Cyklokapron®

tranexamic acid

- is a specific therapy for the control of fibrinolytic bleeding
- is a valuable complement to replacement therapy in haemophilia
- prevents attacks of hereditary angioneurotic oedema

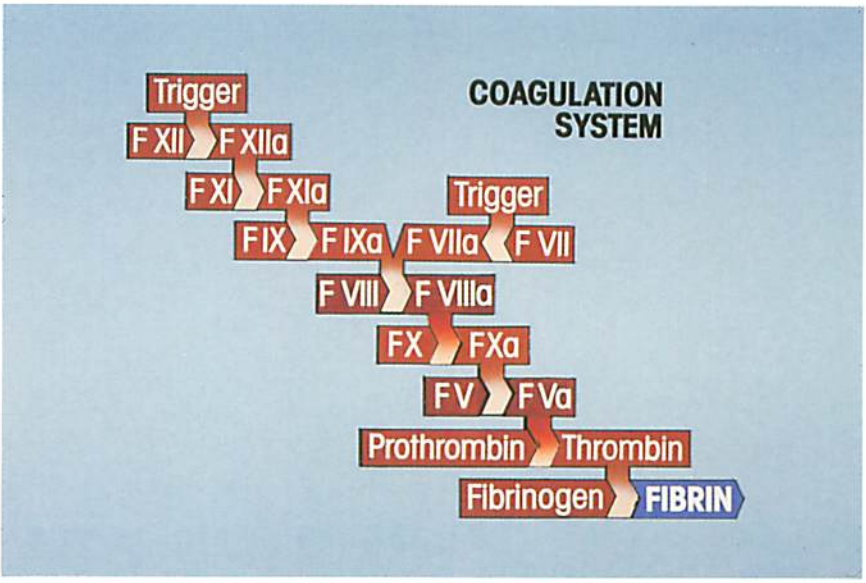
KabiVitrum 

Contents

Haemostatic equilibrium

The coagulation of blood takes place in a complex series of consecutive activation reactions finally leading to the active proteolytic enzyme thrombin.

The reaction sequence is usually described as follows

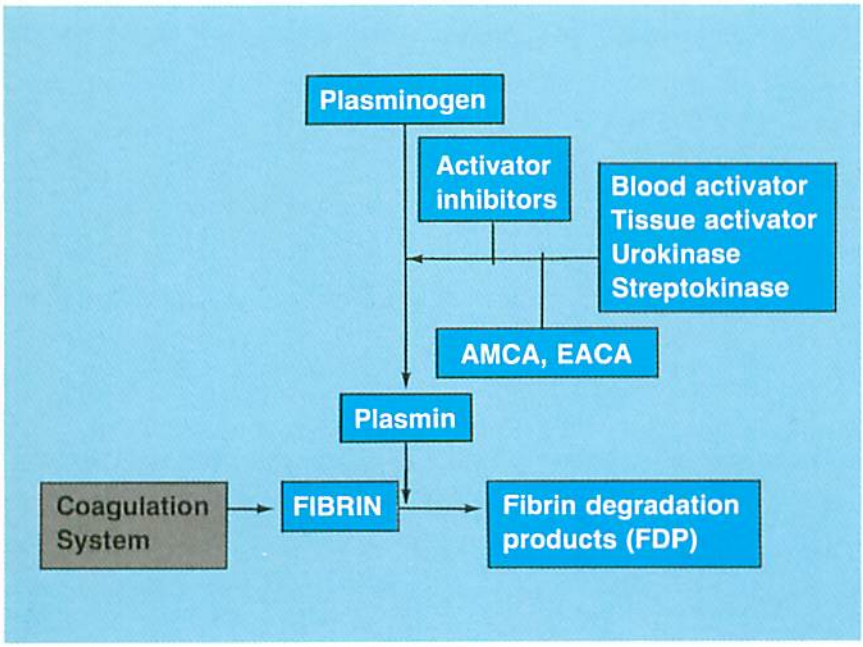


The coagulations factors XII, XI, IX, VII, VIII, X, V, and II (prothrombin) are all inactive precursors of proteolytic enzymes (XII_a...II_a), which, in an accelerated sequence of events, finally generate the fibrin meshwork necessary for effective haemostasis. This occurs primarily at sites of bleeding in the presence of aggregating platelets whose surfaces serve as catalysts for rapid thrombin formation.

In a subsequent step thrombin catalyses the conversion of fibrinogen to fibrin. This final step in blood coagulation also marks the initial step of the opposite process, dissolution of fibrin or fibrinolysis.

The fibrinolytic system has two main functions: to counteract an overproduction of fibrin and to regulate tissue repair processes. The fibrinolytic system is briefly outlined below.

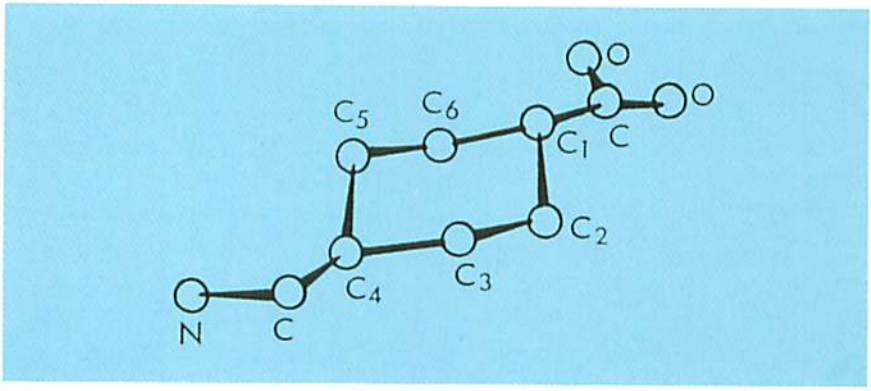
Fibrinolytic system



The coagulation and fibrinolytic systems normally balance one another in such a manner that neither thrombosis nor bleeding occurs. In a series of steps, vascular trauma will finally trigger the formation of fibrin and the bleeding will cease. However, defective fibrin formation or excessively rapid dissolution of fibrin results in continued bleeding or rebleeding.

It was realized early on that it ought to be possible to master the fibrinolytic haemorrhages with suitable inhibitors of plasmin, and, in order to meet the need for therapeutically useful agents, Okamoto and co-workers (1968) started a comprehensive programme for the screening of synthetic compounds, especially those of the amino acid type, as early as 1948. This work soon led to the discovery of ε-aminocaproic acid, EACA, which was extensively studied both in vivo and in vitro during the early 1950s.

With the development of high-purity streptokinase for clinical use, the sudden interest in thrombolytic treatment of thrombotic disorders made the availability of efficient inhibitors as antidotes even more urgent than before and the work was continued by many groups to find more active inhibitors. Okamoto & Okamoto (1962) discovered the derivative 4-aminomethylcyclohexane-carboxylic acid, which was later shown independently by Okamoto and co-workers (1964) and Melander et al (1965) to consist of two isomers, one of them being responsible for all of the activity. Okamoto et al (1964) identified it as the isomer trans-4-aminomethyl-cyclohexane carboxylic acid with the following structure:



Steric configuration of tranexamic acid as determined by X-ray crystallography.

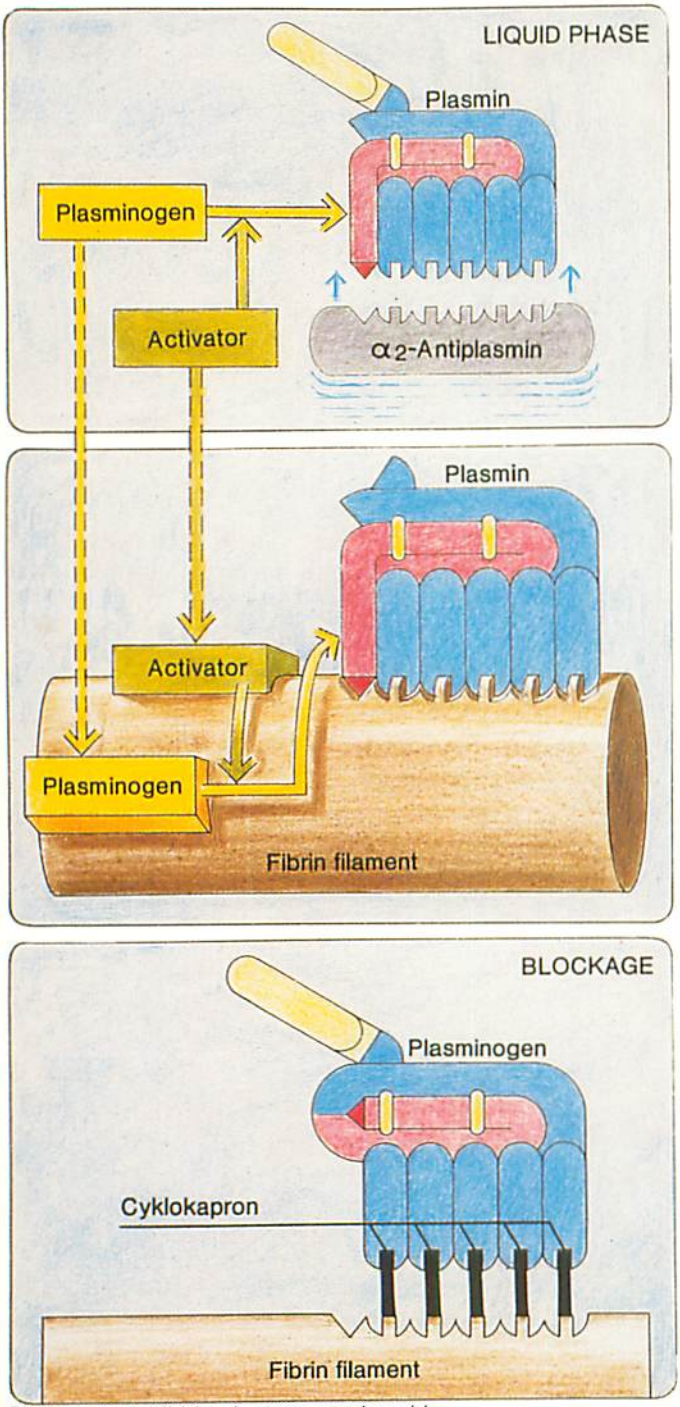
It was shown to have about 10 times the activity of EACA.

During this early period of development very little was known in detail about the mechanisms underlying the fibrinolytic system. Only during the last ten years or so, after extensive research into the structures of fibrinogen and plasminogen and its activator has a clearer picture gradually developed.

When fibrinogen is transformed into fibrin, sites in the molecule containing structures that adsorb activator and plasminogen in strategic positions for activation to plasmin and subsequent efficient lysis of the fibrin clot are opened up.

How fibrinolysis is inhibited by Cyklokapron

Tranexamic acid



Fibrinolytic inhibition by tranexamic acid

1. Normally
The small amounts of plasmin formed in the blood stream are inhibited by the natural inhibitor, α_2-*antiplasmin*.

2. In the presence of fibrin
Here the plasminogen-plasmin-activator complex is bound to the *surface of fibrin*.
Since the inhibitor – α_2-antiplasmin – remains in the liquid phase, it cannot prevent activation.
This means that there is no natural means of inhibition in the system; consequently, there is a risk of bleeding owing to *clot dissolution*.

3. Blockage by Cyklokapron
Cyklokapron blocks the plasminogen molecule so that it cannot be bound to the fibrin surface. As a result of this blockage, the fibrin is not broken down, which allows the formation of a stable clot and thereby *reduces the risk of recurrent bleeding*.

Synthetic inhibitors of the amino acid type act by occupying the sites in the plasminogen molecule that would normally have taken part in the adsorption to fibrin.

In this way, the activation of plasminogen in situ is effectively inhibited and no fibrinolysis takes place since the systemic activation is a comparatively slow process.

Inhibition of fibrinolysis by tranexamic acid is illustrated on page 6 by molecular models from the film, "The Fibrinolytic System", produced by KabiVitrum AB in co-operation with Dr Sixtus Thorsen, Chief Physician, Department of Clinical Chemistry, Hvidovre, Hospital, Denmark.

For further information about haemostatic equilibrium, please consult:

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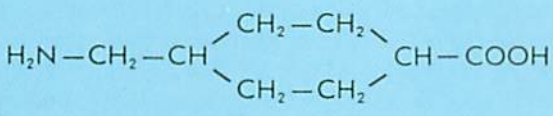
Cyklokapron®

tranexamic acid

Tranexamic acid (AMCA) is a synthetic amino acid with P^{K}_{a} values of 4.3 and 10.6 respectively. It forms white crystals, which are solublekin water, acids and alkalies, but insoluble in organic solvents. The molecular weight is 157 and the structural formula is askfollows:



Trans-4-aminomethyl cyclohexane carboxylic acid

Pharmacodynamics

Tranexamic acid in therapeutic concentrations, 5-20 mg/l produces an antifibrinolytic effect by competitively inhibiting the activation of plasminogen to plasmin (Andersson, 1965, Dubber et al, 1965; Maki & Beller, 1966; Skoza et al, 1968). As a result of this inhibition, fibrin is not broken down, and this allows the formation of a more stable clot and thereby reduces the risk of recurrent bleeding.

Fibrinolytic activity can be determined by various methods, e.g. the euglobulin clot lysis test and the fibrin plate method. As the activity determined by these methods is the net effect of fibrinolytic activators and inhibitors, they can also be used to determine the antifibrinolytic effect of synthetic inhibitors.

Comparative in vitro investigations of the inhibiting effect of tranexamic acid (AMCA), aminocaproic acid (EACA) and para-aminomethylbenzoic acid (PAMBA) on plasminogen activation induced by streptokinase or physiological activators, such as urokinase or tissue activators, have produced different results, presumably because of differences in the test methods used. As a rule, however, AMCA is found to be twice as strong as PAMBA (Maki & Beller 1966) and 6-10 times stronger than EACA in vitro (Andersson, 1965; Andersson et al, 1968).

Tranexamic acid in a concentration of 1 mg/ml did not aggregate platelets in vitro (Cronberg, 1968).

Tranexamic acid did not affect the fibrinolytic activity in the vessel walls after daily treatment during 3 weeks (Åstedt et al, 1978). This finding is of importance from the safety point of view and can be regarded as a possible explanation of the fact that tranexamic has not been found to increase the incidence of tromboembolic complications in controlled clinical studies.

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Pharmacokinetics

Gastrointestinal absorption of tranexamic acid in the therapeuticdose range of 0.5 - 2 g amounts to 40%. Individual variations in serum concentrations are very small and the maximum concentration is reached within 2 - 3 hours after the first oral dose. The synthetic amino acid is chiefly distributed in the extra cellular liquid volume and is eliminated through the kidneys. The biological half live is 2 - 3 hours.

In therapeutic concentrations, 5 to 10 mg/l, the protein binding of the drug , about 3%, can be neglected and appears to be fully accounted for by its binding to plasminogen (Widlund & Strömberg, 1979).

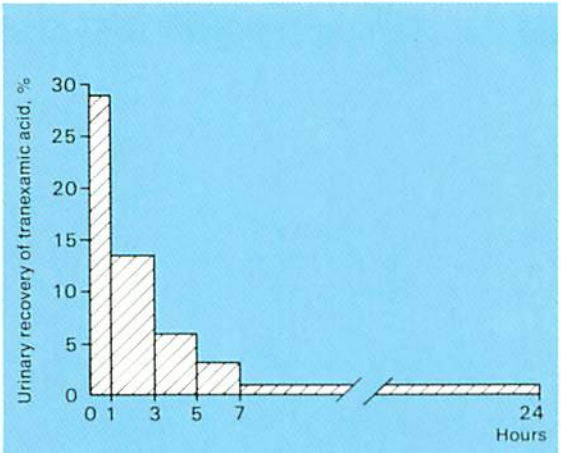
Absorption and elimination

Andersson et al (1965, 1968) first studied the absorption, distribution and excretion of AMCA in man. They measured the acid in serum by a biological method as well as by high-voltage paper electrophoresis, and in urine by high-voltage paper electrophoresis. After intravenous administration of 10 mg tranexamic acid per kilo body weight, about 30% was recovered in the urine during the first hour, 45% during the first 3 hours and 90% within 24 hours. The corresponding values after oral administration of 10-15 mg tranexamic acid per kilo body weight were about 1%, 7% and 39%.

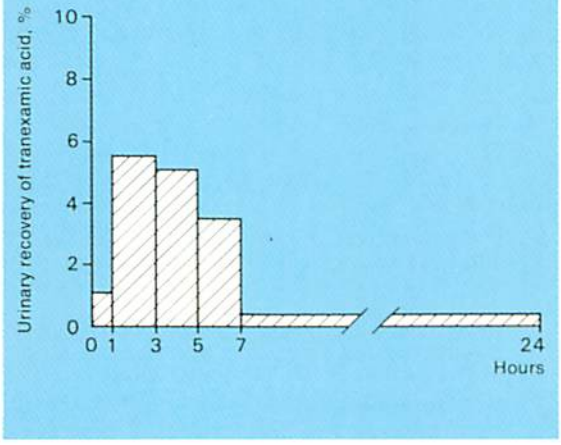
After intravenous administration of 10 mg per kilo body weight Kaller (1967) found plasma concentrations of 18, 10 and 5 mg/l after 1, 3 and 5 hours respectively. The biological half-life was calculated to be about 80 minutes.

Oral administration of 1 g of tranexamic acid in tablets and aqueous solution to 12 healthy normal volunteers gave mean peak plasma concentrations of 8.4 and 8.2 mg/l, respectively, noted 3 hours after dosing. The mean urinary recovery after 24 hours was 38.7 and 40.5% and after 48 hours 40.5 and 42.1% (Eriksson et al, 1971a).

In a study by Eriksson et al (1974) 1 g of tranexamic acid was given intravenously to two healthy normal volunteers. One hour after administration the plasma concentrations were 27.8 and 28.5 mg/l, respectively. Five and a half hours after dosing 4.6 and 3.6 mg/l and 8 hours after dosing the plasma tranexamic acid level was 2.8 and 2.0 mg/l, respectively. More than half of the dose was recovered in the urine as unchanged tranexamic acid within 2 hours after dosing and about 90% within 24 hours. The renal clearance was 135 and 132 ml/min/1.73 m^2, indicating that the elimination is by glomerular filtration. The plasma concentration levels and the urinary recovery reported in this study have later been confirmed by Pilbrant et al (1981) using a more sensitive analytical method. They also showed that food had no effect on the absorption of the drug. The mean peak plasma concentration, noted at 3 hours, was 14.4 mg/l without food and 14.8 mg/l with food (see Fig. page 12). The urinary recoveries over 24 hours were 33.4 and 34.9%, respectively.



Urinary recovery of tranexamic acid after i.v. administration of 10 mg/kg (mean values for 10 males). Average recovery during 24 hours: 91 per cent.

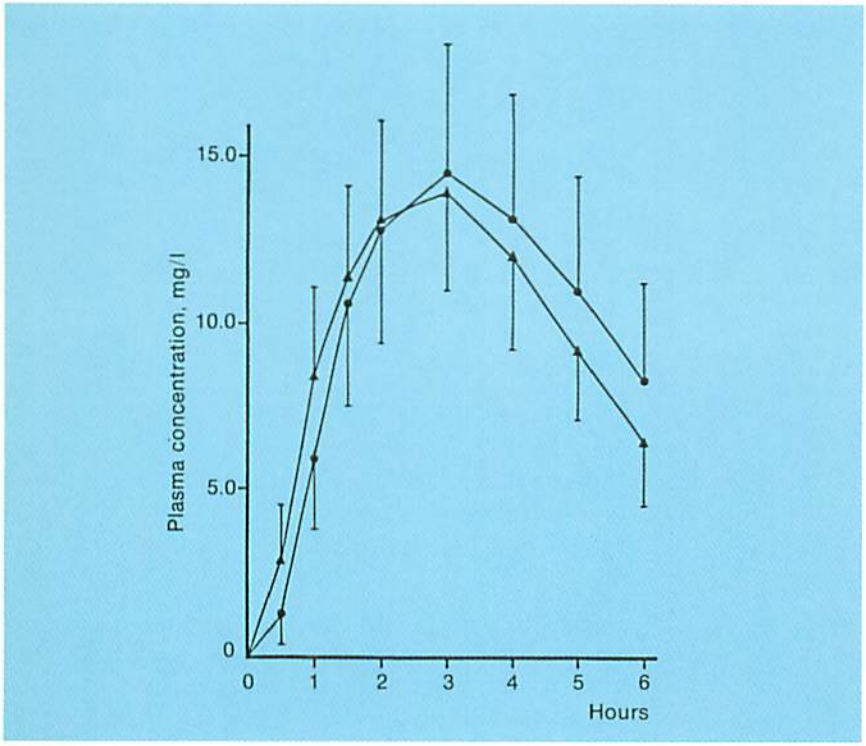


Urinary recovery of tranexamic acid after oral administration of 10–15 mg/kg (mean values for 11 males). Average recovery during 24 hours: 38.5 per cent.

Distribution

The concentration of tranexamic acid has been determined by high-voltage electrophoresis in serum and human tissue fragments (e.g. from the large intestine, kidneys and prostate) removed at surgery. Tranexamic acid was administered 36-48 hours before surgery in four doses of 10-20 mg/kg body weight. The results showed that an antifibrinolytically active concentration of 10 mg/l remained up to 17 hours in the tissues investigated. (Andersson et al, 1968).

Given by mouth or intravenously, tranexamic acid diffuses into semen and inhibits its fibrinolytic activity but does not influence sperm migration (Liedholm et al 1973). The inhibitory effect of tranexamic acid on the plasminogen activators in human seminal plasma has been demonstrated by Hisazumi (1970).



Mean plasma concentration (n = 10) of tranexamic acid after a single oral dose of 2 g. ▲ = fasting conditions. ● = with a meal. Bars indicate + or − one SD.

Tranexamic acid passes into the placenta (Kullander & Nilsson, 1970; Walzman & Bonnar, 1982). After intravenous injection of the mother with 10 mg/kg body weight the concentration in the cord blood may be fairly high: about 30 mg/l. Tranexamic acid passes into the breast milk during lactation at a concentration of about 1% of the corresponding serum levels (Eriksson et al, 1971b).

Ahlberg et al (1976) gave 10 mg tranexamic acid/kg body weight to patients before knee-joint operations. They found that tranexamic acid rapidly diffused into the synovial fluid and synovial membranes and reached the same concentration in the synovial fluid as in the serum. The biological half-life in the synovial fluid was about 3 hours.

Bramsen (1979) investigated the aqueous humour concentration of tranexamic acid after oral administration. After a dose of 25 mg/kg body weight three times daily the peak concentraton reached within three hours was 1.6 mg/l in acqueous humour and 15 mg/l in serum. The tranexamic acid disappeared slowly from the aqueous humour.

In patients with aneurysmal subarachnoid haemorrhage tranexamic acid also enters the cerobrospinal fluid at a concentration of about 2-5 mg/l after a dose of 1 g given intravenously 4-hourly (Tovi & Thulin,1972).

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Toxicology

The acute toxicity of tranexamic acid (TA) as studied in several species is low. Chronic toxicity studies on rats and dogs revealed significant organ toxicity only in the dogs in the form of zonal retinal atrophy after high daily oral doses (800 mg/kg body weight and above). However, the safety margin for treatment in man with TA is considered good. Dogs receiving 800 mg/kg/day had mean peak TA plasma levels of approximately 200 mg/l, which is of the order of 10-20 times that obtained in man after the therapeutic oral dose of about 30 mg/kg body weight. Carcinogenicity studies of TA (in mice and rats) have given no indication of a carcinogenic potential, and no mutagenic activity was observed in a battery of mutagenicity tests. No adverse effects of TA on the reproductive process were found in a series of reproduction toxicology studies (in mice, rats and rabbits).

Tranexamic acid has low acute toxicity. The oral lethal doses exceed 3-10 g/kg body weight in all species studied and the LD_{50} value after i.v. injection is about 1-1.5 g/kg body weight in mice, rats, rabbits and dogs (1-4).

No specific toxicity of TA was found in rats given daily oral doses of up to 1000 mg/kg body weight for 6 months, however, dose-related loose stools or diarrhoea and decreased body weight gain were observed at the highest dose levels (5-7).

In 12-month toxicity studies on dogs (8-13), partial retinal atrophy was observed in a dose related pattern. The retinal atrophy occurred after daily oral doses of 800 mg/kg body weight and above (1200 and 1600), whereas doses of 400 mg/kg body weight/day and below were not associated with retinal toxicity. The retinal atrophy had a typical zonal distribution being located either in the posterior retina, i.e. around the optic disc, and or involving the anterior retina at the far retinal periphery (ora ciliaris retinae, which constitutes the canine equivalent to the ora serrata in man). The anterior retinal atrophy had a slowly progressing course, mimicking that of senescence. It is manifested initially in a gradual decrease in the length of the photoreceptor outer segments (13) (the canine retina is dominated by rods). In later stages, the inner layers of the retina are in direct contact with the pigment epithelium. It should be noted that this retinal atrophy is not associated with any proliferation or hyperpigmentation of the pigment epithelium.

Total atrophy of the photoreceptor layer is incompatible with restitution, this was verified in the recovery segment of one of the studies (9). In dogs with ophthalmoscopically manifest retinal (posterior) atrophy treated for 12 months with 1600 mg/kg/day, the condition proved to be irreversible after cessation of treatment for 13 months, however, the atrophy did not progress during the treatment-free period (11). The mean peak plasma levels of tranexamic acid for dogs treated for 4 weeks with retinotoxic doses of 800 and 1200 mg/kg/day were about 200 and 300 mg/l, respectively (12). From 13 weeks onwards the corresponding values were 150 and 150-220 mg/l (12). At the 1200 mg/kg/day dose level the majority of the dogs developed retinal atrophy (12). The period preceding appearance was 5-14 weeks for the posterior atrophic zone, as verified by ophthalmoscopy (12). The zonal retinal atrophy was not associated with impairment of retinal function, as assayed by electroretinography (12).

In some instances it has been possible to produce retinopathy after

short-term treatment with very high (sublethal) i.v. doses of tranexamic acid in experimental animals. Focal retinopathy was described in a dog subjected to 7 daily i.v. infusions of 2 g/kg/day, whereas a single dose of 2 g/kg to another dog was uneventful (14). Cats given sublethal doses, i.e. 250 or 500 mg/kg/day i.v., for 4-6 days developed retinopathy, whereas those given 125 mg/kg/day for 14 days did not (15). Daily i.v. doses of 2 g/kg/day to monkeys for 7 or 14 days were not associated with drug induced retinal changes.

The preclinical toxicology and experimental pathology studies on TA in animals indicate a good safety margin in man. The oral (therapeutic) dose of tranexamic acid of about 30 mg/kg body weight yields a peak plasma level in the range of 10-20 mg/l (17). After a single i.v. infusion of about 15 mg/kg in man the plasma level of TA is 85 mg/l after 10 minutes and 20 mg/l after 2 hours (17). Ophthalmoscopic examinations of patients on long-term treatment (i.e. for several years with a total consumption of several kilograms of tranexamic acid) have failed to disclose any drug induced retinal changes (18).

Drugs intended for long-term treatment in man call for chronic carcinogenicity studies in experimental animals the animals been treated for nearly their entire life span. Several carcinogenicity studies in rodents have been performed with tranexamic acid. In one of the earlier studies a low incidence of biliary malignancies was found at the highest dose level together with a dose-related increase in biliary hyperplasia occurring at a very early stage in the study (19, 20). One remarkable fact was the unusual high incidence of biliary hyperplasia in the concurrent control group in this study compared to the historical incidence in controls of the same strain of rats. The findings of this study have been invalidated by the results of more recent studies (21-24) which did not confirm reproduce the biliary tract hyperplasias and malignancies.Furthermore, no mutagenic activity of tranexamic acid has been demonstrated in several in vitro and in vivo test systems (25-28).

No adverse effects of tranexamic acid were observed in the reproduction toxicology studies, which included teratology studies in mice (29), rats (29) and rabbits (30, 31), perinatal postnatal studies in rats (32) and a fertility study in rats (34).

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29. MORITA H, TACHIZAWA H, AKIMOTO T: Evaluation of the safety of tranexamic acid (3). Teratogenic effects in mice and rats. Oyo Yakuri 5, 415–420, 1971.

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31. PALMER A K, READSHAW M A: Effect of tranexamic acid on pregnancy of the New Zealand White rabbit. 2. Intravenous administration. Huntingdon Research Centre Confidential Report No 4157/71/315, 1971b.

32. STRIPPOLI N, JACKSON B A: Tranexamic acid, CL 65, 336. A perinatal and postnatal study of tranexamic acid in rats. Study 17438. Lederle Laboratories Confidential Report No 20, 1971b.

34. STRIPPOLI N, JACKSON B A: Tranexamic acid, CL 65, 336. Effect of tranexamic acid on fertility and general reproductive performance of female rats (Segment I, female). Study 17437. Lederle Laboratories Confidential Report No 19, 1971a.

Safety

Safety studies with tranexamic acid include laboratory investigations and ocular examinations. Such studies have been performed in connection with clinical trials and as follow-up studies in patients and in normal volunteers. Furthermore experience from a limited number of pregnant women is available.

Laboratory investigations

Altogether, 159 patients and normal volunteers have been followed, 121 in clinical trials, 25 in follow-up studies and 13 were normal volunteers.

The daily intravenous dose varied between 3 and 6 g of tranexamic acid and the longest period of treatment was six weeks. The daily oral dose varied between 0.5 and 9 g of tranexamic acid and in many patients the treatment has been continuous. The total amount of drug ingested varied between some ten grams and more than 20 kg.

There were no drug-related changes in the laboratory investigations. However, the streptokinase-induced plasma clot-lysis time was prolonged to more that 180 minutes. The range during placebo treatment was five to ten minutes.

Laboratory investigations have been performed in connection with clinical trials in aneurysmal subarachnoid haemorrhage, corneal oedema and hereditary angioneurotic oedema, as well as in follow-up studies of patients with coagulopathies, hereditary angioneurotic oedema and menorrhagia and in normal healthy volunteers.

Three of the reports have been published, all dealing with long-term treatment, one in connection with aneurysmal subarachnoid haemorrhage and two in hereditary angioneurotic oedema. Data on the remaining patients and on normal volunteers are on file at KabiVitrum AB, Stockholm, Sweden.

The influence of tranexamic acid on serum transaminases, LDH, AST (or ASAT, formerly SGOT) and ALT (or ALAT, formerly SGPT) was investigated in 46 patients with subarachnoid haemorrhage who took part in a controlled clinical trial (Dahlerup & Fodstad, 1982). During the first week of treatment 1 g was given intravenously 6 times daily, during the second week 1 g was given intravenously 4 times daily and during the following four weeks 1.5 g were given orally 4 times daily. Treatment was stopped in connection with surgery and discharge. Thus, the length of the treatment period varied.

The results showed that tranexamic acid had no influence on the serum levels of these enzymes.

Fifteen patients, 13 adults and two children, ten and 13 years of age, were treated with tranexamic acid for hereditary angioneurotic oedema in an open study (Agostoni et al, 1978). The daily dose varied between 1.5 g and 3 g of tranexamic acid. Eleven of these patients were checked with laboratory investigations after having been treated for between six months and one and a half years. The laboratory investigations consisted of blood chemistry (AST, ALT, alkaline phosphatase, GGT, bilirubin, α-foetoprotein), haematology (platelets, prothrombin time) and determination of the fibrinolytic activity.

The laboratory data show that hepatic function tests and blood fibrinolytic activity were not influenced by long-term oral treatment with tranexamic acid.

One male patient with hereditary angioneurotic oedema has been treated with tranexamic acid for nine years, the dose being rather high: 1.5 g five to six times daily (Lundh, 1973). During this period more than 20 kg of tranexamic acid have been administered. The patient has been followed up with laboratory investigations at intervals during the treatment period. The last investigations reported included sedimentation rate, haemoglobin, serum iron, leucocyte count, differential count, neutrophils, eosinophils, lymphocytes, monocytes, platelet count, serum bilirubin, alkaline phosphatase, glutamyl transferase, aspartate(amino)transferase, alanine(amino) transferase, serum amylase, urinary glucose or protein, serum creatinine, ^{51}Cr-EDTA-clearance, prothrombin, bromsulphthalein retention, α-foetoprotein and carcino-embryonic antigen.

There were no laboratory signs of any damage to the blood, liver, kidneys, muscle tissue or prostatic gland.

Ocular examinations

Altogether, 131 patients and normal volunteers have been followed, 40 in clinical trials, 78 in follow-up studies and 13 were normal volunteers.

The daily intravenous dose varied between 3 and 6 g of tranexamic acid and the longest period of treatment was six weeks. The daily oral dose varied between 0.5 and 9 g of tranexamic acid and in many patients the treatment has been continuous. The total amount of drug ingested varied between some ten grams and more than 20 kg.

There were no drug-related changes in the ocular examinations.

Ocular examinations have been performed in connection with clinical trials in aneurysmal subarachnoid haemorrhage and in hereditary angioneurotic oedema as well as in follow-up studies of patients with aneurysmal subarachnoid haemorrhage, coagulopathies, hereditary angioneurotic oedema, leukaemia and in normal healthy volunteers.

Only one of the reports has been published. It deals with long-term treatment in patients with hereditary angioneurotic oedema.

Fourteen patients with hereditary angioneurotic oedema have been treated with tranexamic acid for an average period of six years, range 1.5 months to eight years (Theil, 1981). The total dose of tranexamic acid ranged between 1500 and 8000 g.

The ocular examinations included dark adaptometry, visual acuity, colour vision, visual field, bulbar motility, pupillary reflexes, slit-lamp examination, central corneal thickness, intraocular pressure, ophthalmoscopy, fundus photography, fluorescein angiography and electroretinography.

No retinal changes were found that could have been caused by the tranexamic acid therapy. The central corneal thickness was normal.

Experience during pregnancy

So far, 21 patients have received long-term treatment for bleeding during pregnancy and 67 have been given a single dose of 1 g immediately before caesarean section. The long-term treated women were treated for one to 18 weeks, the total doses ranging from 42 to more than 700 g of tranexamic acid. No further bleeding complications occurred when on treatment and they all gave birth to live, normal children.

The limited experience with tranexamic acid in the treatment of pregnant women indicates no negative effect on the mother or child or on the course of the pregnancy. Instead, there are indications that treatment with tranexamic acid will be of importance in preventing bleeding during pregnancy and thereby reducing perinatal mortality and morbidity.

The question of using tranexamic acid during pregnancy and at delivery can be discussed along two lines: safety and therapeutic effect. The safety of the drug is most important.

Reproduction studies have been performed in mice, rats and rabbits at doses up to 75 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to tranexamic acid (Morita et al, 1971; Data on File, KabiVitrum, Stockholm, Sweden).

Since animal reproduction studies are not always predictive of human response, experience gained from the use of the drug in the pregnant woman is of great importance.

The therapeutic effect of drug treatment during pregnancy must be evaluated and a risk-benefit analysis made. There are as yet no controlled studies in pregnant women, but there have been a couple of reports on the use of tranexamic acid during pregnancy.

It is a well-known fact that bleeding during pregnancy is associated with a three- to fourfold increase in perinatal mortality. Maternal mortality is also increased. An effective method of treating bleeding during pregnancy could reduce the high perinatal mortality and morbidity in pregnancies complicated by bleeding.

The rationale of treating bleeding during pregnancy with antifibrinolytic drugs is based on the assumption that activation of the fibrinolytic system plays a role in the occurrence of bleeding during pregnancy. In all papers dealing with tranexamic acid and bleeding during pregnancy evidence is presented that the fibrinolytic system is activated and that this activation is inhibited by treatment with tranexamic acid.

Kullander & Nilsson (1970) showed that tranexamic acid crosses the placenta.

Storm & Weber (1976) treated a woman with fibrinolytic bleeding in the fourth month of pregnancy with tranexamic acid for a total of 64 days, 1 g p.o. every six hours. The total dose was 256 g. Delivery occured spontaneously in the 30th week of pregnancy and was normal in all other respects. The infant was healthy.

A pregnant woman with Glanzmann's thrombasthenia was treated with tranexamic acid to prevent haemorrhage (Sundqvist et al, 1981). The patient had antibodies against tissue antigen and thus platelet transfusion was of no

benefit. The patient was treated from the 24th gestational week to delivery in the 42nd week with 1 g p.o. every four hours. The delivery was uneventful and the child was normal.

Svanberg et al (1980) treated 73 women in the acute stage of abruptio placentae. Of these, 67 were in late pregnancy and were delivered immediately by caesarean section after first having been given 1 g of tranexamic acid i.v. The remaining six were in early pregnancy with less pronounced symptoms. They were treated acutely with 1 g of tranexamic acid i.v. and were then switched to oral treatment with 1 g every four hours until delivery 1 to 12 weeks later, which was also by delivered by caesarean section. In the 67 patients the perinatal mortality was 8 per cent and the maternal mortality was nil. All in the group of six patients gave birth to normal children. None of the cases were complicated by haemorrhagic diathesis or thrombosis. Two patients on long-term therapy had laboratory tests to check the coagulation and fibrinolytic systems. The fibrin-fibrinogen degradation products (FDP) disappeared and the fibrinogen levels increased, as did the concentration of plasminogen. No changes in the other coagulation factors occurred.

Treatment with tranexamic acid was investigated in 12 women with vaginal bleeding in the second half of pregnancy (Walzman & Bonnar, 1982). The aim of the therapy was to accelerate haemostasis in the uteroplacental circulation and to prevent further bleeding at the placental site. Tranexamic acid 1 g 8-hourly was given for 7 days. Serial investigations of coagulation and fibrinolysis were carried out. Plasma fibrinolytic activity, plasminogen, antiplasmin and platelet counts decreased significantly during treatment, while antithrombin III (AT III) and factor VIII related antigen (F VIII R:Ag) showed a significant increase. Plasma tranexamic acid levels ranged from 5 mg/l to 17 mg/l. Two patients on treatment at the time of delivery had plasma tranexamic acid levels of 9 mg/l and 12 mg/l detected in the umbilical cord venous blood. No adverse effects were detected in any of the mothers and all 12 were delivered of live infants.

In a case of threatened placental abruption prevented by giving tranexamic acid, the patient had already lost two children in connection with placental abruption. Bleeding occurred in the 26th week of her third pregnancy, indicating abruption. Pathological proteolysis with predominant activation of the fibrinolytic system was established.

Between the 26th and 33rd week of pregnancy about 250 g of tranexamic acid were given, both intravenously and orally (1 g 4-hourly). The bleeding was arrested and a healthy child was delivered by caesarean section (Åstedt & Nilsson, 1978).

General comments

Up to now more than 3000 patients have been treated with tranexamic acid in clinical studies. The number of controls, untreated or placebo-treated, is almost 4000. There is only one type of side-effect that occurs more frequently in the tranexamic acid-treated patients, namely diarrhoea, or loose stools. This is known from experience to be a dose-dependant effect, and by lowering the dose this could be avoided.

Care must be taken when treating patients with renal insufficiency with tranexamic acid as the drug is excreted via the kidneys. In order to avoid the risk of accumulation, the following dosage schedule should be followed:

Serum creatinine	Dose, i.v.	Dose frequency
120–250 mmol/ml	10 mg/kg	twice daily
250–500 mmol/ml	10 mg/kg	every 24 hours
500 mmol/ml	5 mg/kg	every 24 hours

AGOSTONI A, MARASINI B, CICARDI M, MARTIGNONI G, UZIEL L, PIETROGRANDE M: Hepatic function and fibrinolysis in patients with hereditary angioneurotic oedema undergoing long-term treatment with tranexamic acid. Allergy 1978, 33, 216–221.

KULLANDER S, NILSSON I M: Human placental transfer of an antifibrinolytic agent (AMCA). Acta Obstet Gynecol Scand 1970, 49, 241–242.

LUNDH B: Tranexamic acid in hereditary angioneurotic oedema-A progress report. N Engl J Med 1973, 288, 53.

MORITA H, TACHIZAWA H, AKIMOTO T: Evaluation of the safety of tranexamic acid (3). Teratogenic effects in mice and rats. Oyo Yakuri 1971, 5, 415–420.

STORM O, WEBER J: Langvarig behandling med traneksamsyre (Cyklokapron®) under graviditet. (Prolonged treatment with tranexamic acid (Cyklokapron®) during pregnancy.) In Danish, summary in English. Ugeskr Laeg 1976, 138, 1781–1782.

SUNDQVIST S-B, NILSSON I M, SVANBERG L, CRONBERG S: Glanzmann's thrombasthenia: Pregnancy and parturition. Thromb Haemostas 1981, 46, 225/0710.

SVANBERG L, ÅSTEDT B, NILSSON I M: Abruptio placentae- Treatment with the fibrinolytic inhibitor tranexamic acid. Acta Obstet Gynecol Scand 1980, 59, 127–130.

THEIL P: Ophthalmological examinations of patients in long-term treatment with tranexamic acid. Acta Ophthalmol 1981, 59, 237–241.

WALZMAN M, BONNAR J: Effects of tranexamic acid on the coagulation and fibrinolytic systems in pregnancy complicated by placental bleeding. Arch Toxicol 1982, Suppl 5, 214–220.

ÅSTEDT B, NILSSON I M: Recurrent abruptio placentae with the fibrinolytic inhibitor tranexamic acid. Br Med J 1978, 1, 756–757.

Clinical studies

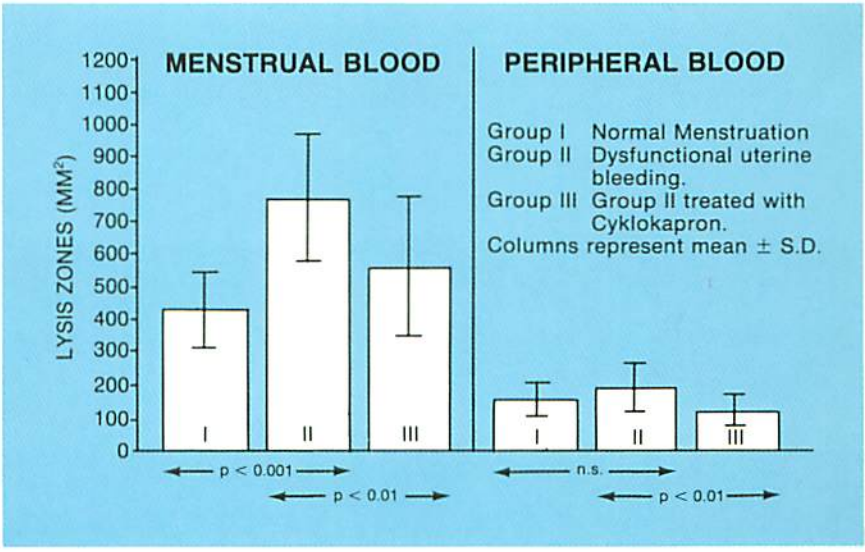
Gynaecology

Menorrhagia

Iron deficiency anaemia in women may be due to excessive menstrual blood loss. In a population study comprising 476 randomly selected women Hallberg et al (1966) investigated the relations between menstrual blood loss and the haemoglobin concentration, the plasma iron concentration and mean corpuscular haemoglobin concentration (MCHC) in order to define the normal limits in menstrual blood loss.

In the 61–80 ml range of menstrual blood loss there was a decrease in the mean values of Hb, MCHC and plasma iron concentration and this decrease was more marked in subjects losing more than 80 ml per menstrual period. On comparing the values obtained in the 1–60 ml range and >80 ml ranges the decrease was statistically significant. Also the number of subjects with a haemoglobin concentration below 12 g per 100 ml, a MCHC below 30 per cent and a plasma iron concentration below 80 μg per 100 ml, respectively, was significantly higher in the >80 ml range compared with the 1-60 ml range. On the basis of these findings the authors consider the upper limit of the menstrual blood loss to be situated between 60 and 80 ml and

Fibrinolytic activity of euglobulin fractions in menstrual and peripheral blood



This study demonstrates that in patients receiving antifibrinolytic therapy, the fibrinolytic activity in menstrual blood is significantly reduced, while in peripheral blood it remains within the normal range.

state that a blood loss above 80 ml should be regarded as pathological. These results were later confirmed by Cole et al (1972).

The reason for using antifibrinolytic drugs in menorrhagia is that women with menorrhagia have a significantly higher plasminogen activator content in the endometrium on the first day of the period than women with a normal menstrual blood loss (Rybo, 1966). Furthermore, Bonnar et al (1983) showed that the fibrinolytic activity in the menstrual fluid of women with excessive menstrual blood losses is increased compared to women with normal menstruation (see figure on page 23).

BONNAR J, SHEPPARD B L, DOCKEREY C J: The haemostatic system and dysfunctional uterine bleeding. Res Clin Forum 1983, 5, 27–36.

COLE S, THOMSON A M, BILLEWICS W Z, BLACK A E: Haematological characteristics and menstrual blood losses. J Obstet Gynecol Br Commonw 1972, 79, 994–1001.

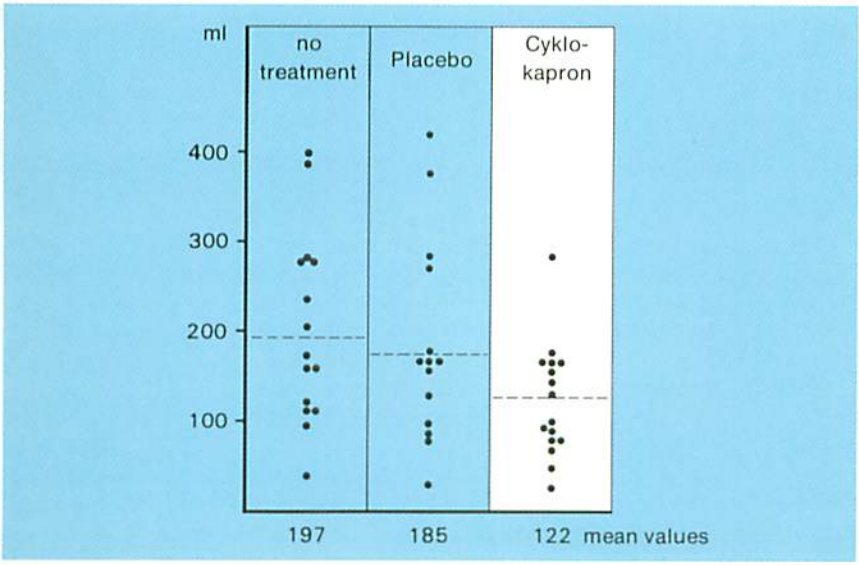
HALLBERG L, HÖGDAHL A-M, NILSSON L, RYBO G: Menstrual blood loss. A population study. Acta Obstet Gynecol Scand 1966, 45, 320–351.

RYBO G: Plasminogen activators in the endometrium. II. Clinical aspects. Acta Obstet Gynecol Scand 1966, 45, 429–450.

Callender S T, Warner G T, Cope E: Treatment of menorrhagia with tranexamic acid. A double-blind trial. Br Med J 1970, 4, 214–216.

No of patients: 16

In this double-blind cross-over trial tranexamic acid was administered 1 g 4 times daily for the first four days of menstruation to 16 women with menorrhagia for which no organic cause was found. The blood loss was measured by labelled Fe and a total body counter. The results are shown in the Figure below:



Mean menstrual blood loss.

A mean reduction of about 34 per cent was obtained when compared to a placebo treatment, and of 41 per cent compared to the control periods ($p < 0.05$) when no treatment was given. There was no difference in the duration of the menstrual period but a significant reduction in the number of pads used when tranexamic acid was administered ($t = 3.37$, $p < 0.01$).

There was no difference in the frequency or type of side effects between the active and placebo treatments.

Nilsson L, Rybo G: Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid (AMCA). A double-blind investigation. Acta Obstet Gynecol Scand 1967, 46, 572–580.

No of patients: 36

In this double-blind, cross-over study, tranexamic acid was administered at two dose levels, either 0.5 g 6 times daily for four days or 1 g 6 times daily for four days. The Table below shows the mean blood loss for all patients during the periods when no treatment was given (controls) and during treatment with placebo and tranexamic acid.

	Controls				AMCA	
	1st period X_1	2nd period X_2	Mean value	Placebo Z	high dosage Y_1	low dosage Y_2
Blood loss (mean value ± S.E. of mean)	134.8±10.9	134.3±13.7	134.5±11.3	123.4±12.9	70.9±9.6	87.6±9.2

Table. Mean blood loss (ml) during various periods (n = 36)

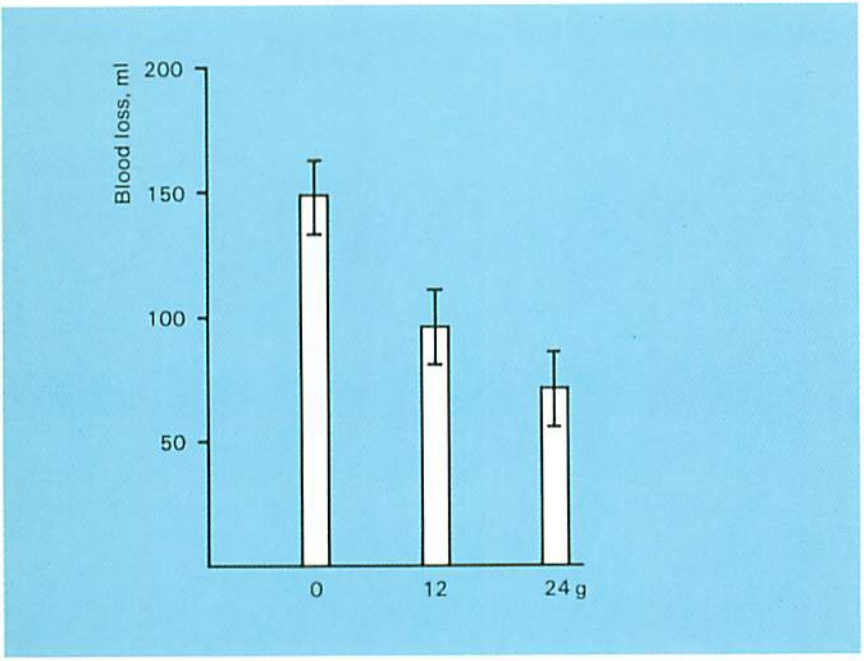
The mean reduction with the low dose, amounting to a total of 3 g, was 38 per cent compared to the control periods, and with the high dose, totally 6 g, 51 per cent. The differences are statistically significant.

Side effects were slight and the treatment did not have to be discontinued in any case.

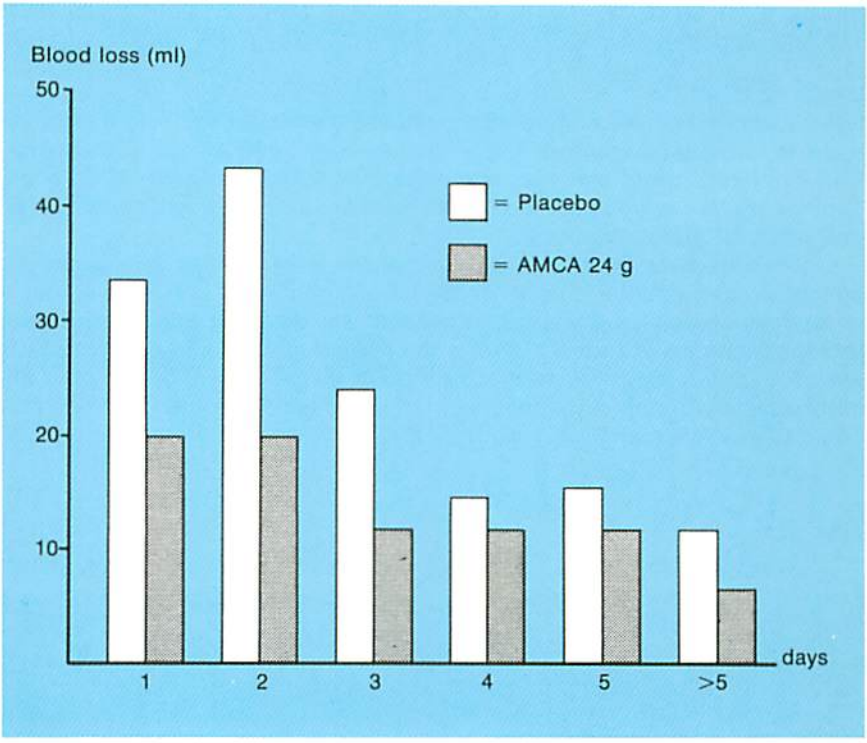
In order to investigate to what extent the reduction in blood loss was due to the size of the dose, 19 women were selected from the earlier series, each of whom received 3 g of tranexamic acid per day (a total dose of 11–12 g) and during another period 6 g per day (a total dose of 23–24 g). There was a significant difference in the effect of these two dosages: with the higher dose, the mean reduction of blood loss compared to the control cycles was 51 per cent; with the lower dose the corresponding figure was 38 per cent (Table below and Figures). The reduction in daily menstrual blood loss was most pronounced during the first three days of menstruation and increased with increasing dosage. Side effects were slight and there were none related to either the tranexamic acid of the placebo treatment.

Dosage (g)	Blood loss Mean value ± S.E. of mean	Reduction in per cent of controls
0	149.1±17.1	
12	96.1±15.2	38±4.47
24	71.0±14.6	51±5.23

Table. Dose-response to tranexamic acid in 19 women with menorrhagia



Blood losses during a single menstrual period in 19 women treated with different doses of tranexamic acid.



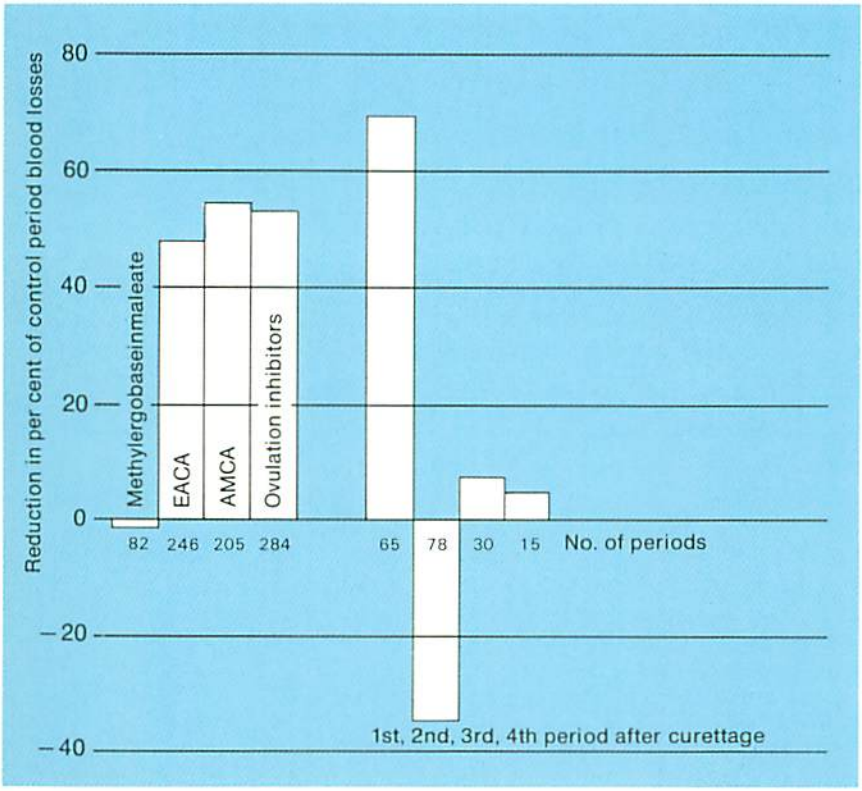
Decrease in the daily blood loss during the menstrual period in 24 women treated with a total of 24 g Cyklokapron (tranexamic acid).

Nilsson L, Rybo G: Treatment of menorrhagia. Am J Obstet Gynecl 1971, 110, 713–720.

No. of patients: 85

Nilsson and Rybo have compared the effect of curettage, methylergobaseine maleate, ovulation inhibitors of the combined type and two antifibrinolytics, EACA (aminocaproic acid) on menstrual flows exceeding 80 ml. PAMBA, another antifibrinolytic agent, was also tested, but on too small a scale for an evaluation of the optimal effect.

It can be seen from the Figure that the effect of the antifibrinolytic agents is comparable to that of ovulation inhibitors. On an average, a reduction of blood loss by about 50 per cent was obtained with both forms of therapy regardless of the volume of the menstrual flow and the size of the uterus. In one respect the methods differ, however: the antifibrinolytics are more effective in reducing the menstrual blood loss in women with fibroids. The difference is statistically significant.

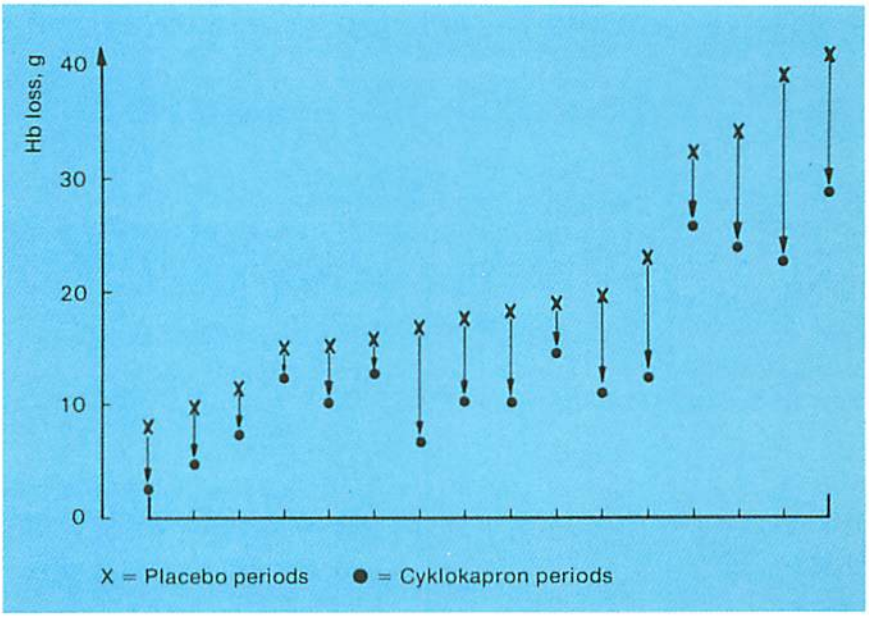


The effect of different methods of treatment in menorrhagia.

Vermylen J, Verhaegen-Declercq M-L, Verstraete M, Fierens F: A double-blind study of the effect of tranexamic acid in essential menorrhagia. Thromb Diath Haemorrh 1968, 20, 583–587.

No of patients: 16

In this double-blind cross-over trial 16 women were treated with tranexamic acid, 3 g daily from the first day of menstruation onwards until bleeding had completely stopped. The mean reduction in haemoglobin loss during the menstrual periods was 35 per cent. In absolute figures, the decrease during the tranexamic acid treatment, compared to the placebo values, ranged from 1.9 to 15.6 g haemoglobin per period, and, expressed as a fraction of the haemoglobin loss during the placebo period, the decrease ranges from 12 to 60 per cent with a mean of 35 per cent ($p < 0.001$). The individual values are shown in the Figure below.



Mean Hb loss during three periods in 16 women with essential menorrhagia.

Fourteen of the 16 women admitted to the trial with a history of essential menorrhagia did indeed have profuse menstrual haemoglobin losses (more than 10 g per period) during the placebo periods. In only two of these 14 women could the haemoglobin loss be considered to have completely normalized during active treatment with the dosage used in this trial.

It was also observed that in 10 of the 16 patients in the study there was a decrease in the duration of the menstrual periods during the tranexamic acid treatment.

One woman got pregnant when on tranexamic acid (last menstrual period). The pregnancy was normal and the baby was in good health.

Petersen K, Jelert H, Diernaes E, Detlefsen G U: Treatment of hypermenorrhagia with tranexamic acid. In Danish, summary in English. Ugeskr Laeg 1983, 145, 2759–2760.

No. of patients: 17

In this double-blind cross-over trial 17 women with menorrhagia were treated with 4–5 g of tranexamic acid daily when active treatment was given. This treatment reduced the menstrual blood loss by 13–229 ml with a mean of 71 ml. The blood loss was normalized in nine women, i.e. reduced to less than 80 ml. The individual values are shown in the Table below. Fourteen of the women continued the treatment after the study was ended.

A Patient	Control	Placebo (1)	Tranex-amic acid (2)	1–2	B Patient	Control	Tranex-amic acid (1)	Placebo (2)	2–1
1	147	119	56	63	2	98	56	121	65
4	113	87	55	32	3	305	277	305	28
6	175	89	45	44	5	122	36	92	56
7	336	244	257	–13	8	274	82	234	152
10	151	119	67	52	9	325	134	285	151
11	222	75	79	– 4	12	114	84	120	36
13	86	50	37	13	15	263	99	328	229
14	160	96	76	20	17	190	128	278	150
16	112	127	30	97					

A 1st period placebo, 2nd tranexamic acid B 1st period tranexamic acid, 2nd period placebo

Menorrhagia after insertion of an intrauterine contraceptive device (IUCD)

The increased menstrual blood loss experienced by many women fitted with an IUCD has also been shown to be reduced by tranexamic acid. The mechanism of this increase has been studied by Larsson et al (1975), Kasonde & Bonnar (1976) and Bonnar et al (1976). Larsson et al found that the fibrinolytic activity increased in 10 out of 15 of the women investigated and this increase, the authors state, is probably a contributory cause of menorrhagia in patients with IUCDs. When an IUCD is used IUCDs stromal oedema and fibrosis as well as invasion of inflammatory cells and partial necrosis of the endometrium occur, and this may induce the release of plasminogen activators. These findings were confirmed by Kasonde & Bonnar, who reported increased fibrinolytic activity in the endometrium in 16 out of 20 women following IUCD insertions. Bonnar et al investigated the fibrinolytic activity around IUCDs removed from 80 women. The reasons for the removal of the devices were heavy and prolonged menstrual bleeding in 56 women and the desire to have another baby in 24. In 15 of the women complaining of excessive menstrual blood loss, an endometrial biopsy was

also performed at the time of removal of the IUCDs. The fibrinolytic activity surrounding the IUCDs removed from patients complaining of excessive bleeding was much higher than around the IUCDs from the women not complaining of excessive bleeding. The difference was statistically significant ($p < 0.001$). The endometrial biopsies showed that the fibrinolytic activity in the endometrium on unheated fibrin plates correlated well with the activity around the IUCDs for 12 of the women. The fibrinolytic activity was due to plasminogen activator and not to plasmin. The authors conclude that the findings indicate that the bleeding complication which occurs with the IUs may be due to enhancement of the fibrinolytic activity in the endometrium and thus can be modified by fibrinolytic inhibitors.

BONNAR J, KASONDE K, HADDON M, HASSANEIN M K, ALLINGTON M J: Fibrinolytic activity in utero and bleeding complications with intrauterine contraceptive devices. Br J Obstet Gynecol 1976, 83, 160–164.

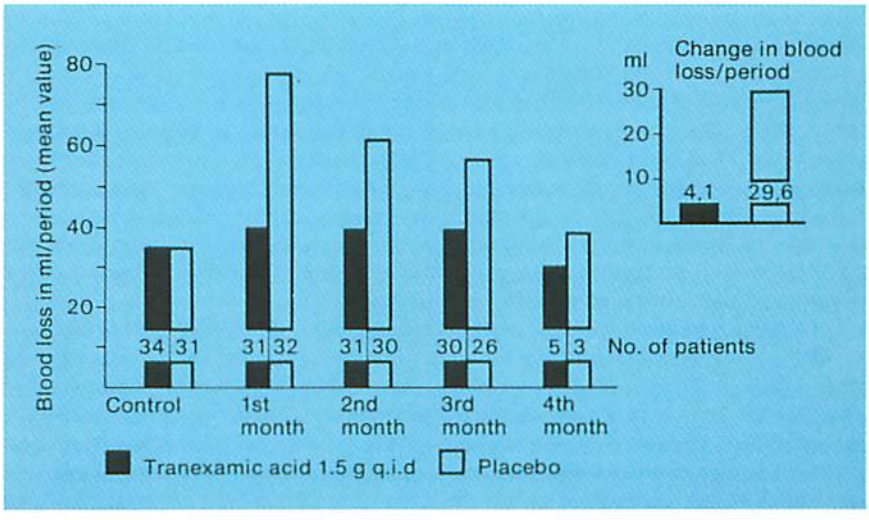
KASONDE J M, BONNAR J: Plasminogen activators in the endometrium of women using intrauterine contraceptive devices. Br J Obstet Gynecol 1976, 83, 315–319.

LARSSON B, LIEDHOLM P, ÅSTEDT B: Increased fibrinolytic activity in the endometrium of patients using copper IUD (Gravigard). Int J Fertil 1975, 20, 77–80.

Weström L, Bengtsson L P: Effect of tranexamic acid (AMCA) in menorrhagia with intrauterine contraceptive devices. J Reprod Med 1970, 5, 154–161.

No. of patients: 65

The women were randomly allocated to either tranexamic acid or placebo treatment. When tranexamic acid was given the dose was 6 g daily for five days.



Blood losses during a control menstrual period and four treatment periods after the insertion of Lippes' loop.

The blood loss was estimated for four consecutive periods. In the first cycle, prior to the IUCD-insertion, no medication was given and this menstruation served as a control period.

In the group of women receiving placebo, the increase in menstrual blood loss after the insertion of the IUCDs was 29.6 ml per menstruation or 82.7 per cent in the three periods after the insertion of the device when compared with a control menstruation before the insertion. In women treated with a control menstruation before the insertion. In women treated with tranexamic acid the corresponding figure was 4.1 ml per menstruation, or 11.5 per cent. The differences are statistically significant.

It is also of interest to note that unexpectedly heavy blood flow led to difficulties for some women in collecting all the blood in the sanitary towels and tampons, and this was more pronounced in the group of women receiving placebo. Thus, in 24 menstruations in women receiving placebo and in one menstruation in a woman receiving tranexamic acid, the blood losses were probably underestimated.

None of the women receiving tranexamic acid had a haemoglobin value lower than 10.5 g per 100 ml at the end of the investigation, while three women receiving the placebo had decreased values.

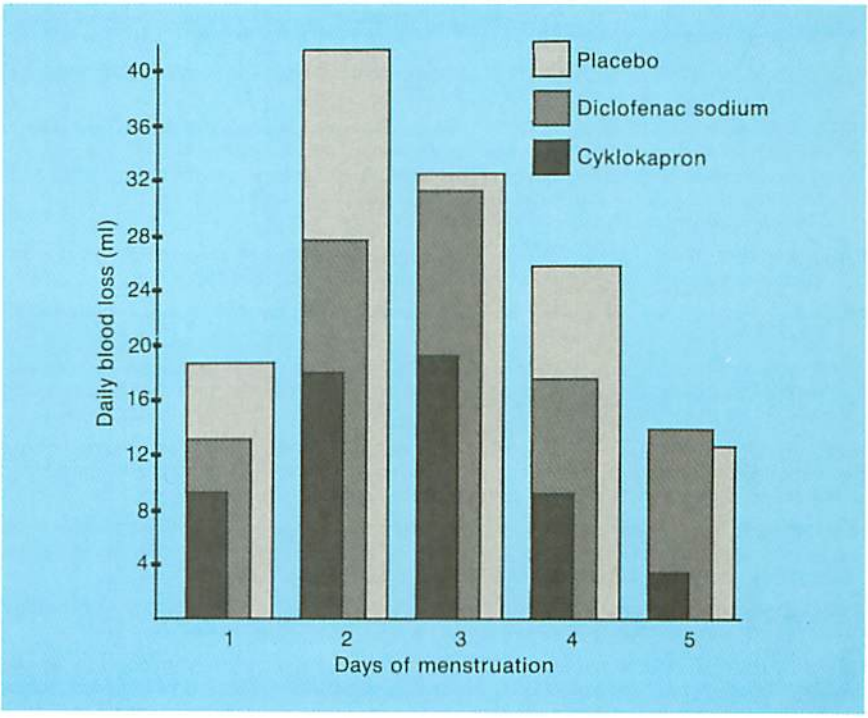
Ylikorkala O & Vilnika L: Comparison between antifibrinolytic and antiprostaglandin treatment in the reduction of increased menstrual blood loss in women with intrauterine contraceptive device. Br J Obstet Gynecol 1983, 90; 78–83.

No. of patients: 19

This study is a double-blind cross-over trial, comparing with diclofenac sodium, (Voltaren®, Ciba-Geigy) using a double dummy technique.

The mean menstrual blood loss during the placebo period was 128 ± 68 ml (MV $\pm$ SD) and did not differ from the value obtained during the control period (135 ± 74 ml). The blood loss during the tranexamic acid treatment was 59 ± 16 ml, a reduction of 54 per cent compared with the placebo period ($p < 0.001$). The corresponding values for the diclofenac sodium treatment were 102 ± 16 ml and 20 per cent ($p < 0.01$). On comparing the two treatment periods, it appears that diclofenac sodium reduces the menstrual blood loss by a further 43 ± 16 ml, or 34 per cent, compared with diclofenac sodium ($p < 0.001$). In 16 women the mean blood loss during the diclofenac sodium periods was reduced to below 80 ml. The corresponding figure for the diclofenac sodium periods was 10 women.

Neither treatment had any effect on the duration of the period.



The reduction in daily menstrual blood loss is shown in the Figure.

Conization of the cervix

Conization of the cervix has become more common as a result of the cytological screening of women for carcinoma of the cervix and is used as treatment for cancer in situ.

Conization may be complicated by postoperative haemorrhage, either as a continuous, successively decreasing postoperative blood loss or as a sudden heavy blood loss usually occurring within two weeks after surgery. This bleeding often requires extra measures, such as repeated surgery and blood transfusions. This type of bleeding occurs in about 14 per cent of the cases (Kinn, 1970) when the open technique (no suturing) is used. Later figures between 6 and 37 per cent in different techniques, including laser, have been reported (Claman & Lee, 1974; Davis et al, 1972; Karjalainen et al, 1974; Larsson, 1983).

The recurrent haemorrhage is partly due to increased local fibrinolytic activity. Endometrial tissue contains a rather high concentration of plasminogen activators (Rybo, 1966) and plasminogen activators are also present in the vaginal tissue (Kullander, 1968; Herschlein & Steichele, 1970). Treatment with antifibrinolytic drugs has been shown to suppress the fibrinolytic activity in the endometrium (Koutsky et al, 1969; Koutsky & Jirasek, 1969) and myometrium (Schmidt-Matthiesen & Schreinert, 1968).

CLAMAN A D, LEE N: Factors that relate to complications of cone biopsy. Am J Obstet Gynecol 1974, 120, 124–128.

DAVIS R M, COOKE J K, KIRK R F: Cervical conization. An experience with 400 patients. Obstet Gynecol 1972, 40, 23–27.

HERSCHLEIN H J, STEICHELE D F: Untersuchungen über die Wirkung intravenös injizierter Fibrinolyseinhibitoren auf die lokalen Fibrinolyseaktivatoren in menschlichen Scheidengewebe. (The effect of intravenous administration of antifibrinolytic drugs on the local fibrinolytic activators in human vaginal tissue.) In German. Zentralbl Gynäkol 1970, 92, 1624–1627.

KARJALAINEN O, AITO M, TIMONEN S: Sequelae of combined amputation on conization of the cervix. Ann Chir Gynaecol Fenn 1974, 63, 160–165.

KINN A-C: Konisation vid cancer in situ. (Conization in cancer in situ.) In Swedish. Läkartidn 1970, 67, 2529–2532.

KOUTSKY J, JIRASEK J E: Histochemical study of the changes in endometrial fibrinolytic activity during treatment of menometrorrhagia with antifibrinolytics. Gynaecol 1969, 168, 241–247.

KOUTSKY J, RYBAK M, JIRASEK J E, HLADOVEC J, MANSFELD V: The changes of the tissue plasminogen activator levels in the endometrium during antifibrinolytic therapy. Gynaecol 1969, 167, 265–270.

KULLANDER S: L'utilisation de l'acide amino caproique comme hemostatique dans les conisations du col uterin. (The use of aminocaproic acid as a haemostatic agent in conization.) Grenoble Med Chir 1968, 6, 505–508.

RYBO G: Plasminogen activators in the endometrium. II. Clinical Aspects. Acta Obstet Gynecol Scand 1966, 45, 429–450.

SCHMIDT-MATTHIESEN H, SCHREINERT B: Bestimmung von Gewebegängligkeit und therapeutischer Dosis von E-Aminokapronsäure, AMCHA und Trasylol mittels direkter Homogenat-EigenplasmaThromboelastographie am Beispiel des fibrinolytisch aktiven Myometrium. (Determination of bioavailability and therapeutic dose of ε-aminocaproic acid, AMCHA and Trasylol by direct homogenate-plasma-thromboelastography in the myometrium.) In German, summary in English. Klin Wochschr 1968, 46, 730–731.

Landin L E & Weiner E: Late bleeding after conization. The effect of tranexamic acid (Cyklokapron®). Opusc Med 1975, 20, 280–284.

No. of patients: 75

The women were referred to the department because of cancer of the cervix, stage 0. The conization was performed with suturing.

The women were randomly allocated to either tranexamic acid or placebo treatment, and the treatment lasted for 14.5 days. The treatment started on the day before operation with 1.5 g at lunch and 1.5 g at night. In the morning of the day of operation 1 g was given i.v., the dose being repeated immediately before surgery. After surgery treatment was continued orally with 4.5 g daily for 13 days.

Thirty-eight women were treated with tranexamic acid and 37 with placebo.

There was only one case of rebleeding in the tranexamic acid treated group and four in the placebo group. All four cases rebleeding in the placebo group required extra measures such as resuturing or tamponade. Thus, antifibrinolytic agents and/or suturing of the wound should be utilized to reduce bleeding after conization.

Lundvall F & Nielsen N C: The hemostatic effect of tranexamic acid in conisatio colli uteri. Acta Obstet Gynecol Scand 1984, 63, 81–84.

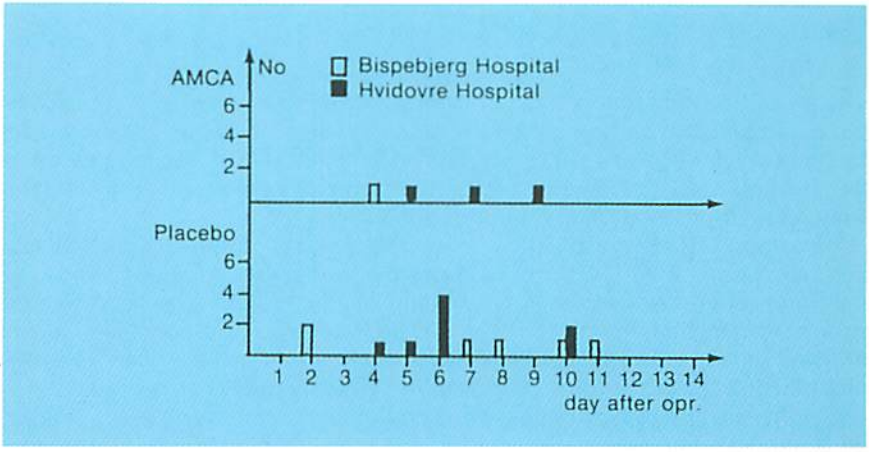
No. of patients: 230

In this double-blind investigation, running at two hospitals, the effect of tranexamic acid on the rebleeding frequency after conization was evaluated.

Altogether, 115 women were treated with tranexamic acid 1.5 g 3 times daily for 12 days and 115 with placebo.

Eighty patients were operated on by an open method and 150 suturings with Sturmdorff sutures were performed.

A statistically significant reduction in rebleeding was obtained in the "open" group, 1 versus 7, 2.5% versus 17.5%. The tendency was the same in the sutured group even though the difference was not statistically significant, 3 versus 8, 4.1% versus 10.7%. All cases of rebleeding required extra measures. The time when rebleeding occurred is shown in the Figure below:



Two patients treated with tranexamic acid had to discontinue treatment due to diarrhoea. Two additional treated patients suffered from diarrhoea. Otherwise there was no difference in side effects between the two groups.

Rybo G & Westerberg H: The effect of tranexamic acid (AMCA) on postoperative bleeding after conization. Acta Obstet Gynecol Scand 1972, 51, 347–350.

No. of patients: 45

This double-blind randomized trial was performed in order to elucidate the effect of tranexamic acid on the postoperative blood loss after conization of the cervix without suturing and on the frequency of sudden profuse rebleeding. Forty-five women remained for the final analysis, 22 treated with tranexamic acid and 23 with placebo.

Tranexamic acid was given in a dose of 1.5 g eight-hourly starting in the evening of operation an continuing for 12 days.

There was no sudden profuse postoperative haemorrhage in the treated

group but there were seven instances in the placebo group occurring from the fifth to the 10th postoperative day. All cases of rebleeding in the placebo group required extra measures.

No. of patients	Treatment	No. of patients with postop. profuse bleeding (Period of observation 12 days)	Total blood loss during first 7 postop. days, ml
22	Tranexamic acid	0	23 ± 3.2
23	Placebo	7	79 ± 20.4

Postoperative blood loss after conization in patients receiving tranexamic acid or placebo.

Grundsell H, Larsson G & Bekassy L: Use of an antifibrinolytic agent (tranexamic acid) and lateral sutures with laser conization of the cervix. Obstet Gynecol 1984, 64, 573–576.

No of patients: 140 and 220

The present investigation was performed to ascertain whether it was possible to simplify the carbon dioxide laser conization technique in outpatients by omitting the use of antifibrinolytics and the lateral sutures, and by omitting the antifibrinolytic agent in laser mini conization, without increasing the frequency of postoperative haemorrhage.

A group of 140 women underwent laser conization for severe dysplasia and carcinoma in situ. A further 220 women underwent mini conization for mild and moderate dysplasia. Sixty-eight of the 140 patients were treated with tranexamic acid and 110 of the 220. No lateral sutures were used in any of these patients. The dose of tranexamic acid was 1 g given in an intravenous infusion during surgery, followed by 3 g daily orally for two weeks.

None of the 68 patients who underwent laser conization treated peroperatively and postoperatively experienced late bleeding compared to 8 of 72 controls ($p < 0.01$). Three women had to be hospitalized. Six of the 110 patients who underwent laser miniconizations treated peroperatively and postoperatively had late bleeding compared to 10 of the 110 controls. However, three of the six bleeds in the tranexamic acid treated group were of arterial origin, a situation in which antifibrinolytic therapy cannot be expected to have any effect. Among the 220 patients with laser miniconizations no hospitalization was necessary for late bleeding in any groups. No hospitalization was necessary for late bleeding in the tranexamic acid group as opposed to one case in the control group.

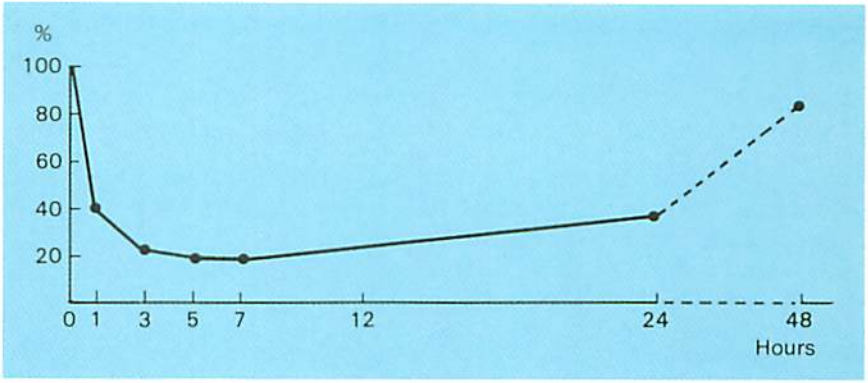
The late bleeding frequency among the 68 women treated with conization was compared with that in a group of 220 women who, apart from tranexamic acid therapy, all underwent ligation of the descending portions of the uterine branches. There was no significant difference in late bleeding frequency, thus indicating that the lateral sutures apparently do not influence the rate of bleeding complications.

The findings in this investigation show that treatment with tranexamic acid results in less postoperative bleeding complications after laser conization.

Urology

The urine contains urokinase which activates the conversion of plasminogen to plasmin, which in turn induces the lytic breakdown of clots in the urinary tract (Andersson et al, 1962, a, b). Increased fibrinolytic activity sustains bleeding in the urinary tract as after surgery or in essential haematuria.

Tranexamic acid effectively inhibits fibrinolytic activity in urine by counteracting the activation of urokinase (Andersson et al, 1968). When 10 mg of tranexamic acid per kg body weight were administrated orally to five normal subjects, the fibrinolytic activity in the urine was decreased one hour after administration, and 3, 5 and 7 hours after administration it amounted to only about 20 per cent of the value before administration. Even after 24 hours the activity was still substantially reduced.



Fibrinolytic activity in urine after oral administration of 10 mg of tranexamic acid per kg body weight. (Mean values for five normal subjects.)

ANDERSSON L ET AL: Role of urokinase and activator in sustaining bleeding and the management thereof with EACA and AMCA. Ann NY Acad Sci 1968, 146, 642–658.

ANDERSSON L: Treatment of so-called essential haematuria with fibrinolytic inhibition (epsilon-aminocaproic acid). Acta Chir Scand 1962 a, 124, 355–364.

ANDERSSON L: Studies on fibrinolysis in urinary tract disease and its treatment with epsilon-aminocaproic acid. Acta Chir Scand 1962 b, suppl 301.

Prostatectomy

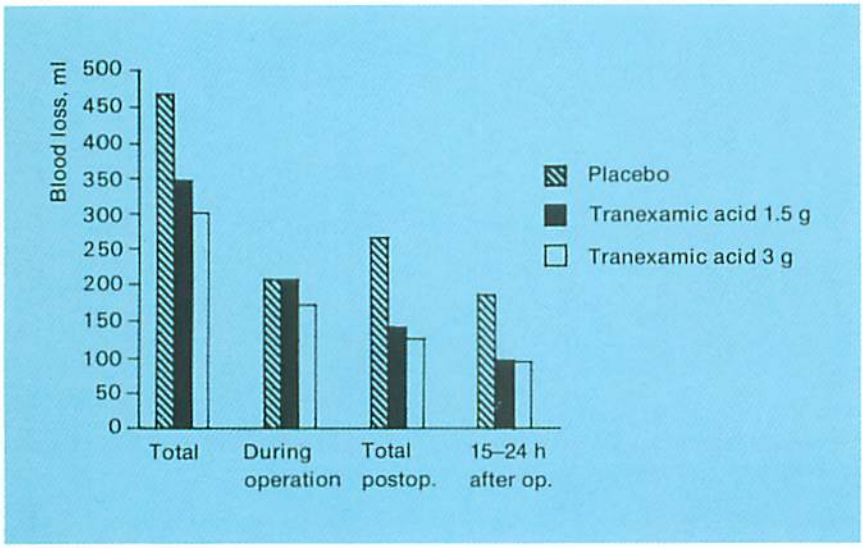
Hedlund P O: Antifibrinolytic therapy with Cyklokapron in connection with prostatectomy. Scand J Urol Nephrol 1969, 3, 177–182.

No. of patients: 92

In this randomized double-blind trial comprising 92 transvesical prostatectomy patients, the effect of tranexamic acid, at two dose levels, on the blood loss in connection with this type of surgery was investigated. Thirty-three patients were treated with a daily dose of 1.5 g for four days, 29 with 3 g and 30 with placebo.

No effect was seen on the peroperative blood loss but a 47 per cent reduction in postoperative blood loss was obtained with the low dose, and a 52 per cent reduction with the high dose compared to placebo treatment. The difference is statistically significant. There was no statistical difference in effect between the two dose levels.

About 70 per cent of the total postoperative blood loss occurred during the first 15–21 hours. As can be seen from the Figure and Table, the blood loss had already been reduced during this initial period in the patients treated with tranexamic acid. This is of paramount importance since the risk of complications (clotting in catheters, poorer bladder drainage, perivesical leakage, infection, pain and impaired mobilization) is reduced if postoperative bleeding can be decreased at an early stage.



Blood loss during and after prostatectomy. Mean values after administration of tranexamic acid, 1.5 g and 3 g daily, and placebo.

	Blood loss, ml			
	During operation	Total postop.	15–24 h after op.	Total
Placebo	205	264	181	469
Tranexamic acid, 1.5 g daily	206	140	97	346
Tranexamic acid, 3 g daily	172	126	92	298

Blood loss during and after prostatectomy

The only possible dose-related side effect was nausea, ocurring only in the high-dose group.

Kaufmann J & Siefker K: Medikamentöse Senkung postoperativer Blutungen nach Prostatektomien. (Erfahrungen mit dem Fibrinolysehemmer AMCA). (Reduction in postoperativa blood loss in conection with prostatectomies. Experiences with the antifibrinolytic drug AMCA.) In German, Sumary in English. Der Urologe 1969, 8, 57–59.

No. of patients: 63

In this study 36 patients subjected to prostatectomy were treated with 1 g intravenously twice daily for three days, starting on the day of operation.

Controls were 27 patients operated on during the same period of time.

The blood loss, measured as haemoglobin loss, was reduced by 36.4 per cent on the second postoperative day and by 52.6 per cent on the third. The blood loss on the first postoperative day was not affected by the treatment.

	Haemoglobin Loss					
	Postop. day 1		Postop. day 2		Postop. day 3	
Group	g/24 h	%	g/24 h	%	g/24 h	%
Tranexamic Acid (n = 36)	5.7±0.9	101	2.1±0.4	63.6	1.8±0.3	47.4
Control (n = 27)	5.6±1.2	100	3.3±0.6	100	3.8±1.0	100
Significance	$p > 0.05$		$p < 0.05$		$p < 0.05$	

Table. Blood loss in haemoglobin, g per 24 h, MV ± SD.

One tranexamic acid treated patient died of pulmonary embolism on the 14th postoperative day after having been orchidectomized for cancer on the tenth postoperative day. Most patients in both groups experienced minor venous thrombosis in the lower limbs, which did not affect their general clinical condition.

Miller R A, May M W, Hendry W F, Whitfield H N, Wickham J E A: The prevention of secondary haemorrhage after prostatectomy: the value of antifibrinolytic therapy. Br J Urol 1980, 52, 26–28.

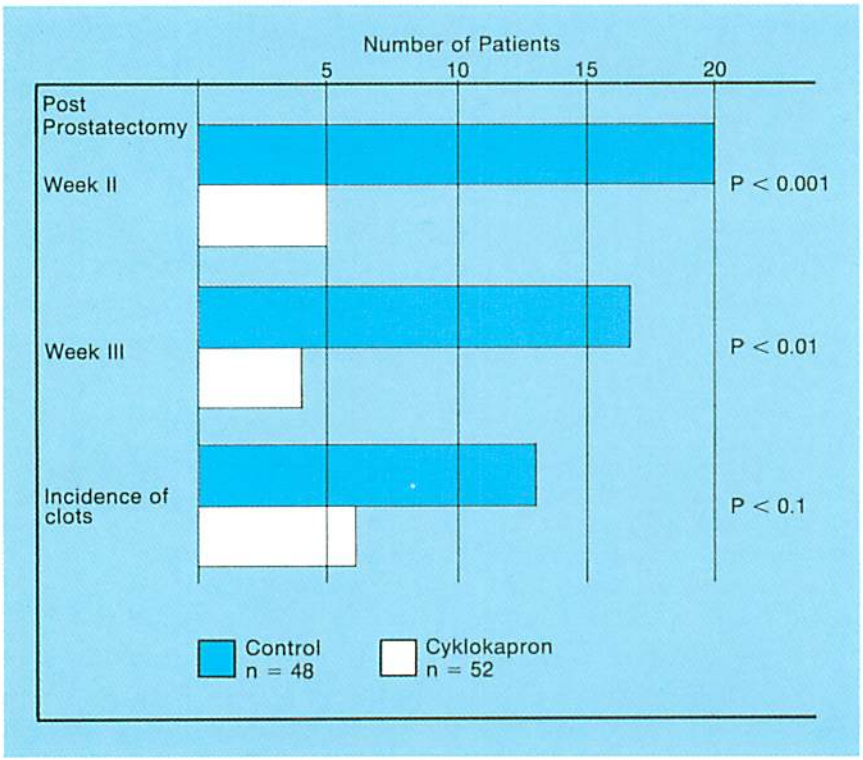
No. of patients: 100

Diagnosis: Bleeding after transurethral prostatectomy or endoscopic bladder tumour resection.

In this study 52 patients subjected to transurethral prostatectomy/endoscopic bladder tumour resection were treated with 1 g tranexamic acid t.d.s. for three weeks postoperatively, starting on the first postoperative day. Controls were 48 patients operated on during the same period of time.

The frequency of secondary haemorrhage was 24 per cent in the treatment group and 56 per cent in the control group. The difference is statistically significant. The results obtained also indicate that with tranexamic acid treatment clot formation in the urinary tract is reduced (see Figure below). The first postoperative week was not studied.

Analysis of secondary haemorrhage



Clinical evidence of deep venous thrombosis developed in one patient in each group and one control had a small pulmonary embolus from which he recovered.

Vecsey, D ET AL: Blutungsprophylaxe nach Prostatektomie mit AMCA. (Bleeding-prophylaxies after prostatectomy with AMCA). In German. Med Welt 1977, 28, 1100–1102.

No. of patients: 70

Diagnosis: Bleeding after transvesical prostatectomy.

Tranexamic acid was administered both systemically and locally in a controlled trial. Altogether, 1 g tranexamic acid was given intravenously before and during the operation. After the operation the bladder was irrigated for 2–5 days with a solution containing 1 g of tranexamic acid per 1000 ml of isotonic saline. The therapeutic results are shown in the Table.

	No. of patients	Average blood loss (M ± SD)
Tranexamic acid	40	47.4 ± 26.1
Control group	30	376.0 ± 108.7

Postoperative blood loss in prostatectomies with and without tranexamic acid.

As can be seen from the above, tranexamic acid reduced the blood losses sharply. No side effects were reported.

Antireflux surgery

Rö J S, Knutrud O & Stormorken H: Antifibrinolytic treatment with tranexamic acid (AMCA) in pediatric urinary tract surgery. J Pediatr Surg 1970, 5, 315–320.

No. of patients: 22

Diagnosis: Bleeding after reimplantation of the ureter.

The blood loss associated with reimplantation of the ureter into the bladder is generally moderate, but in children it can be great enough to necessitate a transfusion. In order to investigate whether antifibrinolytic therapy has any positive effect on this type of bleeding, Rö et al gave tranexamic acid to 10 children on whom antireflux operations were performed using the technique of Leadbetter-Politano. Twelve children undergoing the same operation served as controls. The ages of the patients ranged from 2½ to 12½ years with a mean of 7 years.

Fifteen milligrams per kg body weight of tranexamic acid were given orally three times on the day before the operation, 10 mg per kg body weight were given intravenously on the day of operation, and thereafter 15 mg per kg body weight twice daily orally for seven days.

	Tranexamic acid	Control
Unilateral reimplantation	9	8
Bilateral reimplantation	1	4
Totals	10	12

Distribution by operation and treatment in 22 children

On an average, the blood loss during surgery was reduced by 50 per cent in the patients who received tranexamic acid, and the decrease in the post-operative blood loss was even more pronounced. The loss in the children having unilateral operations amounted to 26 ml in the tranexamic acid group while those in the control group lost 98 ml of blood, a reduction of 73 per cent. The difference for the entire series was even greater, 27 ml as against 129 ml, corresponding to a reduction of 79 per cent. The reduction in blood loss was most pronounced on the second day after the operation.

A blood transfusion was given to one of the children treated with tranexamic acid. Like two other patients, this child had renewed bleeding when tranexamic acid therapy was stopped. Blood transfusions were necessary in four children in the control group.

In six children in the tranexamic acid group, including those in whom renewed bleeding had occurred, greyish clots were passed with the urine, leading in two children to transient retention of urine. The authors point out the risk of clot retention in antifibrinolytic therapy of haemorrhages in the upper urinary tract.

Haematuria

Andersson L & Nilsson I M: AMCA (Aminomethyl cyclohexane carboxylic acid, Cyklokapron) - A potent haemostatic agent in urinary tract bleeding. Scand J Urol Nephrol 1969, 3, 169–176.

Diagnosis: Bleeding from the lower urinary tract without generalized fibrinolysis.

Of 71 patients with haemorrhages in the lower urinary tract, 69 received 1 g tranexamic acid twice daily while the remaining two were given 0.5 g twice daily. As a rule, the oral route was used. Only immediately after operation or when the patient was under the effect of severe acute bleeding was the drug administered intravenously.

Table 1 shows that the bleeding ceased in 51 patients and decreased in 11. In nine cases involving cancer of the bladder or postirradiation bladder changes, the bleeding persisted unchanged. In the cases in which the bleeding was arrested, the effect was immediate. Clinical signs of thrombosis were not noted in any case.

Diagnosis	No. of patients	Haema-turia	Other bleeding	Period of treatment, days	Effect on bleeding			Side effects
					Ceased	De-creased	No effect	
Prostatic hyperplasia	14	14	–	2–11	14	–	–	0
Prostatic cancer	14	14	2	3–21	12	2	–	0
Bladder cancer	5	5	–	3–14	1	2	2	0
Bladder cancer (post-operative haemorrhage)	17	17	–	2–12	12	3	2	2 { 1 diarrhoea, 1 vertigo
Postirradiation bladder change	8	8	–	5–13	–	3	5	0
Inflammatory changes in bladder	2	2	–	8–10	2	–	–	0
Bladder stone or inflammation	5	5	–	1–15	4	1	–	0
Bladder trauma	1	1	–	3	1	–	–	0
Bladder neck stenosis (postoperative haemorrhage)	5	5	–	3–9	5	–	–	0
Totals	71				51	11	9	

Table 1. Bleeding from lower urinary tract without generalized fibrinolysis

Diagnosis: Bleeding from the upper urinary tract without generalized fibrinolysis.

Four patients in this group received between 3 and 6 g tranexamic acid a day periodically. The remaining seven were given 1 g daily orally.

The most important indication for tranexamic acid therapy in renal haematuria is slight to moderate, but prolonged, haematuria. There is a risk of clot retention, but on the other hand an operation carries an even greater risk.

Diagnosis	No. of patients	Period of treatment, days	Effect on bleeding			Clot retention	Other side effect
			Ceased	De-creased	No effect		
Renal tumour	2	8	2	–	–	–	0
Hydronephrosis	1	2	1	–	–	–	0
Chronic glomerulonephritis	1	16	–	1	–	1	0
Essential haematuria	7	18 days–11 weeks	3	2	2	–	0
Totals	11		6	3	2		

Table 2. Renal haematuria (without generalized fibrinolysis)

Diagnosis: Haematuria after prostatic surgery.

Eighty-seven patients who had undergone operations on the prostate were treated with tranexamic acid for haematuria. All but five of the patients were also given heparin to prevent thrombosis since earlier studies have shown that this reduces the frequency of thrombo-embolism without increasing haemorrhage. Heparin was started the morning after surgery and was usually given over as long a period of time as tranexamic acid.

Phlebography of the legs was performed on 34 patients within a fortnight following surgery. Thrombosis was demonstrated or suspected in four cases. However, with the exception of a patient with a tender calf, there were no clinical signs of thrombosis. Thrombo-embolic complications were suspected in an additional two cases. A patient on whom phlebography had not been performed developed oedema and tenderness in one calf, and another had signs of pulmonary embolism. Both these patients had been given heparin in addition to tranexamic acid.

In most cases the urine was clear macroscopically after 4–5 days, but treatment was continued for eight days or longer in 23 cases.

Diagnosis	Operation	No. of patients	AMCA + heparin No. of patients	Period of treatment, days	Thrombo-embolism No. of patients	Side effects
Prostatic hyperplasia	Transvesical prostatectomy	61	59	3–15	6	1 vertigo
Prostatic hyperplasia	Transurethral electroresection	11	9	2–7	–	1 vertigo
Prostatic cancer	Transvesical prostatectomy or electroresection of prostate	8	8	4–16	–	–
Prostatic cancer	Transurethral electroresection	7	6	2–7	–	–
Totals		87	82		6	

Table 3. Haematuria after operation on prostate.

Diagnosis: Generalized fibrinolysis.

Elevated fibrinolytic activity in the circulating blood was noted in six patients, four of which had haemorrhages. The fifth was treated with tranexamic acid to avoid fibrinolytic bleeding complications in connection with transurethral electroresection of the prostate. The course of treatment was normal in all respects. The sixth patient in this group was a 28-year-old male with hereditary angioneurotic oedema. For several years he had had both superficial and internal oedema with varying localization as well as respiratory and gastrointestinal symptoms. Treatment was started with 30 g aminocaproic acid (EACA) daily, which resulted in elimination of the oedema, but urogenital symptoms developed instead, inter alia, in the form

of dry ejaculations and dysuria. Tranexamic acid 5 g daily was then instituted, and this therapy was found to keep the patient free from oedema without producing side effects.

Diagnosis	Age	Haemorrhagic manifestation	AMCA orally	AMCA i.v.	Period of treatment, days	Fibrinolytic activity (citrated plasma) Stand.pl./heated pl. Before AMCA	After AMCA	Effect on bleeding	Side effects
Prostatic cancer	80	–	1 g×2		5	127/13	25/0	–	–
Prostatic cancer + metastases	68	Haematuria + intestinal haemorrhage		1 g×2	3	83/00	0/0	arrested	–
Prostatic cancer } same		Bleeding in region of operation		1 g×2	3	187/90	29/0	arrested	nausea
Prostatic cancer } patient	57	Haematuria	1 g×2		3	129/25	0/0	arrested	nausea vomiting
Prostatic cancer	75	Haematuria	1 g×2		4	61/12	0/0	arrested	–
Prostatic cancer + bladder stones	79	Bleeding after vesiculotomy	1 g×2		8	106/25	0/0	arrested	–
Hereditary angioneurotic oedema	28	–	1 g×5		long period	67/23	28/0	–	–

Table 4. Patients with generalized fibrinolysis.

Dental extractions in patients with coagulopathies

Before replacement therapy was known, dental extractions in patients with coagulopathies were contraindicated. Concentrates of factor VIII and factor IX are now available and have made surgery in these patients possible but may transmit diseases such as serum hepatitis and acquired immunodeficiency syndrome (AIDS). From time to time there may also be a shortage of factor VIII and factor IX concentrates. The degree of bleeding in connection with tooth extractions depends on the severity of the disease, the type of tooth and number extracted and the amount of force required to remove them and is partly due to increased fibrinolytic activity (Björlin et al, 1975; Ramström & Blombäck, 1975). Furthermore mixed saliva from the mouth has been shown to have fibrinolytic activity (Gersel-Pedersen, 1979; Ramström & Blombäck, 1975).

With antifibrinolytic treatment the need for substitution therapy is reduced and the period of hospitalization is shortened.

BJÖRLIN G, PANDOLFI M, HANSSON L: Fibrinolytic activity in human dental pulp. Oral Surg Oral Med Oral Pathol 1975, 39, 488–492.

GERSEL-PEDERSEN N: Inhibitors of fibrinolysis in saliva after oral surgery measured by enzymic acid immunological methods. Int J Oral Surg 1979, 8, 212–222.

RAMSTRÖM G: Fibrinolytic activity in the saliva of patients with coagulation disorders. Swed Dent J 1975, 68, 49–54.

RAMSTRÖM G, BLOMBÄCK M: Tooth extraction in hemophiliacs. Int J Oral Surg 1975, 4, 1–17.

Björlin G, Nilsson I M: Tooth extractions in haemophiliacs after administration of a single dose of factor VIII or factor IX concentrate supplemented with AMCA. Oral Surg 1973, 36, 482–489.

Seven patients with haemophilia A and five with von Willebrand's disease were given single doses containing 40–60 units of factor VIII per kg body weight immediately before the tooth-extracting operation, and five with haemophilia B received about 50 units of factor IX per kg body weight. As a rule, this produced an increase of more than 40 per cent in the concentration of factor VIII and factor IX with effective haemostasis. After this tranexamic acid, 25 mg per kg body weight, was administered six-hourly for 5–7 days. Additional replacement therapy was required postoperatively only in two cases. The first dose was given intravenously in connection with the administration of clotting factor, and the others were given orally. As a result of the initial normalization of clotting by the administration of blood factor, normal fibrin clots are formed in the area of the extraction. Since the alveoli are abundantly supplied with fibrinolysis activators, such clots are readily dissolved. Tranexamic acid inhibits this local fibrinolysis, however, and the formed clots persist despite falling concentrations of factors VIII and IX.

Two of the 17 patients, one with severe haemophilia B who had 11 teeth pulled and one with severe haemophilia A who had two extractions, required

additional substitution therapy. From one to five teeth were extracted in the remaining 15 patients without haemorrhagic complications.

Thus the method makes it possible to extract more teeth at one time than before without postoperative bleeding complications. This means that the patient's stay in hospital can be substantially shortened and the need for substitution therapy decreased.

van Creveld S, Buchner R, de Bruyn Kops-Akkerman M J: Tandextracties bij hemofilie A en B. (Tooth extractions in cases of haemophilia and Christmas disease. In Dutch. Summary in English.) Ned T Tandheelkd 1971, 78, 90–94.

No. of patients: 14

Before surgery the patients received substitution therapy in order to raise the coagulation factor activity in plasma, usually to at least 10 per cent. After surgery tranexamic acid was given in a dose of 0.5–1.5 g orally 3 times daily for some days postoperatively.

In all but two patients no further replacement therapy was needed. When further transfusions were required this was not the case until the fifth to seventh postoperative day.

Thus when tranexamic acid treatment is given in connection with oral surgery in patients with haemophilia A or B further replacement therapy is seldom needed except that given before surgery. No side-effects were reported.

Forbes C D, Barr R D, Reid G, Thomson C, Prentice C R M, McNicol G P, Douglas A S: Tranexamic acid in control of haemorrhage after dental extraction in haemophilia and Christmas disease. Br med J 1972, 2, 311–313.

No. of patients: 28

Twenty-eight patients were included in the series and they were treated on 32 occasions, 16 with tranexamic acid and 16 with placebo.

Table I. Clinical Data on Patients receiving Tranexamic Acid and Placebo

	Placebo	Tranexamic Acid
No. of episodes of extraction	16	16
No. of patients	14	14
No. with haemophilia	9	11
No. with Christmas disease	5	3
Mean (range) level of plasma factor (%)	4–5 (0–22)	5 (0–23)
Clinical severity:		
Severe	7	8
Moderate	6	5
Mild	1	1

Table II. Comparison of Treated and Placebo Groups after Tooth Extraction

	Placebo	Tranexamic Acid
Mean No. (range) of roots extracted	5.5 (2–12)	6.9 (2–22)
Mean (range) blood loss per patient (ml)	84.1 (4–323)	61.2 (1–749)
Mean (range) blood lost per root extracted (ml)	15.3 (0–5–64)	8.9 (0.5–38.6)
Mean No. (range) of units of replacement therapy per root extracted	617 (0–15,800)	30 and 65 in two patients
Mean fall in haemoglobin (g/100 ml)	1.4	0.3
Mean fall in packed cell volume (%)	5.0	0.9

The mean blood loss in the placebo group was 84.1 ml and in the tranexamic acid group 61.2 ml. The variations were great, however. The blood loss per tooth extracted was 15.3 ml in the placebo group and 8.9 ml in the treated group. The difference is statistically significant ($p < 0.05$).

In only two out of the 14 patients in the tranexamic acid treated group were further infusions of plasma or plasma concentrate needed. In one of these 22 teeth were extracted, the largest number in the series. In the placebo group 11 out of 14 patients needed repeated infusions during the trial. The patient requiring the greatest amount of replacement therapy had moderate haemophilia and had six roots extracted. He was in the placebo group.

In this study, screening tests revealed no toxic effects of tranexamic acid on the liver, kidneys or heart.

Pell G: Tranexamic acid—Its use in controlling dental postoperative bleeding in patients with defective clotting mechanisms. Br J Oral Surg 1973, 11, 155–164.

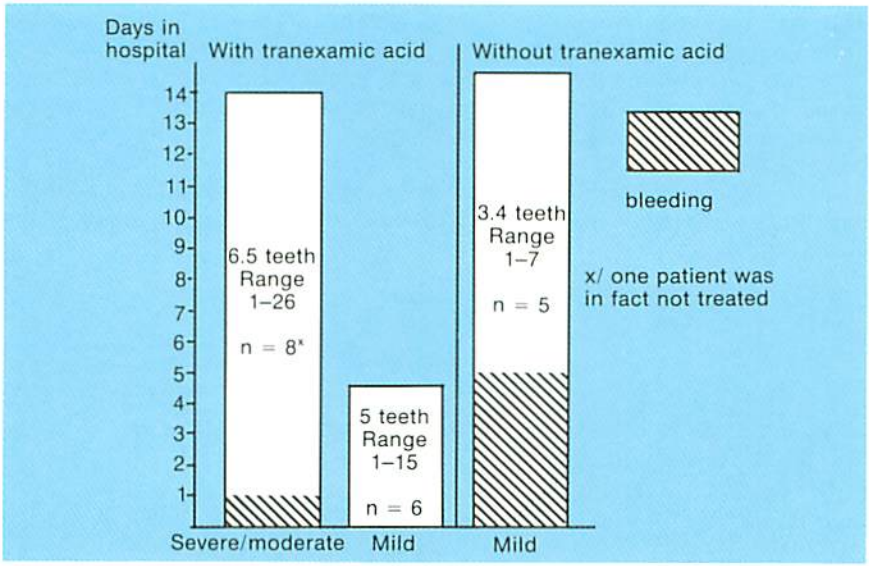
No. of patients: 14

Fourteen patients were treated with tranexamic acid, eight with haemophilia A, three with haemophilia B and three with von Willebrand's disease, the disease being severe to mild. Five patients with mild coagulopathy, four with haemophilia A and one with von Willebrand's disease served as controls.

The dose of tranexamic acid was individual and ranged preoperatively between 1.5 g and 8 g the day before surgery given intravenously and/or orally. The usual postoperative dose was 4 g orally given daily. The results are summarized in the Figure on page 49.

In spite of more teeth being extracted in the tranexamic acid patients than in the controls, the tranexamic acid treated patients bled less. Also, when the severely to moderately diseased patients treated with tranexamic acid were compared with the mildly diseased controls the case was the same. The hospital stay was the same for the severely and moderately diseased treated patients as for the mildly diseased controls. The treated patients with mild disease had a hospital stay of 4.5 days compared with the severe/moderate and control patients who had a hospital stay of 14 days.

The results indicate that tranexamic acid treatment has a beneficial



effect on the management and course of dental extractions in patients with coagulopathies.

There were no complaints of side-effects from the tranexamic acid therapy.

Ramström G, Blombäck M: Tooth extractions in haemophiliacs. Int J Oral Surg 1975, 4, 1–17.

No. of patients: 67

The patients were divided into three groups. Group 1 received substitution therapy only, Group 2 substitution therapy supported by tranexamic acid and Group 3 received the same treatment as Group 2 plus an acrylic splint.

	No. of patients				No. of patients in combinations			
Groups	1	2	3	No. of patients	1+2	1+3	2+3	1+2+3
Hemophilia A								
severe	3	11	6	15	2	1	2	
moderate	7	2	2	9	1	1		
mild	9	8	7	18	4		2	
Hemophilia B								
severe (1.4 %)	2	3	4	6	1		1	1
mild	3	1	1	4	1			
v. Willebrand's disease								
severe		2		2				
mild	7	3	7	13	2	1		1
Total	31	30	27	67	11	3	5	2

Distribution of patients in the different groups and the number of patients treated in more than one group.

The need for substitution therapy, counted per tooth, was 3260 units in the severe haemophilia A cases in Group 1, 1600 units in Group 2 and 440 units in Group 3. The percentage reduction was about the same in the moderate cases and somewhat higher in the mild cases. The reduction in the von Willebrand patients equalled that in the severe and moderate haemophilia A patients. The results in the haemophilia B patients were about the same. The number of days in hospital was correspondingly reduced with the need for substitution therapy. The bleeding complications are summarized in the Table below.

	Group 1		Group 2		Group 3	
Disease	No. of treatm. session	No. of bleeding compl.	No. of treatm. session	No. of bleeding compl.	No. of treatm. session	No. of bleeding compl.
Hemophilia A						
severe	3	3	13	5	6	2
moderate	9	7	3	0	2	0
mild	11	8	9	4	11	1
Hemophilia B						
severe	2	2	3	0	5	1
mild	2	1	2	0	3	0
v. Willebrand's disease	12	2	6	1	13	0
Total	39	23	36	10	40	4

In Group 1 postoperative bleeding ocurred in 59% of the treatment sessions. In Group 2 the bleeding frequency decreased to 28%, and in Group 3 it was reduced to 10%. It should also be pointed out that the bleeds in Group 1 were far more frequent and prolonged than those occurring in Groups 2 and 3. Nine of the bleeds in Group 1 were described as severe and prolonged, but in Groups 2 and 3 there was no such bleeding. Patients with moderate forms of haemophilia A were found to be relatively difficult to treat by the method used for Group 1. Many of the postoperative haemorrhages recorded were particularly prolonged and complicated. This patient category responded very well to tranexamic acid and antibiotic therapy and no bleeds were recorded in Group 2.

Several patients with mild, and even moderate, forms of haemophilia and mild forms of von Willebrand's disease could be treated as outpatients when switched to treatment as in Group 2, and later Group 3. This is said to have lightened the hospital's burden considerably.

Tavenner R W H: The use of tranexamic acid in control of haemorrhage after extraction of teeth in haemophilia and Christmas disease. Br Med J 1972, 2, 314–315.

No. of patients: 23

Nineteen patients with haemophilia A, three with haemophilia B and one with von Willebrand's disease were treated with tranexamic acid in connec-

tion with tooth extractions. Altogether 51 episodes were treated. The dose was 1.5 g orally every six hours until the patients were discharged from hospital. None of the patients received replacement therapy before the extractions.

Earlier treatment with aminocaproic acid and plasma or with blood and plasma served as control treatment.

The total number of days the patient spent in hospital was 206.5, giving an approximate average of four days. One patient required six litres of blood and 40 packs of cryoprecipitate and two patients required 12 and 24 packs respectively, giving a total of 76 packs.

In the 25 dental operations in which aminocaproic acid was used, a total of 18.1 litres of plasma was also given. The total number of days spent in hospital was 147, giving an average of 5.9 days for each operation. The average dose of aminocaproic acid given at each operation was 153 g compared with the average dose of 24.5 g of tranexamic acid given at each operation.

In the 25 dental operations in which blood and/or plasma was used, approximately 8.3 litres of blood and 115 litres of plasma were given. The total number of days in hospital amounted to 235, giving an average of 9.4 days for each operation.

Two patients complained of a mild attack of diarrhoea; in both cases this occurred early in the morning and on only one occasion during the treatment. No complications were noted in any of the other patients. When aminocaproic acid was used in these patients, nausea, vomiting, diarrhoea and hypotensive attacks were common findings.

Thus in this study it is shown that, compared to traditional therapy and therapy with aminocaproic acid, treatment with tranexamic acid diminishes the need for substitution therapy in connection with dental extractions in patients with coagulopathies. The number of days in hospital is also reduced. Compared to aminocaproic acid, the side-effects are much less pronounced, and the dosage required is relatively smaller.

Gastroenterology

Gastrointestinal haemorrhage

The theoretical reasons why antifibrinolytic therapy might be beneficial in gastrointestinal haemorrhage were first studied by Cox et al (1967, 1969). They found plasminogen activators in the gastric and duodenal mucosa and that release of free plasmin into the gastric venous blood occurred more often in patients with peptic ulcers than in other patients. They also demonstrated the ability of the gastric wall to release fibrinolytic activators into the blood after digital compression. Later Thomson et al (1973) reported the ability of aminocaproic acid to inhibit this release of plasmin and also the release of plasmin from the stomach into the gastric venous blood (Thomson et al, 1974). This was confirmed by O'Brien et al (1979), but they found no difference between diseased and normal stomachs.

Later studies have also been made to localize the gastric fibrinolytic activity. Eras et al (1970) found plasminogen activator activity in mucosal and submucosal blood vessels in the human stomach and Kondo et al (1975) found increased fibrinolytic activity in the gastric mucosa in the vicinity of active ulcers. The findings of Eras et al were confirmed by Nilsson et al (1977), who also found plasminogen activator activity in submucosal and mucosal vessels, although the type of vessels producing this activity was not defined. Thomson (1979) showed that fibrinolytic activity occurs around submucosal veins in human stomachs. Furthermore, Nilsson et al (1975) reported increased plasminogen activator activity in the gastric juice of patients with haemorrhagic gastroduodenitis, and Buhr et al (1978) found a higher level of fibrinolytic activity in the gastric juice of patients with gastric bleeding than in the gastric juice from normals. However, O'Brien et al (1979) and Low et al (1980) showed that gastric juice from patients without gastric haemorrhage may also exhibit fibrinolytic activity.

BUHR H J, ENCKE A, SEUFERT R M: Untersuchungen zur lokalen Fibrinolyse des Magens. (Investagations of the local fibrinolytic activity in the gastrointestinal tract.) In German. Chirurg 1978, 49, 431–435.

COX H T, POLLER L, THOMSON J M: Gastric fibrinolysis. A possible aetiological link with peptic ulcer. Lancet 1967, I, 1300–1302.

COX H T, POLLER L, THOMSON J M: Evidence for the release of gastric fibrinolytic activity into peripheral blood. Gut 1969, 10, 404–407.

ERAS P, HARPEL P, WINAWER S J: Histological localisation of plasminogen activator and proteolytic activity in human stomach and duodenum. Gut 1970, 11, 851–854.

KONDO M, IKEZAKI M, IMANISHI H, NISHIGAKI T, NAKAI T, HOSOKAWA K: Role of tissue fibrinolytic activity in gastroduodenal ulcer. J Kyoto Pref Univ Med 1975, 84, 1021–1027.

LOW J, DODDS A J, BIGGS J C: Fibrinolytic activity of gastroduodenal secretion—A possible role in upper gastrointestinal haemorrhage. Thrombos Res 1980, 17, 819–830.

NILSSON I M, BERGENTZ S-A, HEDNER U, KULLENBERG K: Haemorrhagic gastritis. Int Soc Haematol, Europ-Afr Div, 4th Meet, Istambul 1977, Abstracts, 587.

NILSSON I M, BERGENTZ S-E, WIKLANDER O, HEDNER U: Erosive haemorrhagic gastroduodenitis with fibrinolysis and low factor XIII. Ann Surg 1975, 182, 677–682.

O'BRIEN T E, HADLEY H, IRVING M H: Fibrinolytic activity in gastric venous blood. Gastroenterol 1979, 76, 509–514.

THOMSON J M: Fibrinolysis and the stomach. Biochemical identification of the "plasmin-like" enzyme. Thromb Diath Haemorrh 1974, 31, 291–298.

THOMSON J M: Haemostasis in the upper gastrointestinal tract. Proc 1st Florence Conf Haemostas Thrombos, Eds NERI SERNERI, GG, PRENTICE CRM, London Academic Press 1979, 237–245.

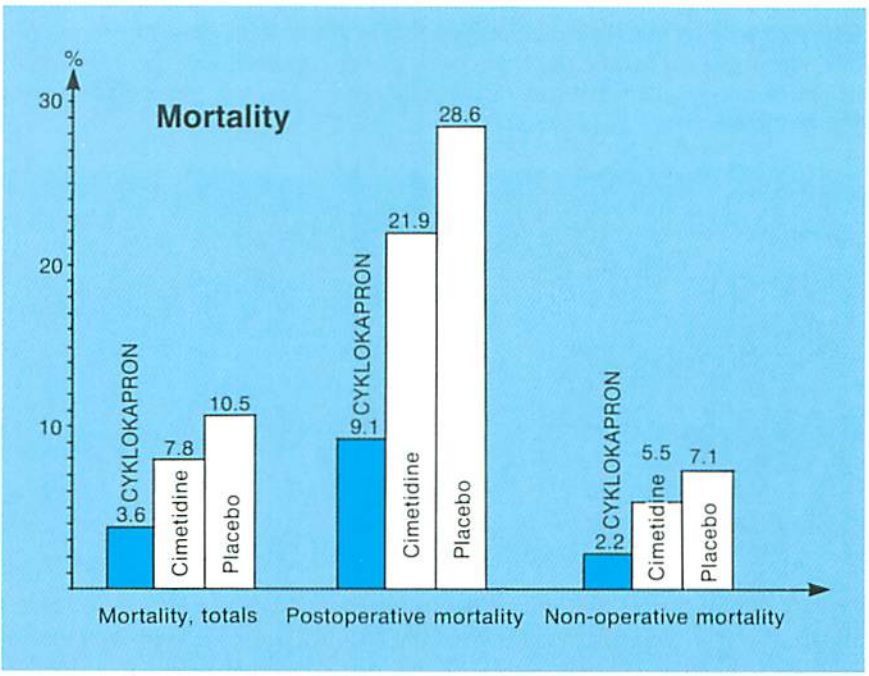
THOMSON J M, TURNER L, POLLER L: Inhibition of gastric plasmin activity by epsilon-aminocaproic acid. Ann Roy Coll Surg 1973, 53, 340–347.

Barer D, Ogilvie A, Coggon D, Henry D, Atkinson M, Langman M J S: Cimetidine and tranexamic acid in the treatment of acute upper gastrointestinal bleeding. New Engl J Med 1983, 308, 1571–1575.

No. of patients: 697

This study was a double-blind trial in which the effects of tranexamic acid and cimetidine on acute upper gastrointestinal haemorrhage were compared. A third group of patients received placebo.

Tranexamic acid was given 1 g intravenously every six hours for 48 hours followed by 1 g orally every six hours for five days. Treatment started as soon as possible and before any diagnostic procedure had been performed. It continued as stated above or until discharge from hospital, operation, withdrawal or death.



Acute upper gastrointestinal bleeding treatment with cimetidine or Cyklokapron (tranexamic acid)

The results obtained showed that the death rate was more than twice as high in patients receiving placebo or cimetidine as in those receiving tranexamic acid. This distribution is unlikely to have occurred by chance ($p < 0.025$). A comparison of death rates in placebo and tranexamic acid treated patients yields a statistical significance of $p < 0.01$. The value for a comparison of placebo and cimetidine is $p > 0.03$.

Side-effects are not commented on, but the immediate causes of death during treatment, before rebleeding or surgery, were pulmonary embolism in two cimetidine-treated patients and in one placebo-treated patient, myocardial infarction/heart failure in two cimetidine-treated patients, one tranexamic acid-treated patient and in one placebo-treated patient, pneumonia and respiratory failure in one placebopatient, cancer in two placebopatients and, finally, other cause in one cimetidine-treated patient.

Biggs J C, Hugh T B, Dodds A J: Tranexamic acid and upper gastrointestinal haemorrhage.—A double-blind trial. Gut 1976, 17, 729–734.

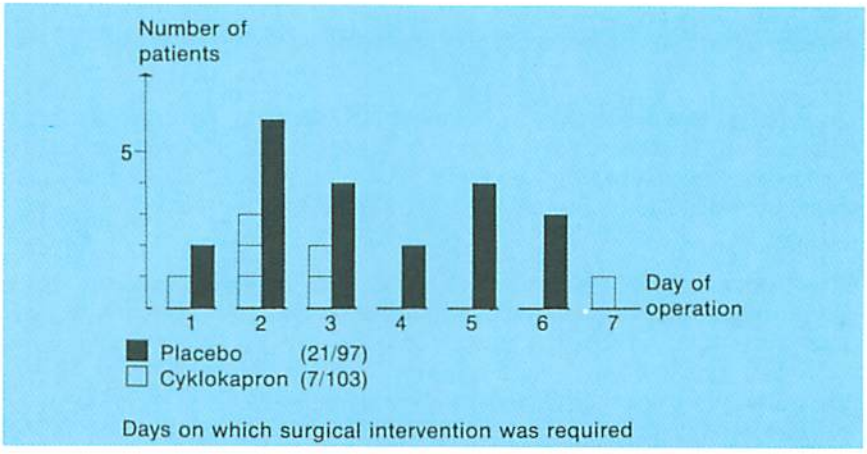
No. of patients: 200

Haemorrhage was observed by a medical officer or confirmed by gastric aspiration and examination of the faeces for melaena. Only patients who required admission to hospital entered the trial. Patients who were pregnant, had chronic renal impairment, previous vascular surgery, or a history of a thromboembolic episode during the preceeding 12 months were excluded. When tranexamic acid was administered the dose was two ampoules intravenously and two tablets orally eight-hourly for 48 hours, followed by two tablets orally eight-hourly for an additional 72 hours. This corresponds to a total daily dose of 6 g of tranexamic acid for the first 48 hours and 3 g daily for the additional 72 hours. The trial period comprised the first seven days in hospital.

Lesions causing blood loss	Tranexamic acid	Placebo
Duodenal and pyloric ulcer	35	40
Gastric ulcer	20	13
Acute gastric erosions	19	27
Oesophageal varices	5	7
Mallory-Weiss tear	4	4
Oesophagitis	5	1
Not determined	14	5
Other	1	0
Totals	103	97

Twenty-one of the 97 patients (22%) in the placebo group and seven of the 103 in the treatment group (7%) required surgery within the period of study. The indications for surgery were usually continuing or recurrent haemorrhage, although two patients in the placebo group were treated in this way because of a long history of duodenal ulceration. This difference in opera-

tion rates was significant ($p < 0.05$). After the first three days surgical intervention was required in only one patient in the treatment group and in nine patients in the placebo group (see below). The lesions found at operation largely reflected the distribution of lesions in the whole series. The overall mortality rates in both groups were 2 and 4 per cent, respectively. Massive blood loss played a role in all deaths.



Days on which surgical intervention was required

Reported side effects were nausea three in the treated group and one in the placebo group headache one and four fever one and two and thrombophlebitis at the injection site three and two respectively.

Cormack F, Chakrabarti R R, Jouhar A J, Fearnley G R: Tranexamic acid in upper gastrointestinal haemorrhage. Lancet 1973, I, 1207–1208.

No. of patients: 150

The final evaluation includes 76 tranexamic acid-treated patients and 74 placebo-treated patients. When tranexamic acid was given the dose was 1.5 g orally eight-hourly.

Retransfusion was necessary in eight tranexamic acid-treated patients and in 11 placebo-treated patients. In the tranexamic acid group 43 units were needed compared to 83 in the placebo group. This indicates that antifibrinolytic treatment may reduce the amount of blood required if retransfusion is necessary.

Three patients died in each group. All were over 60 years of age.

Treatment was judged to have failed in 15 tranexamic acid-treated patients and in 20 placebo-treated ones on applying the criteria of continued bleeding, recurrence, need for further transfusions and surgery. If patients with haemorrhage due to hiatus hernia or oesophageal varices were excluded, the figures were 7 out of 62 tranexamic acid patients and 17 out of 63 placebo patients ($p < 0.05$). This indicates that antifibrinolytic treatment is beneficial in the management of bleeding caused by peptic ulceration or erosion, and that inhibition of fibrinolysis is helpful only in such patients.

There was no significant difference in the failure rate between patients

being treated with tranexamic acid and the placebo patients in whom the subsequent barium-meal test was positive. However, in the patients with negative barium-meal tests there were no failures in 27 patients given tranexamic acid compared to six failures among 26 placebo-treated patients ($p < 0.05$).

One patient had continuous nausea and vomiting when on tranexamic acid, but these symptoms did not cease after the drug was stopped. Treatment had to be stopped in one patient because of epigastric pain. There were no symptoms or signs of thromboembolism.

Engqvist A, Broström O, von Feilitzen F, Halldin M, Nyström B, Öst Å, Reichard H, Sandquist S, Törngren S, Wedlund J E: Tranexamic acid in massive haemorrhage from the upper gastrointestinal tract. A double-blind study. Scand J Gastroenterol, 1979, 14, 839–844.

No. of patients: 149

In this double-blind, randomized trial 149 patients were treated for acute haemorrhage from the upper gastrointestinal tract; 76 were treated with tranexamic acid and 73 with placebo. The dose was 1 g intravenously 6 times daily for a maximum of 3 days, followed by 1.5 g orally 4 times daily for a maximum of 4 days when active treatment was given.

The transfusion requirements in the treatment group were smaller than in the placebo group, the difference being statistically significant on the second day after admission.

Ten patients in the treatment group and 18 in the placebo group were operated on. Eleven patients in the treatment group and 12 patients in the placebo group died.

The above date show that there is a favourable trend towards fewer operations and blood-transfusions in the tranexamic acid-treated group and that the number of blood-transfusions given on the second day differed significantly between the two groups. There were two patients with pulmonary embolism in the tranexamic acid group, both after surgery, and two with myocardial infarctions, both preoperatively. Two cerebral infarctions occurred in the placebo group, one preoperatively and one postoperatively.

Ulcerative colitis

The aetiology of ulcerative colitis is still being debated. That the condition involves a fibrinolytic component was first suggested by Kwaan et al (1964, 1969), who found that fibrinolytically active sites occurred more frequently in specimens from patients with active ulcerative colitis than in normal specimens. The aim of treating these patients with antifibrinolytic drugs is to reduce the blood loss and positively influence the healing.

KWAAN H C, COCCO A, MENDELOFF AI: Histologic demonstration of plasminogen activation in rectal biopsies from patients with active ulcerative colitis. J Lab Clin Med 1984, 64, 877.

KVAAN H C, COCCO A, MENDELOFF AI, ASTRUP T: Fibrinolytic activity in the normal and inflamed rectal mucosa. Scand J Gastroent 1969, 4, 441–445.

Hollanders D, Thomson J M, Schofield P F: Tranexamic acid therapy in ulcerative colitis. Postgrad Med J 1982, 58, 87–91.

No. of patients: 12

This study is a randomized double-blind, cross-over trial.

All patients chosen for the study were in a stable phase of the disease but continued to show blood in most or all stools. The diagnosis of ulcerative proctitis or proctosigmoiditis was made on the basis of clinical features, sigmoidoscopic appearances, barium enema tests and the histology of rectal mucosa specimens.

Table. Clinical description of patients with ulcerative colitis in this study. All patients were on oral iron supplements

Patient	Age (years) (Sex)	Haemoglobin (g dl)	Duration of disease (years)	Extent of disease	Other treatment
1	19(M)	13.0	6	Rectum	SASP 1 g thrice/day
2	30(F)	13.14	2	Rectum	SASP 1 g thrice/day
3	65(F)	11.9	15	Rectum	SASP 1 g thrice/day
4	57(F)	12.7	4	Recto-sigmoid	SASP 1 g thrice/day
5	40(F)	13.3	10	Rectum	Folic acid 5 mg
6	38(F)	11.5	5	Rectum	SASP 1 g thrice/day Normacol
7	71(F)	12.8	3	Rectum	Normacol
8	20(M)	11.6	5	Recto-sigmoid	SASP 1 g thrice/day
9	47(M)	13.5	2	Recto-sigmoid	SASP 1 g thrice/day Pred. 5 mg twice/day
10	26(F)	12.3	1	Rectum	SASP 1 g thrice/day Normacol
11	37(F)	9.7	2	Recto-sigmoid	SASP 1 g thrice/day
12	56(M)	13.2	1	Rectum	SASP 1 g thrice/day Ibuprofen 200 mg thrice/day

SASP = sulphasalazine

The study periods comprised 3 + 3 weeks and the dose of tranexamic acid was 1.5 g 3 times daily for 3 weeks when active treatment was given.

Table. Effects of tranexamic acid therapy on rectal appearance and bleeding. Patients marked with an asterisk* received tranexamic acid first. The blood in stool data are presented as stools with visible blood (upper number) over the total number of stools passed (lower number) in each treatment period

	Sigmoidoscopic prading			Blood in stool	
Patient	Before trial	Tranexamic acid	Placebo	Tranexamic acid	Placebo
1	2	0	1	1/15	7/23
2	3	1	0	0/43	0/40
3	4	4	4	24/63	20/66
4	4	2	4	1/21	8/38
5	4	2	2	15/39	35/38
6*	2	3	3	10/29	37/43
7*	3	1	1	1/45	0/31
8*	3	1	3	26/76	66/71
9	3	2	2	10/131	27/158
10*	3	2	3	18/18	16/16
11*	4	4	4	60/60	63/63
12*	4	3	3	67/67	63/63

No time effect was noted as a result of the order in which the two treatments were given. Consequently, the patients could be pooled into a single group.

Six patients experienced a substantially lower proportion of stools containing visible blood when on tranexamic acid. Two patients bled slightly less on placebo and in the remaining four patients no difference between the two treatments was found. Overall, the proportion of stools containing visible blood was significantly lower on tranexamic acid than on placebo ($p < 0.05$).

The sigmoidoscopic gradings were lower at the end of both treatment periods compared with the baseline grading before the trial. The grading improvement during the tranexamic acid treatment was statistically significant ($p < 0.05$).

There were no changes regarding stool frequency or stool consistency during either treatments.

Nine patients reported no side effects. Two patients experienced some nausea, one with vomiting, which lasted from 24 to 48 hours, but in neither case did it require discontinuance of treatment. One was on tranexamic acid and the other on placebo when symptoms occurred. One female patient volunteered the information that menstruation had been uncharacteristically light while taking tranexamic acid.

Routine haematology and biochemical profiles of venous blood samples taken at the beginning and close of the trial showed no abnormality which could be attributed to the medication.

It is felt that oral tranexamic acid in an oral dose of 1.5 g t d s is of value in controlling mucosal haemorrhage in some patients with ulcerative colitis but not in terms of reducing stool frequency or improving stool consistency.

Otolaryngology

Epistaxis

The aetiology of epistaxis is not quite clear and several factors, such as hypertension, upper respiratory tract infections, and intake of acetylsalicylic acid, have been reported to play a role in the occurrence of this type of haemorrhage. There have also been reports on high fibrinolytic activity in nasal tissue (Sasaki et al, 1959; Buch Rasmussen, 1966; Petruson, 1971).

BUCH RUSMUSSEN A: Epistaxis treated with Epsilon-Amino-n-Caproic Acid. Acta Oto-Laryngol 1966, 61, 221–227.

PETRUSON B: Fibrinolysens roll vid epistaxis. (The Role of Fibrinolysis in Epistaxis.) In Swedish. Nord Med 1971, 85, 574–575.

SASKAKI Y, OKAMOTO S, OHWADA K, NISHIHATA T: Some Observations on a Remarkable Fibrinolytic Activity in the Extract of Nasal Tissues and the Related Tissuse. Keio J Med 1959, 8, 235–246.

Petrusson B: A double-blind study to evaluate the effect on epistaxis with oral administration of the antifibrinolytic drug tranexamic acid (Cyklokapron®). Acta Oto-Laryngol 1974, Suppl. 317, 57–61.

No. of patients: 68

In this double-blind study treatment started as soon as the primary bleeding was arrested with a dose of 1 g 3 times daily when active treatment was given. The treatment continued for 10 days, thus continuing also after the patient had left the hospital.

The effect of the therapy was evaluated by means of a point scale. When the treatment had begun the severity and the number of recurrent bleeds were recorded and given bleeding scores. In each patient the bleeding scores for the ten days of treatment were then added and presented as the total number of points.

The hospitalization time was used as another criterion for the effect of the treatment. The hospitalization time depended on whether renewed bleeding occurred, how quickly the tampons could be removed and whether new tampons had to be used.

There was no difference between the two groups regarding history of upper respiratory tract infections, intake of acetylsalicylic acid and hypertension. The mean age in the two groups was the same as well as the localization of the bleeding source and the primary local treatment.

Thirty-one patients were treated with tranexamic acid and 31 with placebo.

Table. Total amount of bleeding points in the two groups of patients. The bleeding point scale: 1 = unimportant bleeding 2 = small bleeding during some minutes, not treated 4 = repeated small bleedings, not treated 6 = large bleeding which required treatment with tampons

	Patients treated with Cyklokapron® Bleeding points				Placebo Bleeding points			
	1	2	4	6	1	2	4	6
Number of classified bleedings in the group:								
Total	26	11	6	6	47	36	19	18
After 3 days therapy	0	1	0	1	18	19	3	7
After 5 days therapy	0	0	0	0	13	4	0	3

Table. Number of patients with at least one recurrent bleeding

	Patients treated with Cyklokapron®	Placebo
Total	16 (52 %)	30 (81 %)
After 3 days therapy	2 (6 %)	15 (41 %)
After 5 days therapy	0	10 (27 %)

The differences in bleeding scores and recurrent bleeds were stastically significant ($p < 0.01$). Furthermore, the hospitalization time was significantly shorter in the patients who were treated with tranexamic acid than in those who received placebo.

No side-effects occurred that were attributable to the tranexamic acid treatment.

Tonsillectomy

The most common complication in tonsillectomy is rebleeding, the frequency varying with the surgical technique used and with the definition of rebleeding.

It has been suggested that increased local fibrinolysis may be involved in the occurrence of rebleeding (Ghilardi et al, 1965).

GHILARDI F, VOENA C, BUSCA G: Osservazioni sull attivazione della fibrinolysi nelle emorragia da tonsillectomia e sull trattamento con l'acido EACA. (Observations on the fibrinolytic activation in haemorrhage after tonsillectomy and the treatment with aminocaproic acid.) In Italian. Ann Laringol 1965, 64, 55–61.

Castelli G & Vogt E: Der Erfolg einer antifibrinolytischen Behandlung mit Tranexamsäure zur Reduktion des Blutverlustes während und nach Tonsillektomien. (Experience of antifibrinolytic treatment with tranexamic acid in reducing blood loss during and after tonsillectomy.) In German, summary in English. Schweiz Med Wochenschr 1977, 107, 780–784.

No. of patients: 80

Tranexamic acid therapy was started two hours before surgery with 0.5 g i.v. in a controlled trial. Following surgery 250 mg were given intravenously t.i.d. at four-hourly intervals. On days 2, 3 and 4 after surgery the patients were given tranexamic acid by mouth in a dosage of 0.5 g t.i.d.

Tranexamic acid brought about a significant reduction of bleeding during the operation compared with placebo. Bleeding recurred in only 11 (27.5%) of the patients in the treatment group and stopped after two hours, on the average. The corresponding figures in the control group were 27 (67.5%) and 5.6 hours. The haemorrhages in the tranexamic acid group were considerably milder than those in the controls.

Verstraete M, Tybeghein J, Greef Y, Daems L, van Hoof A: Double-blind trials with ethamsylate, batroxobin or tranexamic acid on blood loss after adenotonsillectomy. Acta Clin Belg 1977, 32, 136–141.

No. of patients: 207

The investigators tested the drugs over a period of three years in separate prospective, randomized double-blind studies. Ethamsylate was given in an i.v. dose of 250 mg 15 minutes before surgery. Tranexamic acid was injected i.v. 30 minutes before surgery in a dose of 20 mg per kg body weight. In the batroxobin trials 0.5 ml of the drug was given intramuscularly one hour before and two hours after surgery.

If all patients are regarded as a single group regardless of the type of operation, none of the three preparations brought about any significant reduction of blood loss. In contrast, it was established that in combined adenotonsillectomy tranexamic acid significantly reduced the blood losses in patients losing more than 5 ml of blood per kg body weight. The two other preparations caused no definite reduction of blood loss.

Drug	No. of patients	Blood loss		
		< 5 ml/kg	> 5 ml/kg	
Ethamsylate	30	21	9	x^2 : 0.018
Placebo	25	17	8	P > 0.05
Tranexamic acid	37	32	5	x^2 : 3.532
Placebo	45	31	14	0.05 > P > 0.025
Batroxobin	33	31	2	x^2 : 2.574
Placebo	37	30	7	0.10 > P > 0.05

Ophthalmology

Hyphaema

Ocular trauma, accidental or surgical, is often accompanied by haemorrhage in the anterior chamber of the eye. The most serious complication of traumatic hyphaema is the secondary bleeding usually occurring on the second to the seventh posttraumatic day. This bleeding may be disastrous for the patient and result in impaired vision or blindness. The occurrence rate has been reported to be 9 to 38 per cent. A variety of therapeutic procedures has been tried in order to prevent the occurrence of secondary bleeding. Binocular padding, bedrest for one week and the use of topical steroids can be mentioned as examples of measures taken to avoid secondary haemorrhage.

Local fibrinolysis may play a part in intraocular haemorrhage. Local sites with plasminogen activator have been demonstrated in the vessels of the human iris, the ciliary body and the sclera (Pandolfi & Kwaan, 1967). In addition, the endothelium of the canal of Schlemm and the collecting channels have been found to have active sites. Thus, treatment with antifibrinolytic drugs may be beneficial in preventing secondary haemorrhage in such patients.

PANDOLFI M, KWAAN H C: Fibrinolysis in the anterior segment of the eye. Arch Ophthalmol 1967, 77, 99–104.

Bramsen T: Traumatic hyphaema treated with the antifibrinolytic drug tranexamic acid. Acta Ophthalmol 1976, 54, 250–256.

No. of patients: 72 + 135 case history controls

All patients were treated with complete rest and stenopeic spectacles. The 72 patients were also treated with tranexamic acid, 25 mg/kg body weight orally 3 times daily for six days. The patients were discharged on the fifth day.

Among the tranexamic acid-treated patients secondary haemorrhage occurred in only one patient (1.4 per cent; 1/72) 58 hours after the trauma. In the control group the frequency of secondary haemorrhage was 6.7 per cent (9/135). The recurrence occurred two days after the trauma.

The series presented is small, but the results indicate that with a dose of 25 mg tranexamic acid per kg body weight 3 times daily for six days after trauma, the incidence of secondary haemorrhage is reduced, compared with similar series of patients treated with bed-rest and stenopeic spectacles.

Some patients complained of gastrointestinal disturbances which did not result in discontinuation of treatment.

Bramsen T: Traumatic hyphaema treated with the antifibrinolytic drug tranexamic acid. II. Acta Ophthalmol 1977, 55, 616–620.

No. of patients: 75

The same dose of tranexamic acid was used as in the previous study. All patients were allowed to walk around during their stay in hospital, to read and to watch television.

There were no secondary haemorrhages in this group of patients.

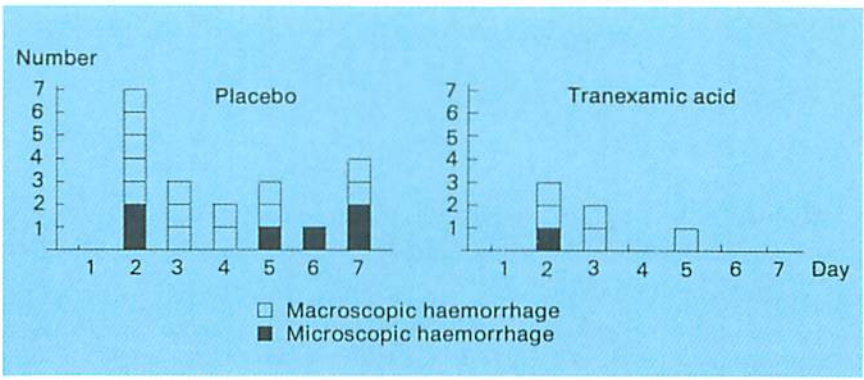
Jerndal T, Frisen M: Tranexamic acid (AMCA) and late hyphaema. A double-blind study in cataract surgery. Acta Ophthalmol 1976, 54, 417–429.

No. of patients: 244

Patients admitted for cataract surgery were entered in this randomized double-blind trial. The treatment started at lunchtime immediately after surgery with a dose of 1 g 3 times daily orally for 7 days when active treatment was given.

The effect was measured as a reduction in the frequency of rebleeding. The patients were examined by slit-lamp microscopy once daily during the first seven days. Every pre-existing hyphaema on day 1 and subsequent rebleeding in the anterior chamber were noted on a special daily record card.

Altogether, rebleeding occurred in six tranexamic acid-treated patients and 20 placebo-treated ones. The difference is statistically significant ($p<0.05$). A rebleeding peak is seen in both groups on the second post-operative day. No rebleeding occurred after day 5 in the tranexamic acid treated group and none after day 7 in the placebo group.



An interesting observation in a number of cases in the tranexamic acid group was the coagulation of a primary postoperative hyphaema which did not seem to hamper its resorption. This observation is interpreted as visible evidence of the depression of intraocular fibrinolysis by tranexamic acid.

There were no serious side-effects in either group and no difference between the groups. No thrombotic complication occurred.

Missotten L, de Clippeleir L, van Tornout I, Beenders P: The value of tranexamic acid (Cyklokapron) in the prevention of secondary bleeding, a complication of traumatic hyphaema. Bull Soc Belg Ophthalmol 1977, 179, 47–52.

No. of patients: 20 + 43 case history controls

The series comprises 20 patients with traumatic hyphaema consecutively admitted to the department. Forty-three patients, admitted earlier to the

department, served as controls. There was no difference between the two groups regarding the type of trauma or the size of the initial hyphaema.

The dose of tranexamic acid was 3 g orally daily for seven days. Furthermore, treatment consisted of bed-rest, eye patching and some were also treated with atropine. One patient also received ethamsylate. The patients in the control group were treated with bed-rest and eye patching and most of them also with atropine.

There were no secondary haemorrhages among the 20 tranexamic acid-treated patients while there were six among the 43 controls. The rebleeding occurred on days 3 and 4. A summary of the material, treatment and results is given in the Figure below. No side-effects were observed.

	Group 1: treated without Cyklokapron		Group 2: treated with Cyklokapron	
Group	43 patients		20 patients	
Treatment	– bedrest + eyepatching		– bedrest + eyepatching – Cyklokapron: 3 g a day; 7 days	
	– Atropin (32), Dicynone (4) – Varidase (7), Chymar (9)		– Atropin (15), Dicynone (1)	
	– Aceatazolamide if eyepressure 1		– Aceatazolamide if eyepressure 1	
Results	Rebleeding	No rebleeding	Rebleeding	No rebleeding
	6 patients (14 %) – young males – Atropin: 3 – Chymar: 3 – Salicylates: 3 – Varidase: 0 – Dicynone: 0	37 patients (86 %) – Atropin: 29 – Chymar: 6 – Salicylates: 0 Varidase: 7 – Dicynone: 4	0 patients	20 patients

Fig. Treatment given to 63 patients with traumatic hyphaema, 57 males, 6 females.

Uusitalo R J, Saari M S, Aine E, Saari K M: Tranexamic acid in the prevention of secondary haemorrhage after traumatic hyphaema. Acta Ophthalmol 1981, 59, 539–545.

No. of patients: 239 including case history controls

Altogether, 239 patients with traumatic hyphaema and admitted to hospital are included in the final evaluation.

Table. Age and sex distribution of 239 patients with traumatic hyphaema

	Non-tranexamic acid treated patients				Tranexamic acid treated patients	
	1972–1976 group		1977–1980 group		1977–1980 group	
Age (years)	Male	Female	Male	Female	Male	Female
0– 9	13	4	7	2	7	1
10–19	36	7	12	5	16	1
20–29	24	4	5	0	11	1
30–39	10	1	13	1	9	0
40–49	9	2	3	3	5	1
50–59	6	2	2	1	2	1
60–69	4	2	0	0	2	0
70–79	1	1	1	0	1	0
Total	103	23	43	12	53	5

Patients in the 1972–76 group were treated with bed-rest and in some cases also with steroids and mydriatics. In the 1977–80 group the patients were allowed to walk around on the ward. No eye patching was employed.

The dose was 0.5 g of tranexamic acid 3 times daily to 23 tranexamic acid treated patients and 2 tablets three times daily to the remaining 35, i.e. the ones with the large hyphaemas. Treatment usually lasted three to seven days.

There were no secondary haemorrhages in the tranexamic acid group (0/58) while three patients (3/55) in the parallell control group had secondary haemorrhages. In the case history control group the rebleeding frequency was 7.1% (9/126).

The resorption time was prolonged in the tranexamic acid group and the difference in resorption time between the tranexamic acid and control groups is highly significant. The effect of tranexamic acid in this condition has been postulated to be due to prolonged lysis of the formed clot.

Visual acuity was somewhat poorer in the tranexamic acid group than in the control group, but all patients presenting with hyphaemas involving more than half of the anterior chamber were entered in the tranexamic acid group.

None of the patients experienced other side-effects.

Vangsted P, Nielsen P J: Tranexamic acid and traumatic hyphaema. Acta Ophthalmol 1983, 61, 447–453.

No. of patients: 112

This study is an open randomized trial with two groups of hyphaema patients, one treated conservatively with complete bedrest for seven days, whereas the other patients were allowed to walk about and received oral tranexamic acid, 25 mg/kg body weight 3 times daily for seven days. The former group consists of 53 patients and the latter of 59.

Tranexamic acid was given orally, 25 mg per kg body weight 3 times daily for seven days.

Because of the persisting absence of rebleeding in both groups and incoming reports on the efficacy of tranexamic acid, it was felt inappropriate to continue to prescribe bed-rest to one group. The study was therefore terminated before sufficient clinical material to allow statistical analysis had been collected. These results tend to support the belief that it is safe to mobilize patients with hyphaema if they are treated with antifibrinolytic drugs.

Also in this investigation it was noted that the resorption of blood from the anterior chamber was delayed in the tranexamic acid group. However, no complication resulting from the prolonged presence of blood in the anterior chamber was recorded during the observation period.

Varnek L, Dalsgaard D, Hansen A, Klie F: The effect of tranexamic acid on secondary haemorrhage after traumatic hyphaema. Acta Ophthalmol 1980, 58, 787–793.

No. of patients: 232

Included into the study were all patients with traumatic hyphaema who showed at the inital slit-lamp examination either a sedemented hyphaema or visible clots in the anterior chamber. Only patients admitted less than 24 hours after sustaining the injury were included in the study.

The frequency of secondary haemorrhage, resolution of the clot, visual acuity and the duration of the stay in hospital were the variables studied. All patients were treated as in-patients with bed-rest and stenopeic glasses for five days. Tranexamic acid was given to patients admitted on even days and placebo to patients admitted on odd days in an oral dose of 25 mg/kg body weight 3 times daily for six days. Altogether, 102 patients were treated with tranexamic acid and 130 served as controls.

Two patients out of the 102 in the tranexamic acid group developed secondary haemorrhages compared to 12 patients among the 130 controls. The difference is statistically significant ($p < 0.02$). The secondary haemorrhages in the tranexamic acid group both occurred three days after the trauma and their course was uneventful, without increase in intraocular tension or visual defects. The secondary haemorrhages in the control group occurred two to seven days after the trauma. In six patients the course was disturbed by poorer final visual acuity accompanied by increased intraocular pressure in five of them. The duration of follow-up necessary for these 12 patients was 60 days compared to 12 days for the whole control group. The follow-up for the patients with secondary haemorrhage in the tranexamic

acid group lasted for 12 days and did not differ from that of the group as a whole.

To sum up, the treatment with tranexamic acid proved to be useful in preventing secondary haemorrhage after traumatic hyphaema. Furthermore, the final visual acuity was not affected in the two tranexamic acid treated patients while the controls with secondary haemorrhages also experienced poorer visual acuity.

Welsh N H: The effect of Cyklokapron in traumatic hyphaema: A double-blind study. S A Arch Ophthalmol 1983, 10, 67–74.

No. of patients: 39

Adult male and female in-patients with a history of hyphaema of no more than five days were included in this randomized double-blind trial. At the onset of treatment a full report on the cause of the hyphaema was noted as well as the appearance and extent of the lesions. The visible surface area of the hyphaema was assessed daily for a period of seven days and the estimated percentage involvement of bleeding in the anterior chamber of the eye was recorded diagramatically. In addition, intraocular pressure recordings were made on a daily basis. The affected eye was padded and dressings were changed daily.

When active treatment was given the dose of tranexamic acid was 1.5 g 3 times daily for seven days.

Variables studied were reduction in the frequency of secondary haemorrhage after traumatic hyphaema, the area of the hyphaema and intraocular pressure. The diagnosis of secondary haemorrhage was based on an increased hyphaema area.

One patient in the tranexamic acid group of 19 patients and six patients out of 20 in the placebo group developed secondary haemorrhages. On the average, the hyphaema on any particular day was 84.9% of that of the previous day in the tranexamic acid treated patients, compared to 91.6% in the placebo ones. Thus, on the average, the hyphaema on any particular day decreased by 15.1% in the tranexamic acid group, compared to 8.4% in the placebo group. The improvement rate with tranexamic acid was significantly higher than with placebo, $p < 0.05$. The avarage intraocular pressure on any day was 89.7% of that of the previous day in the tranexamic acid group, compared to 99.2% in the placebo group. Thus, the average intraocular pressure on any particular day decreased by 10.3% with tranexamic acid and by 0.8% with placebo. The difference is statistically significant, $p < 0.05$.

One patient complained of nausea while on tranexamic acid therapy.

Dermatology

Hereditary angioneurotic oedema (HANE)

Hereditary angioneurotic oedema is characterized by recurrent, circumscribed, transient and non-itching oedema of the skin and oedema of the mucosa of the gastrointestinal and upper respiratory tracts. Involvement of bowel mucous membranes leads to acute attacks of abdominal pain with associated vomiting and occasionally diarrhoea. When the oedema affects the upper respiratory tract there is a great risk of death by asphyxiation (Landerman, 1962).

Hereditary angioneurotic oedema is an autosomal dominant disease. The onset of symptoms usually occurs in infancy or childhood. Acute attacks usually last from one to about four days and may be separated by periods of remission ranging from days to years. Prodromal symptoms are sometimes reported and vary from patient to patient and from site to site. Triggering factors are not clearly understood. Oedema of allergic origin has to be distinguished from this entity.

Hereditary angioneurotic oedema has been shown to be due to an inherited deficiency of the functional plasma inhibitor of the activated first component (C1) of the complement system. The episodic swellings are secondary to a deficiency of this C1esterase inhibitor. C1 is normally found in the serum in an inactive state but under certain conditions becomes activated and then triggers the complement cascade. C1-esterase inhibitor closely regulates the initial reaction of the cascade. A deficiency of this enzyme may thus lead to an uncontrolled activation of the complement cascade and an excessive production of fragments of other complement factors such as C2, C3 and C5, many of which have vasoactive properties. During acute episodes of angiooedema the amount of activated C1 is markedly increased. Plasmin can trigger C1. C1-esterase inhibitor also inhibits plasmin and plasma kinogenase. A minor trauma can activate the fibrinolytic system. Exercise, anxiety, minor trauma, emotional trauma and profuse menstrual bleeding are all common triggering factors in this disease.

Treatment of hereditary angioneurotic oedema is directed towards preventing the acute attacks of oedema and reducing the severity of symptoms in connection with them, such as abdominal disturbances and the worst complication, laryngeal oedema, which still carries a high mortality.

LANDERMAN N S: Hereditary angioneurotic oedema. J Allergy 1962, 33, 316–329.

TAYLOR F, FUDENBERG H: Inhibition of the C'1 component of complement by amino acids. Immunology 1964, 7, 319–331.

Blohme G: Treatment of hereditary angioneurotic oedema with tranexamic acid. A random double-blind cross-over study. Acta Med Scand 1972, 192, 293–298.

No. of patients: 5

Blohme' treated five HANE patients in a randomized double-blind cross-over study, three continuously and two intermittently, i.e. treatment was started in the latter when the prodromal symptoms appeared. The dosage was 1.5–4.5

g tranexamic acid daily in the continuously treated patients and 2–4.5 g for 1–5 days in the patients treated intermittently. The improvement after therapy was dramatic in two of the patients in the former group and in one in the last-mentioned group.

Intermittent therapy may be sufficient in patients in whom there is a marked periodicity of symptoms.

Champion R H, Lachmann P J: Hereditary angio-oedema treated with ε-aminocaproic acid. Br J Dermatol 1969, 81, 763–765.

No. of patients: 1

A man, 38 years old, with hereditary angioneurotic oedema who had been treated earlier with aminocaproic acid at a dose of 30 g daily was switched to tranexamic acid therapy. Apart from slight nausea and a tendency to nasal stuffiness, the treatment with aminocaproic acid was successful. He was then put on tranexamic acid, 0.5 g twice daily. At the time of the report, the patient's condition had been nearly completely controlled for seven months and he had had only four mild attacks while taking this low dose.

This case report indicates that when tranexamic acid is used in hereditary angioneurotic oedema in order to reduce the frequency and severity of attacks, very much lower doses can be employed compared with the doses needed when aminocaproic acid is used.

Lundh B, Laurell A-B, Wetterquist H, White T, Granerus G: A case of hereditary angioneurotic oedema, successfully treated with ε-aminocaproic acid. Clin Exp Immunol 1968, 3, 733–745.

No. of patients: 1

The patient was a 26-year-old man, with hereditary angioneurotic oedema, who noted nasal stuffiness an slight dizziness and had dry ejaculations during treatment with aminocaproic acid at a dose of 5 g 6 times daily. After six months' treatment with aminocaproic acid a prostatovesiculitis interpreted to be a side-effect of the aminocaproic acid treatment, developed. The patient was then put on tranexamic acid, 5 g daily. At the time of the report the patient had been on tranexamic acid for six months. The ejaculations became normal and the prostatovesiculitis disappeared. The nasal stuffiness and dizziness also disappeared.

This case report indicates that by treating with tranexamic acid instead of aminocaproic acid some side-effects, such as nasal stuffiness, dizziness and dry ejaculations, can be avoided. Furthermore, much a smaller dose of tranexamic acid is sufficient to prevent attacks and symptoms.

This patient was later reported on by Lundh (New Engl J Med, 1973, 288, 53). At that time the patient had been on continuous tranexamic acid treatment since June 1967. The dose had been 1.5 g 6 times daily. At a check-up in July 1972 he had ingested altogether more than 12 kg of tranexamic acid. The only side-effect was increased gastrointestinal motility. There were no laboratory signs of impairment of haematopoiesis or damage to the liver and kidneys. There was no demonstrable effect on muscle tissue and the prostate gland. The authors conclude that 11 pretreatment attacks of laryngeal oedema against none afterwards weigh heavily against discontinuation of therapy.

Marasini B, Cicardi G C, Martignoni G C, Agostoni A: Treatment of hereditary angioedema. Klin Wochenschr 1978, 56, 819–823.

No. of patients: 15

Fifteen patients, 10 females and five males, aged 10 to 48, with hereditary angioneurotic oedema were studied during long term prophylactic treatment with tranexamic acid. All had had more than one debilitating attack per month.

Eleven of the adults were treated with 2 g of tranexamic acid daily, one with 2–3 g and one with 3 g daily. The two children were treated with 1.5 g daily. The treatment period ranged from one to 16 months.

Complete remission of symptoms was observed in two patients. In 10 patients the frequency of the attacks was reduced and the symptoms were less pronounced. In three patients no effect at all was achieved.

Side-effects reported were gastrointestinal disturbances, anal pruritus and polymenorrhoea. In no case did the drug had to be withdrawn.

Ohela K: Treatment of hereditary angioneurotic oedema with tranexamic acid and cinnarizine. Acta Dermato-Venerol 1976, 56, 61–67.

No. of patients: 7

This study was an open one, and partly cross-over, with cinnarizine. All patients were treated with tranexamic acid during attacks and three were also on continuous treatment. Cinnarizine was given to four of the seven patients.

The acute treatment consisted of 1–1.5 g of tranexamic acid 2–3 times daily and the continuous therapy of 0.5–1.5 g 3 times daily. Cinnarizine was given as continuous, 20–30 mg daily.

The results are presented in the Table below.

Table. The results of treatment with AMCA and cinnarizine in 7 HANE patients ++ = good response, a few mild attacks, + = moderate response, the attacks shorter and milder

	AMCA				Cinnarizine	
	During the attacks		Continuously		Continuously	
Case No.	Duration of treatment (months)	Response	Duration of treatment (months)	Response	Duration of treatment (months)	Response
1	22	+				
2	25	+				
3	15	+	9	+	21 days	–
4	3	+			9	+
5	11	–	11	++		
6	11	+	1.5*	++	10	++
7	13	+				

* Interrupted therapy due to side effects

Tranexamic acid given during attacks seemed to be effective in six of the seven patients. The best effect was obtained when the drug was taken immediately at the start of the attack and in a dose of 1.5 g 3 times daily. The follow-up period was three to 25 months. Two of the three patients treated continuously were almost symptom-free on a dose of 1 g 2–3 times daily. The follow-up period was three to 11 months. Two of the three patients given cinnarizine were obviosly helped by the treatment. One of these had to interrupt her tranexamic acid treatment due to fatigue, nausea and vertigo. Follow-up was nine to 10 months.

Sheffer A L, Austen K F, Rosen F S: Tranexamic acid therapy in hereditary angioneurotic odema. N Engl J Med 1972, 287, 452–454.

No. of patients: 12

In this randomized, double-blind, cross-over trial tranexamic acid was given in a dose of 1 g 3 times daily when active treatment was given.

Each patient remained on the active or placebo regimen for two successive periods of three months each. In some cases the study period was less than six months, however.

Frequency of attacks in patients with hereditary angioneurotic oedema during treatment with tranexamic acid or placebo

	Tranexamic acid		Placebo	
Case no.	Duration of treatment (mo)	No. of attacks	Duration of treatment (mo)	No. of attacks
Excellent results				
1	9	2	5	4
2	11	2	4	5
3	4	0	9	6
4	13	0	3	3
5	1	0	4	6
6	4	0	7	10
7	13	0	3	3
	55	4	35	37
Good results				
8	13	5	3	3
9	11	5	3	4
10	4	1	11	9
11	5	5	1	4
	33	16	18	20
Poor results				
12	6	12	4	6

The difference between the frequency of attacks during the two treatment periods was statistically significant ($p < 0.005$).

All patients, except the one who was not helped by tranexamic acid during the trial, continued the tranexamic acid treatment upon completion of the trial period at a reduced daily dose of 1 g. They continued to experi-

ence attenuation of their symptoms without noticeable side-effects.

One patient complained of puritis ani and four of mild abdominal discomfort and diarrhoea when treated with tranexamic acid.

No significant alteration was noted in any of the laboratory investigations performed except for the streptokinase-induced plasma clot lysis time. Ingestion of tranexamic acid prolonged the lysis time to more than 180 minutes (range during placebo treatment: 5 to 30 minutes).

Sheffer A L, Fearon D T, Austen F, Rosen F S: Tranexamic acid: preoperative prophylactic therapy for patients with hereditary angioneurotic edema. J Allerg Clin Immunol 1977, 60, 38–40.

No. of patients: 14:

Traumata frequently induce attacks of hereditary angioneurotic oedema. Sheffer et al describe 14 patients with an average of 6 spontaneous attacks a year. In the majority of cases dental extractions had led to laryngeal oedema in these patients. They were now treated with tranexamic acid in connection with different surgical procedures. The dosage used was 1 g orally every six hours for a total of 96 hours before and after the procedures. No other medicines for angiooedema were given. The prophylactic treatment with tranexamic acid was very successful. All the operative procedures could be carried out without inducing attacks of the disease.

Zachariae H, Laurberg G, Hjortshöj A: Tranexsamsyre (Cyklokapron®) ved hereditaert angioneurotisk ödem (Tranexamic Acid (Cyklokapron®) in hereditary angioneurotic oedema). In Danish, summary in English. Ugeskr Laeg 1975, 137, 1106–1108.

No. of patients: 8

In this open study the medication period was compared to non-medication periods regarding the frequency and severity of the attacks. Usually, 1 g of tranexamic acid was given 3–4 times daily.

Patient No. (sex, age)	Attack Frequency	
	Before Treatment	During Treatment
1. ♀ 30 y.	1 per month	3 per year
2. ♀ 70 y.	2–3 per month	1–2 per month
3. ♂ 31 y.	4 per year	0
4. ♀ 17 y.	1 per month	0
5. ♂ 50 y.	1 per month	0
6. ♂ 12 y.	1 per month	1 per year
7. ♀ 67 y.	1 per day	4–8 per month
8. ♀ 40 y.	1 per month	0

All eight patients studied responded to the treatment with tranexamic acid, experiencing fewer attacks of oedema and less severe symptoms when attacks occurred.

In one patient the treatment had to be interrupted for investigational reasons and this resulted in an attack which necessiated hospitalization and treatment with tranexamic acid intravenously.

Two patients complained of headache and dizziness. These side-effects disappeared when the dose was lowered. Two other patients complained of being sleepy. Laboratory investigations revealed nothing of a pathological nature.

Urticaria/angiooedema

Urticaria and angiooedema, in combination or alone, are rather common diseases. Urticaria usually involves the superficial skin layers and may be intensely pruritic. The wheals usually disappear within 48 hours but may recur for long periods. Angiooedema involves the deeper skin layers and is usually not pruritic. Both conditions may be accompanied by disabling gastrointestinal disturbances, life-threatening upper respiratory tract obstruction or hypotension. Most of the time the cause of the attack cannot be defined and thus the treatment is symptomatic. Antihistamines have been used, and adrenaline and steroids in the acute stage.

Laurberg G: Tranexamic acid (Cyklokapron) in chronic urticaria. A double-blind study. Acta Dermatovenerol 1977, 57, 369–370.

No of patients: 17

All patients had low levels of the C1-esterase inhibitor. The study was a double-blind cross-over one and active treatment was given.

The treatment periods comprised four weeks each and were separated by a one-week wash-out period. The dose of tranexamic acid was 1 g 3 times daily for four weeks when active treatment was given. The efficacy of tranexamic acid was evaluated in terms of less severe symptoms.

The results obtained did not show any difference between the two treatments regarding the severity of symptoms. Thus, these findings do not support the use of tranexamic acid in the management of patients with urticaria.

While on tranexamic acid, one patient complained of diarrhoea.

Martens B P M: Clinical experience with tranexamic acid (Cyklokapron) in urticaria and angioedema. Br J Dermatol 1984, 111, 481–482.

Number of patients: 74

The patients were selected because of an inadequate response to conventional therapy. Tranexamic acid was given in a low dose, 0.5 g 3 times daily for four weeks. The results are presented in the Table on page 74:

	n	Cured	Improved	Equal or worsened
Acute angio–oedema	8	6	0	2
Recurrent angio–oedema	4	2	0	2
Factitious urticaria	7	1	3	3
Cholinergic urticaria	9	2	1	6
Pressure urticaria	6	2	2	2
Delayed pressure urticaria	11	8	1	2
Cold urticaria	5	2	0	3
Chronic idiopathic urticaria	16	5	6	5
Cyclic urticaria	3	1	0	2
Urticaria–vasculitis	5	3	1	1
Totals	74	32 (43 %)	14 (19 %)	28 (38 %)

Adverse reactions were observed in ten patients (13.5%). They consisted of headache (3), nausea/abdominal pain (3), increased urticarial activity (2), flushing/perspiration (2), weakness/tiredness (2). These patients were all classified as unchanged or worsened.

It is concluded that a favourable effect of low-dose treatment with tranexamic acid in patients with urticarial disorders can be obtained, especially in those who are only partly responsive to antihistamines.

Munch E P, Weeke B: Non-hereditary angioedema treated with tranexamic acid. Allergy, 1985, 40, 92–97.

No. of patients: 10

All patients had previously been treated according to several regimens, including antihistamines and oral steroids, without any improvement.

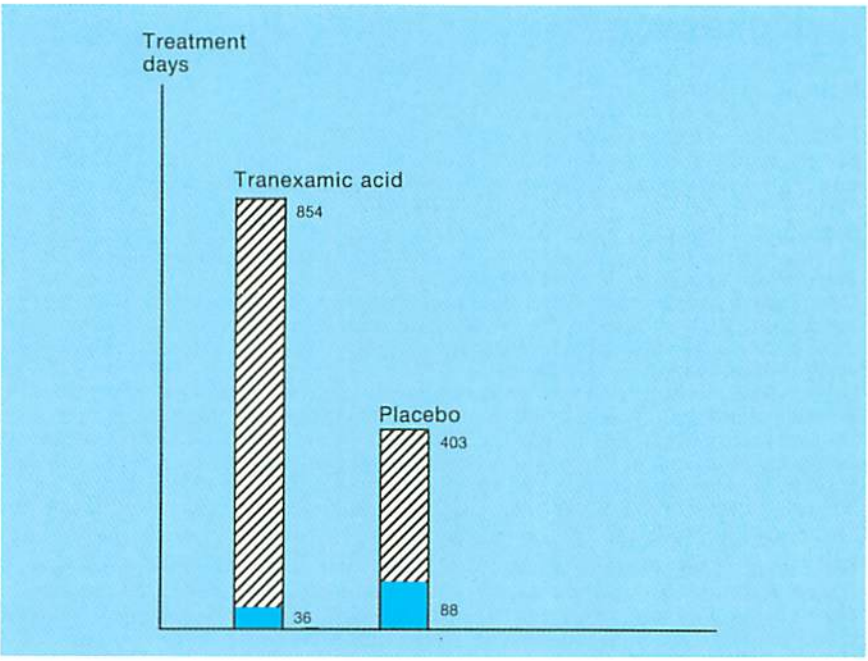
The treatment periods comprised three months each and the dose of tranexamic acid was 1.5 g 3 times daily.

During tranexamic acid treatment nine patients were symptomfree or improved substantially and one did not improve ($p < 0.01$). Five patients completed the study according to the protocol, while five did not complete the placebo period. The total number of treatment days and days with oedema in the active and placebo periods are shown in the figure below. Itching was a main complaint in four patients. It disappeared during the tranexamic acid treatment.

Gastrointestinal disturbances were more pronounced during the tranexamic acid treatment and necessitated a dose reduction in one patient.

Four years after the study it was possible to get in touch with eight of the nine responders. Six were still taking tranexamic acid regularly. Two patients had improved during this period and did not use the drug regularly.

The finding that some patients with urticaria/angiooedema may benefit from treatment with tranexamic acid is further supported by several case reports on patients with urticaria (Yamamoto & Hatano, 1965; Hellenbroich & Welke,



Total number of days of treatment with tranexamic acid and placebo. Hatched area: days of treatment without symptoms: black area: days with symptoms (oedema).

1975; Tant, 1979) and angiooedema (Sundin, 1977; Thompson & Felix-Davies, 1978; Freed et al, 1980; Jörnö, 1981).

FREED D L J, BUISSERET P D, LLOYD M J, PUMPHREY R S H, GARRETTS M: Angiooedema responding to antiprotease treatment but without abnormalities of the complement system. Clin Allerg 1980, 10, 21–23.

HELLENBROICH H, WELKE S: Tranexamsäure (AMCA)—eine therapeutische Möglichkeit bei endogenem Ekzem und chronisch rezidivierender Urtikaria. (Tranexamic acid (AMCA) - a therapeutic agent in endogenous eczema and chronic urticaria.) In German. Akt Dermatol 1975, 1, 137–143.

JÖRNÖ C: Icke-hereditärt angioneurotiskt ödem behandlat med tranexamsyra (Cyklokapron). (Non-hereditary angioneurotic ooedema treated with tranexamic acid [Cyklokapron].) In Swedish. Ronden 1981, 6, 90.

SUNDIN B: Ett fall av icke hereditärt angioödem framgångsrikt behandlat med tranexamic acid. (A case of non-hereditary angiooedema successfully treated with tranexamic acid.) In Swedish. Läkartidningen 1977, 74, 3098–3099.

TANT D: Tranexamic acid in chronic urticaria. Br Med J 1979, 1, 266.

THOMPSON R A, FELIX-DAVIES D D: Response of "idiopathic" recurrent angioneurotic oedema to tranexamic acid. Br Med J 1978, 3, 608.

YAMAMOTO K, HATANO H: Clinical uses of trans-form of AMCHA (4-Aminomethyl-Cyclohexane-1-Carboxylic Acid) on several skin diseases. Keio J Med 1965, 14, 99–105.

ZACHARIAE H, LAURBERG G, HJORTSHÖJ A: Tranexamsyre (Cyklokapron) ved hereditaert angioneurotiskt ödem. (Tranexamic acid (Cyklokapron) in hereditary angioneurotic oedema.) In Danish, summary in English.

Product presentation

Cyklokapron®

Tablets 0.5 g, mixture 0.1 g/ml, injection solution 0.1 g/ml.
Fibrinolysis inhibitor.

Declaration *1 tablet contains:* Acid. tranexamic. 0.5 g, constit. q.s. *1 ml mixture 0.1 g/ml contains:* Acid. tranexamic. 0.1 g, sorbitol. 0.18 g, constit. et aroma q.s., aq. purif. ad 1 ml. *1 ml injection solution contains:* Acid. tranexamic. 0.1 g, aq. steril. ad 1 ml.

Properties Cyklokapron contains tranexamic acid (AMCA), which in the fibrinolytic system exercises a strongly inhibitory effect on plasminogen activation, i.e. the transformation of plasminogen into plasmin.
Cyklokapron is absorbed very well orally, though somewhat less well than ε-aminocaproic acid (Epsikapron). Intravenous administration is only indicated when there is difficulty in giving the required dose by the oral route. Cyklokapron is excreted via the kidneys in unchanged form.
Cyklokapron mixture has a licorice taste and is sugar-free. The antifibrinolytic activity of tranexamic acid is about 10 times greater, gram for gram, than that of ε-aminocaproic acid, on fibrinolysis brought about by urokinase or tissue activiators.
Cyklokapron is used in fibrinolytic haemorrhage conditions, which may arise in various clinical situations involving an abnormal stimulation of the mechanism of activation.

Toxicology Tranexamic acid has low toxicity. After oral administration to mice the LD_{50} is about 12500 mg/kg and after intravenous administration 1300 mg/kg. The corresponding values when given to rats are about 11250 mg and 850 mg/kg. Tests in mice, rats and rabbits have shown no teratogenic effect.
Retinal changes have been reported in the dog after administration of massive dosis of tranexamic acid for long periods of time, and in the cat after i.v. administration of 250 mg/kg/day for 14 days. Such changes were not seen in the rat after administration of maximum tolerable dose for long periods of time.
No retinal changes have been reported or established in eye examinations performed on patients treated with CYKLOKAPRON over periods ranging from several weeks to months. For patients who are to receive continual treatment with CYKLOKAPRON for several weeks, an ophthalmological examination is advisable (including visual acuity, colour vision, eyegrounds, field of vision etc.) if possible before commencing treatment and at regular intervals during treatment.

Indications Increased fibrinolysis or fibrinogenolysis with haemorrhage or risk of haemorrhage. Hereditary angioneurotic oedema.
Local fibrinolysis may occur in such cases as after prostatectomy or bladder operations of any kind, in haematuria, recurrent gastric haemorrhage, ulcerative colitis and menorrhagia, and after dental surgery (extractions) on patients with haemorrhagic diathesis.
General fibrinolysis may occur in cases of cancer of the prostate or pancreas, after thoracic surgery and other major surgical interventions, in obstetrical complications such as ablatio placentae and post-partum haemorrhage, in leukumia, liver disease and in thrombolytic therapy with streptokinase (Kabikinase). In cases of fibrinolysis concurrent with diagnosed increased intravasal coagulation — defibrination syndrome — an anticoagulant such as heparin should also be given at very carefully controlled dosages.

Contraindications Care should be taken in cases of renal insufficiency due to the risk of accumulation, and where there is pronounced haematuria from the rest of the urinary tract, since in isolated cases obstacles to passage have been observed in the tract. Patients with a marked risk of thrombosis should not be given Cyklokapron, unless at the same time it is possible to give treatment with anticoagulants. The preparation should not be given to patients with acquired disturbances of colour vision. If disturbances of colour vision arise during the course of treatment the administration of the preparation should be discontinued.

Pregnancy and nursing Tranexamic acid passes into the maternal milk, but in such small quantities there should not need, generally, to be any risk of the infant being affected by therapeutic doses.

Side effects Gastrointestinal disturbances (nausea, vomiting, diarrhoea) may occur but disappear when the dose is reduced. Exceptional cases of giddiness have been reported when intravenous injection is too fast.

Dosage
Recommended normal dosages are 5—10 ml intravenously or 2—3 tablets 0.5 g or 10—15 ml mixture 2—3 times a day.
For the indications given below, however, the following standard dosage can be used:
General fibrinolysis: 10 ml intravenously 3—4 times a day.
Prostatectomy: 5—10 ml intravenously 2—3 times a day (with the first dose during the operation) during the first three days after the operation, after which 2—3 tablets or 10—15 ml mixture 2—3 times a day until macroscopic haematuria is no longer present.
Haematuria: 2—3 tablets or 10—15 ml mixture 2—3 times a day until macroscopic haematuria is no longer present.
Menorrhagia: 2—3 tablets or 10—15 ml mixture 3—4 times a day. Cyklokapron treatment should only be started when copious bleeding has begun.
Hereditary angioneurotic oedema: some patients can feel when attacks are coming on, and are best treated intermittently with 2—3 tablets or 10—15 ml mixture 2—3 times a day for several days. Others should be treated continuously with this dose.
Dental surgery: immediately before the operation, AHF concentrate or Preconativ should be given as well as Cyklokapron, 10 mg per kg body weight intravenously. After the operation, 25 mg/kg is given orally 3—4 times an day for 6—8 days. After the operation the patient does not generally require AHF concentrate or Preconativ.

Note Cyklokapron injection solution is administered slowly intravenously at the rate of 1 ml per minute. For intravenous drip, Cyklokapron injection solution can be mixed with most infusion solutions, such as electrolyte, carbohydrate, amino acid and dextran solutions. The mixing must be done on the day of use. Heparin may be added to Cyklokapron injection solution. Cyklokapron injection solution must not be mixed with blood or with infusion solutions containing penicillin.

Packs Ampoules 0.1 g/ml 10 × 5 ml, 10 × 10 ml.
Tablets 0.5 g (white, round flat with CY engraved in arcs, diam. 13 mm or white, film-coated, capsule-shaped with CY engraved in arcs, 8 × 18 mm): 20 tablets, 50 tablets, 100 tablets.
Oral solution 0.1 g/ml 300 ml.

Notes