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Monitoring antacid preparations in the stomach using gamma scintigraphy

J.R.F. Jenkins, J.G. Hardy * and C.G. Wilson

*Department of Physiology and Pharmacology and *Department of Medical Physics, Queen's Medical Centre, Nottingham NG7 2UH (U.K.)*

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Summary

Aluminium hydroxide particles have been radiolabelled with indium-113m, and incorporated into antacid preparations. Following administration to human subjects, the radiolabelled preparations were monitored in the gastrointestinal tract using a gamma camera. The results show considerable inter-subject variability in the rate of gastric-emptying of the preparations. The presence of dimethicone did not affect the gastric-emptying rates.

Introduction

The efficacy of antacids is influenced by the chemical properties of the preparations and physiological factors such as the gastric-emptying rate (Grossman, 1956). Aluminium hydroxide is used widely as a constituent of antacid preparations, and it has been shown that dissolved aluminium ions reduce the rate of gastric-emptying (Hurwitz et al., 1976). Most antacid preparations comprise a mixture of compounds. In addition to the materials present to neutralize the acid, the pharmaceuticals may contain substances such as alginic acid or polydimethylsiloxane (dimethicone). Alginic acid is used in the treatment of gastro-oesophageal reflux. It acts by forming a foam which floats in the stomach and is refluxed preferentially (Malmud et al., 1979). Dimethicone has mucosal protective properties and is also an antiflatulent. Its antifoaming action is enhanced by the addition of silica (Birtley et al., 1973).

A method of radiolabelling the aluminium hydroxide particles with indium-113m has been devised. The use of gamma scintigraphy has enabled the distributions of radiolabelled antacid preparations to be monitored in the gastrointestinal tracts of

volunteer subjects. This technique facilitates the investigation of factors such as gastric-emptying, which affect the efficacy of antacids.

Materials and methods

Materials

The antacid comprised 840 mg dried aluminium hydroxide gel and 140 mg magnesium oxide per 10 ml. One preparation contained 270 mg dimethicone activated with 5% w/v silica, and the other no dimethicone. Both pharmaceuticals were supplied by Berk Pharmaceuticals, Guildford. To facilitate monitoring of the antacids, aluminium hydroxide radiolabelled with indium-113m was added to the preparations.

Radiolabelled indium chloride solution was obtained by elution of an indium-113m generator (Amersham International, Amersham) with 0.04 M hydrochloric acid. To 1.5 ml 0.3 M aluminium chloride solution was added 1.5 ml of the generator eluate, followed by 10 ml 9 M ammonia solution with continuous stirring. Following centrifugation the supernatant was discarded and the aluminium hydroxide was suspended in water. The washing procedure was repeated 6 times to remove all traces of ammonia. The resulting [$^{113}In^{m}$]-labelled aluminium hydroxide was re-suspended in 4 ml water, and contained approximately 9 mg/ml aluminium hydroxide. To 10 ml of each of the antacid preparations was added 1 ml radiolabelled suspension containing 3 MBq indium-113m.

Sizing of the particulate phases of the preparations was undertaken using a Coulter Counter Model ZBI and Coulter Channelyzer C-1000. The equipment was calibrated using latex particles 0.79, 1.15 and 4.6 μm diameter. Measurements were carried out both before and 1 h after the addition of human gastric juice (pH 1.5–3.0) to the suspensions.

In vivo studies

Five healthy adult male volunteers each received 10 ml of the radiolabelled antacid preparation orally on two occasions. The subjects had not eaten during the 4 h nor drunk during the hour immediately preceding administration of the antacids. On the first occasion 3 subjects received the preparation containing the dimethicone and two subjects the other preparation. A week later each subject received the alternative preparation.

The 393 keV gamma rays emitted by indium-113m were monitored using a gamma camera having a 40 cm diameter field of view and fitted with a medium energy (400 keV maximum energy) parallel hole collimator. The data from the gamma camera were recorded by computer for subsequent analysis. Imaging was undertaken with the subject standing and facing the gamma camera detector. The stomach was at the centre of the field of view, and a small source of indium-113m was taped to the abdomen, overlying the right lobe of the liver to provide an anatomical reference point. With the radiolabelled antacid in the mouth, the subject was instructed to swallow and the imaging commenced. Data were recorded continu-

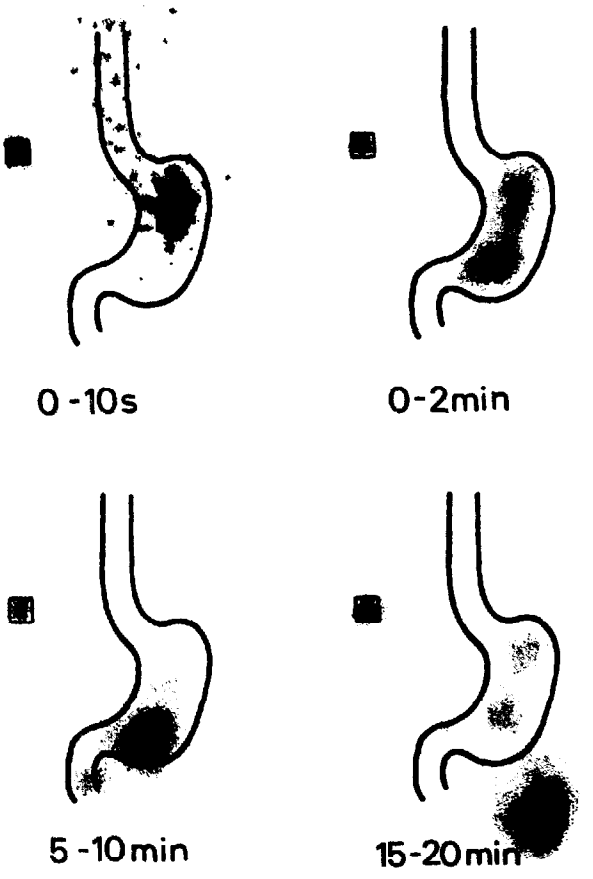

Fig. 1. Gamma camera images of the radiolabelled antacid in the stomach. The square defines the position of the anatomical reference point.

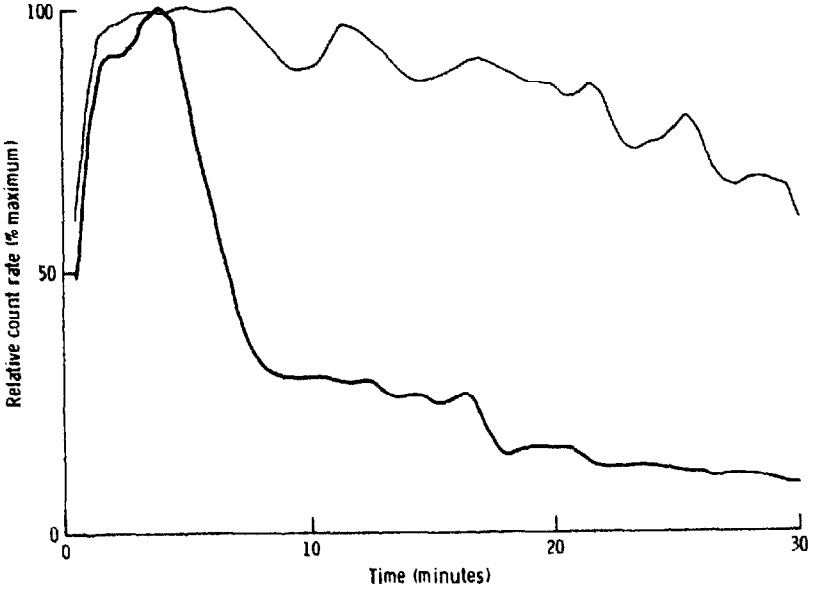

Fig. 2. The transit of an indium-113m-labelled antacid preparation through the stomachs of two subjects.

ously for 30 min. For the first 2 min each image was of 5 s duration and subsequently the images were of 30 s duration. Count rates from regions of interest defined over the lower oesophagus and the stomach were determined from each image.

Results

In vitro experiments

Particle sizing was undertaken to ensure that the [$^{113}In^{m}$]-labelled aluminium hydroxide particles were of similar dimensions to those of the antacid. Additionally, the effect of dimethicone on the antacid particles was investigated. In all the preparations the majority of the particles had diameters of less than 0.8 μm. Accurate measurements of the sizes could not be obtained using the Coulter Counter due to the small diameters of the particles. The distribution profiles, however, were similar for all the preparations. The addition of the radiolabelled aluminium hydroxide did not result in the introduction of larger particles, and the presence of dimethicone did not seem to affect the size distributions. A slight reduction in the particle sizes was detected following interaction with gastric juice for 1 h and 90% of the indium-113m remained associated with the particulate phase.

In vivo studies

The transit of the radiolabelled preparations from the oesophagus to the small intestine could be observed in the gamma camera images. Fig. 1 shows computer prints of summated images. There was a rapid transit of the preparations down the oesophagus with no evidence of particulate retention in the oesophagus with either

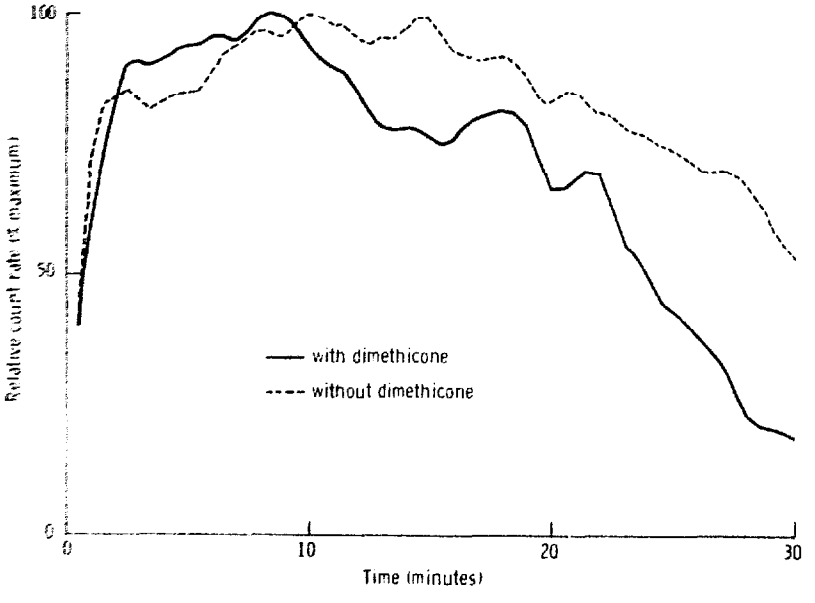

Fig. 3. The gastric-emptying of radiolabelled antacid, with and without dimethicone, in one subject.

preparation.There was considerable inter-subject variability in the rate of clearance of each preparation from the stomach (Fig. 2). The rates were similar in the same individual for the preparations with and without dimethicone (Fig. 3).

Discussion

Radionuclide-imaging techniques are well established for the monitoring of gastric-emptying (van Dam, 1974; Tothill et al., 1978). Studies have been undertaken using gamma camera imaging to investigate the effects of antacids on gastric-emptying (Hurwitz et al., 1976), and the mode of action of alginic acid when incorporated into an antacid preparation (Malmud et al., 1979).

It is essential for the accurate interpretation of the results that the radiolabel remains associated with the components under investigation. Ideally the antacid preparation would be radiolabelled with an isotope of one of its consitituent elements. None of the elements in the preparations has a readily available, suitable radioisotope. Indium-113m was chosen as the tracer since it can be obtained at a high specific activity and has similar chemical properties to aluminium, both being elements in group IIIb of the periodic table. The indium was co-precipitated with aluminium as hydroxides, with a ratio of aluminium atoms to indium atoms of approximately 10^{10}: 1. Such a small amount of indium would not be expected to affect significantly the behaviour of the aluminium hydroxide particles. Although accurate particle sizing was not achieved, the results indicate that the antacid particles were relatively unaffected by the interaction in vitro with gastric juice for 1 h. At the end of 1 h 90% of the radiolabel remained associated with the particulate phase.

Following administration of radiolabelled antacid to the subjects, the particles passed rapidly down the oesophagus, and most of the preparation was located in the lower part of the body of the stomach within a few minutes of swallowing. Similar findings were obtained with both preparations indicating that dimethicone does not affect the adhesion of the particles to the lining of the oesophagus or stomach. There was considerable inter-subject variability with regard to the rate of emptying of the tracer from the stomach. Since the efficacy of an antacid preparation is influenced by the residence time in the stomach, consideration should be given to the factors influencing the rate of gastric-emptying. The use of radiolabelled preparations will enable the effects of stomach contents, posture and disorders of the gastrointestinal tract to be monitored, and may result in the production of better pharmaceutical products. The technique described provides a means of undertaking studies non-invasively, and under normal physiological conditions.

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