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Monitoring radiolabelled antacid preparations in the stomach

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Summary

Radiolabelled antacid preparations have been monitored in the stomach using gamma scintigraphy. The stomach contents were labelled with technetium-99m and two antacid preparations with indium-113m. It has been shown that the antacid containing aluminium hydroxide and magnesium oxide mixed and emptied with the other stomach contents. An alginate containing preparation tended to float on the food and emptied only slowly from the stomach.

Introduction

An extensive range of products is available designed to reduce the concentration of acid in the stomach. Various in vitro and in vivo techniques have been devised in order to assess the efficacy of these preparations. A list of the ingredients of an antacid provides only an indication of its acid neutralizing capabilities. The chemical properties of the constituents can be modified considerably by their methods of production. Additionally, the same antacid dose can cause greatly different pH changes in different subjects with a similar initial level of gastric acidity (Fordtran et al., 1973).

Studies of the acid neutralizing properties of antacids have been undertaken in vitro by titration with hydrochloric acid (Keyriläinen, 1982). It is important to standardize the experimental conditions when comparing different products. Al-

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though in vitro tests provide a convenient means of assessment, these procedures are only an approximation of the situation in the stomach. The acidity of the stomach contents is dependent on factors such as the extent of gastric acid secretion, the buffering capacity of any food present, and the rate of gastric emptying (Fordtran et al., 1973). Monitoring of gastric acidity can be undertaken by the aspiration of stomach contents. This procedure, however, is invasive and may interfere with the normal physiological functions. Ekenved and Walan (1975) used radiotelemetry capsules to monitor intragastric pH. This technique offers the advantage of allowing continuous recording, and is relatively non-invasive.

In the evaluation of antacids, it is useful to be able to visualize the distributions of the preparations within the stomach. Jenkins et al. (1983) monitored the transit of radiolabelled antacid preparations through the stomachs of fasted subjects using gamma scintigraphy. In the present investigation the same technique has been employed to compare the gastric emptying rates of two preparations, and to follow their distributions relative to those of the other stomach contents.

Materials and Methods

Materials

Two antacid preparations were studied, "Asilone Suspension" (Berk Pharmaceuticals, Shalford) and "Gaviscon Liquid" (Reckitt and Colman, Hull). The "Asilone Suspension" ("Asilone") contained 840 mg dried aluminium hydroxide, 140 mg light magnesium oxide and 270 mg activated dimethicone in 10 ml; and the same volume of the "Gaviscon Liquid" ("Gaviscon") contained 500 mg sodium alginate and 267 mg sodium bicarbonate. "Clinifeed ISO" ("Clinifeed") (Roussel Laboratories, Wembley Park) was used to simulate a 375 ml meal having an energy content of 1575 kJ.

Both the antacids were radiolabelled with indium-113m. The "Asilone" was radiolabelled by addition of [^{113m}In]-labelled aluminium hydroxide (Jenkins et al., 1983). Briefly, 1.5 ml of 0.6 M aluminium chloride solution was mixed with 1.5 ml of eluate from an indium-113m generator (Amersham International, Amersham), and 10 ml of 9 M ammonia solution added. The resulting aluminium hydroxide was washed repeatedly with water to remove all traces of ammonia, and resuspended in 3 ml water. To 9 ml "Asilone" was added 1 ml of the suspension which contained approximately 20 mg [^{113m}In]-labelled aluminium hydroxide. The "Gaviscon" was radiolabelled by the addition of 0.1 ml indium-113m chloride generator eluate to 9.9 ml of the pharmaceutical. In vitro studies showed that the indium-113m remained almost completely associated with the solid phase of "Gaviscon" when mixed with 0.1 M hydrochloric acid. The "Clinifeed" was labelled with technetium-99m by addition of 0.2 ml [^{99m}Tc]-labelled diethylenetriaminepentaacetic acid ([^{99m}Tc]-DTPA) solution (kit for labelling DTPA with technetium-99m, CIS (UK), London) to 375 ml "Clinifeed".

In vivo studies

Experiments were undertaken to assess the reproducibility of gastric emptying of

"Asilone", and to compare the findings with those for "Gaviscon". The distributions of the two antacid preparations were studied in 8 healthy male subjects (aged 19–23 years), all of whom gave written informed consent. The subjects fasted for at least 4 h prior to the commencement of each experiment. Each subject drank the contents of a can of "Clinifeed" which had been radiolabelled with a 4 MBq technetium-99m, followed 30 min later by 10 ml antacid labelled with 2 MBq indium-113m. The experiment was undertaken on two occasions in each volunteer. Four subjects received radiolabelled "Asilone" both times, and the other four, "Asilone" on one occasion and "Gaviscon" on the other.

The gastric emptying rates of the preparations were measured using a gamma camera and associated computer. The gamma camera had a 40 cm diameter field of view and was fitted with a medium energy (400 keV maximum energy) parallel hole collimator. The 141 keV and 393 keV gamma rays emitted by technetium-99m and indium-113m, respectively, were imaged simultaneously and the data from each energy window recorded separately by the computer.

Immediately following administration of the "Clinifeed", anterior and posterior images of the stomach, each of 1 min duration, were recorded with the subject standing. Imaging was repeated at 5 min intervals during the first 15 min following dosing, and subsequently at 10 min intervals. After 30 min each subject drank 10 ml radiolabelled antacid and monitoring was continued for a further 2 h.

The radioactivity remaining in the stomach was quantified using the computer. The count rate was measured from a region of interest defined around each image of the stomach displayed on a television monitor. The count rates were corrected for background counts, and additionally the values from the 141 keV energy window were corrected for counts due to scattered radiation arising from the indium-113m. Finally, a correction was applied to allow for radioactive decay. For each imaging time the count rate for each radionuclide was taken to be the geometric mean of the count rates from the anterior and posterior views (Tothill et al., 1978). The radioactivity in the stomach at a given time was expressed as a proportion of the maximum count rate for each preparation.

Results

The gamma camera images (Figs. 1 and 2) show clearly the size and shape of the stomach, thus facilitating definition of the region of interest. The reproducibility of the gastric emptying rates was assessed by comparing the rates of emptying of the [^{99m}Tc]DTPA in the group of subjects who took "Clinifeed" followed by "Asilone" on two occasions. Fig. 3 shows very similar average emptying rates for the two sets of studies.

From Fig. 1 it is apparent that the "Asilone" preparation rapidly mixed with the other stomach contents. It can be seen in the images recorded 46 and 72 min after administration of the "Asilone" that the antacid had partially emptied from the stomach, and Fig. 4 confirms that the "Asilone" emptied along with the "Clinifeed". Table 1 lists the amount of each preparation remaining in the stomach expressed as

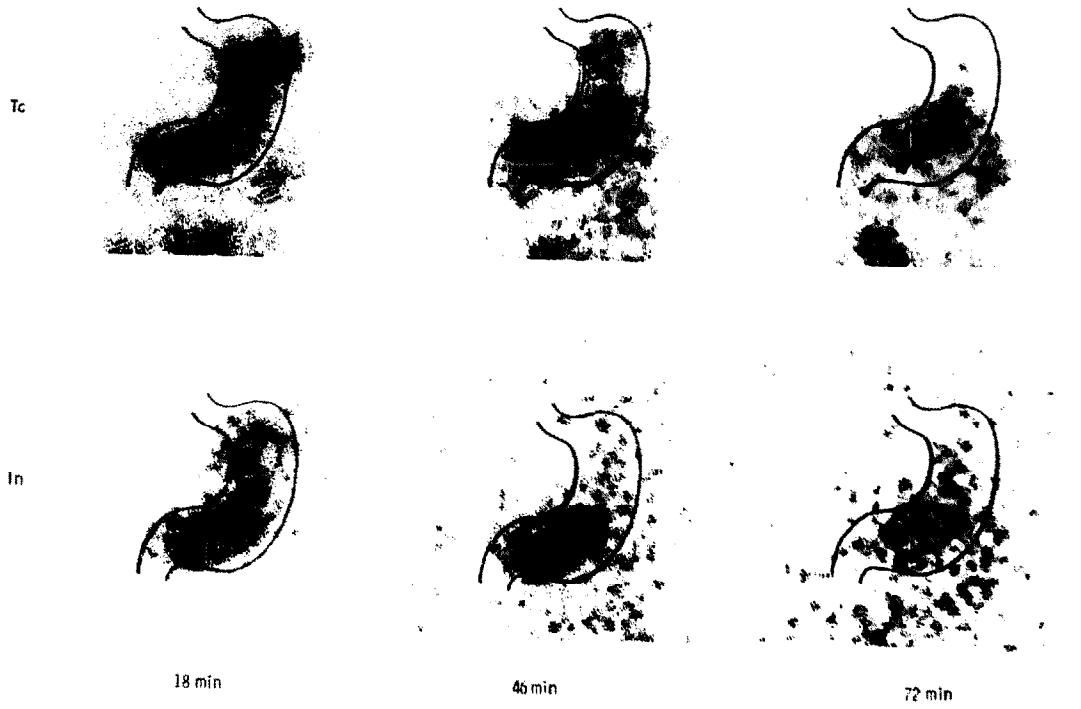

Fig. 1. Radionuclide images of [^{99m}Tc]-labelled "Clinifeed" and [^{113m}In]-labelled "Asilone" in the stomach, 18, 46 and 72 min after administration of the antacid.

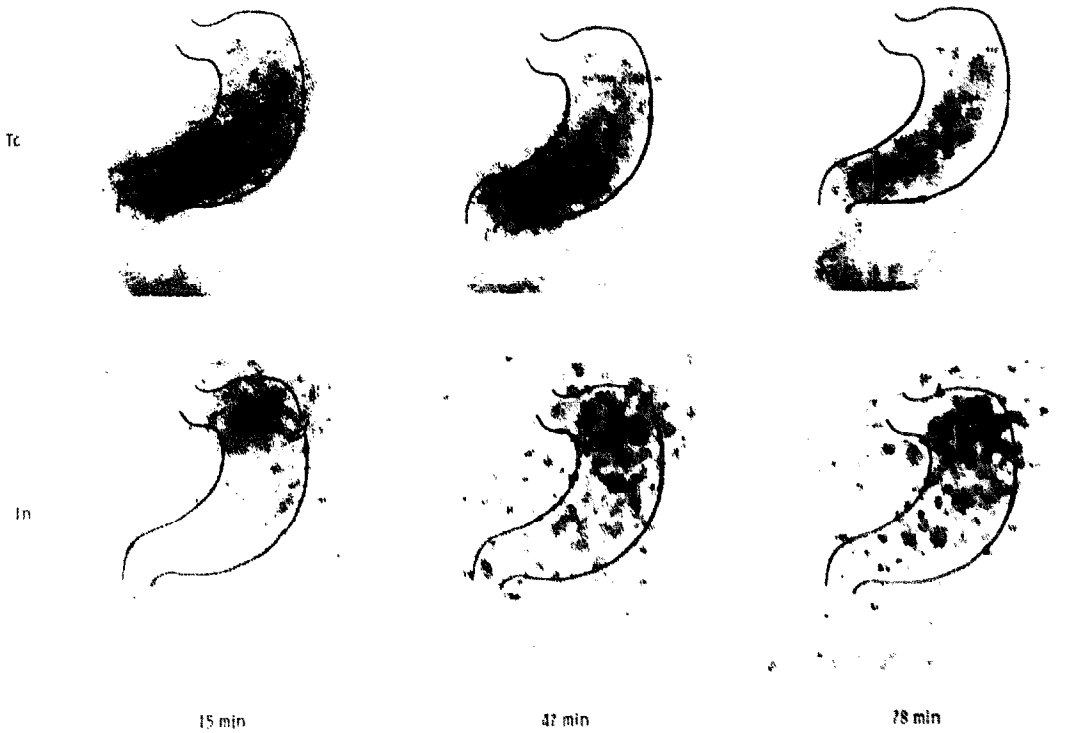

Fig. 2. Radionuclide images of [^{99m}Tc]-labelled "Clinifeed" and [^{113m}In]-labelled "Gaviscon" in the stomach, 15, 47 and 78 min after administration of the antacid.

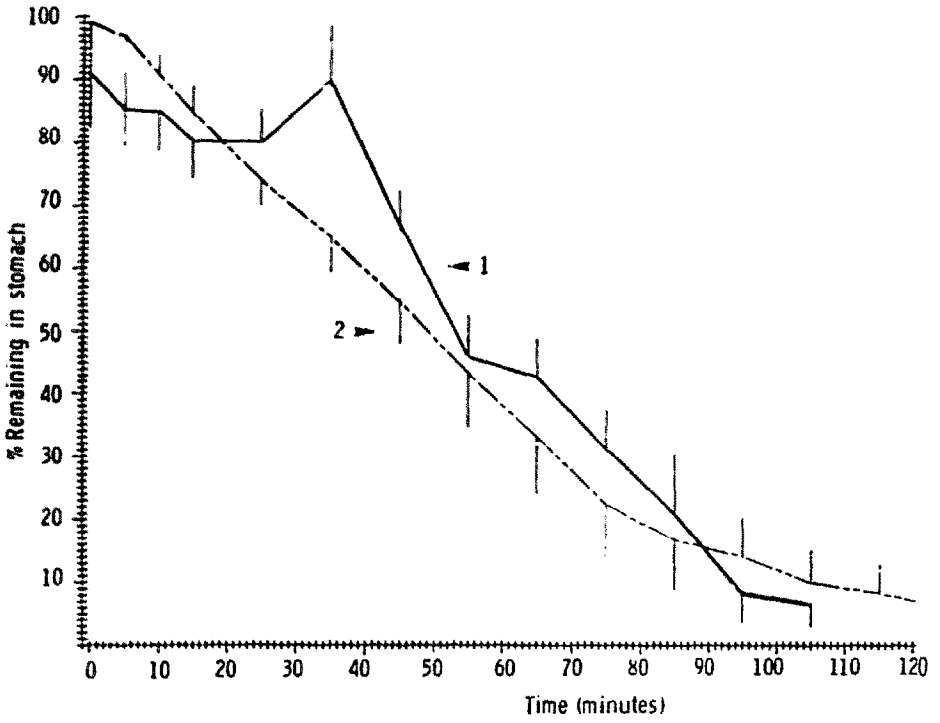

Fig. 3. Comparison of the gastric emptying of [^{99m}Tc]-labelled "Clinifeed" on two occasions (mean ± 1 S.D. for 4 subjects).

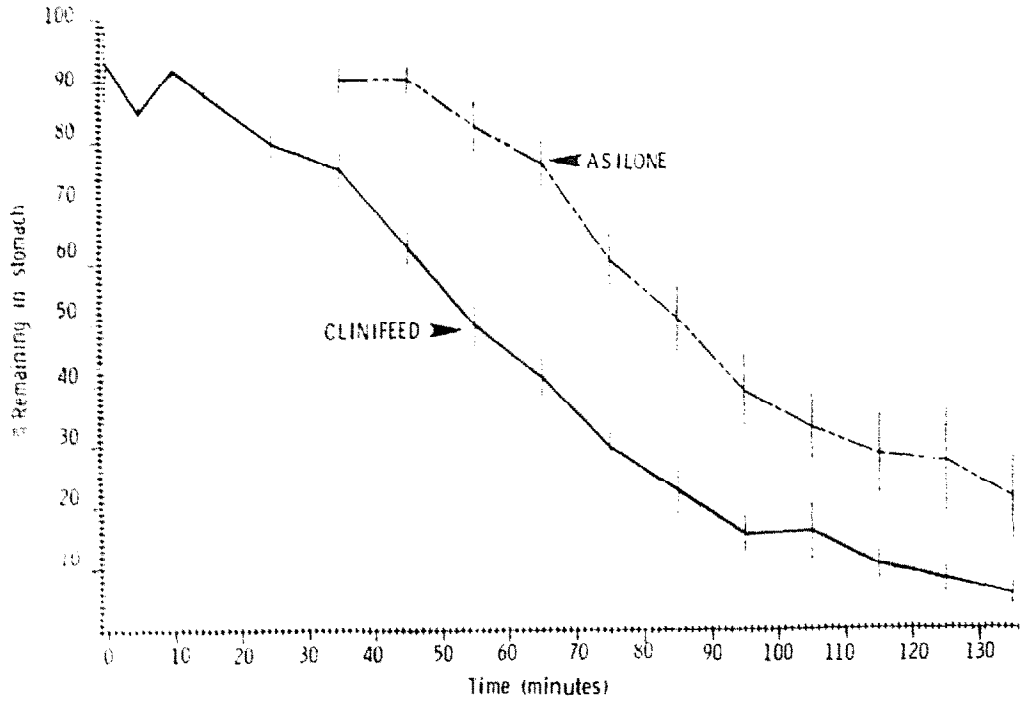

Fig. 4. Comparison of the gastric emptying of radiolabelled "Asilone" and "Clinifeed" (mean ± 1 S.D., n = 12).

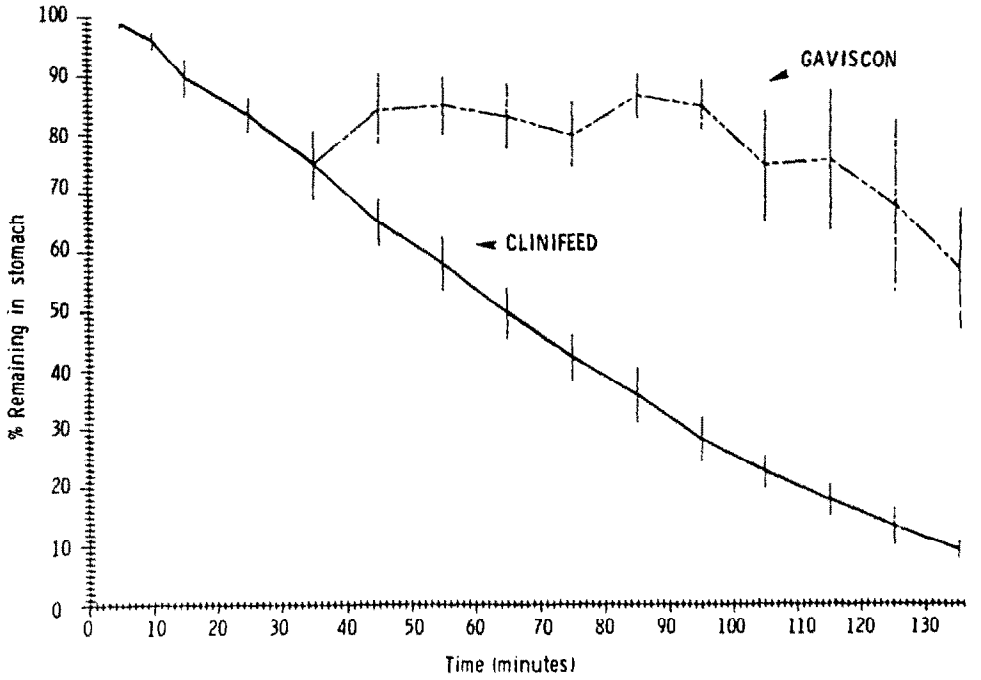

Fig. 5. Comparison of the gastric emptying of radiolabelled "Gaviscon" and "Clinifeed" (mean ± 1 S.D. n = 4).

a percentage of that present 15 min following administration of antacid. The differences ($P < 0.001$) between the proportions of "Clinifeed" and "Asilone" remaining in the stomach, over the time period 30–75 min following antacid administration, indicate that these preparations had not mixed uniformly by 15 min. From 45 min to 75 min, however, approximately the same proportion of each of these preparations emptied suggesting that a homogeneous mixture was eventually achieved.

The "Gaviscon", unlike the "Asilone", tended to remain as a separate layer above the "Clinifeed" (Fig. 2). Little of the "Gaviscon" was observed to empty from the

TABLE 1

GASTRIC EMPTYING OF "CLINIFEED" AND ANTACID

Time after antacid administration (min)	% Remaining in stomach (mean(± 1 S.D.))			
	"Clinifeed"	"Asilone"	"Clinifeed"	"Gaviscon"
	(n = 12)		(n = 4)	
15	100	100	100	100
30	73 (3)	89 (4)	84 (4)	100 (6)
45	48 (4)	68 (5)	65 (4)	99 (5)
60	32 (3)	55 (6)	50 (4)	98 (4)
75	24 (4)	37 (6)	36 (3)	94 (9)

stomach during the period of study. This is confirmed by the gastric emptying plots (Fig. 5), and the data in Table 1 which show slower emptying of "Gaviscon" than either "Asilone" or "Clinifeed".

Discussion

Monitoring of gastric emptying is a well-established technique in nuclear medicine. A wide range of test meals has been devised, but radiolabelled DTPA is generally used as the liquid phase marker. Amongst the factors influencing gastric emptying rates are meal size and composition. In general, the times taken for the stomach to empty half of its contents are shorter for liquids than for solids, and increase with meal size (Christian et al., 1980). In the present study a liquid meal ("Clinifeed ISO") radiolabelled with [^{99m}Tc]DTPA was administered. Although this could not be regarded as typical food, the half-emptying time of about one hour was in agreement with the values reported by Christian et al. (1980) for more conventional fare. Being a liquid, "Clinifeed ISO" provided stomach contents of homogeneous consistency, which simplified interpretation of the antacid distribution studies.

Following administration of radiolabelled "Asilone" the antacid quickly mixed with the "Clinifeed". These observations were supported by the quantitative data (Fig. 4 and Table 1), which show that both components emptied from the stomach simultaneously. Hurwitz et al. (1976) studied the effects of aluminium hydroxide containing antacids on gastric emptying. They found that preparations yielding relatively high concentrations of dissolved aluminium ions inhibited gastric emptying. No such effect was detected in the present study, presumably indicating that the combination of "Asilone" and "Clinifeed" in the stomach resulted in the generation of only low aluminium ion concentrations.

"Gaviscon" did not mix with the "Clinifeed", and remained as a layer floating on the stomach contents. This observation is supported by the findings of Malmud et al. (1979), who investigated the role of an alginic acid containing preparation in subjects with gastro-oesophageal reflux. By monitoring [^{87m}Sr]-labelled alginate, they showed that the antacid floated and refluxed preferentially.

The distributions and residence times of the two preparations were clearly influenced by the constituents. The aluminium hydroxide containing antacid was observed to mix with the test meal rapidly, whilst the alginate containing preparation remained as a separate phase. "Gaviscon" contains sodium bicarbonate, primarily as an agent to aid raft formation by liberation of carbon dioxide on contact with gastric acid. As has been demonstrated, the alginate preparation does not mix with the stomach contents and thus the unreacted bicarbonate associated with the raft will render the top phase alkaline but have little action on the underlying contents. In contrast, the aluminium hydroxide will tend to exert its neutralizing action throughout the gastric contents. Thus it would be expected that the pattern of neutralization would differ for the two preparations. The use of radiotelemetry capsules to allow pH measurement, coupled with radionuclide imaging, is currently being pursued to investigate the efficacy of the two formulations with respect to regional neutralization of gastric contents.

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