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The relationship between gastric emptying of semisolids and paracetamol absorption

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1 The relationship between gastric emptying rate of semisolid Tc-99m labelled Chelex-100 resin/oatmeal and paracetamol absorption was determined simultaneously in seven healthy volunteers.

2 There was no significant correlation between the half-time of gastric emptying and the time of the peak serum paracetamol concentration.

3 There was no significant correlation between the area under the serum paracetamol concentrations at 60 and 90 min and the % meal emptied in 60 and 90 min respectively.

4 Three subjects showed a lag phase in gastric emptying pattern, while the other four showed the emptying curves without evidence of a delayed phase of emptying.

5 Individual values of gastric emptying determined by the methods varied widely.

Keywords gastric emptying paracetamol absorption semisolids radionuclides

Introduction

Gastric emptying of solids and liquids is dependent on motor function of different portions of the stomach (Minami & McCallum, 1984). Several techniques have been described using two radionuclides to measure liquid and solid emptying simultaneously (Heading *et al.*, 1976; Christian *et al.*, 1980). However, the use of multiple radionuclide markers and labelling of a solid phase is a cumbersome procedure (Meyer *et al.*, 1976). Frequently, liquids are used as test meal, although complaints of gastric retention when present, occurs when solids are consumed, and symptoms of dumping occur mostly when semisolids are taken (Jacobs *et al.*, 1982).

In this study we have used Tc-99m-labelled Chelex-100 resin mixed with oatmeal to study the gastric emptying of semisolids. This conveniently prepared Tc-99m-Chelex-100 resin has been shown to have excellent *in vitro* and *in vivo* stability with $t_{1/2}$ of emptying in normal subjects similar to that observed for other small, solid test meals (Wirth *et al.*, 1983). The rate of paracetamol absorption has been demonstrated to reflect the rate of gastric emptying of the liquid phase, when compared with In-113m DTPA chelate scintiscanning studies (Heading *et al.*, 1973; Clements *et al.*, 1978). In the present study the relationship between gastric emptying rate of semi-solids and absorption of paracetamol and Tc-99m Chelex-100 resin/oatmeal mixed in powder form was studied in normal volunteers under standard conditions.

Methods

Seven healthy volunteers, four women and three men (age 25–39 years, body weight 45–85 kg) were the subjects. The study was approved by the local ethics committee and informed consent was given by all subjects.

After an overnight fast, the subjects sat while eating 30 g instant oatmeal, 5 g sugar, 100 ml of cold milk and paracetamol powder 20 mg kg^{-1}

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uniformly mixed with 37 MBq of Tc-99m Chelex-100 resin. Starting 5 min after the test meal, with the subjects in supine position, the gastric emptying study was performed in the anterior projection using a gammacamera (Maxi 400 T, G.E.) with low-energy parallel-hole collimator on line to computer system (gamma 11, D.E.C., Maynard, M.A.). Successive 60 s images were obtained over a 90 min period. The quantitative examination of emptying was based on a series of 5 min images. In three subjects images of the stomach area were accumulated alternately from the anterior and the posterior aspects of the body. Assuming that the 1 min delay between the anterior and posterior recording was not believed to introduce any significant error in the calculations, the geometric mean of the anterior and posterior counts (the square root of the product) was then calculated.

The stomach was outlined using an irregular region of interest and the activity curve from this region was calculated over the period of the study after correction for decay of the 99m-technetium marker. Isotope counts, were expressed as percentage of meal emptied from stomach in 60 (E_{60}) and 90 min (E_{90}), gastric emptying half time ($E_{½}$) and duration of the lag period. Time 0 was taken as the time of the first count, immediately after meal ingestion. On the same occasion venous blood samples were taken from an indwelling cannula before and with 15 min intervals after the end of 'the meal' ingestion. Serum was separated and stored at −20° C until measurement of serum paracetamol concentration was performed by high performance liquid chromatography (Knox & Jurand, 1978).

Statistics

The relationships were assessed by Spearman's rank correlation coefficient.

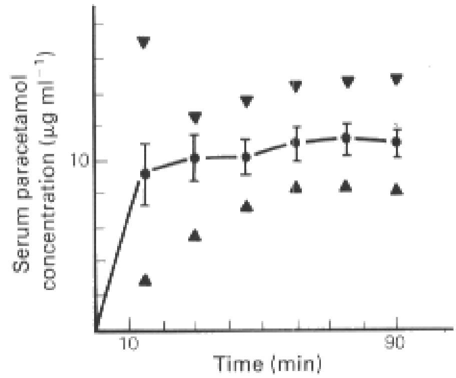

Figure 1 Mean ± s.e. mean paracetamol concentrations for seven volunteers at each sampling time. ▼▲ range.

Results

Mean serum paracetamol concentrations at each sampling time are given in Figure 1, the individual values of C_{max}, t_{max} and AUC are presented in Table 1. Gastric emptying parameters are presented in Figure 2 and Table 1. There was no statistically significant relations between the half time of gastric emptying and peak serum paracetamol concentration ($r = 0.13$; $P < 0.05$) or time of the peak serum paracetamol concentration ($r = 0.39$; $P < 0.05$). There was no statistically significant correlation between the area under the serum paracetamol concentration at 60 min and % of the meal emptied in 60 min ($r = 0.38$; $P < 0.05$). There was no statistically significant correlation between the area under the serum paracetamol concentration at 90 min and % of the meal emptied in 90 min ($r = 0.08$; $P < 0.05$). The mean percent retention values of the anteriorly acquired data did not differ from the

Table 1 The individual values of the peak serum paracetamol concentration (C_{max}), the time from administration of paracetamol to its peak concentration (t_{max}), the area under serum paracetamol concentration-time curve from 0–60 min. (AUC_{60}), the area under serum paracetamol concentration-time curve from 0–90 min (AUC_{90}), % of meal emptied from stomach at 60 min (E_{60}), % of meal emptied from stomach at 90 min (E_{90}), gastric emptying half time ($E_{½}$) and duration of lag period (Lag)

Subject	C_{max} (µg ml^{-1})	t_{max} (min)	AUC_{60} (µg ml^{-1} min)	AUC_{90} (µg ml^{-1} min)	E_{60} (%)	E_{90} (%)	$E_{½}$ (min)	Lag (min)
1	15,7	30	722	1098	40	57	80	0
2	11,8	15	554	857	30	61	80	15
3	9,2	75	355	624	50	72	60	0
4	16,8	15	722	1147	22	35	105	30
5	11,8	150	319	611	16	31	135	25
6	8,6	75	375	629	16	17	160	0
7	14,1	60	414	1042	21	39	105	0
Mean	12,6	60	494	858	28	45	104	
1 s.e. mean	1.2	17.9	65	90	4.9	7.3	13.1	

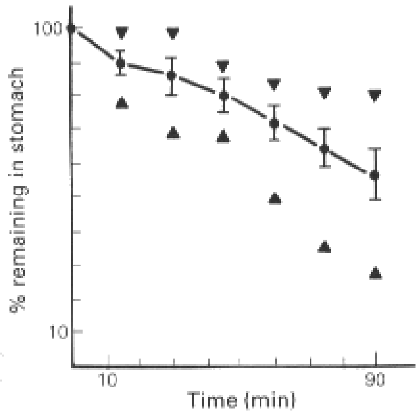

Figure 2 Gastric emptying curve of semisolid for the seven volunteers (mean ± s.e. mean, ▼▲ range).

geometric mean values. The anterior detector alone did at no time underestimate the emptying rate determined by geometric mean by more than 9%.

Three of seven subjects showed an early delay, or 'lag' phase in gastric emptying pattern determined by anterior detection. In two subjects this existence of the lag phase was further classified by the filling curve of the intestine and by geometric mean correction. The other four subjects showed the emptying curves closely conformed to a linear fit, without evidence of a lag phase before emptying.

Discussion

The absorption rate of many drugs has been shown to depend on gastric emptying rate. In particular it is assumed that the absorption of orally administered paracetamol reflects the gastric emptying rate since it is absorbed rapidly from the upper small bowel. Simultaneous measurement of serum paracetamol concentration, the time to reach maximum paracetamol concentration, the area under the serum paracetamol concentration curve at 60 min and gastric emptying rate determined with radionuclide markers have confirmed measurements of the rate of paracetamol administered orally as a reliable expression of liquid phase gastric emptying (Heading *et al.*, 1973; Clements *et al.*, 1978). However, our data suggest no such relationship between paracetamol absorption and scintigraphic measurement of gastric emptying of semisolids.

In this study Tc-99m-labelled polysterene resin was incorporated into a palatable, small semisolid test meal. Heading *et al.* (1973) used a semisolid test meal labelled with In-113m diethylenetriaminepenta-acetic acid chelate, which is a liquid marker. Liquid and solid phase empty at different rates and patterns (Minami & McCallum, 1984; Moore *et al.*, 1985) and patients may demonstrate normal emptying of liquid while actually retaining the solids abnormally with symptoms of gastric retention (Mannell & Esser, 1984). Only rarely complaints occur after drinking liquids (Jacobs *et al.*, 1982).

The emptying of the semisolid test meal in our study was found to be a linear process, similar to the solid phase gastric emptying pattern. The nuclide marker was apparently emptying along with the solid phase, while paracetamol is known to follow the liquid phase (Heading *et al.*, 1973; Clements *et al.*, 1978).

In this concept paracetamol seems to represent the function of proximal stomach which controls the gastric emptying of liquids, while the gastric emptying of semisolid reflects more the distal part of stomach responsible for reducing solids to the form required for emptying (Minami & McCallum, 1984). Food eaten as solids, leaves the stomach more slowly than the liquid portion of a meal (Malmud *et al.*, 1982).

After meal consumption, food material moves anteriorly decreasing tissue attenuation. It has long been known that the geometric mean of counts from opposing views is insensitive to changing source depth (Tothill *et al.*, 1978). The geometric mean can be determined from anterior and posterior computer images of the stomach (Christian *et al.*, 1980). This correction seems to be important for precise quantification of gastric emptying rates in studies using large meals and in obese patients (Christian *et al.*, 1983). Using anterior detection alone, over-estimation of the half emptying time is proportional to the size of the meal: with a 300 g meal the error is approximately 10% (Manell & Esser, 1984; Christian *et al.*, 1980). In this study a meal of approximately 115 ml was used and this error was maximum 9% at 75 min, when corrected by geometric mean as employed by Moore *et al.* (1985). Thus, it was assumed that the more convenient and easier method using single anterior detection with correction for decay was optimal in our study. Similar approximation has previously been used in several clinical studies (Jacobs *et al.*, 1982; Malmud *et al.*, 1982; Sheiner *et al.*, 1980).

It has been postulated that the period of an early delay or lag period in gastric emptying pattern is a measurement artefact, as it has been shown that gastric emptying begins as soon as food reaches the stomach (Mannell & Esser, 1984; Christian *et al.*, 1983) and only represents movement of the labelled meal from the posterior to the anterior part of the stomach where the effect to attenuation is less in relation to the fixed anterior detector (Christian *et al.*, 1980, 1983). There is, however in the literature a diversity in opinion about the existence of a lag phase (Jacobs *et al.*, 1982; Moore *et al.*, 1985; Tothill *et al.*, 1978).

The gastric emptying patterns of semisolid in our study showed that the subjects could be divided in two subgroups. One without evidence of a lag period and the other with a lag pattern. The emptying patterns of the two subgroups differed only in the existence of the lag phase, whereas the emptying rates were similar. There was no significant difference in sex, weight or $E_{1/2}$ between the subgroups and all volunteers were without symptoms or history of gastric/intestinal disease. Since some variation in gastric emptying has been shown due to posture and gravidity (Tothill *et al.*, 1978, 1980) a standard supine position was maintained during the study. We suggest that the explanation could be e.g. different mastication habits or different ability of adequately filling the gastric antrum (Sheiner *et al.*, 1980) or even psychological reaction to the study. However, only assessment of much larger number of subjects will allow recognition of subgroups according to gastric emptying pattern.

Provided the limitations of anterior detection alone, gastric emptying studies of semisolids provides different information than liquid emptying test alone and will suffice for most clinical studies where differences in emptying rates between groups are sought.

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