Continuous monitoring of the effect of pentagastrin on gastric emptying of solid food in man

S. G. HAMILTON, H. J. SHEINER, AND M. F. QUINLAN

From the University Department of Surgery and Department of Nuclear Medicine, Perth Medical Centre, Perth, Western Australia

SUMMARY By continuous monitoring of a solid meal labelled with a radiopharmaceutical it has been possible to determine the effects of drugs on gastric emptying and motility during a single study. Predictably hyoscine delayed, and bethanechol increased, the rate of gastric emptying. Pentagastrin initially produced marked antral activity resulting in a physiological stricture and subsequent delay in the overall rate of gastric emptying. Fundal motility was unaffected though reflux from the antrum occurred.

Gastric emptying tests have been used to assess physiological control mechanisms governing emptying from the intact normal stomach and to compare emptying rates in patients before and after surgery for gastroduodenal disease (Sheiner, 1975). By comparison, there are relatively few reports of studies assessing the effects of drugs on gastric emptying in the intact stomach, presumably because the established methods are relatively insensitive to intra-study manipulations. Hitherto, the actions of drugs on gastric muscle activity have usually been determined from isolated muscle preparations and from pressure and electrical studies in animals and humans.

The purpose of this study was to develop a sensitive, non-invasive technique for continuously monitoring gastric emptying in the intact human stomach, so that changes in rates and patterns of emptying could be determined after drug administration. In order to explain changes in the net rate of emptying from the whole stomach, an assessment of regional muscle activity was attempted by monitoring emptying from subareas of the proximal and distal stomach.

The project was developed in three parts (1) establishment of the method and its reproducibility; (2) study of drugs with known effects on the intact stomach; and (3) study of the action of the drug pentagastrin which is reported to have apparently opposing effects on motility and emptying. (Hunt and Ramsbottom, 1967; Misiewicz *et al.*, 1967; Kelly, 1970; Dozois and Kelly, 1971; Kwong *et al.*, 1971; Cooke *et al.*, 1972).

Methods

TEST MEAL

Composition of meal

The meal consisted of 100 g cooked, lean, minced beef and 28 g of a proprietary potato whip (Edgell) added to 125 ml boiling water. This was lightly homogenized using a commercially available electric blender. One millicurie of Technetium-99 m labelled macro-aggregated ferrous hydroxide particles (^{99m}Tc-MAFH) (Boyd *et al.*, 1969) was then added and the meal again homogenized. This produced a meal of low fat content (6 g), 2123 J (508 calories), of pH 7.0, volume 210 ml, and total weight of 250 g. It contained a moderate protein (100 g) and carbohydrate content (28 g).

Radionuclide label characteristics

The particles of ^{99m}Tc-MAFH (size 5-50 micra) were uniformly distributed throughout the meal phase as shown by counting random samples of equal weights taken from the meal. The distribution was unaffected by centrifugation and acidification to a pH of less than 1.0. Complete aspiration of gastric contents after studies resulted in less than 3% of the radionuclide in the supernatant. The remaining 97% of the activity in the aspirate was uniformly distributed throughout the meal phase.

Six hours after ingestion of the meal and after complete aspiration of the stomach, a gamma camera image failed to show residual radioactivity adsorbed onto the stomach wall. Serial images and counting performed over the thyroid, cardiac blood pool, liver, and spleen for the period up to 24 hours

showed no detectable radioactivity in any of these organs. Urine collections performed over the 24 hour period after ingestion of the meal did not reveal any radioactivity.

In summary, the solid test meal provided a neutral, low fat preparation, uniformly labelled with a particulate radiopharmaceutical from which no significant dispersion, adsorption, or absorption occurred.

Target organ radiation absorption was low as calculated from published nuclear data on ^{99m}Tc (Dillman, 1970) and data for absorbed fraction and organ masses (Snyder *et al.*, 1969). The estimates were similar to previously published data using ^{99m}Tc compounds for gastric emptying studies (Calderon *et al.*, 1971; Chaudhuri, 1974) and significantly less than acceptable radiation exposure to the foetus upon abdominal radiography of pregnant women (Coates, 1971).

EQUIPMENT

Equipment consisted of a high performance, standard sized field of view Toshiba gamma camera (model GCA-102). A 1000 hole medium energy diverging collimator was used for all studies. The gamma camera was linked on line to a Digital Equipment PDP 11/40 computer. A Digital Equipment Gamma 11 Software package was used for data collection. The camera was equipped with a variable persistence storage oscilloscope and the computer terminals included a high resolution Tektronix 611 storage oscilloscope and a Tektronix 4010 key board visual display unit with a graphics capability.

PROCEDURE

All subjects were male medical students from whom consent was obtained in accordance with the proposals laid down by the Medical Research Council (*Medical Research Council Annual Report*, 1962-3).

The subjects were fasted for eight hours and then seated upright in front of the diverging collimator. As ingestion of the meal commenced, data collection started simultaneously. Therefore no initial data were missed. Consecutive 30 second frames were collected on a 64×64 matrix for one hour, 45 minutes (210 frames). A drug or placebo was given after one hour. At the end of the study, a flood field was collected for later correction of the data. This is essential, as there is inherent non-uniformity of response over the field of the gamma camera.

At 60 minutes, a placebo (normal saline) was given as a bolus injection in three subjects. In a further three subjects a bolus injection was added to a continuous infusion of normal saline which had been commenced before the beginning of the study. Four

other subjects in this control group did not receive any injections or infusions of normal saline.

The response by the stomach to the following drugs given at 60 minutes was studied.

1. Hyoscine-*N*-butyl bromide (hyoscine) 20 mg subcutaneously *statim* in four subjects.

2. Bethanechol chloride (bethanechol) 4 mg subcutaneously *statim* in six subjects.

3. Pentagastrin peptavlon (pentagastrin) $1.2 \mu\text{g kg}^{-1} \text{h}^{-1}$ by continuous intravenous infusion in normal saline in nine subjects. In three subjects the rate of infusion was doubled to $2.4 \mu\text{g kg}^{-1} \text{h}^{-1}$, 40 minutes after the commencement of the infusion.

ANALYSIS OF DATA

Flood correction

Each frame of the study was corrected for non-uniformity of response of the camera by means of a correction matrix derived from the flood field. This is automatically done under Gamma 11 Software.

Isotope decay and dead time correction

All data in the studies were corrected for radio-isotope decay resulting from the six hour half life of ^{99m}Tc . A correction was performed to allow for the 27 μs dead time of the camera-computer system.

Curve construction

Using the Gamma II Software, an integrated image of the stomach was displayed on the 611 oscilloscope screen by adding representative frames from the beginning through to the end of the study (Fig. 1a). The total stomach was outlined using an irregular region of interest marker controlled by a joystick. The study was checked to confirm that the stomach remained within the irregular region of interest outlined, throughout the study. Subareas were also defined to enclose the proximal and distal regions of the stomach (Fig. 1b). Then the computer was instructed to extract the counts in each region of interest from each frame in the study and the curves displayed (Fig. 2).

CURVE ANALYSIS

Using a specially written DOS programme, exponential fits were established for parts of the curve which the operator designated on the Tektronix 4010 screen (Fig. 3). The half emptying times for the curves were calculated and the results displayed on the screen. For the assessment of the effects of placebo and drugs, the half emptying times before and after 60 minutes were compared for groups of subjects. In this way, each subject acted as his own intra-study control. Obvious changes in patterns

Fig. 1 (Left) Integrated image of the whole stomach. (Right) Regions of interest enclosing the proximal and distal subareas of the stomach.

Fig. 2

Fig. 3 Exponential fit for the whole stomach curve in a subject given subcutaneous hyoscine at 60 minutes. Note the marked delay in emptying which persisted for 20 minutes.

of emptying were assessed for all curves by visual inspection.

Results

REPRODUCIBILITY

Reproducibility of the technique was assessed from the analysis of 31 separate studies performed on 11 subjects. There was significant variation between subjects ($P < 0.05$) but not between their replicates or meals. A histogram constructed from these data

Fig. 2 Curves showing the raw data for the whole stomach; the proximal subarea; and the distal subarea. The subject received normal saline throughout the period of the study with a bolus injection at 60 minutes.

shows a skewed normal distribution (Fig. 4) and consequently analysis of the results of all the data was normalized using a logarithmic transformation. Then statistical validity was determined using Student's *t* test.

CONTROL STUDIES

A comparison of the rate of emptying before and after one hour in the four subjects who did not receive either placebo or drug showed no significant difference (Table). When intravenous saline was used as a placebo no significant difference was observed in half emptying times before and after 60 minutes (Table).

STUDY OF DRUGS WITH KNOWN EFFECT ON INTACT STOMACH

The effects of hyoscine and bethanechol are shown in the Table. It can be seen that hyoscine significantly prolonged the half emptying time. A reverse situation was found with bethanechol.

EFFECT OF PENTAGASTRIN

As can be seen from the Table, the overall rate of emptying of the stomach was significantly delayed by pentagastrin. Visual inspection of the whole stomach curves showed an immediate decrease in counts suggesting a transient increase in the rate of emptying (Fig. 5). This was seen in all subjects to varying degrees. Towards the end of the study, when the rate of infusion of pentagastrin was doubled, an immediate but transient increase in emptying was observed again. Inspection of the 'subareas' revealed a marked, rapid initial decrease in counts in the distal region which was obvious in all nine

Drug	Number of Subjects	Half emptying time ($T_{\frac{1}{2}}$)		P value
		Before 60 min	After 60 min	
Without drugs	4	61 ± 8	61 ± 15	NS
Saline	6	74 ± 36	60 ± 25	NS
Hyoscine	4	57 ± 22	631 ± 292	< 0.01
Bethanechol	6	54 ± 9	29 ± 8	< 0.01
Pentagastrin	9	73 ± 25	326 ± 415	< 0.01

Table Mean $T_{\frac{1}{2}}$ in all groups

subjects. A simultaneous slight increase in the proximal region was noted (Fig. 5).

Discussion

Since Griffith *et al.* (1966) first used an isotope labelled meal in conjunction with the scintiscanner, a variety of meals have been used together with either the scintiscanner or gamma camera (Harvey *et al.*, 1970). Our technique allows for the continuous acquisition of data from the commencement of the meal. Two advantages are apparent:

1. No initial data is missed and therefore an actual measurement of the 'starting index' initially postulated by Hunt and Spurrell (1951) may be obtained.
2. Intra-study manipulations can be made with each subject acting as his own control. Therefore, the action of a drug can be ascertained from a single study and its effect on net gastric emptying, as well as on antral and fundic emptying, can be monitored immediately after administration.

In the absence of any form of drug administration, there was no change in the rate of emptying before and after 60 minutes. This is in keeping with the

Fig. 4 The frequency distribution of half-emptying times in 31 studies performed on 11 normal subjects.

Fig. 5 Effect of pentagastrin. The first arrow signifies commencement of the infusion at $1.2 \mu\text{g kg}^{-1} \text{h}^{-1}$ and the second arrow the doubling of the infusion rate to $2.4 \mu\text{g kg}^{-1} \text{h}^{-1}$. Note the immediate but transient decrease in counts in the distal stomach with simultaneous increase in counts in the proximal stomach. The whole stomach curve reflects the changes from the distal stomach, but to a lesser degree. The subsequent slow rise in counts in the whole stomach and distal area is presumably related to refilling after reflux (see text).

results of Cowley *et al.* (1972). Normal saline, whether given as a continuous infusion or by bolus injection, had no significant effect on the subsequent rate or pattern of gastric emptying (Fig. 2). The validity of applying this technique to

drugs studies was shown using hyoscine and bethanechol. The former, which is used to inhibit peristalsis in radiology (Solanke *et al.*, 1969) was found to significantly delay gastric emptying. Bethanechol, a cholinergic, should stimulate gastric motility and emptying. Another cholinergic, carbachol, increased emptying in subthreshold doses in the post-vagotomy patient (Tinker *et al.*, 1970). This study, using a pharmacological dose, has shown a similar finding in the intact stomach.

The interpretation of the data using the half emptying time proved satisfactory for measuring the effects of both hyoscine and bethanechol. Visual inspection of the curves in these subjects added little useful information. The curves from the distal stomach, after injection of these drugs, reflected the overall changes in gastric emptying (Fig. 3). However, the fluctuations in counts between 30 second frames were insufficient to directly relate the changes in net emptying to antral muscle activity.

In this study, pentagastrin produced an overall delay in gastric emptying (as measured by $T_{1/2}$) which is in accord with previous reports using both gastrin II and pentagastrin with liquid meals in man (Hunt and Ramsbottom, 1967) and dogs (Dozois *et al.*, 1971; Cooke *et al.*, 1972). The only contradiction is that of Aylett *et al.* (1969) who found no change with pentagastrin. This may be attributed to the type of meal or the presence of duodenal ulcers in their patients. Despite the delay in gastric emptying, visual inspection of the curves showed a marked initial increase in emptying, most evident in the distal stomach (Fig. 5). This suggests strong antral contractions in response to pentagastrin. The slight reciprocal rise in counts noted in the proximal stomach area is interpreted as partial reflux of contents into the fundus. The subsequent delay in gastric emptying can be explained by the intense antral (and probable duodenal) activity producing a physiological stricture. This is supported by photographs of four consecutive 30 second frames showing virtually complete emptying of isotope from the distal stomach within two minutes of commencing the infusion—a situation not seen at any other time during these studies (Fig. 6; compare Figs. 3 and 5). It is probable that this antral contraction is sustained (Dozois *et al.*, 1971; Kwong *et al.*, 1971) and this finding would not support the suggestion that delayed emptying is due to rapid weak antral contractions (Sugawara *et al.*, 1969). The transient rise in counts in the antrum seen after the maximal response to pentagastrin is presumably related to rapid refilling from the fundus. The smaller rise in counts noted in the total stomach curve is a little more difficult to explain. It is possibly related to reflux back into the stomach from the

Fig. 6 Effect of pentagastrin. Four consecutive 30 second frames taken soon after the injection of pentagastrin ($1.2 \mu\text{g kg}^{-1} \text{h}^{-1}$). Note the absence of radioactivity in the distal region, suggesting marked antral contraction. Compare the outline of the stomach in Figure 1.

oesophagus (or duodenum). In the present study, the proximal stomach did not respond to pentagastrin. Any changes appear to be due to passive reflux from the antrum.

Gastrin, or its analogue, directly stimulates isolated smooth muscle preparations (Bennett, 1965; Mikos and Vane, 1967)—more specifically, human antral muscle (Bennett *et al.*, 1967; Cameron *et al.*, 1970). An increase in frequency of electrical waves and a coupling of mechanical and electrical activity has been described in dogs (Sugawara *et al.*, 1969; Kelly, 1970; Dozois *et al.*, 1971; Cooke *et al.*, 1972) and man (Kwong *et al.*, 1971, 1972). These correlate with the pressure changes (Kwong *et al.*, 1971) and are maximal in the antrum (Misiewicz *et al.*, 1967, 1969). No changes in electrical or pressure measurements were found in the fundus or with isolated fundic smooth muscle in these studies. Thus, the finding in the present study of increased antral activity and minimal or absent fundal activity is in keeping with the known action of gastrin.

The dose of pentagastrin used ($1.2\text{--}2.4 \mu\text{g kg}^{-1} \text{h}^{-1}$) was within the suggested physiological range, as gastric motility does not commence until a dose of the magnitude of $0.6 \mu\text{g kg}^{-1} \text{h}^{-1}$ is given with

maximal effect at $6 \mu\text{g kg}^{-1} \text{h}^{-1}$ (Kwong *et al.*, 1971; Misiewicz *et al.*, 1967). An infusion of pentagastrin at $3 \mu\text{g kg}^{-1} \text{h}^{-1}$ produced results identical with endogenously released gastrin (Sugawara *et al.*, 1969). However, despite the effects of pentagastrin on gastric emptying shown in this study, it is not possible to extrapolate further and suggest that they are analogous to endogenous gastrin. The physiological role of gastrin on gastric emptying in man remains uncertain.

Conclusion

A non-invasive technique for the continuous assessment of the emptying of a solid isotope meal from the human stomach is described. Reproducibility of the technique was confirmed. Ability to assess the effects of drugs administered during a study was demonstrated using hyoscine-*N*-butyl bromide and bethanechol chloride. Pentagastrin peptavlon (at $1.2 \mu\text{g kg}^{-1} \text{h}^{-1}$) delayed the overall rate of emptying of food from the normal stomach. There is marked initial increase in emptying due to intense antral contraction, subsequently resulting in a stricture. The proximal stomach is unresponsive and only passive reflux from the distal stomach is seen.

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