Inhibition of gastric secretion and motility by simulated upper gastrointestinal haemorrhage: a response to facilitate haemostasis?

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SUMMARY As gastric acid and pepsin inhibit blood coagulation and platelet aggregation it is surprising that most upper GI haemorrhages stop spontaneously. To investigate this paradox we have studied acid and pepsin secretion, gastric motility and GI hormones after simulated upper GI haemorrhage. In seven healthy volunteers intraduodenal infusion of 160 ml autologous blood decreased pentagastrin stimulated submaximal acid secretion (mmol/h) from 30.0 (3.2) (mean (SE)) in the hour preceding infusion to 21.4 (3.7) in the hour following infusion ($p < 0.02$), representing a mean reduction in acid output of 30%. Pepsin output (mg/h) was also decreased from 207.5 (67.7) (mean (SE)) in the hour preceding blood infusion to 135.7 (54.7) in the hour after infusion ($p < 0.02$) representing a mean reduction in pepsin output of 43%. In six volunteers gastric emptying of a liquid meal was delayed after intraduodenal blood infusion compared with intubation alone with the emptying time (min) to half volume ($t_{1/2}$) being prolonged at 75.0 (8.2) (mean (SE)) after blood infusion compared with 35.5 (6.6) after intubation alone ($p < 0.02$). Plasma GIP concentrations (ng/l) increased to peak levels of 127.9 (62.7) (mean (SE)) after intraduodenal blood infusion compared with the pre-infusion value of 58.3 (2.3) ($p < 0.02$). These changes may represent protective physiological responses to facilitate haemostasis.

Considering the adverse environment for haemostasis, it is surprising that approximately 80% of acute upper GI bleeds stop spontaneously. The resting pH of the stomach and proximal duodenum is usually less than 2 and platelet aggregation and plasma coagulation are abolished *in vitro* at pH values of < 5.4 .¹ Gastric juice is also rich in pepsin, a potent fibrinolytic agent which rapidly digests thrombus in acid medium of $pH < 4$.^{2,3} The fact that haemostasis is usually effective in the upper GI tract suggests the presence of specialised physiological

mechanisms to facilitate haemostasis in this unusual environment. In order to determine whether such mechanisms exist we have studied the effect of simulated upper GI haemorrhage on gastric acid and pepsin secretion, gastric motility and GI hormone release.

Methods

GASTRIC SECRETION STUDY

The effect of simulated intraduodenal haemorrhage on gastric acid and pepsin secretion was studied in seven healthy volunteers (six men, one woman, median age 29 years, range 25-36). After an overnight (12 h) fast, a size 8 duodenal tube (Viomedex)

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and size 14 vented Andersen gastric tube (AN 10, HW Andersen Inc, New York, USA) were passed under fluoroscopic control into the second part of the duodenum and body of stomach respectively. This allowed simultaneous intraduodenal infusion and gastric aspiration without contamination. At time zero, an iv infusion of pentagastrin (Peptavlon, ICI) 0.25 µg/kg/h was commenced and continued throughout the study to stimulate submaximal gastric secretion. After a 30 minute equilibration period, 4×15 min collections of gastric juice were obtained by continuous aspiration. After this (time 90 minutes) each volunteer was blindfolded and received intraduodenally either 160 ml of fresh, unclotted autologous venous blood or 160 ml egg white (which has a similar protein and carbohydrate content to blood). Intraduodenal infusions were administered in random order on separate days at least one week apart. Infusions were given as 4×40 ml aliquots at five minute intervals over 20 minutes. On each study day 40 ml of venous blood was removed from each volunteer's arm every five minutes for 15 minutes (total volume removed=160 ml) and either directly infused into the duodenum before clotting (blood study day) or discarded (egg study day). After the start of duodenal infusion, a further 4×15 min gastric collections were taken (90–150 min). Volumes of each 15 min gastric aspirate were measured and aliquots retained for assay. A summary of this study method is shown in Figure 1.

Corrections were made for pyloroduodenal loss by infusing a non-absorbable marker, phenol red solution (1500 mg/l) at 12 ml/h intragastrically throughout the study.⁴ Corrections for duodeno-gastric reflux of duodenal juice were made by estimating Na⁺ concentration of the gastric aspirate.⁵ Microscopic blood reflux was quantitated spectrophotometrically.⁶ Any study showing macroscopic reflux of blood or egg white was abandoned. Macroscopic egg white reflux was detected visually by its effect on phenol red in the aspirated gastric juice, turning the normal acidic yellow/orange colour to pink. Four studies were repeated because of macroscopic reflux of blood in three, and egg white reflux in one.

GASTRIC MOTILITY STUDY

The effect of simulated intraduodenal haemorrhage on gastric emptying of a 600 ml liquid glucose meal was studied in six healthy volunteers (five men, one woman, median age 29 years, range 25–36) using a double sampling test meal technique.⁷

After an overnight fast, separate intraduodenal and gastric tubes were positioned as described above. At time zero 600 ml of a liquid meal (50 g dextrose diluted to 600 ml in 75 mmol/l NaCl with phenol red

Fig. 1 Experimental study method to determine effects of intraduodenal blood and egg white infusion on pentagastrin stimulated gastric secretion.

solution 45 mg/l) was instilled into the stomach, mixed and 5 ml aspirate kept for analysis. Each volunteer was then blindfolded and received intraduodenally either 160 ml fresh autologous venous blood (4×40 ml aliquots over five minute intervals as described above), 160 ml egg white (4×40 ml aliquots) or intraduodenal intubation alone in random order on separate days. At 10 minutes, a 10 ml gastric aspirate was removed and kept for analysis. Immediately, 10 ml phenol red solution (1500 mg/l) was instilled into the stomach, the gastric contents mixed and a further 10 ml gastric aliquot kept for analysis. This double sampling technique was repeated at 10 minute intervals until time 50 minutes when the stomach was emptied completely, the volume recorded and a 10 ml aliquot retained for analysis. The stomach was then washed with 100 ml water which was aspirated, the volume noted and a 10 ml aliquot also retained for analysis.

GASTROINTESTINAL (GI) HORMONE STUDIES

To study possible hormonal mediation of any responses shown, serial blood samples were taken before and after intraduodenal blood and egg white infusion during the gastric secretory study.

Three basal samples were taken at 30 minute intervals before intraduodenal infusion and thereafter at seven minute intervals until study completion at 150 minutes. Samples were added to heparinised tubes, immediately centrifuged and plasma stored at -20°C. The following GI hormones with known gastric secretory and/or motility effects were studied – gastrin, secretin, gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP), neurotensin and somatostatin.

ANALYSIS

Gastric secretion

Gastric juice was analysed for: (1) Hydrogen ion concentration by titration to pH 7.0 with 100 mmol/l sodium hydroxide. (2) Phenol red concentration by

spectrophotometric absorption (Pye Unicam SP8-100 UV Spectrophotometer) at 550 and 410 nm and at 410 nm alone to quantitate microscopic blood reflux. (3) Sodium concentration by flame photometry (EEL Flame Photometers Ltd). (4) Pepsin concentration by Pipers method.⁸ Results were expressed as mg Sigma porcine pepsin.

GI HORMONES

Gastric inhibitory peptide, gastrin, secretin, somatostatin, VIP, and neurotensin were measured by radioimmunoassay.

CALCULATIONS

Acid output was expressed as total acid output in mmol/h for each hour before and each hour after duodenal infusions after correction of pyloroduodenal losses and duodenogastric reflux. Pepsin output was expressed as the total output in milligrams for each hour before and after intraduodenal infusions.

Intragastric volumes were calculated using the method of George.⁷ The time taken for intragastric volume to decrease to half volume from 600 ml ($t_{1/2}$) was calculated in each case using linear transformation of the data.

For each GI hormone assay preinfusion values were expressed as the mean of the three samples at 0, 30 and 60 minutes.

STATISTICAL ANALYSIS

Results are given as mean (SE). Statistical analysis was performed using the Wilcoxon's signed-ranks

test (two sided) for paired data. Results were considered significant when $p < 0.05$.

Written, fully informed, consent was obtained in each case and all studies were approved by the Local Hospital Ethical Committee.

Results

GASTRIC SECRETION

Acid output

Gastric acid output (mmol/h) decreased in each of the seven volunteers after intraduodenal blood infusion. The mean output being 30.0 (3.2) in the hour preceding intraduodenal blood infusion and 21.4 (3.7) in the hour after infusion ($p < 0.02$) (Fig. 2). This represented a mean reduction in acid output of 30.4% (range 16–67%) and was accounted for by a reduction in both the volume and H^+ concentration of the gastric juice.

With intraduodenal egg white infusion there was no significant change in acid output being 31.8 (2.8) in the hour before infusion and 33.0 (4.4) in the hour after intraduodenal infusion (Fig. 2).

Pepsin output

Pepsin output (mg/h) decreased in each of the seven volunteers after intraduodenal blood infusion (Fig. 3). The mean output being 207.5 (67.7) in the hour preceding intraduodenal blood infusion and 135.7 (54.7) in the hour after infusion ($p < 0.02$). This represented a mean reduction in pepsin output of 43% (range 19–80%) and was accounted for by a

Fig. 2 Effect of intraduodenal blood and egg white infusion on pentagastrin stimulated gastric acid secretion in seven healthy volunteers.

Fig. 3 Effect of intraduodenal blood and egg white infusion on pepsin secretion in seven healthy volunteers.

Fig. 4 Residual gastric volumes after intraduodenal blood infusion and duodenal intubation alone in six healthy volunteers. Values are given as mean (SEM).

reduction in both volume and pepsin concentration of the gastric juice. With intraduodenal egg white infusion, there was no significant change in pepsin output being 372.2 (82.9) in the preinfusion hour and 376.9 (54.6) in the hour after intraduodenal infusion (Fig. 3).

Calculated recovery fractions by phenol red estimation were 91% in the blood infusion group and 94% in the egg white infusion group. The calculated mean volume of blood refluxed in the hour after intraduodenal blood infusion was 3.2 (0.9) ml.

GASTRIC MOTILITY STUDY

Gastric emptying was delayed in all six subjects after intraduodenal blood infusion compared with intubation alone. Figure 4 shows the residual gastric volumes with intraduodenal blood infusion compared with the control study (duodenal intubation alone). The emptying time (min) for the initial intragastric volume (600 ml) to decrease to half volume ($t_{1/2}$) was increased to 75.0 (8.2) after intraduodenal blood infusion compared with 35.5 (6.6) in the control study ($p < 0.02$). At 50 minutes, 355 (18) ml remained in the stomach, compared with 211 (28) ml after the control study ($p < 0.02$).

Compared with intubation alone, intraduodenal egg white infusion also resulted in a delay in gastric emptying although this was less marked than after blood infusion. $t_{1/2}$ (min) after egg white infusion was

Fig. 5 Venous plasma concentrations of GIP before and after intraduodenal infusions of blood and egg white in seven healthy volunteers. Values are given as mean (SEM).

67.7 (12.7) compared with control study 35.5 (6.6) ($p = \text{NS}$). After egg white infusion 291 (36) ml remained in stomach at 50 minutes compared with 211 (28) ml after the control study ($p = \text{NS}$).

GI HORMONES

Intraduodenal blood infusion

Plasma GIP concentrations (ng/l) increased significantly after blood infusion compared with preinfusion values ($p < 0.02$) (Fig. 5). Peak GIP levels were reached 21 minutes after the start of blood infusions being 127.9 (62.7) compared with the preinfusion value of 58.3 (2.3) ($p < 0.02$). Gastric inhibitory peptide concentrations remained significantly raised above preinfusion values at the end of the study 56 minutes after the start of blood infusions.

Plasma concentrations of gastrin, somatostatin, VIP, secretin, and neurotensin showed no significant change after blood infusion compared with preinfusion values.

Intraduodenal egg white infusion

None of the plasma concentrations of hormones studied changed significantly after egg white infusion (Fig. 5).

Discussion

This study has shown that intraduodenal blood infusion in man inhibits pentagastrin stimulated gastric acid and pepsin secretion, delays gastric emptying and increases plasma GIP concentrations.

These responses may represent a locally protective physiological mechanism to facilitate haemostasis.

The normal environment of the upper GI tract is not conducive to haemostasis. The resting pH of the stomach and proximal duodenum is usually less than 2^{9,10} and platelet aggregation and plasma coagulation are abolished at pH<5.4.¹ Gastric juice is rich in pepsin a potent proteolytic enzyme which digests thrombus and fibrin.^{2,3} Furthermore, the highly vascular and motile nature of the upper GIT is likely to promote haemorrhage and inhibit haemostasis. After simulated intraduodenal haemorrhage the three of these factors studied were all altered in a way that would facilitate haemostasis. In clinical terms the 160 ml of blood infused in our study represents a very minor bleed and the changes seen may be more marked after larger bleeds. In a single large clinical study by Chandler and Watkinson in 1953 a temporary achlorhydria was noted in patients with intraduodenal haemorrhage which was not the result of blood reflux but was thought to represent a temporary inhibition of parietal cell function.¹¹

The mechanism by which intraluminal blood inhibits acid secretion and gastric motility is unclear. The increase in circulating GIP concentrations may be relevant. Gastric inhibitory peptide is a polypeptide located primarily in the duodenum and jejunum¹² and its primary role appears to be in glucose metabolism.¹³ It has been shown, however, to inhibit gastric acid secretion and gastric motility in dogs¹⁴ although these effects remain controversial in man.¹⁵

Medical therapy of acute upper GI haemorrhage has mainly been directed at inhibiting acid and pepsin secretion or reducing gastroduodenal blood flow. These therapeutic regimes have been applied without a clear understanding of the physiological changes accompanying upper GI haemorrhage. A clearer understanding of these changes may lead to new and more rational approaches to therapy.

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