Foregut motor function in chronic renal failure

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Abstract

In children with chronic renal failure (CRF) anorexia, nausea, and vomiting are common yet poorly understood symptoms. We studied oesophageal and gastric motor function in 12 children (age 7 months–6.8 years) with severe CRF not undergoing dialysis who had persistent anorexia and vomiting. Eight of 12 patients had significant gastro-oesophageal reflux (reflux index 5.2% to 21.9%, mean 11.3%; controls <5%), 7/10 had altered gastric half emptying times ($T_{1/2}$) for 5% glucose or milk (glucose meal—controls: 8–14 min, two CRF patients: 18–25 min; milk meal—controls: 48–72 min, five CRF patients 27, 28, 82, 83, and 110 min). Gastric antral electrical control activity was abnormal in 6/11 patients, with different types of gastric dysrhythmias whereas the remainder and controls showed a regular dominant frequency of 0.05 Hz. In 7/9 patients fasting serum gastrin concentration was raised (53 to >400, mean 168 pmol/l, controls <40 pmol/l). All CRF patients with anorexia and vomiting had one or more disorder of foregut motility. The nature and variety of the motor disorders and the raised concentrations of circulating gastrin suggest that the normal environment generated by CRF affects the function of the smooth muscle of the foregut.

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Children with chronic renal failure (CRF) commonly suffer from anorexia, nausea, vomiting, and failure to thrive.¹ Our current understanding of the cause of these symptoms is limited and treatment is largely empirical and ineffective. It is generally accepted that vomiting may occur as a result of gastro-oesophageal reflux (GOR) or by initiation of the emetic reflex. The latter is associated with prodromal symptoms such as nausea, gastric and oesophageal dysmotility and reflex contractions of the intercostal, diaphragmatic, and anterior abdominal muscles.² Regurgitation however is effortless and not associated with any prodromal symptoms.³ Whether one or both of these mechanisms is responsible for vomiting in children with CRF has not been previously studied.

In this study we have assessed foregut motor function and its regulation in children with CRF who were failing to thrive and had symptoms of anorexia and vomiting.

Patients and methods

PATIENTS

Twelve children (10 boys and two girls, mean

age 2.17 years, range 7 months–6.8 years) with CRF (mean estimated glomerular filtration rate 11 (range 6–25) ml/min/1.73 m²) receiving conservative medical management but not requiring dialysis were studied. The primary cause of renal disease was renal dysplasia (n=7) or obstructive uropathy (n=5). At the time of study the mean height SD score was –2.6 (–4.0 to –1.7) and mean weight SD score was –2.5 (–3.8 to –1.3). All children were anorexic and/or had a history of vomiting at the time of study. Eleven of the 12 required nasogastric tube feeding in order to achieve an adequate energy intake.

CONTROLS

Overall 50 subjects (age 3 months–17 years) acted as controls: 22 for GOR, 12 for gastric emptying, and 16 for gastric electrical activity. Twelve were normal healthy children and the others had eating disorders (n=23), recurrent respiratory infections (n=6), cyclical vomiting (n=5), postenteritis enteropathy (n=2), Crohn's disease in relapse (n=2); none had irritable bowel syndrome or were referred for a suspected gastrointestinal motility disorder. After detailed motility investigation including intra-oesophageal pH monitoring, antroduodenal manometry and electrogastrography, no evidence of such a disorder could be found.

METHODS

All patients with a history of vomiting had a barium meal and follow through examination. Foregut motor function was assessed by measuring intraoesophageal pH, gastric emptying, and gastric antral electrical activity. Regulation of gastrointestinal motility was assessed by measuring polypeptide hormones. The study was approved by the ethical committee of the Hospital for Sick Children, Great Ormond Street.

GOR

A well validated ambulatory intraoesophageal pH monitoring system (Synectics Medical) utilising an antimony electrode was used over a six hour postprandial period, which has been shown to be comparable with a 24 hour recording for the detection of GOR in children with vomiting and feeding problems.⁴ Two parameters were considered: (1) percentage of time spent with an intraoesophageal pH below 4 (reflux index or RI) and (2) duration of the longest reflux episode. GOR was graded as

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glucose meal: difference between medians -1.0 , 95% confidence interval -11.0 to 5.0 ; $p=0.87$), the variability of their $T_{1/2}$ was clearly higher than that of controls. Of those patients with abnormal gastric emptying, half were intolerant of the test meal. Among the patients with delayed emptying, two vomited during the

test and one received a reduced meal volume. One patient with accelerated emptying vomited at the end of the test.

Gastric antral electrical control activity

Electrical control activity occurred at a mean frequency of 0.05 (0.04 – 0.06) Hz in 16 controls and in five patients. In 6/11 children with CRF a number of different dysrhythmias of antral electrical control activity were detected. One patient had a tachyarrhythmia (0.15 Hz), two had a bradyarrhythmia (0.02 and 0.03 Hz respectively), and three had an unstable electrical control activity (no dominant frequency detectable). All dysrhythmias occurred during the fasting as well as the postprandial period. These dysrhythmias are shown as pseudo three dimensional running spectral frequency plots in fig 3.

Polypeptide hormones

Fasting serum concentrations of vasoactive intestinal polypeptide, pancreatic polypeptide, glucagon, and neurotensin were within the reference range in all but two patients, one with vasoactive intestinal polypeptide values of 48 pmol/l (reference range <30) and another with pancreatic polypeptide values of 393 pmol/l (reference range <300). Fasting serum gastrin was significantly raised in 7/9 patients. These seven had a mean value of 168 pmol/l and a range

Figure 2 Gastric half emptying times ($T_{1/2}$) after a milk meal and a 5% glucose meal in 12 healthy controls and 12 children with CRF. Note that the time scale on the Y axis of the right hand scatterplot is expanded.

Figure 3 Pseudo three dimensional running spectral frequency plots of electrogastrography recorded in four children with chronic renal failure. Normal electrical control activity (A), a tachyarrhythmia (B), a bradyarrhythmia (C), and unstable electrical control activity (D) are shown. Frequencies are expressed as cycles per minute (cpm), where $3 \text{ cpm} = 0.05 \text{ Hz}$.

Results of foregut motility assessment

Patient No	GOR	Gastric emptying	Gastric antral electrical control activity
1	Moderate	Delayed	—
2	Mild	Delayed	Normal
3	Normal	Normal	Tachyarrhythmia
4	Moderate	Accelerated	Unstable
5	Severe	Normal	Normal
6	Mild	Accelerated	Unstable
7	Mild	Normal	Bradyarrhythmia
8	Normal	Delayed	Normal
9	Normal	Normal	Bradyarrhythmia
10	Mild	Delayed	Normal
11	Mild	Normal	Unstable
12	Normal	Delayed	Normal

of 53–>400 pmol/l (reference range <40, remaining two patients 29 and 39 pmol/l). This finding was not related to any abnormality of blood chemistry or foregut motor function.

In summary—as can be seen from the table, all patients with CRF had some foregut motility disorder, either in the form of GOR (66·7%), abnormal gastric emptying (58·3%), or antral dysrhythmia (54·5%), and seven out of 12 (58·3%) had more than one abnormality, the most common association being between GOR and disordered gastric emptying.

Discussion

There is increasing evidence to suggest that anorexia, nausea, and vomiting result from a disturbance of foregut motility and its control mechanisms.⁷ This study clearly demonstrates that there are widespread motility disorders affecting the foregut of children with CRF who present with these symptoms. The prevalence of GOR was high (66·7%) and GOR was moderate to severe in 25%. These findings confirm the observations of Ruley *et al*, who found GOR in 16/22 (73%) infants with CRF and feeding problems.⁸

In this study, however, GOR was not the only cause of vomiting and abnormalities of gastric motor activity were as common. There have been no previous studies of gastric motor function in children with CRF, but studies in adults with CRF have yielded contradictory results. Some have shown delayed gastric emptying in symptomatic patients⁹ and during continuous ambulatory peritoneal dialysis,¹⁰ whereas normal gastric emptying has been reported in patients receiving haemodialysis, whether symptomatic or not.^{11–12} Our findings of both delayed and accelerated gastric emptying might be surprising, but both are in keeping with the patients' symptoms of fullness, nausea, and vomiting.¹³

During the pre-ejection phase of the vomiting reflex gastric antral dysrhythmias commonly occur in association with nausea and other autonomic symptoms.² Gastric antral dysrhythmias have been described in different conditions in which the emetic reflex has been evoked^{14–18} and in both adults and children with severe unexplained vomiting.^{19–21} Although it might be expected that gastric electrical activity would affect gastric emptying, in only two patients was an antral dysrhythmia found as well as a disordered gastric emptying. The most likely

explanation is that dysrhythmias result in impaired motor function of the gastric antrum which is mainly involved in grinding and emptying of solid foods. Emptying of a liquid meal depends mainly upon tonic pressure changes of the gastric fundus²² and thus antral dysrhythmias may not affect emptying of a liquid meal such as 5% glucose or milk. Furthermore, some of the dysrhythmias that we detected were more subtle and less striking than the continuous 'tachygastria' observed by others in patients with intractable vomiting. They may have been sufficient to induce nausea (and thereby a reduced food intake) but insufficient to affect gastric emptying. Secondly, some patients did not have the same meal volume (as they did not all tolerate the full meal) or the same test meal during the applied potential tomography and electrogastrography studies and a different challenge on the stomach might have resulted in different functional consequences. Finally, in nearly all patients gastric electrical control activity and gastric emptying were studied on two different occasions. Thus day to day variations might have been responsible for the lack of correlation between gastric emptying and gastric electrical control activity, perhaps due to fluctuations of some polypeptide hormones metabolised by the kidney and active on gut motility and food intake.

Gastrointestinal motility is modulated by myogenic, neural, and humoral factors,²³ which may themselves be altered when the renal function is deranged. The variability of antral electrical control activity found in this study is in sharp contrast to the persistent dysrhythmias we have recently described in patients with disease of enteric nerves or smooth muscle.²⁴ Thus it is likely that our present findings result from an altered humoral environment. In adults with CRF abnormally raised serum concentrations of several polypeptide hormones have been reported and hypergastrinaemia is a prominent biochemical feature.^{25–26} In response to a meal, gastrin increases and stimulates gastric acid secretion and gastrointestinal motor activity by increasing antral contractions and disrupting the fasting motility pattern.²⁷ At pharmacological doses, like those seen in CRF, gastrin stimulates oesophageal, gall bladder and small bowel contractions, as well as gastric acid and pancreatic exocrine secretion. Acid hypersecretion and disruption of the fasting motility pattern with increased but incoordinate small bowel contractions all result in delayed gastric emptying.²² Therefore gastrin could be partly responsible for some of the motility disorders found in our study. However, other polypeptide hormones involved in the regulation of gut motility and the modulation of hunger and satiety are markedly increased in adults with CRF.²⁵ It is therefore very likely that in children with CRF hypergastrinaemia is only part of a more complex biochemical disorder that may be expected to have considerable effects on gut motility and food intake. In summary, this study demonstrates that children with CRF who suffer from anorexia, nausea, and vomiting have several motility disorders of the upper gastrointestinal tract. GOR is the

cause of much vomiting, but reflex vomiting, with gastric dysrhythmias and disordered gastric emptying, is at least as common. We speculate that the altered humoral environment indicated by the hypergastrinaemia and generated by the CRF is at least in part responsible for the foregut motility disorders and the persistent anorexia.

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