Aliment. Pharmacol. Ther. (1992) **6**, 389–394.

Short report: twenty-four-hour hyperpepsinogenaemia in Helicobacter pylori-*positive subjects is abolished by eradication of the infection*

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Accepted for publication 16 January 1992

SUMMARY

Twenty-four-hour plasma pepsinogen I and II concentrations were determined in 8 healthy subjects with antibody to *Helicobacter pylori*, before and after treatment with tripotassium dicitrato bismuthate, amoxycillin and metronidazole, Therapy was successful in the 5 subjects with active *H. pylori* infection. In these subjects, median integrated 24-h plasma pepsinogen I and II concentrations significantly decreased from 2288 and 357 μg.h/L before treatment, respectively, to 1811 and 171 μg.h/L at 4–6 weeks after treatment, and 1643 and 150 μg.h/L at 20–24 weeks. By contrast, in the 3 subjects without evidence of active *H. pylori* infection, pre-treatment plasma pepsinogen I and II concentrations were similar to values found in the *H. pylori*-infected subjects after successful therapy, and they did not change significantly in response to therapy. *H. pylori* infection is associated with reversible hyperpepsinogenaemia.

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INTRODUCTION

Duodenal ulcer patients usually show increased serum concentrations of pepsinogen I (PG I)[1,2] and it has been suggested that hyperpepsinogenaemia may be a sub-clinical marker of the genetic predisposition to duodenal ulcers.[1] We have demonstrated that asymptomatic healthy volunteers with *H. pylori* infection have an elevated integrated 24-h plasma gastrin concentration but normal integrated 24-h intragastric acidity,[3] and that normal gastrin concentrations are restored after eradication of *H. pylori*.[4] Fasting pepsinogen I and II has been reported to be elevated in *H. pylori* infection,[5,6] therefore, we analysed plasma samples from our previous study,[4] with respect to the effect of eradication of *H. pylori* infection on 24-h plasma PG I and PG II concentration.

SUBJECTS AND METHODS

The selection of subjects, the experimental protocol and results obtained using the Royal Free Hospital protocol for simultaneous measurement of 24-h intragastric acidity and plasma gastrin concentration have been described previously.[4] Briefly, 8 healthy subjects, 7 males and 1 female ranging in age between 21 and 25 years, were selected based on positive serology for *H. pylori*.[7] They were studied on 3 occasions: before treatment, and at 4–6 weeks and 20–24 weeks after treatment. The treatment regimen was tripotassium dicitrato bismuthate (De-Noltab, Gist-Brocades, Weybridge, UK) 1 tablet q.d.s. for 6 weeks, with amoxycillin 250 mg t.d.s. and metronidazole 400 mg t.d.s. during the first week. For this study, samples of frozen plasma, which had been obtained hourly between 08.00 and 24.00 hours and 2-hourly between 24.00 and 08.00 hours, were coded and shipped in dry-ice to Los Angeles where they were analysed for PG I and PG II by radioimmunoasssay.[8] In all subjects, antral biopsies were obtained at endoscopy before and 20–24 weeks after treatment. A [^{13}C]urea breath test was performed before treatment, and at 4–6 weeks and 20–24 weeks after treatment. Integrated 24-h plasma PG I and PG II concentrations were calculated by the trapezoidal rule and expressed as μg.h/L. The statistical significance of observed differences was determined by the Wilcoxon matched pairs signed rank test.

RESULTS

Five subjects had active *H. pylori* infection, whereas 3 subjects were negative for rapid urease test, histology and [^{13}C]urea breath test. The latter, having received a full course of treatment to eradicate presumed infection, were continued in the study as negative controls. Therapy was successful in the 5 subjects with active *H. pylori* infection.

H. pylori *infected subjects*

In each *H. pylori*-infected subject, the 24-h integrated plasma PG I concentration fell in response to eradication (Figure 1). Reductions ranged between 12.2 and 57.9% at 4–6 weeks and between 19.2 and 55.4% at 20–24 weeks. Median 24-h integrated plasma PG I concentrations were 2288 μg.h/L before treatment, 1811 μg.h/L at 4–6 weeks after treatment, and 1643 μg.h/L at 20–24 weeks after treatment. Each post-treatment median value was significantly less ($P < 0.05$) than the pre-treatment value; the difference between the 4–6 week and 20–24 week values was not statistically significant.

Twenty-four-hour integrated PG II concentrations also fell in response to treatment (Figure 1). For this zymogen, individual reductions ranged between 24.4 and 74.6% at 4–6 weeks and between 29.5 and 68.8% at 20–24 weeks. Median 24-h integrated plasma PG II concentrations were 357 μg.h/L before treatment, 171 μg.h/L at 4–6 weeks after treatment, and 150 μg.h/L at 20–24 weeks after treatment. Each post-treatment median value was significantly less ($P < 0.05$) than the pre-treatment value; the difference between the 4–6 weeks and 20–24 weeks concentrations was not statistically significant.

Antral chronic active gastritis, which was moderate to severe before treatment,

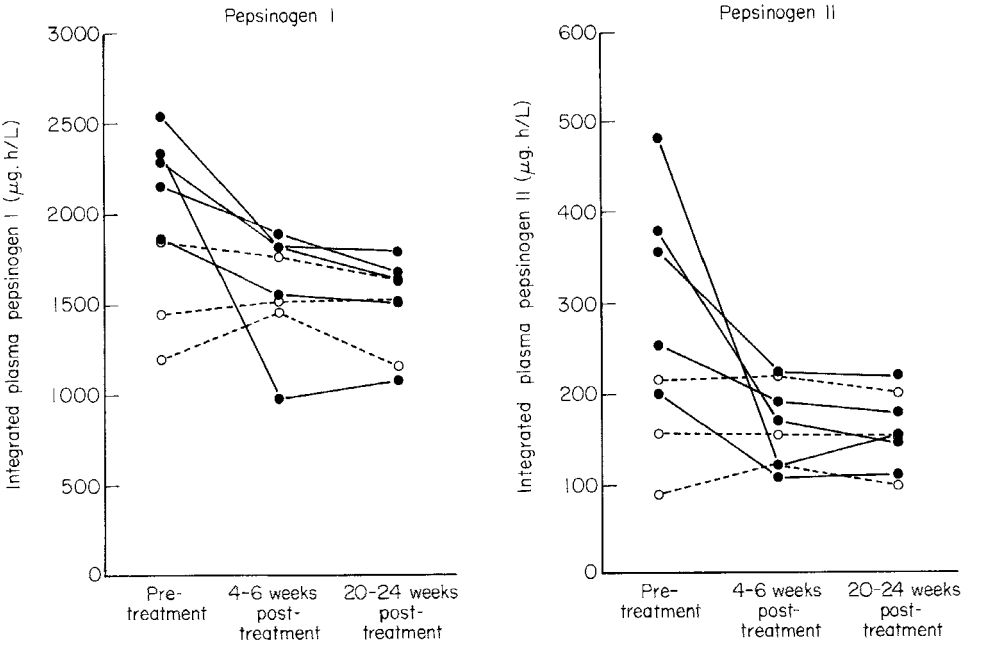

Figure 1. Integrated 24-h plasma pepsinogen I (left) and pepsinogen II (right) concentrations for the 5 *H. pylori*-positive subjects (——) and the 3 *H. pylori*-negative subjects (– – –) before and after treatment to eradicate *H. pylori*. Compared with pre-treatment, in the *H. pylori*-positive subjects there were significant decreases in median plasma pepsinogen I and II concentration 4–6 weeks and 20–24 weeks after treatment ($P < 0.05$ for both zymogens at both time intervals).

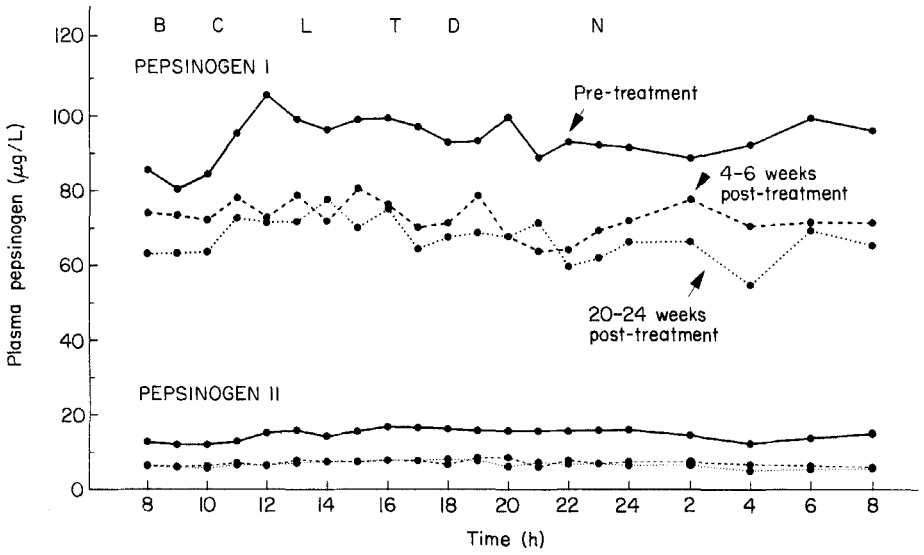

Figure 2. Median 24-h plasma pepsinogen I and II profiles before treatment to eradicate *H. pylori*, and 4–6 weeks and 20–24 weeks post-treatment, in 5 *H. pylori*-positive subjects. B, Breakfast; C, coffee; L, lunch; T, tea; D, dinner; N, nightcap.

was resolved by the time of follow-up biopsy 20–24 weeks post-treatment. The 24-h profiles of median plasma PG I and PG II concentration in the 5 *H. pylori*-infected subjects before treatment, and at 4–6 weeks and 20–24 weeks after treatment, are shown in Figure 2.

Subjects without H. pylori *infection*

In the 3 subjects without active *H. pylori* infection, median 24-h integrated concentrations of PG I and PG II before treatment, 1450 and 157 μg.h/L, respectively, were similar to the concentrations found in the *H. pylori* infected subjects after eradication of their infection. In these non-infected subjects, treatment had no effect on integrated 24-h PG I and PG II concentrations. For the PG I, the median concentrations at 4–6 weeks and 20–24 weeks after therapy were 1517 and 1515 μg.h/L, respectively. The corresponding values for PG II were 155 and 152 μg.h/L. These subjects showed no evidence of chronic active gastritis on antral biopsy, either before or after treatment.

DISCUSSION

Twenty-four-hour profiles of plasma PG I and PG II concentration have not been reported previously. This study shows that there is little variation of hourly median PG I concentration throughout the 24-h period, although some individuals show a delayed meal-associated increase. Waldum *et al.* found that PG I concentrations showed a non-significant increase after a light meal.[9] The unchanged values for the

three *H. pylori*-negative subjects demonstrate that therapy with bismuth and 2 antibiotics had no direct effect on 24-h plasma pepsinogen concentration.

We have reported that integrated 24-h intragastric acidity in these 5 *H. pylori*-positive patients was unchanged by triple therapy, but eradication of *H. pylori* resulted in a halving of the median integrated 24-h plasma gastrin concentration.[9] Although plasma gastrin and plasma pepsinogen concentrations fell dramatically after eradication of *H. pylori* infection, there was no direct correlation between these two variables.

This study has demonstrated that healthy subjects with active *H. pylori* infection of the gastric mucosa have elevated levels of plasma PG I and PG II, and that successful eradication of the infection is accompanied by a prompt decrease in their concentrations with a proportionally greater fall of PG II than PG I. The latter change is consistent with the unique presence of PG II in antral mucosa and with the finding that therapy resulted in healing of the antral gastritis in each of the 5 *H. pylori*-infected subjects. Based on three earlier observations, these findings might have been anticipated: firstly, superficial gastritis is associated with increased levels of serum PG I and PG II and with a proportionally greater increase in PG II than PG I;[10] secondly that *H. pylori* infection is a major cause of superficial gastritis; finally that successful treatment of *H. pylori* infection results in rapid improvement of the gastritis.

There is an increased predisposition to duodenal ulcer disease in hyperpepsinogenaemic asymptomatic subjects.[1, 11] The observation in this study that elevated PG I concentrations are related to active *H. pylori* infection may explain these findings. *H. pylori* infection is now well established as an associated factor for most duodenal ulcer disease,[12] and *H. pylori*-positive patients have a much higher risk of relapse than *H. pylori*-negative patients.[13] *H. pylori*-induced inflammation in the gastric mucosa may allow PG I and PG II to back diffuse into circulation. An alternative explanation is that *H. pylori* lipopolysaccharide may induce pepsin secretion.[14] Oderda *et al.* reported that the observed elevation of serum PG I, gastrin and IgG antibody to *H. pylori* in children with *H. pylori*-associated gastritis decreased significantly after a 6-week course of amoxycillin and tinidazole.[15] The fasting PG I concentration decreased by 32%, similar to the 28% fall in integrated 24-h pepsinogen concentrations in our study. The same authors have shown a strong correlation between PG I concentration and the degree of antral gastritis in 44 *H. pylori*-infected children; no values for PG II were reported.[5] Wagner *et al.*[6] also found a fall in serum PG I and PG II concentration in response to successful treatment of *H. pylori*, but the magnitude of the decrease was similar for the two zymogens and only the fall in serum PG I was statistically significant.[6]

In conclusion, we have shown that in healthy subjects eradication of *H. pylori* infection results in a significant fall of 24-h integrated plasma PG I and PG II concentration, and in a fall of 24-h plasma gastrin concentration, without any change of intragastric acidity.

ACKNOWLEDGEMENTS

This study was supported by a grant from Glaxo Group Research Ltd. Technical assistance was provided by Nurse Judith Sercombe. Dr A. P. Dhillon and Dr E. A. Sankey performed the histological examination of gastric mucosal biopsies. The manuscript was prepared by Ms Doris Elliot.

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