Fibrinolysis and gastrointestinal haemorrhage

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Most human tissues contain fibrinolytic activators. The alimentary tract organs, however, were not considered to be a site of importance and were not included in a comprehensive survey of human necropsy tissues studied by Albrechtsen.¹ But since Cox, Poller, and Thomson² found local organ fibrinolysis in the stomach and free plasmin in gastric vein blood there has been much interest in the possible role of fibrinolysis in gastrointestinal bleeding. There is also some evidence that similar influences might contribute to bleeding at other sites in the alimentary tract.

Blood fibrinolytic activity

Our initial study² was on two clinical contrast groups undergoing upper abdominal laparotomy—that is, patients with peptic ulcer and controls undergoing cholecystectomy. Gastric vein blood samples were obtained directly at laparotomy in both groups and compared for their fibrinolytic activity with blood from gastric arteries and peripheral veins. In all patients the fibrinolytic activity in blood leaving the stomach was much more than in the blood entering it through the gastric arteries and in blood from the peripheral venous circulation. The most remarkable and unexpected finding, however, was the presence of a potent plasmin-like activity in gastric vein blood which could be clearly differentiated from pepsin. Later its non-identity to trypsin was established.³ The difference was shown by gel filtration using chromatography Sephadex G200. This showed that the plasmin-like activity in gastric vein blood and peripheral vein blood was the same and identical to purified plasmin.³ The results were also confirmed later by Thomson in an amidolytic assay for plasmin using chromogenic substrate S-2251 (unpublished data).

Therefore the first report suggested that anti-fibrinolytic drugs might be of value in the management of gastric bleeding.² We were at first reluctant to accept without further proof the unexpected finding of appreciable amounts of free plasmin in the gastric vein specimens. The original reports have now been substantiated by further work and by

complementary studies from other centres using a variety of different techniques and approaches.⁴⁻⁸

In a subsequent study from Manchester⁹ the fibrinolytic potential of the stomach was found in all subjects. Stimulation was applied to the stomach wall by controlled manipulation at laparotomy. There was a gradation of activity. Fig. 1 shows the shortening of the euglobulin lysis time in serial

Fig. 1 Fibrinolytic activity on plasmin-free fibrin plates with peripheral vein samples at 10-minute intervals after gastric compression. P1 = base line. P2-P3 = 10-minute intervals. G = gastric vein samples.

samples obtained at 10-minute intervals. After 30 minutes the activity tended to disappear. The additional observation that free plasmin was present in over half the patients in peripheral venous samples collected after gastric manipulation was of extreme interest. The thrombelastogram tracings obtained were consistent with the extreme, activated fibrinolytic state encountered after streptokinase infusion (Fig. 2). This pattern was also obtained by a later, independent study.⁸

Fig. 2 Thrombelastograms of peripheral venous blood obtained at base line (PI) and of gastric vein specimen (GI) immediately after manipulation.

In-vivo neutralisation of the gastric fibrinolytic activity was next attempted by giving epsilon aminocaproic acid before laparotomy.¹⁰ EACA preoperatively in therapeutic dosage prevented the release of plasmin activity after manipulation of the stomach in 13 out of 14 duodenal ulcer patients. All 15 duodenal ulcer patients in a control group not given EACA showed evidence of plasmin in both gastric and peripheral venous blood and raised fibrin breakdown products (FDP) in these same blood samples. The EACA-treated series (apart from one patient with pyloric stenosis), in contrast, had an increase of plasminogen activator only, which was presumably due to the stress of operation and anaesthesia.

A further study reported that high concentrations of FDP were also associated with a recent gastrointestinal haemorrhage but not with other types of bleeding.¹¹ Patients with haematemesis and melaena were studied and compared with patients bleeding into other sites, most of whom were suffering from menorrhagia, and patients having operations. The concentrations of FDP in haematemesis and melaena patients were significantly higher than in other groups, suggesting increased fibrinolysis (Fig. 3).

Tissue fibrinolytic activity

In our original study² fresh gastric tissue examined by extraction in saline contained plasminogen activator activity. In a further study¹² on 19 samples of the ulcer-bearing area of pyloric antrum from patients with chronic peptic ulcer obtained at laparotomy plasminogen activator was extracted

Fig. 3 FDP measured by TRCHII in patients with haematemesis and other groups.

according to the technique of Astrup *et al.*¹³ The tissues were rich in plasminogen activator, comparable with extracts from uterus which is known to contain high concentrations of activator activity. Russian investigators¹⁴ prepared extracts from gastric ulcer which considerably increased the fibrinolytic properties of plasma. They commented that, as a result, a stomach ulcer was often complicated by haemorrhage.

By histochemical fibrin slide techniques it was found that plasminogen activator was localised to blood vessels in the wall of the gastrointestinal tract and sites along the epithelium of gastric and intestinal mucosa and submucosa.^{15 16} In a further histochemical study in gastric tissue,¹⁷ aimed at locating the site of plasminogen activator in the tissues, the modification of Todd's original technique¹⁸ described by Pandolfi *et al.*¹⁹ was used. Fresh samples for biopsy were obtained at laparotomy from patients with duodenal ulcer. Sections from various regions of the gastrointestinal tract were examined, including pylorus, fundus, and body of stomach. Results indicated a rich supply of plasminogen activator in the areas surrounding the submucosal veins (Fig. 4). Fibrinolytic activity appeared to be extensive throughout the organ. Similarly, Nilsson and colleagues²⁰ examined normal gastric mucosa using a histochemical method and identified plasminogen activator localised around the small vessels in the submucosa as well as in the mucosal cells. This activator, shown to be stable, could be released into the gastric juice after damage to the gastric mucosa.

In experimental and clinical tissue studies in support of the role of local fibrinolysis in the stomach, a Japanese group⁷ produced an experimental model of gastric ulcer in dogs by injecting intramucosally an antigen/antibody complex. Specimens of gastric mucosa were obtained close to the injection site and from distal parts of the stomach. Areas near the ulcer showed increased fibrinolytic activity which lasted for up to seven days and disappeared as the

Fig. 4 (a) (b) Gastric mucosa studied by Todd technique showing areas of lysis.

ulcer healed. Similarly in man areas near gastric ulceration showed high fibrinolytic activity. Anti-fibrinolytic drugs significantly reduced these tissue fibrinolytic activities and areas of ulceration viewed endoscopically. Protein-losing gastropathy associated with Menetrier's disease was associated with increased fibrinolytic activity in gastric mucosa at biopsy, and the use of an anti-fibrinolytic agent blocked the cycle of membrane disorder and increased vascular permeability and hypoproteinaemia.²¹

In 1975 Nilsson and her Malmö colleagues published the results of a study on gastric juice as confirmatory evidence of local fibrinolysis in the stomach and duodenum.⁵ They found that gastric juice from patients with erosive haemorrhagic gastroduodenitis had very high fibrinolytic activity but gastric juice from normal or from bleeding ulcer patients had no activity. Plasmin was identified chemically and immunologically in the gastric juice of these patients. Low concentrations of plasminogen and α_2 -macroglobulin and raised

concentrations of FDP were recorded in the peripheral blood. The activity was inhibited *in vitro* by adding EACA and *in vivo* by giving AMCA (Cyklokapron). The authors stated that these findings suggested that gastric fibrinolysis, presumably from blood which had leaked from the stomach, contributed substantially to the bleeding tendency.

Gastric juice from patients with bleeding ulcers was found by Buhr and colleagues⁶ to contain higher fibrinolytic activity than normal and that this produced lysis on plasminogen-free fibrin plates—that is, it had plasmin-like activity. It has recently been shown²² that about 20% of samples of gastric juice in normal people without gastric haemorrhage exhibit 'pure' (plasmin) fibrinolytic activity. Giving aspirin, a known gastric irritant, did not increase the number of samples of gastric juice showing this fibrinolytic activity.

The mechanism of the release of plasminogen tissue activator is still an enigma. Astrup²³ suggested that during cellular differentiation and maturation plasminogen tissue activator is produced. Plasmin-

ogen activator is released when active cells degenerate. From this it could be postulated that during increased cell degeneration in acute and chronic gastric ulceration increased amounts of tissue activator are released. The resultant free plasmin activity may either cause bleeding or delay healing when the venous blood flow permeates the ulcer area. Should overt bleeding occur into the lumen the presence of plasmin in the blood, described by Nilsson *et al.*,⁵ may impair haemostasis and healing.

Fibrinolytic activity of the epithelial surfaces and of the submucosal blood vessels may be of importance in interfering with haematemesis and even delay healing in acute and chronic ulcers. From the evidence, the presence of blood in the gastric juice may, because of its plasmin content, interfere with clot formation in the lumen and prolong bleeding. Furthermore, plasmin has been found in the gastric juice of some patients who have no evidence of bleeding,²² suggesting that this activity does not necessarily arise from blood contamination. The additional question whether excessive fibrinolysis is of importance in the aetiology of peptic ulcer, as we originally suggested, remains to be resolved. If it were the case anti-fibrinolytic drugs might be important in the management of peptic ulceration as distinct from bleeding complications. There appears to be enough scientific evidence to mount clinical studies of fibrinolytic inhibitor administration in these states.

Clinical trials

Anecdotal experience of the benefit of anti-fibrinolytic drugs in gastric bleeding has been common in the last few years, including the successful management of haemostasis in at least one European monarch. But their role can be evaluated only in carefully controlled double-blind clinical trials. The reports of two such trials are encouraging and emphasise a need for more detailed and lengthier evaluations. Cormack *et al.*²⁴ in a double-blind randomised study of tranexamic acid (Cyklokapron) in upper gastrointestinal haemorrhage used a dosage of 1.5 g eight-hourly for seven days. The controls received a placebo at similar time intervals.

The results are summarised in the Table. Cases in which bleeding continued or further transfusion or surgery were needed were regarded as failures. Overall, the difference between the treated and the control group was not significant, but when patients with hiatus hernia or bleeding varices were excluded tranexamic acid was shown to produce a significant benefit ($P < 0.05$).

In a second double-blind trial of tranexamic acid in upper gastrointestinal bleeding²⁵ the drug was given both intravenously and by mouth for 48 hours and then only by mouth for a further 72 hours. In this unselected group, which included at least 11 patients with oesophageal varices, the failure rate was significantly lower—that is, the number of patients in the treated group requiring surgery for continued bleeding or for recurrence ($P < 0.005$) (see Table).

The patients in the treated group who required surgery included two who were operated on not for bleeding but because of the long history of duodenal ulceration. The results of these two careful prospective studies are therefore encouraging and underline the need for a more thorough clinical appraisal of the drugs in the management of bleeding in the upper gastrointestinal tract. As the *Lancet* stated,²⁶ the favourable results have thrown the gauntlet to physicians and surgeons to amplify their claims that anti-fibrinolytic drugs are beneficial.

The function of fibrinolysis in the lower gastrointestinal tract and its role in bleeding is less certain. Kwaan and coworkers²⁷ showed by histochemical methods that there was a high concentration of plasminogen activator in the rectal mucosa of patients with ulcerative colitis.

Fibrinolytic activity has been found in the small and large bowel and the stomach of the rat.¹⁵ Plasmin-like activity similar to that in gastric vein blood has been found in colonic vein blood at laparotomy (unpublished data). It is reasonable to assume, therefore, that anti-fibrinolytic agents might be of some value in managing the bleeding complications of ulcerative colitis. No evidence of excess fibrinolysis in the blood of these patients was detected but they improved clinically on anti-fibrinolytic drugs.^{28, 29} Results of a later, small,

Table Clinical trials of tranexamic acid in upper gastrointestinal bleeding

	Total	Treated	Control	Failure rate		Mortality	
				Treated	Control	Treated	Control
Cormack <i>et al.</i> ²⁴	150	76	74	15	20	3	3
*Cormack <i>et al.</i> ²⁴	125	62	63	7	17		
Biggs <i>et al.</i> ²⁵	200	103	97	7	21	3	3

*Patients with hiatus hernia and oesophageal varices excluded.

double-blind, cross-over trial of oral tranexamic acid in the management of bleeding from patients with ulcerative colitis have been disappointing.³⁰ The patients did not show a significant benefit from placebo and there was no diminution in chromium-labelled red cells in the stools.

As well as the fundamental problems of gastric physiology and pathology the physiopathological function of the fibrinolytic mechanism in other parts of the gastrointestinal tract demands more investigation. A further review, perhaps in a few years' time, may produce firm conclusions on the status of fibrinolytic inhibition in the management of such states and their bleeding complications.

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