Gastric emptying with gastro-oesophageal reflux

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SUMMARY The time taken for gastric emptying of a liquid (milk) or a semi-liquid (pudding) meal was evaluated in 477 infants and children. These patients were referred for suspected gastro-oesophageal reflux and underwent gastro-oesophageal scintigraphy, prolonged oesophageal pH study, manometric evaluation of the lower oesophageal sphincter pressure, and fiberoptic endoscopy. No difference in gastric emptying was observed in children aged under 3 years, regardless of the presence or absence of the gastro-oesophageal reflux, the pressure of the lower oesophageal sphincter, or the presence of oesophagitis. In children over 6 years, however, gastric emptying was significantly delayed in those presenting with reflux compared with those without reflux; in children over 3 years there was slower gastric emptying in those with a decreased lower oesophageal sphincter pressure compared with those with higher pressure and in those with overt oesophagitis compared with those without oesophagitis. This study suggests that gastro-oesophageal reflux is more severe in childhood than in infancy, probably due to more complex motor disorders affecting the gastric fundus as well as lower oesophageal sphincter function.

Several techniques are currently available for measurement of gastric emptying of a liquid or semi-liquid meal, such as the marker dilution technique,¹ radiological studies,² radioisotopes,³ and, more recently, ultrasound scanning.⁴ It has been shown that gastric emptying is delayed in infants with congenital heart disease⁵ and with respiratory distress syndrome,⁶ while it seems to be accelerated when pancreatic insufficiency is present.⁷ There is some controversy, however, about the evaluation of the time taken for gastric emptying in infants and children who present with gastro-oesophageal reflux: some authors have found significantly delayed gastric emptying in children with reflux,^{8,9} while others have not.¹⁰⁻¹²

We have reviewed about 500 gastro-oesophageal scintiscans performed in our department during the last five years, firstly, to compare the time taken for gastric emptying in children with and without gastro-oesophageal reflux and, secondly, to assess whether delayed time for gastric emptying to take place could be associated with decreased lower oesophageal sphincter pressure with or without concomitant reflux peptic oesophagitis.

Patients and methods

A total of 477 infants and children referred with symptoms that suggested gastro-oesophageal reflux (vomiting or regurgitation, or both, 64%; recurrent pulmonary disease, 21%; near miss 'sudden infant

death syndrome', 10%; retrosternal pain, 5%) were investigated. Gastro-oesophageal scintigraphy was performed in all of them. In addition to this radionuclide investigation, 89 were also studied by means of 24 hour continuous oesophageal monitoring of pH, 202 underwent fiberoptic endoscopy for diagnosis of oesophagitis, and 188 had manometric evaluation of the lower oesophageal sphincter pressure.

The series of 477 patients was subdivided in six groups according to age: (1) less than 3 months (mean 1.8 months), (2) 4 to 6 months (mean 4.9 months), (3) 7 to 12 months (mean 8.9 months), (4) 13 to 36 months (mean 20.9 months), (5) 3 to 6 years (mean 4.4 years), and (6) 7 to 14 years (mean 11.2 years). As a result of the smaller number of patients investigated the results of pH study, endoscopy, and manometry were analysed in five age groups (groups 5 and 6 were considered together).

Gastro-oesophageal scintigraphy. The technique of gastro-oesophageal scintigraphy has been well described.¹³ In our department a large field scintillation camera (Toshiba) and a mini-computer Simis 3 (Informatek) were used. A 7.4 MBq dose of ^{99m}Tc sulphur colloid was mixed with a small amount of the usual meal and given orally. The rest of the meal was given immediately after to wash down the remaining radioactivity in the mouth. The meal consisted of the usual milk formula for children aged under 1 year or pudding for those 1 year or over.

The patient was allowed to belch and then placed in supine position over the detector for a recording period of one hour, using 20 second frames. Regions of interest were drawn over the oesophagus and stomach and the time activity curve of the oesophagus was obtained and expressed as a percentage of the gastric activity. Each reflux peak was checked by inspecting the corresponding image to exclude artificial peaks due to gastric displacement into the oesophageal area. The number, intensity, and duration of the reflux peaks were noted and a reflux index calculated by taking these three variables into account.¹⁴

The number of counts over the gastric region of interest was measured during the one hour recording, allowing estimation of the time taken for gastric emptying. We used the residual gastric activity at 60 minutes expressed as a percentage of the initial activity (R60) as the variable. We chose this variable in preference to the half life of the radioactive isotope ($T_{1/2}$) because R60 does not require an *a priori* hypothesis concerning the shape of gastric emptying curve.

pH study. Continuous 24 hour oesophageal pH was monitored using a flexible MI-506 glass pH probe (Microelectrode Inc), the distal end being placed at 87% of the total distance from the nares to the lower oesophageal sphincter. pH was determined continuously and the data, recorded every 7.5 seconds, were stored into a portable system (Memolog 600-Novo) and processed with an Apple IIe computer, using our own program. An oesophageal pH under 4 was regarded as abnormal. Each episode of reflux was analysed and the reflux index (percentage of total time of oesophageal pH inferior to 4) was considered to be abnormal when greater than 5.

Oesophageal manometry. A three lumen tube assembly was employed to study oesophageal motility. The recording catheters were arranged to measure pressure through side orifices, spaced at 2.5 cm intervals. Each pressure catheter was infused with distilled water by a syringe pump at a rate of 0.8 ml/min. Resistance to infusion was transmitted to external Statham transducers. The pressure profiles were continuously recorded with a multichannel polygraph recorder. The resting lower oesophageal sphincter pressure in each patient was measured by the pull through technique.¹⁵ No premedication was used to perform this examination.

Oesophagoscopy and histology. Endoscopic examination was performed with paediatric fiberoptic panendoscopes (Olympus GIF-XP, GIF P-10). Two or more biopsy specimens were obtained using conventional endoscopic biopsy forceps either from an area where lesions were evident or 2–3 cm above the squamocolumnar junction if the mucosa seemed

to be normal. If there were obvious oesophageal ulcers no biopsy specimen was taken. All specimens were reviewed by a pathologist. A classification of the histological findings was made on the basis of the following criteria:

- (a) Normal biopsy;
- (b) Oesophagitis grade 1 (hyperplasia of the epithelium, vascular papillae extending more than two thirds to the free luminal margin, ingrowth of vessels in the vascular papillae);
- (c) Oesophagitis grade 2 (abnormal infiltration of neutrophilic or eosinophilic polymorphonuclear leucocytes, or both);
- (d) Oesophagitis grade 3 (erosion or complete ulceration of the mucosa, columnar lined oesophagus).

This series of examinations was performed for each child during a period ranging from two to seven days.

Statistical analysis. Statistical analysis was carried out by the non-parametric Wilcoxon rank sum test.

Results

The total population of 477 patients was divided into two groups, those with and those without reflux, on the basis of the results of scintigraphy or pH study, or both. Group 1 was formed of the 291 children who had abnormal results in at least one of these two examinations. Group 2 was formed of the 186 children with normal results.

The comparison of the time taken for gastric emptying in these two groups of patients is presented in Figure 1. A significant difference ($p < 0.001$) was found only in the children over 6

Fig. 1 Mean (SEM) of age related R60 (residual activity in the stomach after 60 minutes): relation with gastro-oesophageal reflux (●—● = those with reflux; ■—■ = those without reflux).

* $p < 0.001$.

Table Mean (SEM) age related R60 (residual activity in the stomach after 60 minutes) in patients with normal and abnormal results of gastro-oesophageal scintigraphy and pH study

	Age group					
	<3 months	4-6 months	7-12 months	1-3 years	4-6 years	>6 years
Scintigraphy results:						
Normal	65.5 (1.4)	68.0 (1.7)	68.9 (2.6)	64.2 (3.4)	51.0 (5.0)	44.2 (4.5)*
Abnormal	70.6 (2.3)	71.2 (1.7)	70.2 (2.8)	60.5 (3.7)	53.0 (4.5)	25.1 (2.5)*
pH study:						
Normal	61.7 (4.0)	67.5 (4.9)	70.2 (4.4)	77.7 (4.2)	47.0 (6.5)**	
Abnormal	68.9 (4.3)	70.5 (5.7)	74.5 (5.0)	58.8 (10.0)	26.2 (5.3)**	

* $p < 0.005$; ** $p < 0.05$.

years, gastric emptying being delayed in patients with reflux (mean (SEM) R60: 41.6 (3.8) in those with reflux ν 23.7 (2.8) in those without reflux). A further comparison of R60 between those with and those without reflux was performed by analysing separately the results of pH study on one hand and of reflux scintigraphy on the other. No difference was observed between the two populations, except for the oldest subgroups (Table).

The lower oesophageal sphincter pressure, determined in 188 children, was >12 mm Hg in 119 patients and ≤ 12 mm Hg in 69. No significant difference in gastric emptying was found in children under 3 years with low and normal lower oesophageal sphincter pressures (Fig. 2). The difference was significant, however, in children over 3 years (mean (SEM) R60: 55.5 (6.6) in children with low

Fig. 2 Mean (SEM) of age related R60 (residual activity in the stomach after 60 minutes): relation with values of lower oesophageal sphincter pressure (●—● = those with lower oesophageal sphincter pressure ≤ 12 mm Hg; ■—■ = those with lower oesophageal sphincter pressure >12 mm Hg).

* $p < 0.05$.

Fig. 3 Mean of age related R60 (residual activity in the stomach after 60 minutes): relation with endoscopic and histological findings (■—■ = those with normal findings; ●—● = those with oesophagitis grade 1; ▲—▲ = those with oesophagitis grades 2 and 3).

* $p < 0.05$.

pressure ν 29.4 (5.9) in children with normal pressure; $p < 0.05$).

Endoscopic and histological findings were available for 202 children: there was no oesophagitis in 108 children, slight oesophagitis (grade 1) in 64, and overt oesophagitis (grades 2 and 3) in 30. Only in the oldest age matched subgroups was a significant difference in gastric emptying found between the children with overt oesophagitis and those without oesophagitis (mean (SEM) R60: 53.4 (7.8) ν 30.4 (4.1); $p < 0.05$) (Fig. 3).

Discussion

Since the very first studies of Cannon¹⁶ many data have been published about gastric emptying in humans. Among the techniques currently used, scintigraphy with ^{99m}Tc is a suitable method for the

study of gastric emptying of a liquid or a semi-liquid meal. It is more physiological and better accepted than the marker dilution technique and its radiation hazard is less than the conventional radiological method. As a matter of fact, using 7.4 MBq of ^{99m}Tc sulphur colloid, the total body absorbed dose is less than 0.05 mGy and the gonadal dose is less than 0.2 mGy.¹⁷ This exposure is less than a tenth that of conventional barium meal.¹⁸

Most of the previous studies have been performed in adults, whereas the mechanisms of gastric emptying in childhood have been investigated only recently, although the motor behaviour of the stomach seems to be altered in many childhood diseases. Unfortunately, because of the differences in the techniques used and in the ages of the patients investigated, previously reported data are not always comparable. It has been shown, for example, that the patterns of emptying of a liquid, a digestible solid, or an indigestible solid are different.¹⁹ It has become clear that tonic fundal activity is mainly responsible for the emptying of liquids, while the distal stomach is much more concerned with the elimination of solids from the gastric cavity.²⁰

Osmolality and fat composition,²¹ protein,²² and amino acid²³ contents of the ingested meal have an important influence on gastric emptying and often the different nutrients chosen by different authors for evaluating gastric emptying make comparison of their results difficult. It should also be emphasised that some technical problems may be related to the use of milk: when milk reaches the stomach there is a precipitation of casein, the radiotracer is sequestered into this fraction, and the time taken for gastric emptying describes mainly the emptying of the casein phase.²⁴ This could explain the low emptying rates found in infants when milk was used as a meal using scintigraphy. Another source of controversy is the variable employed to express the rate of gastric emptying. In our experience fitting a straight line to the gastric time activity curve, to measure the half time of gastric emptying, seems to be a questionable technique. When using milk formulas the pattern of gastric emptying is variable, a sudden decrease of activity being preceded or followed by periods during which no emptying is observed at all. For that reason, we preferred to use the residual gastric activity after 60 minutes as the variable. In this study we used milk in children under 1 year because it represents the physiological meal at this age.

To evaluate the gastric emptying of children with suspected gastro-oesophageal reflux, our population was subdivided into two groups, those with reflux and those without reflux, according to the results of gastro-oesophageal scintigraphy and prolonged pH study, these two techniques being considered as the most reliable methods for the detection of reflux disease.^{14 25}

A significant delay in the time taken for gastric emptying was found only in those children over 6 years with reflux. Whatever the technique used for the diagnosis of reflux (pH study or scintigraphy), no difference was seen in the time taken for gastric emptying of children, with or without reflux, in the lower age groups. A significant difference between those with and without reflux was observed from the age of 3 years, when pH study was used as the only criterion for the diagnosis of reflux, and from the age of 6 years when only scintigraphy was used. This difference might be due to the fact that the criteria that we have chosen for diagnosis of reflux by pH study were more selective and picked up patients with a more severe reflux disorder.

The delay in emptying of a liquid or semi-liquid meal is mainly due to abnormal gastric fundal function.²⁶ A delay in gastric emptying occurred in those children over 3 years with low lower oesophageal sphincter pressures, one of the major pathogenetic factors in patients with reflux.²⁷ Lower oesophageal sphincter and fundus can probably act as a synergic functional unit, both showing a relaxation reflex in response to swallowing, which is almost entirely mediated by the non-adrenergic, non-cholinergic nerve fibres.²⁸ Our findings that important abnormalities of the lower oesophageal sphincter can be associated with altered gastric emptying support the concept of an interrelation between lower oesophageal sphincter and fundic function.

In infants no correlation was found between oesophagitis and gastric emptying. These data are consistent with those of Baulieu, who found normal gastric emptying in very young children with reflux oesophagitis.⁹ The findings that older children with obvious oesophagitis also have a slower rate of emptying of the stomach agrees with the increasing severity of the reflux disease with age, the fundal function seeming to be affected as well.

It has been shown in adults that this disease can be part of a more complex disorder in which the gastrointestinal tract distal to the oesophagus may also be involved. McCallum *et al* showed an abnormal motor function of the stomach in a high percentage (41%) of adult patients with reflux,²⁹ and Behar and Ramsby showed an antral dysmotility in reflux oesophagitis.³⁰ After the first few years of life children probably develop reflux disease, therefore, that resembles the adult form more, with a motor disorder not always confined to the lower oesophageal sphincter but that also involves other upper gastrointestinal structures.

The evidence that delayed gastric emptying can be significantly associated with a low lower oesophageal sphincter pressure and with a severe reflux oesophagitis strongly supports the role of prokinetic drugs, which can enhance the emptying of the stomach, in the treatment of reflux disease.

To our knowledge, this paper is the first report to compare gastric emptying in children, with and without reflux, and evaluates a large series of patients according to their age. Rosen *et al* have studied gastric emptying using a 5% dextrose solution in two groups of children, those under and those over 2 years of age.¹⁰ They found no difference in children with or without reflux. Our data, even if we used another meal, are not significantly different from those of Rosen: if the patients of the different subgroups above 2 years are considered together, the difference for the older children (>6 years) is masked and no difference can then be shown between those with and without reflux.

On the other hand, Hillemeier *et al* claimed that in infants with reflux complicated by failure to thrive or recurrent pulmonary disease, or both, gastric emptying was slower than in controls.⁸ These data are not incompatible with our own as, unlike in Hillemeier's patients, severe complications were seldom observed in our population.

Our study also shows a correlation between the age of the patients investigated and the rate of their gastric emptying, older children showing a faster emptying than younger children. Part of the difference can, of course, be explained by the change of meal (pudding) given to the older children. The age related differences are also obvious, however, comparing children aged 1 to 3 years, 4 to 6 years, and older than 6 years, who all received the same type of meal. The evaluation of the gastric emptying in children should therefore take into consideration the age of the patient investigated as well as the type of meal used for the study.

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