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Absorption of acetylsalicylic acid from enteric-coated tablets in relation to gastric emptying and in-vivo disintegration

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The absorption of acetylsalicylic (ASA) acid from enteric coated tablets was studied in relation to gastric emptying and in-vivo disintegration. ASA tablets labelled with ^{51}Cr were given to six healthy subjects under fasting and non-fasting conditions. The position and disintegration of the ^{51}Cr-labelled tablets was followed by external radiation measurement and the amount of salicylic acid in blood and urine was analysed. The absorption of ASA from the studied enteric coated tablets was usually correlated with gastric emptying and in-vivo disintegration. However in some cases the absorption can be delayed between 10–20 h even if gastric emptying and disintegration of the tablet have occurred.

That absorption from enteric-coated tablets can be erratic is well known. When such products are taken with food, absorption of drug can be delayed by more than 10 h (Bogentoft et al 1978). The underlying mechanism is thought to be slow gastric emptying. We have set out to test the validity of this hypothesis, using a profile scanning technique in combination with radionuclide labelling of the dosage form (Alpsten et al 1976; Faxén et al 1978).

Methods

Enteric-coated acetylsalicylic acid (ASA) tablets (diameter 10 mm) were prepared in the conventional manner. The tablets were labelled in the granulation step with a radionuclide and coated in an Accela-Cota with cellulose acetate phthalate dissolved in methylene chloride and isopropanol. Each tablet contained 0·5 g of ASA and 1·85 MBq ^{51}Cr. Care was taken to limit the in-vitro release of ^{51}Cr from an intact tablet. According to radiation measurements, no detectable amount of ^{51}Cr was released during the in-vitro studies at pH 1. With a modified USP rotating basket procedure (150 rev min^{-1}), 3% of the ASA was found to be released in 4 h at pH 1 and 100% in 1 h at pH 6·5.

Six healthy subjects participated, according to a randomized cross-over design. One tablet was swallowed with 150 ml of water immediately after a standardized breakfast or after the subjects had been fasting for 10 h. Food was allowed 4 h after tablet intake. Blood samples (10 ml) were drawn hourly for 10 h and an additional sample was taken after 24 h. All urine was collected for 48 h. The samples were stored in frozen condition until analysed for salicylic acid by liquid chromatography and uv-detection at 280 nm (Edgard et al 1983).

The radiation measurements were made in a low activity laboratory (Sköldborn et al 1972). The position of the ^{51}Cr-labelled tablets was followed by external measurement with a moveable NaI (Tl)-crystal while

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Table 1. Gastric emptying of tablets.

Subject	Food status	Gastric emptying of tablet (min)	Tablet disintegration (min)	C_{pmax}[1]	T_{max}[2] (h)	Plasma salicylate at 24 h (mmol $litre^{-1}$)
RW	Fasting	246–285	285–305	187	7	0
	Nonfasting	224–270	305–324	—	—	162
JL	Fasting	145–162	126–145	151	7	0
	Nonfasting	>480	100–120	—	—	Missing
GS	Fasting	148–168	299–278	119	7	0
	Nonfasting	45–66	82–130	180	6	0
AT	Fasting	62–140	144–160	184	4	0
	Nonfasting	164–180	160–219	165	7	0
GR	Fasting	45–85	102–140	122	6	0
	Nonfasting	229–245	245–277	160	7	0
CD	Fasting	103–124	140–163	—	—	18
	Nonfasting	267–292	100–127	—	—	108

[1] Maximal plasma concentration mmol $litre^{-1}$.
[2] Time (h) to reach maximum plasma concentration.

the subjects were resting in an armchair (Faxén et al 1978; Alpsten et al 1982). Measurements were taken every 20 min for 8 h. Each measurement took 3–6 min. The subjects were allowed to move about freely between the measurements. In this manner, the gastric emptying and time of disintegration of the tablets could be determined and correlated with the rate of absorption. The tablets were considered to have disintegrated when the measurement indicated a change from the initial approximately point-shaped to a broad distribution of the ^{51}Cr-activity.

Results

The results are given in Table 1. Gastric emptying and tablet disintegration are expressed as the time interval between two measurements where gastric emptying and tablet disintegration, respectively, occurred. The amount of total salicylate excreted in urine was found to be 79–101% of the dose given under fasting conditions and 89–103% under non-fasting conditions, indicating almost complete absorption of ASA from all tablets.

The mean gastric emptying time was about 2 h (range 0·5–4 h) under fasting conditions and about 5 h (range 3–>8 h) when the tablets were taken with food. These results are within the range reported for tablets by Blythe et al (1959) and Dragsted et al (1979), although Bechgaard et al (1981) recently reported longer periods in a study in ileostomy patients.

As expected, the tablets normally disintegrated directly upon entering the small intestine. However, in two cases, tablet disintegration occurred in the stomach and in one of the subjects the tablet fragments were retained in the stomach longer than the 8-h study period.

In eight of the 12 experiments, the time of onset of absorption correlated well with the time of tablet disintegration. In the other four experiments, three under postprandial conditions and one under fasting conditions, the absorption of ASA was delayed more than 10 h in spite of the fact that complete disintegration and gastric emptying of the tablet seemed to have occurred. In three of these cases, relatively high plasma salicylate levels were found 24 h after intake of tablets, indicating that the absorption of ASA had started about 20 h or more after administration. The explanation for this finding is not clear but may be physical/chemical interference with the dissolution of ASA.

This study shows that the absorption of ASA from enteric-coated tablets is usually correlated with gastric emptying and in-vivo disintegration. However, especially under postprandial conditions, the absorption of ASA can be delayed between 10–20 h even if gastric emptying and disintegration of the tablet have occurred. The erratic absorption from enteric-coated tablets reported for several drugs, e.g. ASA (Bogentoft et al 1978), dichlophenac (Willis et al 1981) and prednisolone (Henderson et al 1979), may thus be explained by two factors, slow gastric emptying and some as yet unknown mechanism.

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