INHIBITION OF GASTRIC PLASMIN
ACTIVITY BY EPSILON-
AMINOCAPROIC ACID

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Summary
PREOPERATIVE ADMINISTRATION OF the antifibrinolytic drug epsilon-aminocaproic acid (EACA) prevented the release of plasmin activity following digital compression of the stomach at operation in 13 out of 14 patients with duodenal ulceration. In a parallel control series all of 15 duodenal ulcer patients not given EACA showed evidence of plasmin in gastric and peripheral venous blood and of fibrin/fibrinogen breakdown in these same blood samples following similar gastric manipulation. The EACA-treated series, apart from one patient with pyloric stenosis, showed an increase of plasminogen activator only, presumably due to stress, anaesthesia, etc., and no increase of fibrin/fibrinogen breakdown products. Antifibrinolytic drugs may become an important new factor in the management of bleeding from acute gastric erosions.

Introduction
IN PREVIOUS STUDIES gastric venous blood was shown to have considerably more fibrinolytic activity than gastric arterial blood1, 2. The most striking finding was the demonstration of free plasmin in gastric venous blood which could be liberated into the circulation by digital compression of the stomach at operation. Patients with peptic ulcer showed significantly increased activity compared with controls, a fact that may have an important bearing on the mechanism of peptic ulceration and particularly on the pathogenesis of bleeding from peptic ulcers.

The purpose of the present study was to discover whether gastric fibrinolytic activity could be blocked by the prior administration of the antifibrinolytic drug epsilon-aminocaproic acid (EACA) in pharmacological doses, a possibility suggested by our previous observation that the fibrinolytic activity present in gastric venous blood was neutralized in vitro by EACA. We therefore investigated the possible 'blocking effect' of EACA in a group of patients with duodenal ulceration.

Patients and methods
Twenty-nine patients were studied. All had clinical and radiological evidence of duodenal ulceration and had been admitted for surgical treatment. They were divided into two groups as follows:

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Group 1. The ‘untreated’ group consisting of 15 patients who were not prescribed EACA.

Group 2. The ‘treated’ group consisting of 14 patients who were prescribed EACA before operation.

The patients were admitted by L.T. seriatim from his waiting list, none being excluded. Allocation to the 2 groups was arranged by one of us (L.P.) who had no prior knowledge of the clinical features of any of them, so as to have balanced numbers in each group.

EACA was given to the 14 patients in Group 2 by mouth in a recommended dosage—0.1 g/kg body weight. In 3 instances one dose or more was inadvertently omitted. These 3 cases are discussed separately.

The first 11 patients in Group 2 were prescribed 3 doses of EACA syrup preoperatively at 6-hourly intervals up to 8 hours before operation. Because the time interval between the last dose of EACA and the start of the operation was thus greater than the optimum the timing was altered for the last 3 patients, the final dose being given only 2–3 hours before operation. The amended time schedule was introduced to make absolutely certain that adequate inhibition had been achieved.

A standard technique of gastric compression was used at operation on each of the 29 patients. Specimens of gastric venous blood were collected immediately after gastric compression from a tributary of the left gastric vein. The first (baseline) peripheral vein samples were collected almost simultaneously from a vein in the antecubital fossa. Two further peripheral vein samples were collected at 10-minute intervals.

Laboratory methods. Standard and heated fibrin plate assays of fibrinolytic activity were performed. Euglobulin lysis time was measured by both acid and CO₂ precipitation methods; the former additional microtechnique was included because aspiration of blood from gastric veins must be done quickly and carefully to avoid clotting or the release of tissue activator due to tissue injury, so that it was usually possible to withdraw only 3–4 ml of gastric venous blood. Measurement of fibrin/fibrinogen breakdown products (FDP) was by a staphylococcal clumping test (SCT) and by the modified tanned red cell haemagglutination inhibition immunoassay (TRCHII).

Results

Group 1—Untreated. Euglobulin lysis times. Results indicated a marked increase in fibrinolysis in all 15 subjects in this group, shown by progressive shortening of the lysis times in the serial venous speci-
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Fig. 1  Euglobulin lysis times of serial peripheral and gastric venous blood samples from patients with peptic ulcer; effective blocking of fibrinolysis is shown in the group adequately treated with EACA. P1 = first, P2 = second, P3 = third peripheral vein blood sample; G = gastric vein blood sample.

e samples from the first to the third peripheral sample. The shortest times were recorded from the gastric venous blood. The most marked difference was observed between the lysis times of the first and second peripheral venous blood specimens. This indicates a dramatic increase of activity within the first 10 minutes following gastric compression. The mean values given by the microtechnique are shown in Figure 1. The same trend was also shown by the CO₂ method.

Standard fibrin plate assay. A similar pattern of graded increase of fibrinolytic activity was also apparent in all cases with the standard fibrin plate assays, confirming the findings of euglobulin lysis time.

Heated fibrin plate assay. Areas of lysis indicating plasmin activity* were seen in the gastric and third peripheral venous samples in each of the 15 patients. In 13 patients the activity was also present in the second peripheral venous samples. There was no observable activity in the baseline samples. The mean values of the areas of lysis are illustrated in Figure 2. Individual patients' results are given in Figure 3.

Measurement of FDP. The second and third peripheral venous samples, in addition to the gastric venous blood, showed an increase in FDP levels above the normal range. In all patients the results were

*The possibility of peptic or tryptic digestion had previously been discounted (see Discussion).
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Fig. 2. Lysis on heated fibrin plates of peripheral and gastric venous blood samples from peptic ulcer patients showing the blocking effect of EACA. 
(For key see Fig. 1.)

similar with both techniques used (TRCHII and SCT). The results by the TRCHII method are illustrated in Figure 4.

**Group 2—Treated.** This group was subdivided into Group 2a, consisting of the 11 patients who received the full prescribed dose of EACA, and Group 2b, consisting of the 3 cases in which at least one of the prescribed doses was inadvertently omitted.

_Euglobulin lysis time._ In Group 2a the lysis times of the 3 peripheral venous samples from each patient were all within normal limits, in contrast to the progressively shortened times in Group 1. Observations were continued in all cases for a minimum period of 90 minutes. The gradation of activity was less marked than in Group 1. Figure 1 underestimates the effect of EACA on the lysis time because observation was discontinued in many cases long before the time of complete lysis. The lysis times of the gastric blood samples were shorter than those of the peripheral blood but not as short as in Group 1.

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Fig. 3. Individual heated fibrin plate results in patients with peptic ulcer showing the inhibitory effect on plasmin of EACA administration.
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The 3 patients inadequately treated with EACA (Group 2b) showed a progressive shortening of the euglobulin lysis time in the serial blood samples. The effect was more marked than in Group 2a but the lysis times were not as short as in Group 1 (see Fig. 1).

*Standard fibrin plates.* In Group 2a the majority of patients showed an increase of fibrinolytic activity in the second and third serial peripheral blood samples and an even greater zone of lysis from the gastric venous sample. However, the areas of lysis from all of the serial venous samples were considerably less than those observed in Group 1.

![Graph showing FDP titres from peripheral and gastric venous blood in peptic ulcer patients, treated and untreated with EACA.](image)

Fig. 4. Contrasting results of FDP titres from peripheral and gastric venous blood in peptic ulcer patients, treated and untreated with EACA.

In Group 2b all 3 patients showed zones of lysis with the second and third peripheral samples and also with the gastric venous blood. The areas of lysis were greater than those in Group 2a but smaller than those in Group 1.
Heated fibrin plates. There was no lysis detectable from the serial peripheral and gastric venous samples from 10 of the 11 patients in Group 2a. The one exception was in a case of severe pyloric stenosis.

In Group 2b areas of lysis were measurable with the second and third peripheral venous samples and also with the gastric venous samples, where the activity was more marked (see Figs. 2 and 3).

Fibrin/fibrinogen breakdown products. In Group 2a there was no rise in the level of FDP measured by either technique (TRCHII or SCT) in any of the serial peripheral or gastric venous samples, apart from one patient with raised levels of FDP in the baseline peripheral sample which persisted throughout (Fig. 4). There was a slight increase in the level of FDP in the gastric vein blood from only one of the 3 patients in Group 2b. No increases were detected in any of the other serial peripheral and gastric venous blood samples tested.

Discussion

The lytic activity on the heated fibrin plates in the serial peripheral and gastric venous samples has recently been identified on biochemical grounds and has been shown to be due to plasmin, not trypsin. It had previously been differentiated from gastric peptic activity.

The present results demonstrate the inhibition of gastric plasmin activity by the oral administration of a standard dose of EACA. The effectiveness of this inhibition was most clearly demonstrated in the 11 patients receiving the full number of 3 standard doses (Group 2a). The absence of plasmin activity is in complete contrast to the results in the untreated patients (Group 1) (see Fig. 3). The results in the 3 patients in Group 2a who were given their last dose of EACA about 2–3 hours before operation did not, however, indicate more effective inhibition than was demonstrated in the other 8. Therefore it may be assumed that the original dose regimen was sufficient to block plasmin activity.

In one patient only was inhibition of plasmin activity not achieved with EACA. This was a case of pyloric stenosis secondary to active duodenal ulceration. The presence of pyloric stenosis may explain the ineffectiveness of EACA, for in this condition there is excess motility of the stomach. The greater the motility, the more the likelihood that tissue activator could be released locally from the stomach.

In Group 2a, in spite of the inhibition of plasmin, there was still some evidence of stimulation of fibrinolytic activator activity shown by the graded zones of lysis on the standard fibrin plates and shortened euglobulin lysis times (see Fig. 1). The activity again appeared to increase.
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progressively from the first to the third peripheral venous sample, and the gastric venous blood showed the most activity. It is of interest that, unlike the plasmin activity, this increase in plasminogen activator—presumably due to the effect of stress, anaesthesia, etc., on the fibrinolytic system—was not blocked by EACA.

The 3 patients inadequately treated with EACA (Group 2b) all showed some increase in fibrinolytic activity, but unlike the patients in Group 2a measurable amounts of plasmin were present in each instance, shown by lysis of the heated plate (Fig. 3). This finding clearly distinguishes these 3 patients from the 11 adequately treated. It demonstrates the incomplete blocking by the inadequate dose and confirms the need for all 3 oral doses for inhibition of gastric plasmin.

The raised levels of FDP detected in Group 1 paralleled the appearance of plasmin in the same peripheral and gastric venous specimens. Their presence confirms that activation of the fibrinolytic mechanism had proceeded to the final stage, resulting in the breakdown of fibrin/fibrinogen by plasmin. In contrast, in Group 2a there was no evidence of increased fibrin/fibrinogen breakdown in the absence of plasmin release.

We suggested¹ that activation of gastric fibrinolytic activity might be important in the pathogenesis of gastric and duodenal bleeding and that antifibrinolytic drugs might have a place in treatment. A double-blind trial recently reported¹⁰ has confirmed that, particularly where bleeding has occurred from acute gastric erosions, antifibrinolytic drugs can influence their management, reducing the need for blood transfusion and operation in a significant number of patients.

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