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Local Inhibition of the Fibrinolytic System in Patients with Massive upper Gastrointestinal Hemorrhage

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ABSTRACT

The effect of oral tranexamic acid on massive upper gastrointestinal hemorrhage was evaluated in a randomized double-blind study. Totally 50 patients entered the trial and seven were excluded, leaving 22 placebo treated and 21 tranexamic acid treated for analysis. The groups were comparable regarding sex, age, diagnosis, and initial laboratory data. Transfusions requirements and operation frequency did not differ. Mortality was slightly reduced and death delayed in tranexamic acid treated patients.

INTRODUCTION

In cases of gastroduodenal ulcers an increased content of plasmin has been obtained in gastric venous blood (5). Cormack et al. (4) found an effect of peroral antifibrinolytic treatment in cases of upper gastrointestinal bleeding with negative barium meal, which was therefore interpreted as erosive gastritis. In patients with hemorrhagic gastroduodenitis very high fibrinolytic activity has been found in the gastric juice, and antifibrinolytic agents have been shown to have an inhibitory effect (9).

In this study we wanted to investigate the effect of a rather high dose of tranexamic acid as antifibrinolytic treatment in patients with massive upper gastrointestinal hemorrhage in a randomized double-blind trial. This treatment should be the only treatment given.

MATERIAL AND METHODS

Fifty patients with massive upper gastrointestinal bleeding were included in the study. A massive bleeding was defined as hematemesis and/or maelena and the patient showing circulatory involvement on arrival or in anamnesis. Patients in chock or prechock on admission were immediately given dextran 70 and then blood if necessary. Blood transfusions were given to obtain a hematocrit of about 30 per cent. A gastroduodenal tube for blood evacuation was immediately inserted as well as a catheter for measurement of the central venous pressure. Oesophago-gastro-duodenoscopy and a barium meal were performed as soon after arrival as possible. The following blood tests were made: hemoglobin, hemato-

crit, white cell count, platelet count, normotest (NT), thrombotest (TT), fibrinogen degradation products (FDP), bilirubin, ALP, ASAT, electrolytes, pH, HCO_3^-, pO_2, and acetylsalisylic acid.

The patients were randomly allocated to treatment with placebo or tranexamic acid (AMCA, trans-AMCHA, Cyklokapron^R, Kabi, Sweden). The study was double-blind. An oral solution was administered through the gastric tube every four hours for two days. The tube was then closed for the next hour. When active treatment was given an oral dose of 2g was administered on each occasion. The treatment started as soon as the patient had arrived to the intensive care unit, mostly within one hour after arrival.

RESULTS

Totally 50 patients entered the trial. Seven patients were excluded from the final evaluation, three patients from the placebo group and four from the tranexamic acid treated group. In two cases treated with tranexamic acid the inclusion criteria were wrong, and in the rest the patients were treated in other ways which could influcence the hemorrhage (Vasopressin, vitamin K, and/or Sengstaken tube). Thus, 22 patients in the placebo group and 21 in the treated group remained for final analysis. There were no differences between the groups regarding sex, age ranges and diagnosis (Table 1).

TABLE 1. Patients with massive upper gastrointestinal hemorrhage. Distribution regarding sex, age, and diagnosis.

		Placebo	Tranexamic acid
Number of male patients		20	14
Number of female patients		2	7
Age, years, (mean and range)		57.6 (26-85)	60.8 (23-82)
Diagnosis:	ulceration of the stomach	5	5
	ulceration of the duodenum	10	8
	gastritis	4	4
	eosophageal varices	1	2
	gastric cancer	1	1
	other	1	1

None of the patients had any acetylsalisylate in serum. FDP was less than 10 mg/l in 19 of the placebo patients and 14 of the tranexamic treated patients and less than 40 mg/l in all placebotreated patients and all except one tranexamic acid treated patient.

TABLE 2. Laboratory data on arrival from 22 placebo-treated and 21 tranexamic treated patients with massive upper gastrointestinal hemorrhage.

	Placebo	Tranexamic acid
Hemoglobin (g/l)	93.5	89.7
Platelet count x 10^{-3}	226.5	232.6
NT (%)	88	84
Bilirubin (μmol/l)	12	13
ALP [1] (μkat/l)	2.5	3.0
ALAT[2] (μkat/l)	0.43	0.49
CVP[1] (cm H_2O)	+2.5	+2.1

1) ALP - Alkaline phosphatase
2) ALAT - Alanine amino acid transferase
3) CVP - Central venous pressure

Table 2 gives some initial laboratory data showing comparability between the groups. Eleven of the placebo treated patients and 16 of the tranexamic acid treated patients were initially given dextran 70. The minimum hemoglobin level did not differ between the two groups, 77.9 g/l in the placebo and 71.9 in the tranexamic acid treated group. The mean number of preoperative blood transfusion units (one unit = 500 ml) was 6.0 (113 units in 20 patients) in the placebo group and 8.1 (170 units in 20 patients) in the tranexamic acid treated group. The aim to transfuse the patients to a hematocrit of around 30 per cent was kept with these amounts of blood as can be seen from table 3.

TABLE 3. Development of hematocrit (per cent) in 22 placebo treated an 21 tranexamic treated patients with massive upper gastrointestinal hemorrhage. Mean and range.

	Placebo	Tranexamic acid
Day 1 (arrival before transfusion)	28.6 (14-44)	27.2 (15-40)
Day 2	30.0 (23-42)	29.1 (24-38)
Day 3	31.3 (22-41)	31.5 (22-40)
Day 7	28.9 (26-37)	30.4 (25-40)

The operation frequency was the same in the two groups but the mortality was somewhat lower in the tranexamic acid treated group. Moreover, death was delayed in the tranexamic acid treated group compared to the placebo group (Table 4). The causes of death is shown in table 5. There were no differences between the groups regarding liver function tests over time. The platelet count was stable for the three first days during which time it was followed and did not differ between the groups. No difference in acid-base balance or pO_2 were found.

DISCUSSION

In a few cases of erosive hemorrhagic gastroduodenitis an extremely high

fibrinolytic activity in gastric juice has been found (8,9). This was in contrast to findings in healthy persons and patients with gastric ulcer. The activity was inhibited by tranexamic acid. Other investigators have found plasmin like activity in gastric veins in patients with gastric ulcer and gastric hemorrhage (5,6) and this activity was later shown to be due to plasmin (10). These findings motivate studies on antifibrinolytic treatment in cases of upper gastrointestinal hemorrhage.

TABLE 4. Number of operations and deaths among 22 placebo treated and 21 tranexamic treated patients with massive upper gastrointestinal hemorrhage.

	Placebo	Tranexamic acid
Operation on day 1	3	4
2	1	
3		
later	3	3
Operation on day (mean)	4.7	4.4
Mors on day 1	2	
2		
3		
later	3	3
Mors on day (mean)	12.2	29.0
Mortality, per cent[x]	22.7	12.3

TABLE 5. Causes of death

a) Placebo treated group

Continued bleeding postoperatively in two patients.
Bleeding from a gastric cancer with death before operation.
Respiratory failure postoperatively.
Circulatory failure and pneumonia postoperatively.

b) Tranexamic treated group

Respiratory failure postoperatively.
Asystole postoperatively.
Continued bleeding postoperatively (amyloidosis in the duodenum)

A hemostatic plug which seals a bleeding vessel is composed of densely packed platelets and rebleedings are prevented by a fibrin net-work surrounding the plug (1). An increased fibrinolytic activity both in the circulating blood and the milieu around the plug (with normal fibrinolytic activity in the blood) give an increased frequency of rebleedings and thus larger blood loss. From this theoretical viewpoint it is of interest to investigate the effect of fibrinolytic inhibition of gastroduodenal hemorrhage in two ways: with general inhibition (intravenously) and with local inhibition (perorally). A third possibility of course is a combination of both. We have chosen oral administration through the gastric tube in order not to mix the two theoretical

possibilities. A solution was used to get maximal admixture with the gastric juice. This is in contrast to other investigators who used tablets. We found no effect on transfusion requirements or operation frequency but a slightly reduced mortality and delayed death. To obtain statistical significance, however, a much larger material is necessary.

There are few investigations made on fibrinolytic inhibition in cases of acute upper gastrointestinal bleeding. Cronstedt et al (7) and Östberg et al (11) used tranexamic acid in all patients and thus nothing can be concluded on the effect of the drug in this type of patients. Moreover, the mortality in their material is of the same magnitude as in other studies without fibrinolytic treatment.

However, there are three controlled investigations on the effect of tranexamic acid in patients with upper gastrointestinal bleeding. Cormack et al (4) and Biggs et al (2) included all patients, which means a rather large proportion of small and less severe bleedings. Cormack et al (4) used tablets and Biggs et al (2) used tablets and solution for injection, both being able to show an effect, Cormack et al on transfusion requirements in patients with negative barium meal and Biggs et al on operation frequency in all patients. Both used relatively small doses. Brömster et al (3) studied patients with severe gastrointestinal hemorrhage, their material very much resembling ours. They started with tranexamic acid i.v. and continued with tablets in a medium dose and was not able to show any effect but there was a tendency in favour of tranexamic acid. This tendency could be seen also in our study, using a large dose.

To conclude from present data fibrinolytic inhibition can possibly have a small but significant effect in small upper gastrointestinal bleedings. Massive bleedings probably have a larger frequency of arterial hemorrhages and then the theoretical motivation for using this type of treatment is less strong. Based on results from the studies on plasmin content in gastric juice and blood the most interesting group to study is patients with erosive hemorrhagic gastroduodenitis. However, these patients are relatively rare. At present time there is need for a double-blind randomized study with a large dose of tranexamic acid administered i.v. and p.o. in patients with erosive gastroduodenitis.

REFERENCES

1. Bergqvist, D.: Hemostatic plug formation time and stability in the microvasculature of rabbit mesentery. Acta Univ Upsal Abstracts of Uppsala Dissertations from the Faculty of Medicine 167 Uppsala 1973.
2. Biggs, J.C., Hugh, T.B., Dodds, A.J.: Tranexamic acid and upper gastrointestinal hemorrhage - a double-blind trial. Gut 17:729, 1976.
3. Brömster, D., Broström, O., Engqvist, A., von Feilitsen, F., Halldin, M., Nyström, B., Öst, A., Reichard, H., Sandquist, S., Törngren, S., Wedlund, J.E.: Tranexamsäure bei grossen Magenblutungen - Eine Doppelblindstudie.

Akt. Gastroenterologie 6: 225, 1977.
4. Cormack, F., Chakrabarti, R.R., Jouhar, A.J., Fearnley, G.R.: Tranexamic acid in upper gastrointestinal hemorrhage. Lancet 1:1207, 1973.
5. Cox, H.T.. Poller, L., Thomson, J.M.: Gastric fibrinolysis. A possible aetiological link with peptic ulcer. Lancet 1:1300, 1967.
6. Cox, H.T., Poller, L., Thomson, J.: Evidence for the release of gastric fibrinolytic activity into peripheral blood. Gut 10:404, 1969.
7. Cronstedt, J., Östberg, H., Carling, L., Lööf, L., Wennerholm, M., Högberg, N., Vogel, A.: Diagnosis and treatment of acute gastrointestinal hemorrhage in a small district hospital. Acta Med Scand 199:129, 1976.
8. Nilsson, I.M., Bergentz, S-E., Hedner, U., Kullenberg, K.: Gastric fibrinolysis. Thromb Haemostas 34:409, 1975a.
9. Nilsson, I.M., Bergentz, S-E., Wiklander, O., Hedner, U.: Erosive hemorrhagic gastroduodenitis with fibrinolysis and low factor XIII. Ann Surg 182:677, 1975b.
10. Thomson, J.M.: Fibrinolysis and the stomach: biochemical identification of the "plasmin-like" enzyme. Thromb Haemostas 31:291, 1974.
11. Östberg, H.O., Ulfberg, J., Wennerholm, M., Zellner, K.: Acute gastrointestinal hemorrhage. Experience with early panendoscopy and tranexamic acid in a rural hospital. Acta Chir Scand 143:463, 1977.

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