Measurement of plasma group I pepsinogens

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Summary

Plasma group I pepsinogen (PG I) concentration is now a readily available non-invasive marker of gastric secretory function, with several potentially useful applications.

Ninety-eight percent of control subjects had a plasma PG I below 115 ng/ml while values above this level were seen in 43% of duodenal ulcer patients. Plasma PG I levels below the observed normal lower limit of 30 ng/ml were seen consistently in patients with documented achlorhydria or pernicious anaemia.

In 48 patients with a variety of upper gastrointestinal disorders there was a significant correlation between PG I pepsinogens and pentagastrin-stimulated maximal acid output.

Changes in plasma PG I promise to be useful in evaluating both operations on the vagus and newer anticholinergic drugs, whilst in epidemiological and family studies these measurements seem well suited to explore duodenal ulcer heterogeneity.

KEY WORDS: duodenal ulcer, gastric acid, pernicious anaemia.

Introduction

Agar gel electrophoresis of human gastric mucosal extracts yields proteolytic fractions, numbered 1-8 in decreasing order of electrophoretic mobility. The seven fastest fractions have characteristics of pepsinogens, with proteolytic activity resistant to alkalization but destroyed by sequential acidification and neutralization (Samloff, 1969).

Fractions 1-5 inclusive are designated group I pepsinogens (PG I) and originate solely from the chief and mucous neck cells of the gastric oxyntic mucosa (Samloff, 1971). Fractions 6 and 7 are the group II pepsinogens and are found also in pyloric and Brunner's glands (Samloff and Liebman, 1973).

Radioimmunoassay of PG I in serum was first described by Samloff and Liebman in 1974. Samloff was later able to show a correlation between serum PG I and histamine-stimulated peak acid output

(PAO) (Samloff, Secrist and Passaro, 1975b). High serum levels of PG I have been found in approximately 50% of patients with duodenal ulcer (DU) (Samloff, Liebman and Panitch, 1975a). In some families, a high serum PG I level is inherited as an autosomal dominant character (Rotter *et al.*, 1979).

Serum PG I levels are not affected by small test meals (Waldum, Straume and Burhol, 1979) and after more substantial meals a maximum rise of about 8% has been reported (Samloff *et al.*, 1975a). PG I are excreted in urine and high levels occur in patients with renal failure (Samloff and Townes, 1970). Pregnancy is reported to have no significant effect on serum PG I (Waldum, Straume and Lundgren, 1980). Samples taken with subjects standing may give slightly higher results than those taken supine (Waldum, Jorde and Gunnes, 1982).

There have been no published accounts from Britain of plasma PG I measurements. This study is an attempt to evaluate plasma PG I as a non-invasive test of gastric secretory potential and to assess whether the distribution of plasma PG I concentration in ulcer patients and controls matches that seen in other countries.

Materials and methods

Venous blood was obtained from several groups of subjects:

- (1) Healthy male medical staff and students ($n = 17$) age range 22-31 years, mean 25.2 years.
  - (2) Healthy female medical students and nurses ($n = 17$) age range 20-45 years, mean 26.9 years.
- All subjects in groups 1 and 2 (designated normal controls) were non-smokers who denied any history of peptic ulcer or recurrent dyspepsia in themselves or first degree relatives. Blood was taken between 8.00 a.m. and 9.00 a.m. after overnight fast. No attempt was made to control for posture. Four male subjects had blood taken under similar conditions on 3 consecutive days.

- (3) Male medical outpatients with no history of peptic ulcer or recurrent dyspepsia—designated male hospital controls ($n=21$) age range 18–52 years, mean 32 years.
- (4) Ante-natal clinic patients in the third trimester of pregnancy—designated female hospital controls ($n=41$) age range 18–34 years, mean 25.7 years. In groups 3 and 4 no attempt was made to control for family history, smoking, time of last meal or time of sampling.
- (5) Patients about to undergo upper gastrointestinal endoscopy for investigation of pain or bleeding ($n=47$). This group included 17 males with DU and 10 females with DU. Male normal endoscopy—11; female normal endoscopy—7.
- (6) Patients ($n=48$) with a variety of upper gastrointestinal disorders about to undergo pentagastrin tests which were performed by the conventional method using $6 \mu\text{g/kg}$ pentagastrin i.m. Maximal acid output (MAO) was the quantity of acid aspirated in the 1st hr after pentagastrin. In this group there were 24 DU patients, (6 of these were also listed in group 5), 4 gastric ulcer patients and 17 with dyspepsia but normal upper gastrointestinal endoscopic appearances. Also included were 3 patients found to be achlorhydric.
- (7) Six patients with pernicious anaemia.

Blood was collected into heparinized tubes, plasma separated by centrifugation and stored at -20°C until assay which was performed using a commercial radioimmunoassay 'kit' (Pepsik SORIN CIS U.K. Ltd). Manufacturer's instructions were followed but additional tubes were added to check non-specific binding. Counting was done on an LKB Wallac 1260 'Multigamma' counter linked to a Data Dynamics 390 microprocessor and printer.

Results

Intra- and inter-assay coefficients of variation were 8 and 13%, respectively, for samples in the control range. Fig. 1 shows the distributions of plasma PG I in normal and hospital controls.

In normal controls there was no significant correlation between plasma PG I and height, weight or calculated lean body mass.

In 4 normal controls plasma PG I varied by less than 5% when sampled under similar conditions on 3 consecutive days. Fig. 2 shows the distribution of plasma PG I in controls and patients with DU, dyspeptic patients with normal gastroduodenal endoscopy appearances and patients with achlorhydria / pernicious anaemia.

Male and female controls and patients have been grouped together here for clarity and because the sex

FIG. 1. Distribution of plasma PG I concentration in control subjects.

distribution of plasma PG I in patients was much more similar than in the controls.

It will be noted that all 9 patients with achlorhydria/pernicious anaemia had plasma PG I below 30 ng/ml . The only other subject with a level below 30 ng/ml was an endoscopy-negative dyspeptic patient in whom, unfortunately, acid studies were not obtained.

Fig. 3 shows the regression of plasma PG I on pentagastrin-stimulated maximal acid output (MAO) for the group of 48 patients with a variety of upper gastrointestinal disorders.

Discussion

Plasma PG I concentrations in normal control subjects seem to be independent of height, weight and calculated lean body mass, but are generally higher in men than women. Normal controls showed similar PG I concentrations to less rigorously selected hospital controls. Grouping all male and female controls, only 2/96 (2.1%) had plasma PG I concentrations over 115 ng/ml compared with 19/45 (42.2%) of patients with DU. Of symptomatic patients found to have normal endoscopic appearances, 2/18 (11.1%) had plasma PG I over 115 ng/ml , making it unlikely that the stress of an anticipated endoscopy caused the elevated PG I in DU patients.

Although there was a very small day-to-day

FIG. 2. Distribution of plasma PG I concentration in control subjects and patients with upper gastrointestinal disorders.

FIG. 3. Regression of plasma PG I concentration on maximal acid output (MAO) for patients with upper gastrointestinal disorders.

variation of plasma PG I in normal controls under basal conditions, there was more variation with time in the few DU patients so studied, although with no

obvious relationship to ulcer activity. This warrants further study, as a direct correlation between activity of DU and acid/pepsin secretion has been reported (Achord, 1981).

Although there is seldom any need for measurements of plasma PG I (or gastric acid output) in the initial diagnosis and management of individual patients, such a readily available non-invasive marker has several potential applications. It has already been suggested that for identification of ulcer recurrence after surgery, serum PG I is as useful as acid secretory tests, which, after gastric surgery may be particularly subject to errors (Stabile *et al.*, 1978).

For a heterogeneous group of patients there was a significant correlation between plasma PG I and pentagastrin-stimulated MAO. These data resemble those of Samloff for Histalog-stimulated PAO (Samloff *et al.*, 1975b) and support the contention that plasma PG I concentrations tend to reflect steady-state gastric acid secretory capacity.

Although this could prove clinically useful, it may also be worth considering the circumstances in which pepsinogen and acid differ. It is still not clear by what mechanism PG I enters the circulation, or indeed whether plasma PG I more accurately reflects mucosal pepsinogen synthesis or storage (Waldum, Burhol and Straume, 1978; Waldum and Burhol, 1980). Acid and pepsinogen probably have different responses to some stimuli. Cimetidine treatment has no consistent effect on plasma PG I concentration (Gledhill, personal communication) and it has been reported that, at least gastric, peptic activity may particularly reflect vagal activity (Elder and Smith, 1975; Gabrylewicz, Laszewicz and Sarosiek, 1980). More work is needed to clarify the relationship of plasma PG I to intragastric peptic activity (Stabile *et al.*, 1978).

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