablet containing [^{99m}Tc]DTPA and its progress through the gastrointestinal tract was followed by gamma-scintigraphy (Daly et al., 1982). One hour and 15 minutes after intake, the tablets were observed in the stomach, but later they were in the intestine. In five volunteers, Wilson et al. (1984), with the same technique, recorded gastric emptying times of 0.3–5 h for aspirin 800-mg tablets.

The effect of specific gravity and eating on the gastric emptying of capsules was studied by Müller-Lissner and Blum (1981). Four non-digestible capsules ($6 \times 6 \times 20$ mm), two floating and the other two sinking were given to each of 16 fasting volunteers. Eight volunteers swallowed the capsules with 50 ml water and continued fasting; the other 8 took them with 200 ml of a test-meal (milk + cream). The capsules were labelled with ^{57}Co and followed with a gamma-camera. Within 2.5 h the floating capsules had been emptied in all 8 fasting subjects and the sinking capsules in 7; in the last it was emptied immediately after ingestion. In 2 out of the 8 non-fasting subjects, the sinking capsules were emptied within 2.5 h, and in the 6 others within 2.5–5 h. The floating capsules were emptied within 2.5–5 h in 6 of the non-fasting subjects. In one subject they were emptied after 12 h; in another, one

capsule was emptied after 12 h, and the other after 24 h.

The results of the present study are thus in agreement with the few data from the literature. The non-disintegrating OROS tablets remain in the stomach of the different individuals for very variable periods of time.

It is known that the pylorus exerts some screening effect, so that particles larger than around 2 mm are not immediately allowed to pass it. As OROS tablets have a diameter of 8.8 mm, it is not surprising they remain in the stomach, at least partly, until they are evacuated at the end of the digestion of a meal. The rapid initial emptying of 1 or 2 tablets on the other hand might have happened before the breakfast and be due to the arrival of the contraction waves of an interdigestive motor complex in the fasted subjects. Such motor complexes are inhibited by food, and this could result in the prolonged sojourn of OROS tablets in the stomach of some subjects.

Conclusion

The extended residence of OROS tablets in the stomach of some volunteers is certainly beneficial as regards the absorption of the drug they contain. This drug in solution passes into the small intestine, the whole length of which is thus available for absorption. When the OROS tablets are shortly evacuated from the stomach, they deliver the drug solution in the intestine for several hours, and their overall bioavailability may sometimes depend on their intestinal transit.

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