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Scintigraphic investigation of the gastric emptying of 3 mm pellets in human volunteers

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Summary

The gastric residence time of a coated pellet formulation has been investigated in six human volunteers. After labelling with the radionuclide ^{99m}Tc, the pellets were coated with a methacrylic acid resin and the gastric emptying from a fed stomach was measured by gamma scintigraphy. Four volunteers showed extremely slow emptying, two subjects showed substantial gastric emptying after 3 h.

Introduction

Gastric emptying and intestinal transit times of small solid particles such as non-disintegrating tablets and pellets strongly influence bioavailability and absorption velocity of oral pharmaceuticals. Often the variability in gastrointestinal transit is a limiting factor in the controlled release or resorption of sophisticated drug release systems. Several methods such as particle size, particle density, multiple unit systems and bioadhesion have been proposed as controlling factors in gastric emptying and intestinal transit (Khosla and Davis, 1987; Meyer et al., 1988; Parker et al., 1988; Smart and Kellaway, 1989). Spreading of pharmaceuticals in the duodenum mainly originates from gastric emptying and not from dispersion in the intestine itself (Christensen et al., 1985). Whereas gastric emptying of pellets and tablets may be altered by the formulation, intestinal transit hardly seems to be influenced by size and density of the oral dosage system itself (Parker et al., 1988). From studies of Davis (Feely et al., 1987; Davis et al., 1988), it is known that particle size and filling status of the stomach are the most important parameters that determine the gastric emptying rate of the formulation. Particles of 5 mm are retained in the fed stomach until the food contents have passed the pylorus, whereas smaller particles (e.g. 1 mm) are said to empty more rapidly even through a closed pylorus

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in a fed stomach. However, literature data on the relation between particle size and gastric residence time are contradictory.

We investigated the gastric emptying behaviour of a 3 mm pellet formulation in six human volunteers by gamma scintigraphy after radiolabelling the pellets with the gamma-emitting nuclide ^{99m}Tc. Due to its favourable radiation and dosimetry characteristics ^{99m}Tc is the nuclide of choice in diagnostic nuclear medicine; it is readily available, its photon energy (140 keV) is appropriate for scintillation detection by the Angertype gamma camera and its short physical half-life (6 h) results in a low radiation burden.

The pellet formulation we investigated is a coated antacid designed to provide a long gastric residence time and thereby a sustained acid neutralisation. Therapeutic efficacy of such a controlled release antacid will strongly depend on the gastric emptying rate of the pellets. The goal of this study was to investigate whether 3 mm pellets would give a substantial gastric residence after 3–4 h. The pellets were given on a fed stomach to comply with the usual antacid medication.

Materials and Methods

Radiolabelling of pellets

The newly developed antacid formulation consists of spherical particles containing Al and Mg hydroxides (Cascan, Wiesbaden, Germany). To achieve a sustained acid neutralisation these pellets are coated with a mixture of acrylic resins; in vivo this coating will slowly become permeable. However, for the scintigraphy studies a coating was used which only contained a rather insoluble methacrylate resin to prevent any disintegration of the labelled pellets during the scintigraphy. For all studies 10 g of the uncoated pellets (diameter 3 mm) were merged for a few seconds in a ^{99m}Tc-pertechnetate solution in 5 ml of absolute ethanol. Pellets were dried with a hair dryer. With the aid of a small sieve the pellets were then briefly immersed in a methacrylate resin solution (5% in acetone) and immediately dried under constant agitation with a hair dryer. This coating by immersion was repeated twice. After thoroughly drying, the semi-coated labelled pellets were put in a capsule coater (Ter Horst et al., 1989). This is a small apparatus with a bulb of glass in which pellets are rotating in an air stream and film coated by dropwise addition of a coating solution. The coating was terminated after spraying 75 ml of a methacrylate resin solution (1% in acetone) in about 3 h. After drying overnight at room temperature, 3–5 g (containing 5–10 MBq) were administered to each volunteer. An aliquot of each batch was checked for in vitro disintegration and/or Tc leakage in 0.01 M HCl with a tablet disintegration tester without disks (USP XXII) for 4 h. The mean diameter of the labelled and coated pellets was 3.0 mm (range 2.67–3.35) with a density of 1.08 g/cm^3.

Scintigraphy

The measuring equipment involved a large field of view digital gamma camera (Toshiba GCA501S) with a low-energy collimator coupled to a dedicated computer system suitable for continuous data acquisition and data analysis. Continuous data acquisition of anterior images was performed for 2 h followed by intermittent anterior images each 30 min for another 2 h (acquisition time 60 s, matrix 64×64 bytes). A region of interest (ROI) over the stomach area was drawn and the counts per image in this ROI corrected for decay were calculated. These values were normalised by taking the maximum count rate per minute in the stomach during the 4 h acquisition as 100%.

Subjects

Six healthy volunteers (aged 19–23 years) participated in the study, for which the protocol was approved by the Medical Ethics Committee of the University Hospital Leiden. Each subject was investigated twice on separate days; once with a radiolabelled pancake and once with radiolabelled pellets. The volunteers abstained from alcohol for at least 24 h before the studies.

Pancake study

After an overnight fast the subjects were positioned sitting in front of the gamma camera and ingested a pancake (1200 kJ, 8.7 g of proteins, 8.9 g of fat, 43 g of carbohydrates) radiolabelled with ^{99m}Tc-colloid (5–10 MBq). The pancake study, which is a standard procedure in our hospital for gastric emptying studies, was performed to check for interindividual variability in gastric emptying rate to be able to exclude volunteers with abnormal emptying rates and to obtain individual anatomical information about the stomach and intestines. No fluid intake was allowed during the investigation.

Pellet study

0.5 h after a standardised breakfast (3000 kJ, 29 g of proteins, 37 g of fat, 72 g of carbohydrates, 8 g of nutrition fibres) the volunteers swallowed the radiolabelled pellets (3–5 g, 5–10 MBq) with a cup of tea. Scintigraphic data acquisition was the same as for the pancake study, 2 h continuously beginning at the moment of pellet ingestion and 2 h intermittently thereafter. Again no extra drinking was allowed during the study.

Results and Discussion

After 4 h in a tablet disintegration tester no visual disintegration of the pellets could be observed and after correction for radioactive decay they still contained 90.3% (SD 3.7%) of the original activity. A substantial leakage of the nuclide could hamper the interpretation of the scintigraphy as ^{99m}Tc-pertechnetate will partly adsorb to gastric mucosa and partly follow the gastric emptying of fluid. Although the in vitro tablet disintegration tester probably does not completely mimic in vivo gastric conditions, we believe this limited in vitro release is acceptable for reliable gastric emptying rate calculations. Furthermore, the scintigrams do not give evidence of a substantial mucosal uptake and retention in the stomach.

Fig. 1 shows the scintigrams of one volunteer; 0.5, 1, 2.5 and 4 h after ingestion of the radiolabelled pancake. In the 1 h images gastric and intestinal regions of interest are depicted. Fig. 2 shows the gastric emptying curves, calculated from

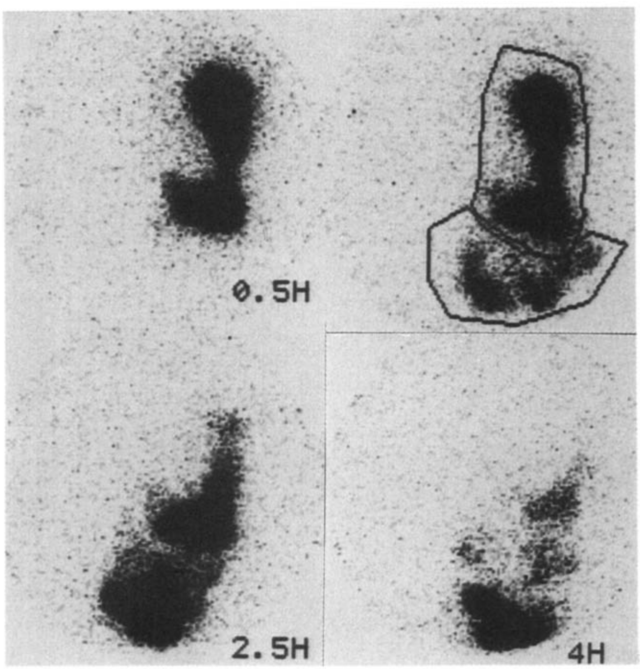

Fig. 1. Scintigrams of volunteer 3, at 30 min, 1, 2.5 and 4 h after ingestion of the radiolabelled pancake. In the 1 h image the regions of interest over the stomach and intestines are drawn.

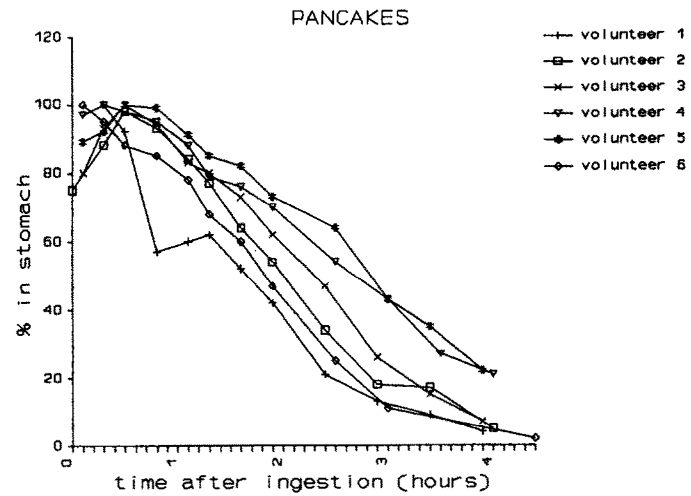

Fig. 2. Gastric emptying curves of the pancakes for the six volunteers. The amount in the stomach is calculated from the counts in the gastric regions. For each volunteer a 100% value in the stomach is assigned to the moment with the highest count rate during the 4 h acquisition.

the counts in the gastric regions, for each volunteer. After intake on an empty stomach the pancake allows a clear delineation of gastric and intestinal regions (Fig. 1). The apparent increase of radioactivity in the stomach after ingestion, typically seen in the emptying curve of volunteers 2 and 3 (Fig. 2), is due to a shift of the labelled pancake to the antrum, which is in a more anterior position towards the gamma camera (Moore et al., 1985). We did not correct for this error in anterior measurements by posterior or lateral images, as minor differences in emptying rate were irrelevant to this study. Nevertheless, the pancake studies reveal a rather uniform gastric emptying rate for these six volunteers even without appropriate attenuation correction. Differences are most pronounced in the first hour but the emptying curves are rather linear with emptying rates ranging from 23 to 37% per h when calculated from the 1–3 h data. At the end of the study none of the volunteers had more than 10% of the pancake left in the stomach. From these pancake studies we conclude that none of the six volunteers showed an abnormal gastric emptying.

Solid-phase gastric emptying is mostly described as a linear process often preceded by a lag time, although this early delay can at least partly be attributed to inappropriate attenuation corrections (Moore et al., 1985). Liquids are more rapidly emptied in an exponential manner. The pellets which were swallowed on a fed stomach hardly reveal gastric contours. Shortly after ingestion the pellets were distributed rather inhomogeneously in the upper part of the stomach, whereas at the end of the study, i.e. 3–4 h after ingestion, the pellets are located mainly in the antrum of the stomach (Fig. 3). Again an apparent increase of activity in the stomach is seen, which is quite prolonged in comparison with the standard pancake study (Fig. 4). Obviously when taken after a meal, it takes a long period for the pellets to reach the antrum. Emptying of particles larger than 2 mm is supposed to take place only when the stomach no longer contains food. At regular intervals an interdigestive myoelectric complex causes the pyloric passage of remaining solid particles (Minami and McCallum, 1984; Fara, 1985). In this study the pellets emptied rather early in two volunteers. Whether the meal had passed the stomach remains unclear but the pancake studies of these subjects did not provide evidence of an accelerated gastric emptying. From studies reported by Davis et al. (1988), it is known that gastric emptying of solid dosage forms is dependent on the quantity of food in the stomach. Hence, it remains to be clarified to what

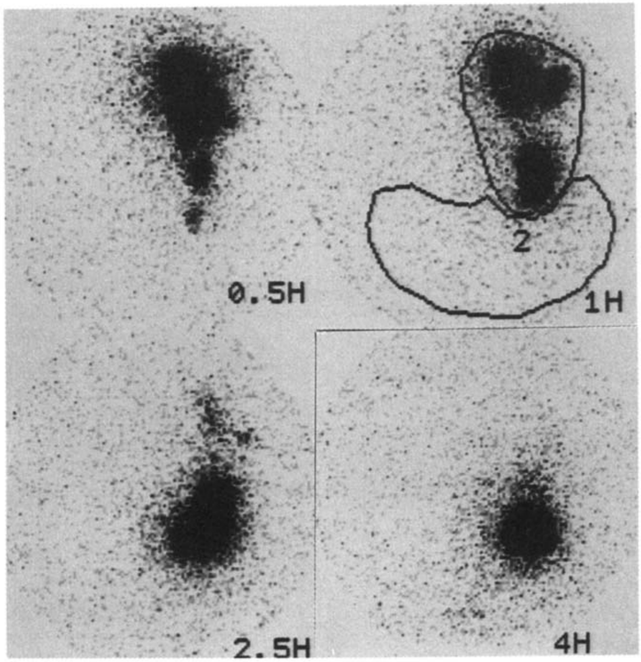

Fig. 3. Scintigrams of volunteer 3, at 30 min, 1, 2.5 and 4 h after ingestion of the radiolabelled pellets. In the 1 h image the regions of interest over the stomach and intestines are drawn.

extent a prolonged gastric residence of the pellets in comparison with the pancake is attributable to the higher calorific value of the meal or to an actively retained delivery system. As the breakfast had a higher calorific value than the pancake (3000 vs 1200 kJ), complete emptying of the food is highly questionable. Obviously, even 3 mm particles sometimes escape from the stomach to-

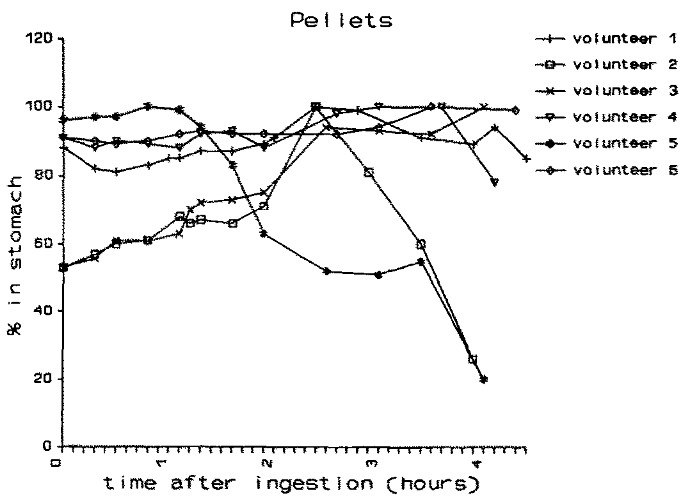

Fig. 4. Gastric emptying curves of the pellets, administered 30 min after a 3000 kJ breakfast, for the six volunteers. The amount in the stomach is calculated from the counts in the gastric regions. For each volunteer a 100% value in the stomach is assigned to the moment with the highest count rate during the 4 h acquisition.

gether with the food. From the literature it is evident that a limit of 2 mm is questionable and contradictory opinions have been published (Davis et al. 1984, 1987). The percentage radioactivity remaining in the stomach at 4 h after ingestion varied from 20 to 100%. However, for four volunteers no substantial emptying was observed.

In conclusion, in comparison with the standard pancake test, pellets of 3 mm diameter definitely were retained in the stomach for a prolonged period, when administered after a breakfast, but interindividual differences are quite marked at 3–4 h after ingestion. Additionally, the influence of fluid intake and meal size on the gastric emptying of these pellets needs to be investigated before a conclusion about the potential therapeutic efficacy of such an antacid, in comparison with normal antacid gel or tablet formulations, can be drawn.

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