Serum gastrin levels in hypertrophic pyloric stenosis of infancy

Response to a gastrin secretion test

MICHEL A. HAMBOURG, M. MIGNON, C. RICOUR, J. ACCARY, AND D. PELLERIN

Department of Paediatric Surgery, Hôpital des Enfants Malades, and Gastroenterology Research Unit, Hôpital Bichat, Paris

SUMMARY The aim of this study was to look for a difference in fasting serum gastrin levels or in serum gastrin response to oral feeding between infants with hypertrophic pyloric stenosis and normal controls. Fasting serum gastrin levels were measured by radioimmunoassay in 10 patients with pyloric stenosis, before pyloromyotomy and 7 and 15 days after it, and in 11 controls. In addition, the serum gastrin responses to a casein hydrolysate meal were studied in both groups (in the patients, 7 days after operation). The fasting serum gastrin levels in the patients did not differ from those in the controls before operation, but they did so after it. The serum gastrin response to feeding in patients after pyloromyotomy was no greater than in controls.

Since the introduction of sensitive methods for measuring gastrin (McGuigan, 1968; Yalow and Berson, 1970), this hormone has been studied in normal children (Sann *et al.*, 1975; Niessen *et al.*, 1976) and it is suggested that serum levels vary with age. The mechanisms responsible for the secretion of gastrin are present at birth. Serum gastrin level is higher in the blood of neonates than in peripheral maternal blood (von Berger *et al.*, 1976; Euler *et al.*, 1977), and rises after the first feed, continuing to rise steeply for a few days after birth (Rogers *et al.*, 1974). The hypothesis that increased gastrin secretion may induce hypertrophic pyloric stenosis in infancy receives support from experimental studies. Pyloric stenosis has been observed in newborn pups after repeated injections of pentagastrin to pregnant bitches during the final stages of gestation, and the most pronounced changes were seen in 30-day-old pups that continued to receive pentagastrin after birth (Dodge, 1970; Karim *et al.*, 1974; Dodge and

Karim, 1976). Moreover a direct action of gastrin on the pyloric circular muscle has been demonstrated (Rogers *et al.*, 1976), in addition to an increase of antral mobility induced by the hormone *in vitro* (Bennett, 1965) and *in vivo* (Heinische, 1967; Isenberg and Grossman, 1969). Gastrin released by vagal reflexes may act in newborn babies as a mediator of perinatal environmental stress factors (Dodge, 1975) to produce pyloric contraction or spasm, or both, and pyloric hypertrophy; alternatively the pyloric hold-up could be increased by a self-perpetuating mechanism: antral distension with milk and gastrin release (Dodge, 1972; Rogers *et al.*, 1975).

The presence of hypergastrinaemia in hypertrophic pyloric stenosis has been denied by some investigators (Rogers *et al.*, 1975) and supported by others (Spitz and Zail, 1976). The aim of this study was to determine fasting serum gastrin levels in infants with hypertrophic pyloric stenosis before and after pyloromyotomy. In addition, the serum gastrin response to oral feeding was determined so as to find out whether the response is exaggerated in infants with hypertrophic pyloric stenosis.

A rise in serum gastrin after feeding different milks to normal newborn babies and infants has been shown (Sann *et al.*, 1975; von Berger *et al.*, 1976). It was found that high or pure protein preparations are capable of producing a gastrin release with a

Department of Paediatric Surgery, Hôpital des Enfants Malades, Paris

MICHEL A. HAMBOURG, consultant paediatrician

D. PELLERIN, professor, chief service

Gastroenterology Research Unit, Hôpital Bichat, Paris

M. MIGNON, associate professor

J. ACCARY, research assistant

Paediatric Gastroenterology Unit, Hôpital des Enfants Malades, Paris

C. RICOUR, associate professor

substantial rise in serum gastrin (Konturek *et al.*, 1974). Hydrolysed proteins, and especially free amino-acids, are potent gastrin stimulants (Elwin, 1974; Walsh *et al.*, 1975). There have been no systematic surveys of amino-acids to determine which one releases gastrin. In man, glycine alone has been tested and shown to be a weak stimulant (McGuigan and Trudeau, 1970). The most active releasers of gastrin (serine, valine, and tryptophan) are amino-acids that are rather poor stimulators of acid secretion (Konturek *et al.*, 1977).

Material

After informed parental consent had been obtained the following groups of patients and controls were studied.

Patients. 10 (9 boys and one girl, age range 3 weeks–4 months) infants with hypertrophic pyloric stenosis without radiologically demonstrable gastro-oesophageal reflux.

Controls. 11 (6 boys and 5 girls, age range 3 weeks–4 months) infants with no gastrointestinal or neurological disease.

Development in both groups of babies was normal. All infants were between 3rd and 97th centiles for length as there is evidence relating gastrin levels to body size.

Methods

All blood samples were drawn via an indwelling catheter already in place or by direct venepuncture at the time an indwelling catheter was placed as part of the patient's treatment. 2.5 ml blood was collected in an unheparinised test-tube, with the separated serum stored at -20°C . Serum gastrin was measured by radioimmunoassay (Yalow and Berson, 1970). The specific antisera used were raised by immunisation with repeated injections of synthetic human gastrin 1 (G1 S(1–17)) conjugated to ov-albumin in rabbits. The G1 S1–17 was labelled with iodine-125 (Inserm U 10, Paris) and standard gastrin was obtained from Imperial Chemical Industries Ltd. Separation of bound antibody from free hormone was by dextran-coated charcoal.

Gastrin secretion test. This was performed by administering casein hydrolysate (Amirige, Nutricia, Netherlands) containing 85.5% nitrogenous substances of which 87.5% are polypeptides (di-, tetra-, and hexapeptides) and 12.5% are free amino-acids. The composition per 100 g Amirige was: polypeptides 74.86; free amino-acids 10.84. Essential amino-

acids: leucine 1.67; lysine 1.51, methionine 1.33, phenylalanine 1.33, isoleucine 0.15, histidine 0.07, threonine 0.07. Non-essential amino-acids: arginine 1.85, tyrosine 1.71, aspartic acid 0.50, glutamic acid 0.45, serine 0.17.

The compound was prepared in such a way as to contain identical protein concentrations for each infant in the same amounts that he would have received with normal feeding (150 ml of half-cream cows' milk/kg per day containing 132 ml H_2O , 4.20 g protein, and with a caloric value of 103, and given in 6 feeds of 25 ml/kg). The amount of the preparation given at each feed was thus 0.70 g peptides/kg (1 g Amirige = 0.855 g peptides). A 15-min gastric drip feed was used to administer these amounts to each infant after a 6-hour fast. The results in the two groups were recorded and plotted on a curve showing changes in serum gastrin levels at -15 , 0, 5, 10, 15, 30, and 60 min from the beginning of the feed. In the patients, gastrin stimulation was carried out on the 7th postoperative day when normal oral nutrition had been resumed. Fasting serum gastrin levels were also determined in these patients before pyloromyotomy and 2 weeks later. The preoperative samples for fasting serum gastrin determination were obtained at least 4 hours after the last feed and the postoperative samples, as in the control group, after a 6-hour fast. Statistical comparison of groups was by Student's *t* test.

Results

Fasting serum gastrin levels. In the control group the mean fasting serum gastrin level ($\pm$ SEM) was 134.2 ± 18.2 pg/ml. The mean fasting level in the patients before pyloromyotomy did not differ from those in the control group, but these levels did differ ($P < 0.025$) after operation. In the patients the mean fasting levels before operation and on the 7th and 15th postoperative days were, respectively, 129.5 ± 23.2 , 222.2 ± 39.6 , and 197.5 ± 21.7 pg/ml. The differences between the preoperative values and those on the 7th and 15th postoperative days were significant ($P < 0.05$ and $P < 0.025$ respectively) (Table 1).

Serum gastrin response to feeding. In the control group a substantial rise was noted within the first minutes after the feed with a maximum peak at 10 min, immediately followed by a decline, which was steep to 15 min, becoming more gradual thereafter to 30 min. Basal gastrin levels were regained after 60 min (Fig. 1). The mean basal and peak serum gastrin levels ($\pm$ SEM) were respectively 134.2 ± 18.2 and 247.5 ± 26.4 pg/ml;

Fig. 1 Mean serum gastrin levels (pg/ml $\pm$ SEM) in 11 control infants and 10 patients with hypertrophic pyloric stenosis after a casein hydrolysate meal. The results are expressed as the mean of all values obtained at each time, less the mean basal serum gastrin levels (BSG) (this explains initial negative values).

Table 1 Fasting serum gastrin levels (pg/ml) in 10 patients with hypertrophic pyloric stenosis before and after pyloromyotomy

Case	Before operation	After operation	
		7 days	15 days
1	260	290	260
2	155	135	295
3	125	113	140
4	215	175	250
5	47	365	135
6	61	415	230
7	190	375	265
8	52	140	160
9	98	89	120
10	92	125	120
Mean $\pm$ SEM	129.5 $\pm$ 23.2	222.2 $\pm$ 39.6	197.5 $\pm$ 21.7

these values differed significantly ($P < 0.02$) (Fig. 2).

In the patients the serum gastrin response to stimulation was represented by a curve with a levelling-off effect between 30 and 60 min, and a more slowly decreasing slope to baseline value beyond 90 min (Fig. 1). The mean basal and peak serum gastrin levels were 222.2 ± 39.6 and 359.5 ± 56.5 pg/ml, and differed significantly ($P < 0.02$) (Fig. 2).

The peak levels obtained after maximum gastrin stimulation were higher in the patients than in the controls ($P < 0.05$), but when the increased values were compared as the percentage of basal gastrin levels ((PSG - BSG)/BSG) there was no significant difference ($P < 0.1$) (Table 2). Analysis of the decreasing slope by comparing the mean gastrin

Fig. 2 Mean basal serum gastrin (BSG) levels and peak serum gastrin (PSG) levels (pg/ml $\pm$ SEM) in 11 control infants and 10 patients with hypertrophic pyloric stenosis after a casein hydrolysate meal. The serum gastrin response to the meal is shown by comparing BSG (for each infant, mean value of 2 fasting levels at -15 and 0 minutes) and PSG (for each infant, mean value of the 2 highest levels obtained).

Table 2 Mean peak serum gastrin levels (pg/ml $\pm$ SEM) in response to a casein hydrolysate meal in 11 control infants and in 10 patients with hypertrophic pyloric stenosis 7 days after pyloromyotomy. Significance of PSG and of percentage of basal gastrin levels

Value	Control infants (n = 11)	Patients (n = 10)
PSG	247.5 $\pm$ 26.4*	359.5 $\pm$ 56.5
(PSG-BSG)/BSG	1.56 $\pm$ 0.42†	0.78 $\pm$ 0.20

PSG = peak serum gastrin level, BSG = basal serum gastrin level.

*Significant ($P < 0.05$) DF 19, †not significant ($P < 0.10$) DF 19.

levels at 30 and 60 min in both groups showed that there was no difference despite the levelling-off effect seen in the patients (at 30 min, $P < 0.25$; at 60 min, $P < 0.15$) (Fig. 1).

In patients, increased fasting gastrin levels were present after pyloromyotomy and were still present 2 weeks after the operation. Test meals did not produce an exaggerated gastrin response and the results were of the same order as those obtained by the same trial stimulation in controls.

Discussion

These findings cast doubt on the hypothesis that increased gastrin levels may promote and/or maintain hypertrophic pyloric stenosis of infancy. This doubt is reinforced by the fact that little difference in serum gastrin levels between the healthy and the affected children was found in the preoperative phase.

Nevertheless higher levels were found in the post-operative period. A marked rise in mean fasting levels was also noted 4 and 5 days after operation by Rogers *et al.* (1975) and Spitz and Zail (1976). Such a hypergastrinaemia does not appear to be induced solely by antral distension secondary to pyloric obstruction, as it was still present in our patients 7 to 15 days after pyloromyotomy. This interpretation can be questioned because, although pyloromyotomy relieves clinical obstruction and motility returns within 30 hours (Schärli and Leditschke, 1968), radiological evidence of improvement of the pylorus does not appear until after some weeks or months (Bishop and Hope, 1962). The possibility that distension of the antrum can persist during the postoperative period is therefore not eliminated.

The postoperative hypergastrinaemia could be explained by an inverse relationship between the serum gastrin levels and HCl secretion. Dodge (1976) found that in preoperative children with pyloric stenosis, acid secretion was raised, probably by increased parietal cell mass. This increased acid secretion may decrease basal gastrin secretion by

lowering the intraluminal pH. After operation, basal gastric acid secretion falls and it seems that gastrin secretion increases. In our series the fasting gastrin levels showed a significant increase after operation in only 5 out of 10 patients, 3 of whom had the lowest preoperative levels (Cases 5, 6, and 8) (Table 1). Perhaps these low levels indicate that their acid secretion was increased to the point where gastrin release was being inhibited. The reduced gastric acidity found after 7 days would allow these patients to revert to a fasting serum gastrin level more in keeping with their true gastrin secretion level. In any event, these 5 patients responded normally to feeding when tested postoperatively. For obvious reasons the gastrin secretory capacity was not tested in preoperative patients.

Long-term follow-up of patients with pyloric stenosis by Wanscher and Jensen (1971) showed an increased incidence of ulcer symptoms, and many had an increased basal gastric acidity. This might indicate that the hypergastrinaemia persists indefinitely and raises another question, whether hypergastrinaemia is the only long-term result of hypertrophic pyloric stenosis.

Although it was confirmed that gastrin levels after feeding were greater in the patients than in the controls, we would emphasise that the differences are insignificant when they are related to the basal gastrin levels. Thus, our findings do not support the hypothesis that patients with pyloric stenosis may have an exaggerated gastrin response to feeding after pyloromyotomy.

Addendum

Since this paper was written, Janik *et al.* (1977) have confirmed that the wide range of serum gastrin levels in normal infants and children is dependent on age, body surface area, and duration of fast. Rogers *et al.* (1978) failed to demonstrate a significant rise in serum gastrin levels after normal newborn infants ingest protein-containing milk. Werlin *et al.* (1978) measured serum gastrin levels in cord blood of infants in whom pyloric stenosis subsequently developed and in controls, and found little difference.

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Correspondence to Dr M. A. Hambourg, Clinique Chirurgicale Infantile, Hôpital des Enfants Malades, 149 rue de Sèvres, 75015 Paris, France.

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