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Gastrointestinal transit time of single-unit tablets

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Information about the transit time of pharmaceutical preparations, i.e. single-unit or multiple-units doses (Bechgaard & Hegermann Nielsen 1978) through the human small intestine, especially through individual segments, is limited.

Two studies have been performed on ileostomy subjects (Bechgaard & Antonsen 1977; Bechgaard & Ladefoged 1978) both aiming to describe the influence of size and density of pellets on intestinal transit time. In the present communication we report the transit time of a single-unit dose administered simultaneously with these pellets to the same ileostomy subjects.

A total of ten ileostomy out-patients, eight females and two males, aged 24–50 years, participated. Six of the subjects had Crohn's disease and four ulcerative colitis. The small intestine was intact in five of the subjects and part of the ileum, maximum 50 cm, resected in the remaining five subjects with Crohn's disease. The time elapsed from ilestomy ranged from 3 months to 15 years (median 4 years).

Gastrointestinal transit time, determined with carmine, showed an average of 4·9 h (range 2·5–9·0 h) estimated on the day before the examination.

Two non-disintegrating dummy tablets made of hard paraffin with diameter 12 mm (spheroid) and density 1·2 (single-unit tablet) were administered together with the pellets in the morning on the day of examination after 12 h of fasting. No restrictions in intake of food or fluid, nor in the locomotive routine were made during the 48 h collection period. (For a detailed description of the design of the studies, see Bechgaard & Ladefoged 1978.)

All single-unit tablets were retrieved within the 48 h observation period.

In three out of 10 subjects the transit times of the two single-unit tablets within subjects were different (Table 1). The intake of fluid was above normal in one subject (IV), who drank 6900 ml, 5000 ml of which was beer. However, normal and uniform consumption of food was observed by the remaining two subjects, showing a maximum intra-subject variation of 9 to 23 h.

One subject repeated the study after a month. On both occasions the two single-unit tablets showed identical transit times but there was a 2 h displacement between the replicates.

The variation in transit time observed between subjects, ranging from 5 to 40 h (Table 1), is surprisingly high compared with the general conception that single-unit preparations tend to follow food, which is assumed to have a normal transit time through the small intestine of between 3 and 8 h (Prescott 1974). Moreover, the data indicate that the transit times of single-unit tablets do not have a random uniform distribution but more likely a bimodal distribution. Within the first 18 h of observation (corresponding to 03 a.m.) 36% (8/22) of the single-unit tablets were retrieved; the remainder were recovered within the observation period, thus a diurnal effect on their transit time cannot be excluded.

In contrast to the high reproducibility of transit times of pellets throughout the small intestine observed both within and between subjects (Bechgaard & Ladefoged 1978), the transit times of the single-unit tablets (administered simultaneously with these pellets) show great variations both between and within subjects (Table 1), in spite of an equal influence of food and habitual behaviour. Therefore, the data support the considerable variation of rate of availability observed after ingestion of single-unit enteric coated tablets (e.g. Hulme et al 1975; Bogentoft et al 1978; Henderson et al 1979) and after single-unit controlled release tablets having a pH-dependent release rate profile (Cramer et al 1974), as drug availability from these types of formulation is only dependent on location of the depot in the gastrointestinal tract. The differences are probably due to variable gastric emptying as few physiological parameters appear to be as variable.

Whether the intestinal transit time of single-unit tablets in ileostomy subjects is comparable to that of healthy

Table 1. Transit times of single-unit tablets. Parentheses indicate number of tablets retrieved at specified time.

Subject	Hours after administration[1]	
I	(1) 9	(1) 23
II	(2) 27	(2) 25[2]
III	(1) 23	(1) 27
IV[3]	(1) 7	(1) 40
V	(2) 25	
VI	(2) 27	
VII	(2) 29	
VIII	(2) 5	
IX	(2) 11	
X	(2) 11	

Range: Intra-subject 9–23 (7–40)[3].
Inter-subject 5–40.

[1] Mean of sampling interval.
[2] Replicate study.
[3] Subject IV had atypical fluid intake (6900 ml, including 5000 ml beer).

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subjects is open to question, but the reasons for ileostomy were different and subjects with a resection were not those showing the shortest transit times.

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Bioavailability of magnesium salicylate

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Intensive salicylate therapy is commonly associated with gastrointestinal disturbances and acute blood losses (Leonards & Levy 1972). Davison et al (1966) have shown that the extent of aspirin-induced gastrointestinal bleeding is higher when the drug is given as a suspension rather than as a solution buffered at pH 6·5. After esterification of the carboxylic group, aspirin retains its pharmacological activity while producing less gastric irritation (Rainsford & Whitehouse 1976). Sorenson (1977) has shown that copper complexes of aspirin and salicylates are as effective as the parent compound but they seem to cause less gastric irritation. Magnesium salicylate has been reported to produce less gastrointestinal irritation than aspirin (Rotschild 1979). Recent reports (Cohen 1978; Cassell et al 1979) suggested that choline magnesium trisalicylate can effectively deliver salicylate without the gastric irritation associated with aspirin. Mason (1980) has shown that commercially available tablets of aspirin, magnesium salicylate and choline magnesium trisalicylate are bioequivalent in man.

In view of the importance of salicylate therapy in the treatment of rheumatoid arthritis, we have investigated the pharmacokinetics of magnesium salicylate and of a commercially available aspirin tablet using a cross-over study in dogs. The tetrahydrate form of magnesium salicylate, which has been shown to be a crystalline, non-hygroscopic material (Alam & Gregoriades 1981) was used in these studies.

Materials

Two tablet formulations of magnesium salicylate were used. Tablet A (Magan, Adria Laboratories, Inc.) contained gelatin as a binder; tablet B contained pregelatinized starch as a binder. A commerial aspirin tablet (Bowman Pharmaceuticals, Inc., U.S.A.) and an aqueous solution of magnesium salicylate were also used in these studies.

In vitro dissolution. The in vitro dissolution of tablets was determined by placing one tablet in the rotating basket which was immersed in 900 ml of distilled water (United States Pharmacopeia 1980). The basket was rotated at 100 rev min^{-1}. At various time intervals, 1 ml sample was withdrawn, filtered through a 0·45 μm membrane filter, diluted to 10 ml with distilled water and an aliquot taken for u.v. absorbance at 296 nm (magnesium salicylate) and 275 nm (aspirin). The amount dissolved was determined and the cumulative percent dissolved was calculated based upon assayed values. Six individual tablets were run for each product. t50% was determined from a plot of cumulative percent dissolved vs time (Alam & Parrott 1971).

In vivo studies. Four female beagle-type mongrel dogs, each ca 10 kg were used. The study was a 4 × 4 Latin square design with a one week wash-out period between treatments. Doses of 325 mg magnesium salicylate (½ tablet) and aspirin, each providing the equivalent of approximately 26 mg salicylic acid per kg were used.

Following an overnight fast, the dogs were given 200 ml water by gavage; 30 min later, the dogs were dosed with one of the test substances. The solution of magnesium salicylate was administered with an oral feeding tube. Immediately following dosing, the dogs were administered an additional 25 ml water to wash down the medication.

Table 1. In vitro dissolution of magnesium salicylate and aspirin tablets in distilled water using USP apparatus at 100 rev min^{-1}.

Product*	Dissolution time means (with s.d.) n = 6	
	t50% (min)	k_d (min^{-1})
Tablet A	12 (2·4)	0·058 (0·012)
Tablet B	33 (8·8)	0·021 (0·003)
Aspirin tablet	3 (1·2)	0·231 (0·039)

* Tablet A, 650 mg magnesium salicylate with gelatin binder.
Tablet B, 650 mg magnesium salicylate with pregelatinized starch binder.
Aspirin (325 mg), commercial tablet.

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