J Clin Pathol 1990;43:762–765

Serum pepsinogen I and gastrin concentrations in children positive for Helicobacter pylori

G Oderda, D Vaira, D Dell'Olio, J Holton, M Forni, F Altare, N Ansaldi

Abstract

Serum pepsinogen I, serum gastrin concentration, and inflammatory scores were measured in a population of 71 children undergoing upper gastrointestinal endoscopy for investigation of upper abdominal pain. Forty four were initially colonised with *Helicobacter pylori*. The indices were measured before treatment (in 71 children), one month (in 41 children), and six months (in 21 children) after stopping treatment. Before treatment there was a significant correlation between serum pepsinogen concentration, total inflammatory score, and *H pylori* state, but no correlation between serum gastrin concentrations and *H pylori* state. Similarly, the total inflammatory score and serum pepsinogen concentrations were significantly correlated. There was no such correlation in children negative for *H pylori*. After treatment the inflammatory score improved in those patients in whom *H pylori* had been eradicated. There was also a significant fall in serum pepsinogen I and serum gastrin concentration in those patients in whom *H pylori* had been eradicated. These results were similar to those found six months after treatment had been stopped.

These findings suggest that the serum pepsinogen I concentration could be considered a useful marker for gastritis and can be used as an index of severity of gastritis in *H pylori* positive subjects. The measurement of serum gastrin concentrations does not give useful information.

Department of Gastroenterology, The Middlesex Hospital, London
D Vaira

Department of Microbiology, The Middlesex Hospital, London
J Holton

Department of Paediatric Gastroenterology, University of Turin, Italy
G Oderda
N Ansaldi
D Dell'Olio

Department of Histopathology, Regina Margherita Children's Hospital, Turin
M Forni

Department of Chemical Analysis, Regina Margherita Children's Hospital, Turin
F Altare

Correspondence to:
G Oderda, Gastroenterology Section, Department of Paediatrics, University of Turin, Piazza Polinia 94, 10126 Torino, Italy

Accepted for publication 30 April 1990

In adults a strong association is now recognised between the presence of *Helicobacter pylori* in gastric mucosa and histologically confirmed gastritis.[1] *H pylori* has also been specifically associated with primary antral gastritis in children, and as in adults the organism is present only in the gastric mucosa with concomitant gastric inflammation.[2,3] Raised serum pepsinogen I concentrations are found in about two thirds of adults with peptic ulcer disease,[4] and are thought to be a useful subclinical marker of genetic predisposition to ulceration. Serum pepsinogen I concentrations and a high titre of antibody to *H pylori* have been found to be raised in children with *H pylori* associated gastritis.[2] Moreover, it has been shown that the concentrations of serum pepsinogen I, gastrin, and IgG antibody to *H pylori* significantly decreased after a six week course of amoxycillin and tinidazole.[5]

The concentration of serum pepsinogen I in adults has been reported to be correlated with the histological gastritis associated with the presence of *H pylori* and to correlate with the degree of inflammation.[6] A significantly raised 24 hour plasma gastrin concentration, which was inappropriate for the gastric acidity, was reported in asymptomatic subjects infected with *H pylori*.[7]

We report the findings of a prospective study in which we used Giemsa staining, culture, and urease testing of antral biopsy specimens obtained from children undergoing upper gastrointestinal endoscopy for investigation of upper abdominal pain. We also report the concentrations of serum pepsinogen I and gastrin compared with the degree of severity of antral inflammatory cells in children positive or negative for *H pylori* associated gastritis before and after antimicrobial treatment.

Methods

Over two years, antral biopsy specimens were obtained from 71 children (46 male) undergoing upper gastrointestinal endoscopy for investigation of upper abdominal pain. The mean age was 10 years (range 1–18 years). None of the children had received any medication which might have affected gastric acidity before endoscopy. Fully informed parental consent was obtained before all endoscopies and biopsies were carried out.

Oesophagogastroduodenoscopy was performed using an Olympus GIF P3 or XP20 gastroscope after oral diazepam had been given. The endoscope and biopsy forceps were disinfected in 2% glutaraldehyde after each use.

Specimens were immediately fixed in 10% buffered formalin and stained with haematoxylin and eosin to determine the presence of gastritis, as described by Whithead *et al*.[8] A diffuse chronic inflammatory infiltrate of the lamina propria was regarded as a "quiescent" chronic superficial gastritis; when polymorphonuclear cells were present in the lamina propria or within the superficial or glandular epithelium, gastritis was considered to be "active". To grade the degree of severity of antral inflammatory cells, Marshall's criteria were adopted.[9] We also quantified the numbers of mononuclear and polymorphonuclear cells infiltrating surface and glandular epithelium as follows:

Mononuclear cells:
(0) No intraepithelial lymphocytes (IELs);
(1) few IELs (less than 10 per high power field) seen in some fields;
(2) less than 10 IELs per high power field seen in every field;
(3) more than 10 IELs per high power field seen in every field.

Polymorphonuclear cells:
(0) No polymorphonuclear cells invading gland necks or surface epithelium;
(1) less than five invading polymorphonuclear cells per high power field seen in some fields;
(2) less than five invading polymorphonuclear cells per high power field in every field;
(3) more than six invading polymorphonuclear cells seen in every field.

Inflammatory cells were counted by two observers (DDO and MF) who were unaware of the patient data, using the same microscope at an enlargement of 400 times on at least 10 fields on four to six haematoxylin and eosin stained sections 5 μm thick. The area covered by a high power field is 0·159 m^2. Only antral biopsy specimens containing muscularis mucosa were considered.

H pylori had to be seen on microscopical examination (Giemsa) for a diagnosis of *H pylori* associated gastritis to be made.[2 10]

Gastric antral biopsy specimens were examined by culture and by urease testing and serum pepsinogen I concentrations were measured.[2] Serum gastrin concentrations were measured by the method of Ansaldi *et al.*[11]

Endoscopy and a fasting blood test were performed before a six week course of oral amoxycillin (50 mg/kg/day) and tinidazole (20 mg/kg/day). Four weeks after stopping treatment endoscopy and fasting blood test were repeated in 41 children. Twenty one children were reinvestigated six months after stopping treatment.

Paired and unpaired parametric data were analysed by the appropriate *t* test, non-parametric data by the Wilcoxon matched pairs signed rank test and Mann-Whitney U test, and correlation between inflammation scores and serum pepsinogen I concentrations, gastrin concentrations and age by Spearman's rank test.

Results

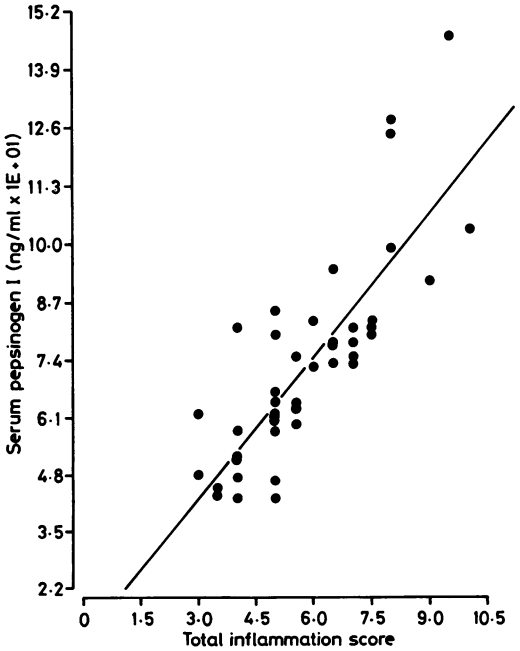
Before treatment the macroscopic endoscopic diagnoses were normal (n = 24), antral gastritis (n = 31), oesophagitis (n = 3), duodenal ulcer (n = 6), gastric ulcer (n = 7). In 44 children histological gastritis was associated with the presence of *H pylori*. Culture was positive in 40 (90%) and urease testing was positive in 34 (77%). There were no false positive culture or urease tests in patients negative for *H pylori* on microscopical examination. The remaining 27 children, although having histological gastritis, were negative for the presence of *H pylori* on Giemsa staining, culture, or urease testing. *H pylori* positive children (n = 44) had significantly higher serum pepsinogen I concentrations than *H pylori* negative patients (n = 27) (72·5 (SD 22·7) ng/ml and 48·4 (8) ng/ml, respectively; p < 0·005). Moreover, *H pylori* positive children did not have a significantly higher serum gastrin concentration than those who were negative (40·7 (12·4) mU/ml and 35·2 (11·9) mU/ml, respectively; p = NS).

Table 1 Inflammation scores in 71 children with H pylori positive or negative gastritis

Inflammation scores	*H pylori positive* (n = 44) Median (range)		*H pylori negative* (n = 27) Median (range)
Total	5·5 (3–10)	*	2·5 (1–3)
Lamina propria	3·5 (2–6)	*	1·5 (1·5–3)
Surface and glandular epithelium	2 (1·5–5)	*	1·1 (0–2)
Mononuclear cells	3 (1–5)	*	2 (1–2·5)
Polymorphonuclear cells	1·5 (0–4)	*	0·5 (0–2)

*p < 0·001.

Table 1 shows the scores of antral inflammation in *H pylori* positive children compared with those who were negative (p < 0·001, respectively). In those *H pylori* positive (n = 44) there was a significant correlation between serum pepsinogen I concentrations and the total inflammation score (r = 0·821; p < 0·001) (figure). The main factor influencing the total score was the lamina propria inflammation score with which serum pepsinogen I concentration was highly correlated (r = 0·751, p < 0·001). Correlation between the other inflammation scores and pepsinogen I concentration were r = 0·542, p < 0·001 for polymorphonuclear cells; r = 0·511 for surface and glandular epithelium score; and r = 0·436, p < 0·001 for mononuclear cells. Total inflammation score was also significantly correlated with age (r = 0·417, p < 0·05). In children negative for *H pylori* (n = 27) the inflammation score was neither correlated with serum pepsinogen I concentration nor with age. Serum gastrin concentrations did



Serum pepsinogen I (PG I) concentrations in 44 children with H pylori positive gastritis in relation to total inflammation score of antral mucosa.

Table 2 Total and lamina propria inflammation scores in H pylori positive children one and six months after stopping treatment

	H pylori positive		*H pylori negative*
	Median (range)		*Median (range)*
One month after treatment	*(n = 5)*		*(n = 36)*
Total	5 (3–6·5)	*	2·5 (0–4·5)
Lamina propria	3·5 (2·5–4)	*	1·7 (0–3)
Six months after treatment	*(n = 7)*		*(n = 14)*
Total	4·4 (3–6)	**	2·5 (0·5–4·5)
Lamina propria	3·1 (2–4)	**	2 (0·5–3)

*p < 0·05.
**p < 0·001.

not correlate with any inflammation score in children positive for *H pylori* nor in those who were negative. Neither serum pepsinogen I nor serum gastrin concentrations correlated with age in children either positive or negative for *H pylori*.

Four weeks after stopping treatment five out of 41 (12%) children had evidence of *H pylori* on microscopical examination of biopsy specimens. Two out of these five had an active antral gastritis but in one inflammation was quiescent. In the 36 children cleared of *H pylori* there was persisting but improved antral gastritis in 29 and normal histological appearances in seven. One month after stopping treatment serum pepsinogen I concentration was significantly decreased in children negative for *H pylori* (49·5 (10·7) ng/ml) compared with 70·6 (26·5) ng/ml ($p < 0·01$) in those who were still positive. Table 2 shows the total median and the lamina propria inflammation scores in treated children negative for *H pylori* compared with treated children positive for *H pylori* ($p < 0·05$). The serum pepsinogen I concentration no longer correlated with the inflammation scores in treated *H pylori* positive children. One month after stopping treatment serum gastrin concentrations were significantly decreased in children cleared of *H pylori* (32 (5) mU/ml) ($p < 0·01$); it was unchanged in children in whom *H pylori* persisted. The serum gastrin concentrations were not correlated with the inflammation score on either positive or negative treated children.

Six months after stopping treatment seven out of 21 (33%) had relapsed with *H pylori* positive gastritis. All seven children had superficial antral gastritis; in four inflammation was unchanged, but in the other three inflammation was less severe. Six months after stopping treatment the serum pepsinogen I and gastrin concentrations were similar to those at one month. Table 2 shows the total median and the lamina propria inflammation scores after six months in children in whom *H pylori* had recurred or in whom it had been eradicated ($p < 0·001$).

Discussion

It has been shown that endoscopy could be completely unhelpful in adults with dyspepsia if endoscopic biopsy specimens are not taken routinely.[12] In our series we confirmed these data in a population of children. Indeed, one third of our children with histological gastritis showed macroscopically normal endoscopic findings.

Serum pepsinogen I concentration has been reported to be predictive of the histological state of the gastric mucosa by Samloff *et al.*[13] In their study 66 patients had superficial gastritis of the gastric body and in 63 of them the inflammation was also found in the antrum. In the Samloff study the concentration of serum pepsinogen I was significantly higher in the population with gastritis. Unfortunately, we do not know about the *H pylori* state in that study.

In our study we did not find any correlation between serum pepsinogen I concentrations and increasing age. Previous epidemiological studies have reported an increase of serum pepsinogen I with age.[14] This discrepancy could have been due to a higher prevalence of *H pylori* infection at older ages[15] or to the increasing severity of antral gastritis. The total inflammation score was indeed significantly correlated with age in our *H pylori* positive children. *H pylori* positive children have a higher prevalence of active gastritis ($p < 0·01$) and significantly higher numbers of polymorphonuclear cells than *H pylori* negative children. The concentrations of serum pepsinogen I correlated with the inflammation score. Thus we suggest that serum pepsinogen I could be used in *H pylori* positive children as a marker of the severity of the histological gastritis.

One month after stopping treatment the inflammation scores decreased by 55% and the serum pepsinogen I concentration by 32%. Six months after stopping treatment the serum pepsinogen I concentration decreased by an additional 12%; the inflammation scores remain unchanged.

Six months after the treatment was stopped a mild inflammatory infiltrate was still present in 78% of patients in whom *H pylori* had been eradicated: it was mild and always comprised mononuclear cells, not correlated with serum pesinogen I concentrations. Similar data have been reported in adults: after eradication of *H pylori* has been achieved a mild mononuclear cell infiltration may persist, while a polymorphonuclear infiltrate is always absent.[9]

Basal serum gastrin concentrations significantly decreased after eradication of *H pylori* but no difference was found between *H pylori* positive and negative children, and no correlation was found with the severity of the inflammation in the gastric mucosa. No association between the presence of *H pylori* and the level of serum gastrin concentration has been found in adults when basal gastrin concentrations were assessed[4 16]; but when gastrin concentration after food was studied in patients with duodenal ulcers, higher gastrin concentrations in *H pylori* positive patients were found.[17] These data suggest that *H pylori* in the gastric antrum may affect gastrin release, but from our data it seemed that the inflammatory infiltrate in the antral mucosa is not affected by gastrin release.

In summary, we suggest that the serum pepsinogen I concentration could be regarded as a marker of gastritis and could be used as an index of severity of gastritis in *H pylori* positive

subjects. Serum gastrin concentrations do not give crucial information about the gastric mucosa.

1 Vaira D, Holton J, Ainley C, Salmon P. Campylobacter pylori and gastritis. *Current Opinion in Gastroenterology* 1989;5:817–23.
2 Oderda G, Vaira D, Holton J, *et al*. Serum pepsinogen I and IgG antibody to Campylobacter pylori in non-specific abdominal pain in childhood. *Gut* 1989;**30**:912–6.
3 Samloff IM, Liebmann WM, Pahitch NM. Serum group I pepsinogens by radioimmunoassay in control subjects and patients with peptic ulcer. *Gastroenterology* 1975;**69**: 83–90.
4 Brady CE, Hadfield TL, Hyatt JR, Utts SJ. Acid secretion and serum gastrin levels in individuals with Campylobacter pylori. *Gastroenterology* 1988;**94**:923–7.
5 Oderda G, Vaira D, Holton J, *et al*. Amoxycillin plus tinidazole for Campylobacter pylori gastritis in children: assessment by serum IgG antibody, pepsinogen I, and gastrin levels. *Lancet* 1989;i:690–2.
6 Schoetensack C, Malfertheiner P, Stanescu A, *et al*. Gastrin and pepsinogen I serum concentration in Campylobacter pylori positive chronic gastritis. In: Megraud F, Lamuliatte H, eds. *Gastroduodenal pathology and Campylobacter pylori*. London: Elsevier, 1989:565–70.
7 Smith GTL, Pounder RE, Nwokolo CV, *et al*. Inappropriate hypergastrinaemia in asymptomatic healthy subjects infected with Helicobacter pylori. *Gut* 1989;**31**:552–5.
8 Whitehead R. Mucosal biopsy of the gastrointestinal tract. In: Bennington JL, ed. *Major problems in pathology. Vol 3*. Philadelphia: WB Saunders & Co, 1985:47–58.
9 Marshall BJ, Armstrong JA, Francis GJ, *et al*. Antibacterial action of bismuth in relation to Campylobacter pyloridis colonization and gastritis. *Digestion* 1987;**37**:16–30.
10 Rathbone BJ, Wyatt J, Heatley RV. Symptomatology in C pylori-positive and -negative non-ulcer dyspepsia. *Gut* 1988;**29**:A1473.
11 Ansaldi N, Santini B, Barbera C, *et al*. Fasting serum gastrin levels and gastric acid output in children. *It J Ped* 1978;**4**:329–35.
12 Vaira D, Holton J, Osborn J, *et al*. Use of endoscopy in patients with dyspepsia. *Br Med J* 1989;**299**:237.
13 Samloff IM, Varis K, Ihamaki T, *et al*. Relationship among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology. *Gastroenterology* 1982;**83**:204–9.
14 Waldum HL, Straume BK, Burhol PG, Bedrup Dahl L. Serum group I pepsinogens in children. *Acta Paediatr Scand* 1980;**69**:215–8.
15 Berkowicz J, Lee A. Person to person transmission of Campylobacter pylori. *Lancet* 1987;ii:680–1.
16 Karttunen T, Niemela S, Lehtola J, *et al*. Campylobacter-like organism and gastritis: histopathology, bile reflux, and gastric fluid composition. *Scand J Gastroenterol* 1987;**22**:478–86.
17 Levi S, Beardshall K, Haddad G, *et al*. Campylobacter pylori and duodenal ulcers: the gastrin link. *Lancet* 1989;i:1167–8.

Serum pepsinogen I and gastrin concentrations in children positive for Helicobacter pylori.

G Oderda, D Vaira, D Dell'Olio, J Holton, M Forni, F Altare and N Ansaldi

*J Clin Pathol*1990 43: 762-765
doi: 10.1136/jcp.43.9.762

Notes