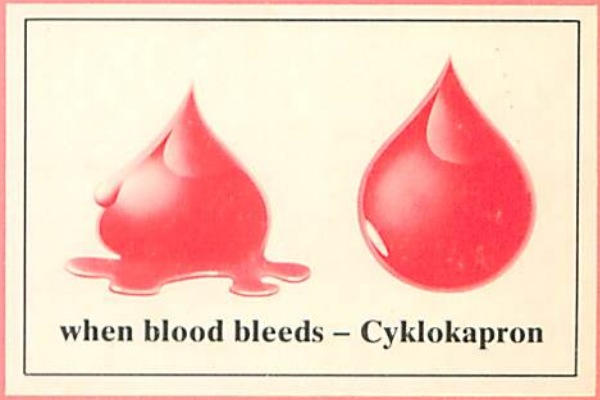
Cyklokapron

tranexamic acid

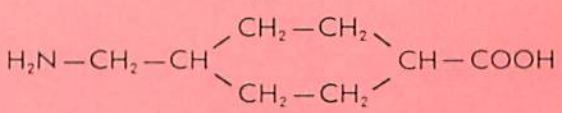


Contents

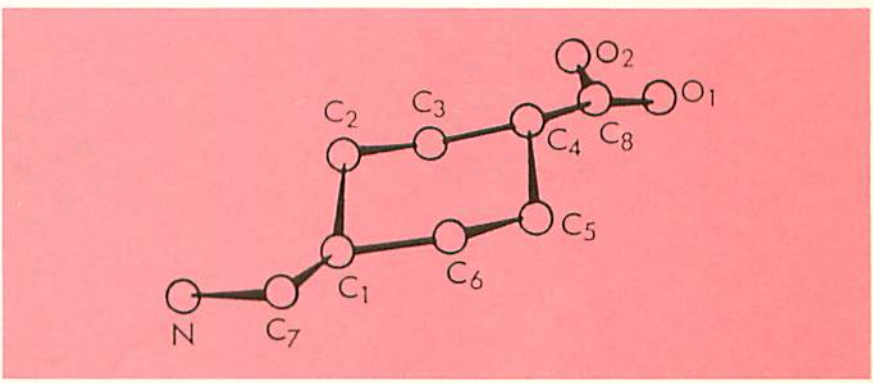
Cyklokapron

tranexamic acid

Tranexamic acid (AMCA) is a synthetic amino acid. It forms white crystals, which are soluble in water, acids and alkalies, but insoluble in organic solvents. The molecular weight is 157 and the structural formula is as follows:



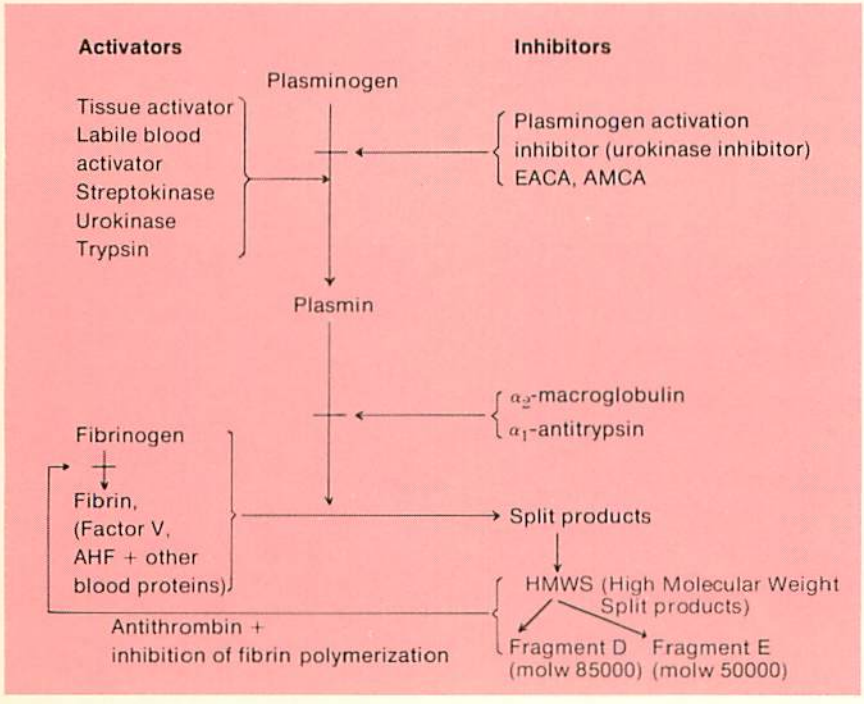
Trans-4-aminomethyl cyclohexane carboxylic acid



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

Pharmacodynamics

The conversion of plasminogen to plasmin requires the presence of an activator. During recent years it has been possible to demonstrate that the walls of blood-vessels and other tissues contain activators (Nilsson & Pandolfi, 1970; Pandolfi et al., 1967). These are released continuously into the blood stream and are responsible for the fibrinolytic activity of the blood.



The fibrinolytic system. According to Nilsson (1971).

Tranexamic acid produces an antifibrinolytic effect by competitively inhibiting the activation of plasminogen to plasmin (Andersson et al., 1965; Dubber et al., 1965). It is also a weak non-competitive inhibitor of plasmin. These properties of tranexamic acid make possible its clinical use as an antifibrinolytic in the treatment of both general and local fibrinolytic haemorrhages.

Thrombi in connection with antifibrinolytic therapy are discussed in the literature. The development of thrombosis is determined by the content of activators in the vascular wall (Pandolfi et al., 1967; Nilsson, 1971). Using a tissue-culture method, Åstedt has demonstrated that this is not affected by tranexamic acid (1973).

ANDERSSON, L, NILSSON, I M, NIHLÉN, J-E, HEDNER, U, GRANSTRAND, B & MELANDER, B: Experimental and clinical studies on AMCA, the antifibrinolytically active isomer of p-aminomethyl cyclohexane carboxylic acid. Scand J Haematol 2 (1965) p 230.

DUBBER, A H, MCNICOL, G P & DOUGLAS, A S: Amino methyl cyclohexane carboxylic acid (AMCHA), a new synthetic fibrinolytic inhibitor. Br J Hematol 11 (1965) p 237.

NILSSON, I M: Haemorrhagic and Thrombotic Diseases. John Wiley & Sons, London. New York. Sydney. Toronto. (1973) p 118.

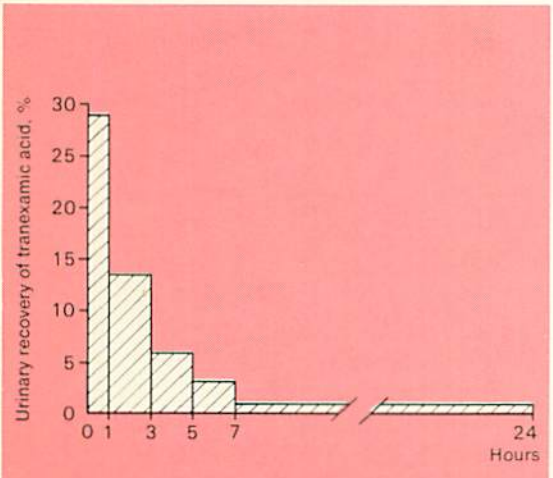
NILSSON, I M & PANDOLFI, M: Fibrinolytic response of the vascular wall. Thromb Diath Haemorrh Suppl 40 (1970) p 231.

PANDOLFI, M, NILSSON, I M, ROBERTSON, B & ISACSON, S: Fibrinolytic activity of human veins. Lancet 2 (1967) p 127.

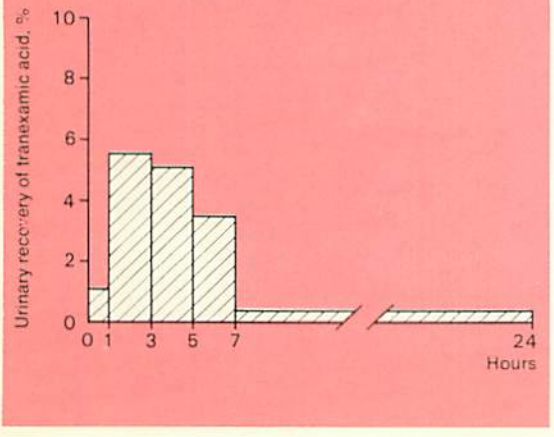
ÅSTEDT, B: Kan fibrinolyshämmare vara trombosdisponerande? Ronden 6 (1973) p 145. (Available in English).

Pharmacokinetics

Andersson and co-workers (1965, 1968) have studied the absorption, distribution and excretion of tranexamic acid in man. After intravenous administration of 10 mg per kg body weight, about 30 per cent of the given dose was recovered in the urine during the first hour after injection. During the first three hours about 55 per cent was excreted, and after 24 hours about 90 per cent had been eliminated. The corresponding values after oral administration of 10–15 mg of tranexamic acid per kg body weight were about 1 per cent, 13 per cent and 39 per cent. Intravenous administration of 10 mg per kg body weight gave plasma concentrations of 18.3 μg, 9.6 μg and 5 μg per ml one, three and five hours after the injection.



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.

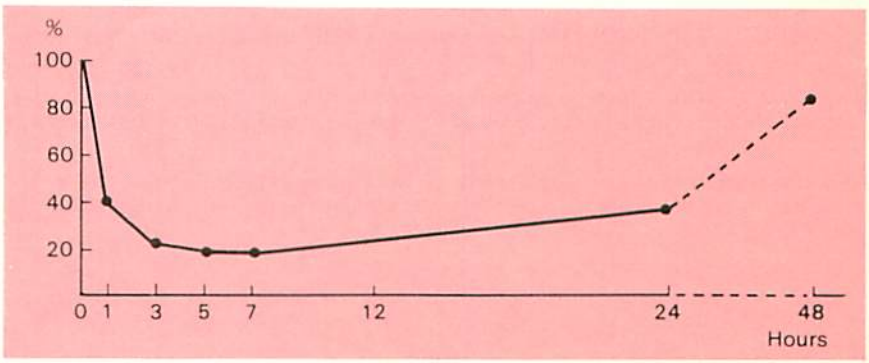


Urinary recovery of tranexamic acid after oral administration of 10–15 mg/kg (mean values for 11 males). Average recovery during 24 hours: 38.5 per cent.

The pharmacokinetics of tranexamic acid has also been studied after intravenous administration to healthy volunteers and can be described as a two-compartment open model (Eriksson et al., 1974). The respective biological half-lives were 2.7 and 1.9 hours. The total urinary recovery in five healthy volunteers was found to average 94.8 per cent. The renal clearence values in the two first-mentioned subjects were 135 and 132 ml per minute per 1.73 m^2 of body surface, which indicates that tranexamic acid is eliminated by glomerular filtration. In an earlier study by Kaller (1967) the biological half-life was reported to be 80 minutes. Since it increases in patients with impaired renal function, the dosage interval should be increased when treating such patients (Andersson et al., 1971).

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 per kg body weight. The results showed that an antifibrinolytically active concentration (10 μg/ml) remained up to 17 hours in the tissues investigated, and up to 7–8 hours in the serum (Andersson et al., 1968).

Tranexamic acid effectively inhibits fibrinolytic activity in urine (Andersson et al., 1968). When 10 mg of tranexamic acid per kg body weight were administered 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.)

Tranexamic acid crosses the placenta (Kullander & Nilsson, 1970). After an intravenous injection of 10 mg per kg the concentration can rise to about 30 μg per ml of fetal serum.

Tranexamic acid also passes over into the breast milk during lactation, but in concentrations 100 times lower than the corresponding serum levels (Eriksson et al., 1971).

After both oral and intravenous administration tranexamic acid passes into the semen and inhibits its fibrinolytic activity, but without affecting the motility of the spermatozoa (Liedholm, 1973).

The ability of tranexamic acid to cross the blood-brain barrier has been demonstrated by Tovi & Thulin (1972), who administered the drug to patients with ruptured intracranial aneurysms.

ANDERSSON, L, NILSSON, I M, NIHLÉN, J-E, HEDNER, U, GRANSTRAND, B & MELANDER, B: Experimental and clinical studies on AMCA, the antifibrinolytically active isomer of p-aminomethyl cyclohexane carboxylic acid. Scand J Haematol 2 (1965) p 230.

ANDERSSON, L, NILSSON, I M, COLLEEN, S, GRANSTRAND, B & MELANDER, B: Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. Ann N Y Acad Sci 146 (1968) p 642.

ANDERSSON, L, NILSSON, I M, LIEDBERG, G, NILSSON, L, RYBO, G, ERIKSSON, O, GRANSTRAND, B & MELANDER, B: Antifibrinolytica. Vergleichende Untersuchungen von trans-4-(Aminomethyl)-cyclohexancarbonsäure, Aminocapronsäure und p-Aminomethylbenzoesäure. Arzneim-Forsch (Drug Res) 21 (1971) p 424.

ERIKSSON, O, KJELLMAN, H & NILSSON, L: Tranexamic acid in human milk after oral administration of Cyklokapron to lactating women. Conf rep, nr 627, AB Kabi 1971.

ERIKSSON, O, KJELLMAN, H, PILBRANDT, Å & SCHANNONG, M: Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. Eur J Clin Pharmacol 7 (1974) p 375.

KALLER, H: Enterale Resorption, Verteilung und Elimination von 4-Aminomethylcyclohexancarbonsäure (AMCHA) und ε-Aminocapronsäure (ACS) beim Menschen. Naunyn Schmiederberg's Arch. Pharmak 256 (1967) p 160.

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

LIEDHOLM, P ET AL: Passage of tranexamic acid (AMCA) to semen in man and its effect on the fibrinolytic activity and on migration of spermatozoa. Fertil Steril 24 (1973) p 517.

TOVI, D & THULIN, C A: Ability of tranexamic acid to cross the bloodbrain barrier and its use in patients with ruptured intracranial aneurysms. Acta Neurol Scand 48 (1972) p 257.

Tranexamic acid during pregnancy?

Clinical experience with tranexamic acid during pregnancy is still too limited to guarantee that it is safe, even though no harmful effects have been reported. In 1976 Storm and Weber reported a case of fibrinolytic bleeding in a women in the fourth month of pregnancy. She was treated with tranexamic acid for a total of 64 days. The total dose was 256 g. The delivery occurred spontaneously in the 30th week of pregnancy and was normal in all other respects. The infant was healthy.

In 1978 Nilsson and Åstedt of the Malmö General Hospital reported a case of threatened placental abruption that was prevented by giving tranexamic acid. The woman had already lost two children in connection with placental abruption. In the 26th week of her third pregnancy bleeding occurred, 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. The bleeding was arrested and a healthy child was delivered by Caesarean section.

Tranexamic acid crosses over to the fetus (Kullander and Nilsson, 1970). After an i v injection of 10 mg per kg the concentration can reach a level of about 30 mg per ml fetal serum. Fibrinolytic activity is very high in neonates. It is not known for certain whether a reduction of this activity during the first hours of life is harmful. Kullander and Nilsson have a wide experience of tranexamic acid in connection with childbirth, however, and they have never observed any negative effect on the infants.

Tranexamic acid is secreted in the mother's milk. The concentration is only a hundreth of the corresponding serum levels, however (Eriksson et al, 1971). The investigators are of the opinion that tranexamic acid can be given during lactation without risk to the child.

ERIKSSON, O ET AL: Tranexamic acid in human milk after oral administration of Cyklokapron to lactating women. Conf report no. 627, AB Kabi, 1971.

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

NILSSON, I M & ÅSTEDT, B: Recurrent abruptio placentae treated with the fibrinolytic inhibitor tranexamic acid. Br Med J I (1978) p 756.

STORM, O & WEBER, J: Langvarig behandling med traneksamsyre (Cyklokapron®) under graviditet. Ugeskr Laeg 138 (1976) p 1781.

Toxicology

The acute toxicity of tranexamic acid is very low. The LD_{50} for mice is reported to be about 12,500 mg per kg after oral administration and 1,300 mg per kg after intravenous administration. The corresponding figures for rats are 11,250 mg and 850 mg per kg respectively. No fetal abnormalities were noted in teratogenic studies on rats, rabbits and mice with doses up to 5,000 mg per kg per day (Melander et al., 1965; Morita et al., 1971; Sirén, 1966).

Light microscopy of the kidney, spleen, myocardium, thoracic and abdominal aorta, and of the carotid artery in dogs given 110 mg or 220 mg tranexamic acid per kg body weight for two weeks revealed no fibrin deposits in these tissues. Faint sings of fibrin have been detected in renal tissue by electron microscopy (Steenblock & Celander, 1968).

Retinal changes have been reported in the dog after the administration, during a period of one year, of doses approximately seven times higher than the maximum recommended for humans per kg body weight per day (Åberg, 1972). Doses about 18 times the maximum recommended for humans per kg per day also produced retinal changes when administered i.v. to dogs over a period of seven days. Such changes were not observed in dogs receiving about 3.5 times the maximum dose recommended for humans per kg body weight per day by the oral route during a period of one year, nor in rats receiving about 27 times the maximum dose recommended for humans per kg per day given orally over a period of 22 months or in monkeys receiving about 18 times the maximum dose recommended for humans per kg per day intravenously during periods of both one and two weeks.

No retinal changes have been reported in eye examinations performed on patients treated with tranexamic acid over periods ranging from several weeks to months. For patients who are to receive continual treatment 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.

In rats receiving oral doses about 27 times higher than the maximum dose recommended per kg per day for humans, adenomas and adenocarcinomas of the liver have been demonstrated after the administration of tranexamic acid for a period of 22 months, but not after 12 months. Such tumours did not occur in rats after oral administration of doses approximately six times higher than the maximum recommended for humans.

MELANDER, B, GLINIECKI, G, GRANSTRAND, B & HANSHOFF, G: Biochemistry and toxicology of Amikapron®; The antifibrinolytically active isomer of AMCHA. (A comparative study with ε-aminocaproic acid.) Acta Pharmacol Toxicol 22 (1965) p 340.

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

SIRÉN, M: Forskningsavdelningen, AB Kabi, Stockholm (1966). In Swedish.

STEENBLOCK, D A & CELANDER, D R: A light and electron microscopic study of arteries and other tissues from dogs subjected to chronic fibrinolytic inhibition with AMCHA. Vasc Surg 2 (1968) p 149.

ÅBERG, B: Receptbeläggning av Cyklokapron begärd. Ronden 5 (1972) p 233. In Swedish.

Side effects

In a few cases gastro-intestinal side effects, such as nausea and diarrhoea, have been reported in connection with tranexamic acid therapy. The frequency has been appreciably lower, however, than with aminocaproic acid (Andersson et al., 1968; Nilsson & Rybo, 1966, 1971). In occasional cases orthostatic reactions have been reported, but the frequency of these too was considerably lower than with aminocaproic acid therapy.

In a few cases pain over the kidneys and obstruction to flow from the upper urinary tract has been reported in the treatment of haemophiliacs with massive haematuria (Itterbeck et al., 1968), and clot retention in the urinary bladder, kidney and urethra in patients with renal haemorrhages and bleeding into the upper urinary tract has also been reported (Andersson & Nilsson, 1969; Rø et al., 1970). Caution is therefore needed in the treatment of patients with profuse haematuria from the upper urinary tract.

A drop in blood pressure has been noted in a few patients after the administration of tranexamic acid (Hedlund, 1969; Vermylen et al., 1968).

ANDERSSON, L, NILSSON, I M, COLLEEN, S, GRANSTRAND, B & MELANDER, B: Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. Ann N Y Acad Sci 146 (1968) p 642.

ANDERSSON, L & NILSSON, I M: AMCA (Aminomethyl-cyclohexane carboxylic acid, Cyklokapron) a potent haemostatic agent in urinary tract bleeding. Scand J Urol Nephrol 3 (1969) p 169.

ITTERBECK, H VAN, VERMYLEN, J & VERSTRAETE, M: High obstruction of urine flow as a complication of the treatment with fibrinolysis inhibitors of haematuria in haemophiliacs. Acta Haematol 39 (1968) p 237.

HEDLUND, P O: Antifibrinolytic therapy with Cyklokapron in connection with prostatectomy. Scand J Urol Nephrol 3 (1969) p 177.

NILSSON, L & RYBO, G: Moderna synpunkter på menorrhagibehandling. Obstet Gynekol 3 (1966) p 243.

NILSSON, L & RYBO, G: Treatment of menorrhagia. Am J Obstet Gynekol 110 (1971) p 713.

RØ, J S, KNUTRUD, O & STORMORKEN, H: Antifibrinolytic treatment with tranexamic acid (AMCA) in pediatric urinary tract surgery. J Pediatr Surg 5 (1970) p 315.

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 20 (1968) p 583.

Clinical studies

Obstetrical and gynaecological bleeding

Some body tissues have an unusually high content of plasminogen activators and are therefore more disposed to bleeding owing to local fibrinolysis than others. One of these tissues is the uterine mucosa, the high activator content of which is a major cause of menstrual blood losses in many women of more than 80 ml per month – menorrhagia. These women run the risk of developing an iron deficiency which in many cases may be difficult to restore by iron therapy as long as the excessive bleeding continues. In connection with IUCDs bleeding may become so troublesome in women who normally have a moderate menstrual flow that the device must be removed.

As can be seen from the following, these different types of heavy menstrual bleeding can be succesfully treated with tranexamic acid. The blood losses can be reduced by 35 to 55 per cent, depending on the dosage.

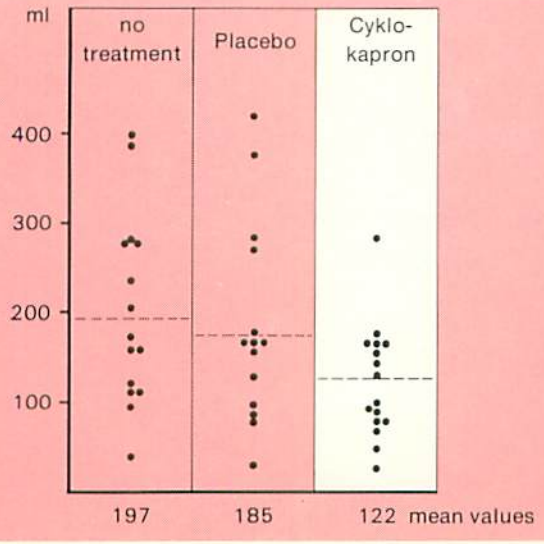
Tranexamic acid has also been found to have a good effect after conization without suturing and obstetrical bleeding.

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

No. of patients: 16.

Diagnosis: Menorrhagia.

Callender and co-workers have assayed iron and blood losses by whole body counting. The study shows that an average total dose of 14 g tranexamic acid per menstrual period decreases the blood loss by 34 per cent



Mean menstrual blood loss.

compared with placebo therapy. As can be seen from the overall results presented in the graph, exceedingly heavy bleeding was involved in most cases and the reduction in blood loss obtained were not sufficient for normalization; the investigators refer to Nilsson & Rybo (1967), who have shown that the reduction is dosedependent.

Hoedt, H Th E: Tranexamic acid treatment of menorrhagia. Data on file, AB Kabi, 1972.

No. of patients: 18.

Diagnosis: Menorrhagia.

The effect of tranexamic acid in menorrhagia was studied in a controlled trial. The investigation comprised two menstrual periods. During the first period no treatment was given, but during the second one tranexamic was administered. Thus the patients served as their own controls. The dosage was three tranexamic acid tablets of 0.5 g in the morning, three in the afternoon and four in the evening for five days. Thus the daily dose was 5 g.

The blood losses were measured quantitatively. The average loss during the control period was 185 ml ± 29.3. The corresponding figure during treatment with tranexamic acid was 83 ml ± 10.8, representing a reduction of about 50 per cent. The difference is statistically significant. No side effects were reported after the tranexamic acid therapy.

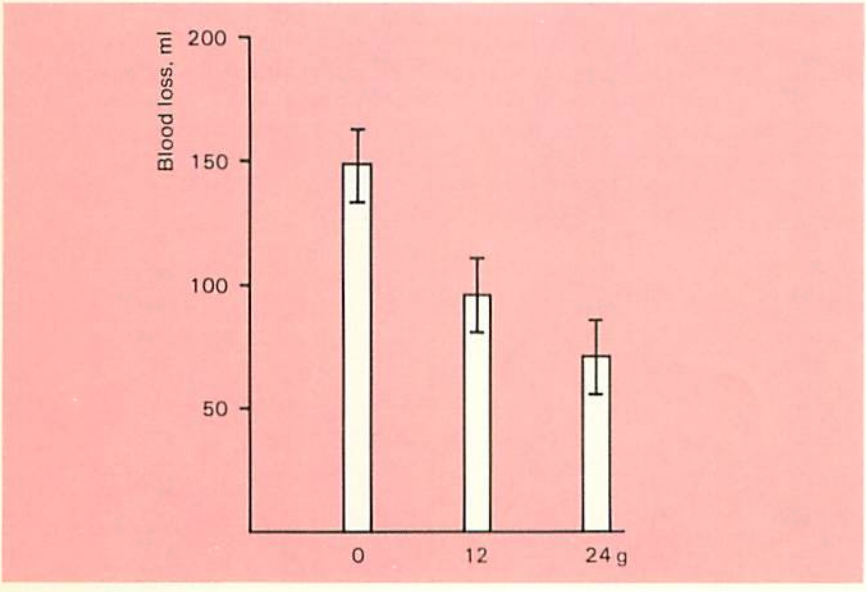
Nilsson, L & Rybo, G: Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid (AMCA). A double-blind investigation. Acta Obstet Gynecol Scand 46 (1967) p 572.

No. of patients: 19.

Diagnosis: Menorrhagia.

During one menstrual period 19 women were treated with 3 g tranexamic acid daily (a total dose of 11–12 g) and during a second period with 6 g daily (a total dose of 23–24 g).

The difference in the blood loss volumes between the two dosage groups was significant. Compared with the control periods, reductions of 51 per cent at the higher dose and 38 per cent at lower dose were obtained.



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

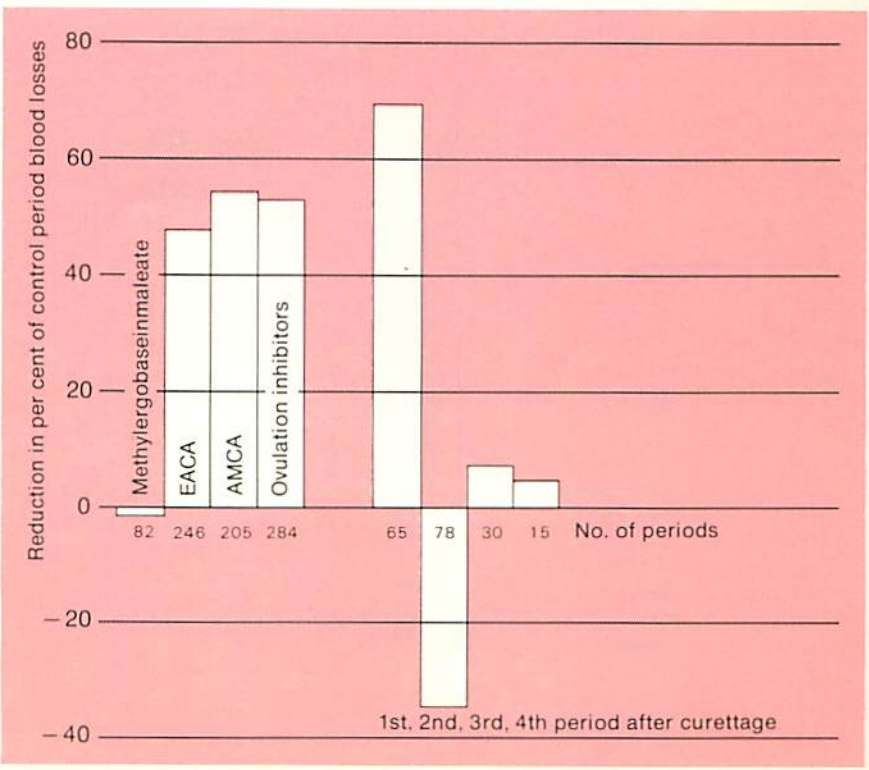
Nilsson, L & Rybo, G: Treatment of menorrhagia. Am J Obstet Gynecol 110 (1971) p 713.

No. of patients: 215.

Diagnosis: Menorrhagia.

Nilsson and Rybo have compared the effect of curettage, methylergobaseinmaleate, ovulation inhibitors of the combined type and two antifibrinolytics, EACA (aminocaproic acid) and AMCA (tranexamic 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 graph 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.



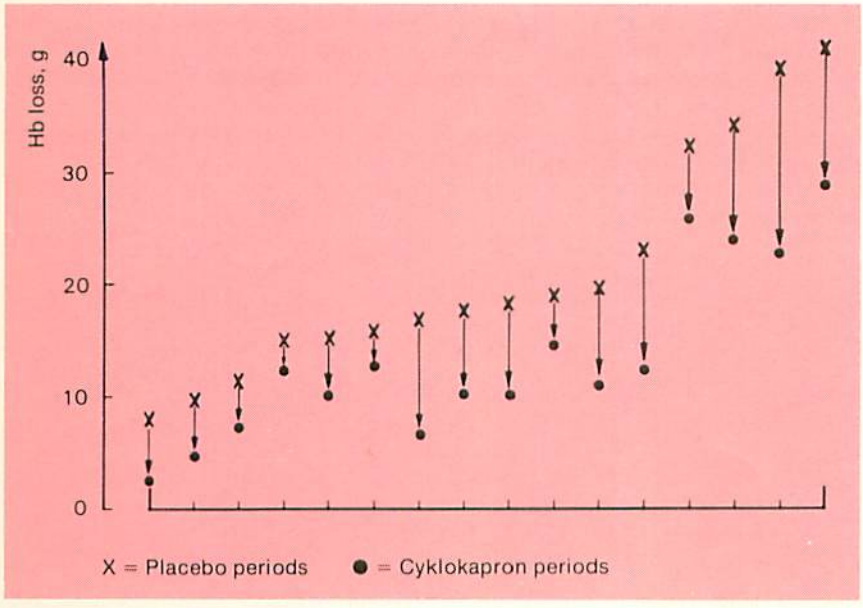
The effect of different methods of treatment in menorrhagia.

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 20 (1968) p. 583.

No. of patients: 16.

Diagnosis: Menorrhagia.

In a double-blind trial Vermylen and co-workers noted a mean reduction of menstrual blood loss of 35 per cent during three menstrual periods with doses of tranexamic acid 3 g daily. The highest value noted was 60 per cent.



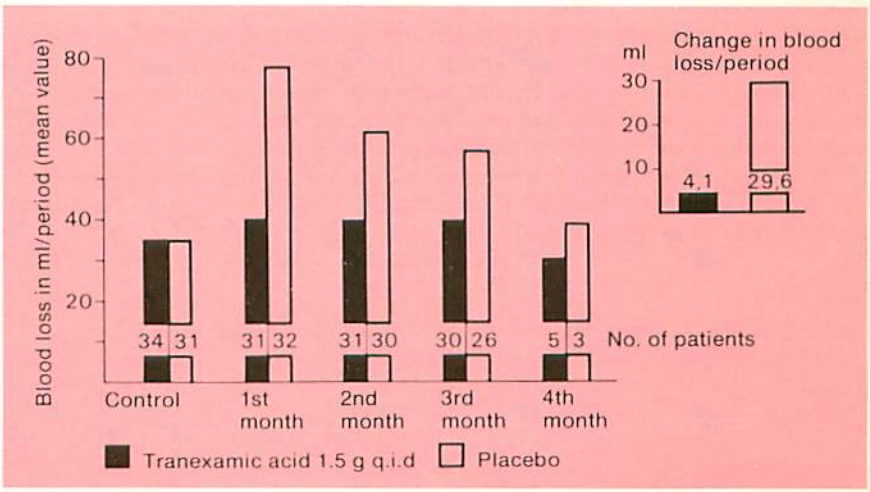
Mean Hb loss during three periods in 16 women with essential menorrhagia.

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

No. of patients: 65.

Diagnosis: Menorrhagia after insertion of IUCD (Lippes' loop B).

The blood losses were determined quantitatively during a control period and during four treatment periods after insertion of the Lippes' loop. In the group of women receiving placebo the menstrual blood loss increased after insertion by an average of 29.6 ml per period, or 82.7 per cent. Corresponding figures in the tranexamic acid group were 4.1 ml and 11.5 per cent, i.e. a significantly smaller increase in bleeding than in the placebo group. The length of the menstrual periods was the same in both groups. The authors draw the conclusion that, by reducing the blood losses in connection with IUCD insertions, tranexamic acid should be able to increase acceptance and retention of the device. It is also of interest to note that the unexpectedly heavy blood losses made it difficult for quite a number of women to collect all the blood in the absorbent. Consequently, the reported blood losses for 24 menstrual periods in women in the placebo group and for one period in the tranexamic acid group may be regarded as being too low.



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

Harms, W: Über die Behandlung geburtshilflicher und gynäkologischer Blutungen mit einem neuen Antifibrinolytikum. Med Welt 19 (1968) p. 643.

No. of patients: 90.

Diagnosis: Obstetrical and gynaecological bleeding.

Harms administered 3 g of tranexamic acid daily for at least four days to eight women with profuse menstrual bleeding; after one day of treatment

the bleeding became normal. All these patients had been treated earlier with hormones without any effect. Tranexamic acid was less successful in three women with fibroids complicated by profuse menstrual bleeding.

Other indications for tranexamic acid therapy were haemorrhages in connection with post-partum atonia, placenta praevia, missed abortion and puerperal haemorrhages. Tranexamic acid was also given during surgery in operations on organs which, owing to a high content of plasminogen activators, have been found to have a marked haemorrhagic tendency (uterus, prostate, lungs). The results of tranexamic acid therapy were very positive excepting four cases of radical vaginal surgery involving vascular haemorrhages which did not respond to antifibrinolytic therapy.

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

No. of patients: 75.

Diagnosis: Bleeding after conization.

The effect of tranexamic acid in recurrent bleeding after "closed" conizations was tested in a randomized double-blind study. The day before the operation three tablets of 0.5 g were given twice. On the day of the operation 1 g was given intravenously twice and, in addition to this, three tablets. During the following 13 days three tablets were given t.i.d. In the tranexamic acid group there was only one instance of recurrent haemorrhage (2.6 %), whereas there were four in the placebo group (10.8 %). Of the five recurrent haemorrhages three, all in the placebo group, had to be sutured or packed. The authors express the opinion that antifibrinolytic agents and/or suturing of the wound should be utilized to reduce bleeding after conization.

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

No. of patients: 50.

Diagnosis: Bleeding after conization.

The cervical tissue contains plasminogen activators and there is also a high concentration in the endometrium. Rybo and Westerberg conducted a randomized double-blind trial to study the effect of tranexamic acid on the incidence of recurrent bleeding after conization and on the postoperative blood loss.

The treatment was started on the evening of the day of operation with three 0.5 g tablets of tranexamic acid or placebo and was continued for 12 days with three tablets every eight hours corresponding to 4.5 g tranexamic acid daily when the active treatment was given. Before breaking the code five patients were excluded from the trial because they had been given other medicine in addition to tranexamic acid by mistake.

The blood loss in the tranexamic acid group was significantly lower than in the placebo group ($P < 0.05$). The number of recurrent bleedings was seven, all being in the placebo group. The cases of postoperative bleeding occurred from the fifth to tenth day after surgery. All cases required resuturing.

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

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

Herschlein, H J & Steichele, D F: Zur postoperativen Blutungsprophylaxe: Ergebnisse einer kombinierten Blutungs- und Antikoagulantienprophylaxe nach vaginalen Operationen. Geburtshilfe Frauenheilkd 31 (1971) p. 62.

No. of patients: 150.

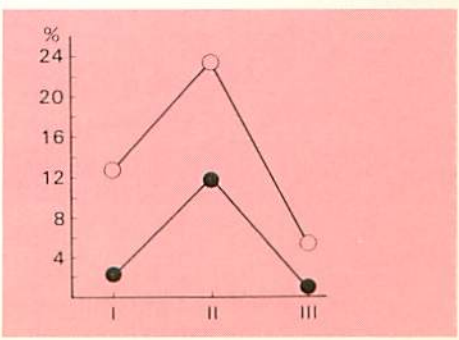
Diagnosis: Bleeding after vaginal surgery.

The object of the investigation was to study the effect of tranexamic acid on bleeding after vaginal operations with or without hysterectomy in conjunction with anticoagulant therapy. During a period of five days after the operation 1 g tranexamic acid was given twice daily i.v. to 150 women. The frequency of vaginal haemorrhage and the degree of wound healing in this group was compared with the corresponding values in a group consisting of 119 women who had undergone the same form of operation but only with anticoagulant therapy.

In addition to significantly better wound healing, the incidence of bleeding was found to be 2 per cent (three patients) in the first group, whereas the frequency was 12.6 per cent in the group not receiving antifibrinolytic therapy (15 patients). No side effects were reported.

Frequency of bleeding after vaginal operations in two different treatment groups, one receiving anticoagulants only postoperatively and the other anticoagulants plus tranexamic acid.

I. Postoperative bleeding
II. Minor superficial wound dehiscence or necrosis in the wound area
III. Major wound dehiscence
Anticoagulant therapy
Combined therapy with anti-coagulants and tranexamic acid



Urinary tract bleeding

Antifibrinolytic agents have found widespread use in urinary tract haemorrhages and in connection with prostate surgery. The urine contains urokinase, which activates the conversion of plasminogen to plasmin. This conversion sustains different types of bleeding in the urinary tract. A haemostatic effect can be obtained by administering tranexamic acid, which counteracts the activation of urokinase.

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

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.

Table 1. Bleeding from lower urinary tract without generalized fibrinolysis

Diagnosis	No. of patients	Haematuria	Other bleeding	Period of treatment, days	Effect on bleeding			Side effects
					Ceased	Decreased	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 (postoperative 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	

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.

Table 2. Renal haematuria (without generalized fibrinolysis)

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		

Diagnosis: Haematuria after prostatic surgery.

Eighty-seven patients who had undergone operation 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.

Table 3. Haematuria after operation on prostate

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	

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 gastro-intestinal symptoms. Treatment was started with 30 g epsilon-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.

Table 4. Patients with generalized fibrinolysis

Diagnosis	Age	Haemorrhagic manifestation	AMCA orally	AMCA i.v.	Period of treatment, days	Fibrinolytic activity (citrated plasma) Stand.pl./heated pl. Before AMCA	Fibrinolytic activity (citrated plasma) Stand.pl./heated pl. 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	–	–

Ennemoser, D & Heidbrink, D: Antifibrinolytische Therapie bei Prostatektomien, Tonsillektomien und Adenotomien. Med Welt 20 (1969) p. 1028.

No. of patients: 17.

Diagnosis: Bleeding after prostatectomy.

Seventeen patients who underwent prostatectomies were given one ampoule of tranexamic acid 250 mg during the operation and one ampoule every four hours subsequently (1.5 g daily). The treatment was continued as long as the urine was not macroscopically clear: in general, for about three days. The results were satisfactory in all cases. Side effects in form of dizziness and nausea developed in three patients.

The study also included 73 children (aged 3–16) in whom bleeding in connection with tonsillectomies and adenotomies could be controlled effectively with tranexamic acid.

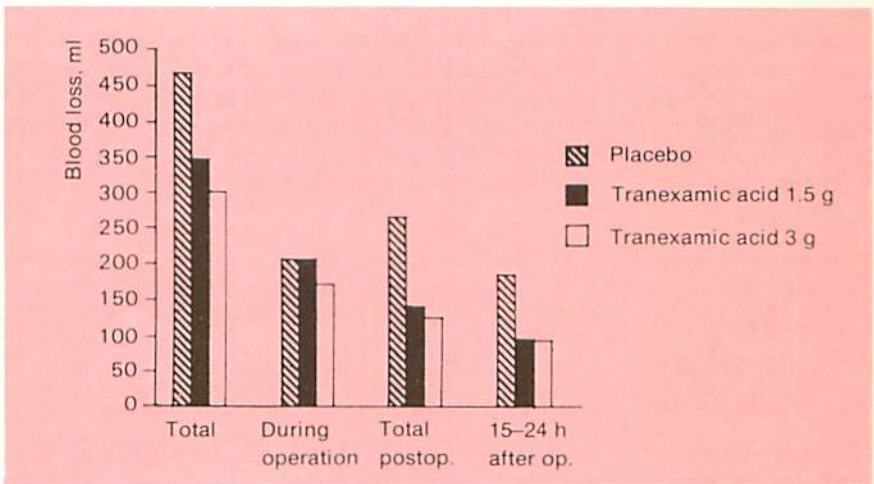
Hedlund, P O: Antifibrinolytic therapy with Cyklokapron in connection with prostatectomy. Scand J Urol Nephrol 3 (1969) p. 177.

No. of patients: 92.

Diagnosis: Bleeding in connection with transvesical prostatectomy.

In a double-blind trial in a non-selected series P O Hedlund studied the effect of tranexamic acid on haemorrhages in 92 patients who had had transvesical prostatectomies. Over a period of four days 3 g tranexamic acid were administered daily to 29 patients, 1.5 g daily to 33 patients and placebo to 30.

The blood loss during surgery was not affected by the treatment (see graph). In contrast, the postoperative blood loss was reduced by 52 per cent in the patients receiving 3 g per day and by 45 per cent in those receiving 1.5 g daily as compared with the placebo group. The differences are statistically significant.



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

About 70 per cent of the total postoperative blood loss occurred during the first 15–21 hours. As can be seen from the graph 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

	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

Hedlund, P O: Postoperative venous thrombosis as a possible complication of antifibrinolytic therapy. In: Postoperative venous thrombosis in benign prostatic disease. Scand J Urol Nephrol (1975) suppl 27.

No. of patients: 201.

Study of possible connections between post-operative thrombosis and antifibrinolytic therapy after transurethral prostatectomy. The test was conducted as a double-blind, random test. Tranexamic acid was given to 100 patients at a daily dose of 1 g intravenously 3 times a day for four days. The remaining 101 patients were given a placebo. Thrombosis was diagnosed by a very sensitive method, the ^{125} J-Fibrinogen Uptake Test (FUT). The incidence of post-operative thrombosis was 18 % in the treated group and 10 % in the placebo group. The difference is not statistically significant.

Kaufmann, J & Siefker, K: Medikamentöse Senkung postoperativer Blutungen nach Prostatektomien. (Erfarungen mit dem Fibrinolysehemmer AMCA). Der Urolog 8 (1969) p. 57.

No. of patients: 36.

Diagnosis: Bleeding after prostatectomy.

The postoperative blood loss was reduced by 45 per cent in 36 patients undergoing prostatectomy by giving 2 g tranexamic acid daily. Twenty-seven patients who were not treated with an antifibrinolytic served as controls. According to the authors, patients who are to have prostatic surgery should also be treated with heparin or some other antiprothrombin preparation in addition to tranexamic acid in order to prevent thrombo-embolic complications.

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

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, Rø 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 (see table).

The ages of the patients ranged from 2½ to 12½ years with a mean of 7 years.

Fifteen mg 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 twice intravenously on the day of operation, and thereafter 15 mg per kg body weight twice daily orally for seven days.

The blood loss was determined by measuring the amount of haemoglobin lost.

The computations were performed separately for the patients who had unilateral operations as well as for the entire series (see diagram).

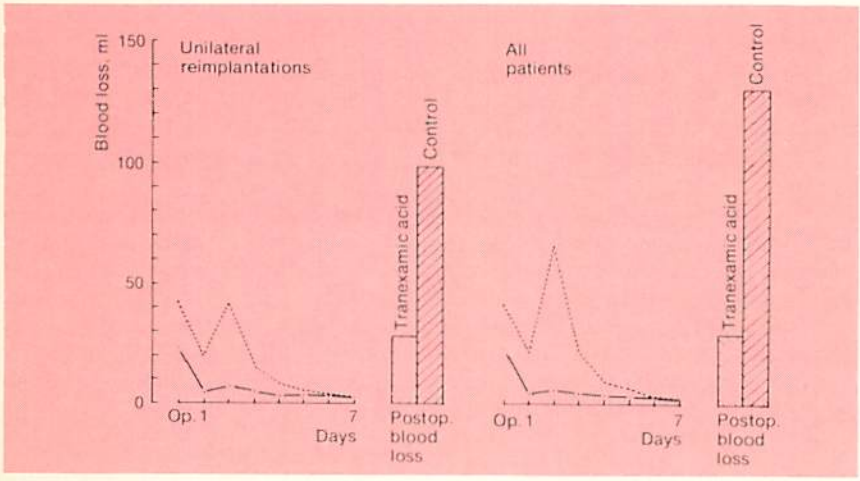
Distribution by operation and treatment in 22 children

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

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 postoperative 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. The principal application of antifibrinolytics in haematuria is the treatment of bleeding originating in the lower urinary tract.



Blood loss on reimplantation of ureter in bladder. Tranexamic acid (·—·), control (····).

Vecsey, D et al: Blutungsprophylaxe nach Prostatektomie mit AMCA. Med Welt 28 (1977) p 1103.

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 100 ml of isotonic saline. The therapeutic results are shown in the table.

Postoperative blood loss in prostatectomies with and without tranexamic acid.

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

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

Haemorrhagic diathesis

For this indication tranexamic acid has found use primarily in dental extractions in haemophiliacs. The effect of antifibrinolytic therapy is to reduce the need for substitution therapy on the one hand and to shorten substantially the period of hospitalization on the other.

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 36 (1973) p. 482.

No. of patients: 17.

Diagnosis: Bleeding after dental extraction.

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 out and one with severe haemophilia A who had two operations, 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). Ned T Tandheelkd 78 (1971) p. 90.

No. of patients: 14.

Diagnosis: Bleeding after dental extraction.

Before the dental extraction the patients were given substitution therapy to increase the concentration of clotting factors in the plasma. After the extraction they were given 0.5–1.5 g tranexamic acid orally thrice daily for a few days. This made it possible to reduce the total number of infusions of clotting factor concentrate. Only a few transfusions were required, and not until 5–7 days postoperatively.

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 2 (1972) p. 311.

No. of patients: 28.

Diagnosis: Bleeding after dental extraction.

In a double-blind trial 20 patients with haemophilia A and eight with haemophilia B (Christmas disease) received 1 g tranexamic acid thrice daily or placebo, beginning two hours before the dental extraction. The treatment was continued for five days. Before the extractions the patients were also given clotting factor concentrates (factor VIII or factor IX) equivalent to 1,000 ml plasma and tetracycline. The average number of extracted roots was 6.9 in the tranexamic acid group and 5.5 in the placebo group.

The patients who had received tranexamic acid had a significantly lower mean blood loss: 61.2 ml as compared with 84.1 ml. When calculated per root, the blood loss was 8.9 ml in the tranexamic acid group and 15.3 ml in the placebo group. Only two patients treated with tranexamic acid required infusions of plasma or plasma concentrate. In one of these 22 root extractions had been performed, the largest number in the series. Repeat infusions were necessary in 11 patients in the placebo group.

Tavenner, R W H: Use of tranexamic acid in control of haemorrhage after extraction of teeth in haemophilia and Christmas disease. Br Med J 2 (1972) p. 314.

No. of patients: 22.

Diagnosis: Bleeding after dental extraction.

Treatment with 1.5 g tranexamic acid every six hours was started half an hour before dental extraction in 19 patients with haemophilia A and three with haemophilia B (Christmas disease). The dosage was changed for two patients during the course of therapy: the dose interval was reduced to four hours in one owing to bleeding and the dose was reduced to 0.75 g six-hourly in the other.

Altogether the patients had 51 tooth-extraction operations, each of which required an average of four days in hospital. Three patients were given substitution therapy in the form of cryoprecipitates, and one of them also received six litres of blood.

Twelve patients who were treated in 25 operations with only blood or plasma required a total of 8.5 litres of blood and 114.7 litres of plasma. The average hospital stay per operation was 9.4 days.

Gastrointestinal haemorrhages

The rationale for using antifibrinolytic agents for haemorrhages in the upper gastrointestinal tract has been discussed by a number of researchers, e g Cox et al (1967, 1969) and Nilsson et al (1975). Cox et al detected local fibrinolytic activity in patients with pyloric and duodenal ulcers. Nilsson et al showed that haemorrhagic gastroduodenitis is associated with high fibrinolytic activity in the gastric juice. In contrast, no such findings were made in gastric ulcers. The authors mentioned are of the opinion that more attention should be given to antifibrinolytic agents in the medical treatment of gastrointestinal haemorrhages. The results of several clinical studies support this point of view.

COX, H T POLLER, L & THOMSON, J M: Gastric fibrinolysis. A possible aetiological link with peptic ulcer. Lancet 1 (1967) p 1300.

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

NILSSON, I M et al: Gastric fibrinolysis. Thromb Diath Haemorrh (Stuttg) 34 (1975) p 409.

Biggs, J C et al: Tranexamic acid and upper gastrointestinal haemorrhage — a double-blind trial. Gut 17 (1976) p 729.

No. of patients: 200.

Diagnosis: Upper gastrointestinal haemorrhage.

Different types of haemorrhage were represented — not only erosive ones. The study was done as a randomized double-blind trial. The dosage used was 1 g tranexamic acid i v during the first 48 hours and 1 g orally every eight hours, followed by 1 g orally for 72 hours. The treatment with tranexamic acid significantly reduced the number of operations necessary to stop continuous or recurrent bleeding. Transfusion requirements were also reduced. Thus the findings in Biggs' trial indicate that tranexamic acid is effective not only in haemorrhages due to erosions in the gastric mucosa.

Brömster, D et al: Tranexamsäure bei grossen Magenblutungen — Eine Doppelblindstudie. Akt Gastrologi 6 (1977) p 225.

No. of patients: 148.

Diagnosis: Massive gastric haemorrhages.

The effect of tranexamic acid was studied in a controlled trial. Using the double-blind technique, placebo or tranexamic acid i v in a dosage of 1 g six times daily was administered in the intensive care unit. This was followed by 1.5 g orally q.i.d. There was no difference in mortality in the two groups. On the other hand, the number of operations was lower in the tranexamic acid group: only 10 patients required surgery, compared with 18 in the placebo group. Transfusion requirements were also reduced in the tranexamic acid group. The required amount of blood per patient in this group was only 4.3 units, compared with 5.1 in the placebo group.

Cormack, F, Charkrabarti, R R, Jouhar, A J & Fearnley, G R: Tranexamic acid in upper gastro-intestinal haemorrhage. Lancet 1 (1973) p. 1207.

No. of patients: 150.

Diagnosis: Upper gastrointestinal haemorrhage.

The patients with bleeding from the upper gastrointestinal tract were treated with tranexamic acid (76 patients) or placebo (74 patients). There was no significant difference in the results between the groups when calculated for the entire series. But when the patients whose haemorrhages were due to hiatus hernia or oesophageal varices were excluded, the number of successful treatments was significantly higher in the tranexamic acid group: 55 of 62 as compared with 46 of 63. These results indicate that antifibrinolytic therapy is warranted in bleeding from the gastrointestinal tract due to peptic ulceration or erosion. This appears to apply particularly to bleeding from erosions since the best results were obtained in patients with negative barium-meal examinations.

Retransfusion was required in eight patients in the tranexamic acid group and in 11 control patients. The amount of blood given was lower in the treated group, however: 43 units as against 83 units.

Östberg, H et al: Acute gastrointestinal haemorrhage. Acta Clin Scand 143 (1977) p 463.

No. of patients: 159.

Diagnosis: Acute gastrointestinal haemorrhage.

150 of these patients suffered from haematemesis and/or melaena and nine from fresh rectal haemorrhages. On admission 53 of the 150 patients had a haemoglobin concentration of less than 89 g/l and 11 showed signs of shock.

Early panendoscopy was performed on all patients with haematemesis and/or melaena. These patients were given antacids.

To all but two patients with minor bleeding tranexamic acid was given over a period of six days in a daily dosage of 3 g. The drug was given intravenously during the first three days and orally thereafter. The mortality was only 4.5 per cent. In the remaining cases the acute bleeding ceased. Only in eight cases was emergency surgery necessary during the first six days.

Ear – nose – throat

Recurrent nose-bleeds that are difficult to manage may be caused by increased local fibrinolytic activity. This can be reduced with antifibrinolytic agents. Treatment of nose-bleeds with tranexamic acid results in fewer and milder recurrent bleeds as well as a shorter period of hospitalization.

The commonest complication in connection with tonsillectomy is bleeding. Antifibrinolytic therapy with tranexamic acid produces both per- and postoperative bleeding.

Nose-bleeds

Petruson, B: Epistaxis. A clinical study with special reference to fibrinolysis. A double-blind study to evaluate the effect on epistaxis with oral administration of the antifibrinolytic drug tranexamic acid (Cyklokapron®), Acta Oto-Laryngolog Suppl 317 (1974) p 57.

The effect of oral tranexamic acid was studied in 68 patients with severe nose-bleeds. Using the double-blind technique, 1 g of tranexamic acid or a placebo was given t.i.d. for 10 days. Recurrent nose-bleeds were checked twice daily during this period. The number of recurrent bleeds was significantly lower in the tranexamic acid group and, in addition, the bleeds were considered to be milder in this group. The period of hospitalization was also affected by the antifibrinolytic therapy: it was significantly shorter for the patients in the tranexamic acid group.

Tonsillectomies

Castelli, G & Vogt E: Der Erfolg einer antifibrinolytischen Behandlung mit Tranexamsäure zur Reduktion des Blutverlustes während und nach Tonsillektomien. Schweiz Med Wochenschur 107 (1977) p 780.

No. of patients: 80.

Diagnosis: Haemorrhage in connection with tonsillectomy.

Tranexamic acid therapy was started two hours before surgery with 500 mg 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 500 mg 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 et al: Double-blind trials with ethamsylate, batroxobin or tranexamic acid on blood loss after adenotonsillectomy. Acta Clin Belg 32 (1977) p 136.

No. of patients: 207.

Diagnosis: Haemorrhage after adenotonsillectomy.

The haemostatic effect of ethamsylate (a haemostatic agent that increases capillary resistance which is not sold in Sweden), tranexamic acid and batroxobin has been studied by Verstraete and his co-workers. 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 were given intramuscularly one hour before and two hours after surgery.

If all patients are regarded as a group irrespective of the type of operation, none of the three preparations brought about any significant reduction of blood loss. By contrast, in combined adenotonsillectomy it was established that 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 (see table).

Double-blind trials to assess the haemostatic effect of different drugs in connection with adenotonsillectomy.

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

Eyes

In recent years antifibrinolytic agents have proved to be of great value in ophthalmological practice. The healing of hyphaema, i.e. blood in the anterior chamber of the eye, is often complicated by secondary haemorrhages. This risk is reduced by tranexamic acid. The prognosis is improved and hospitalization can be shortened.

Fuchs' endothelial dystrophy is a progressive disease of the cornea which results in severe pain and impaired vision if left untreated. Tranexamic acid decreases the thickness of the central cornea, visual acuity is improved and the pain disappears.

Operations for cataract lead to more or less pronounced thickening of the central cornea, which is counteracted by tranexamic acid.

Hyphaema

Bramsen, T: Traumatic hyphaema treated with the antifibrinolytic drug tranexamic acid. Acta Ophthalmol 54 (1976) p 250.

No. of patients: 72.

Diagnosis: Secondary hyphaema following ophthalmic trauma.

Bramsen has investigated the effect of tranexamic acid in a study with a retrospective control series. The treatment group consisted of 72 patients treated during 1975. They received traditional treatment in the form of bed-rest and stenopeic spectacles. In addition, tranexamic acid was given orally in a dosage of 25 mg per kg body weight t.i.d. for six days. The treatment group was compared with 135 patients admitted to the department during 1965—68. These patients had received the same traditional treatment but *not* tranexamic acid. In this group the frequency of recurrent bleeding was 6.7 per cent. The corresponding figure in the tranexamic acid group was only 1.4 per cent.

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

No. of patients: 75.

Diagnosis: Secondary hyphaema following ophthalmic trauma.

In 1977 Bramsen published another study on traumatic hyphaema. The traditional type of treatment was abandoned, and the patients were given tranexamic acid orally as the only from of therapy. As in the previous study, the daily dosage was 25 mg per kg body weight t.i.d. for six days. There was no recurrent bleeding. Bramsen concludes that bed-rest, which is inconvenient to both staff and patient, is not necessary to prevent secondary hyphaema. Treatment with an antifibrinolytic agent is adequate.

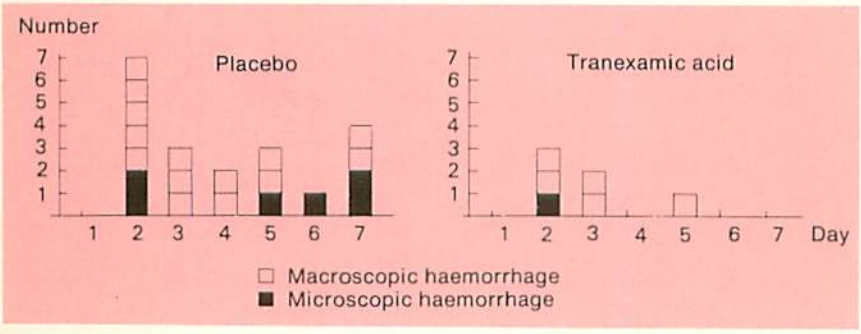
Jerndal, T & Frisén, M: Tranexamic acid (AMCA) and late hyphema. A double-blind study in cataract surgery, Acta Ophthalmol 54 (1976) p 417.

No. of patients: 244.

Diagnosis: Secondary hyphaema following cataract surgery.

The effect of tranexamic acid was tested in a randomized double-blind study. The dosage was 1 g t.i.d. for seven days. Altogether, there were 26 secondary haemorrhages, 20 of which were in the placebo group (see figure). The difference was statistically significant.

Number of secondary haemorrhages after cataract surgery. The patients received placebo or tranexamic acid for seven days.



Corneal oedema

Bramsen, T & Ehlers, N: Bullous keratopathy (Fuchs' endothelial dystrophy) treated systemically with 4-trans-aminocyclohexano-carboxylic acid. Acta Ophthalmol 55 (1977) p 665.

No. of patients: 20.

Diagnosis: Fuchs' endothelial dystrophy.

The series consisted of 15 females and 5 males. They were treated as outpatients, the only form of therapy being oral tranexamic acid in a dosage of 1 g t.i.d. The treatment was continued for 3—16 months and was given intermittently in nine cases. Thus the patients were their own controls. In all cases the central corneal thickness decreased and slit-lamp examinations indicated improvement. Visual acuity was also improved and all the patients were relieved of pain.

Bramsen, T, Corydon, L & Ehlers, N: A double-blind study of the influence of tranexamic acid on the central corneal thickness after cataract extraction. Acta Ophthalmol 56 (1978) p 121.

No. of patients: 34.

Diagnosis: Corneal oedema following cataract surgery.

The patients were operated on for cataract using a standardized technique. No other ophthalmic diseases existed. The study was in the form of a randomized double-blind trial. Tranexamic acid was given from the day before surgery. The daily dose was 25 mg t.i.d. per kg body weight. The treatment was continued for six days after the operation. On measuring the central corneal thickness postoperatively, the investigators found that the increase in thickness was significantly smaller in the tranexamic acid group than in the placebo group.

Hereditary angioneurotic oedema (HANO)

Hereditary angioneurotic oedema, HANO, is manifested in the form of recurring local oedema of the skin, the mucosa of the upper urinary tract and in the gastro-intestinal tract. The mortality is about 30 per cent. The condition is inherited as an autosomal dominant (Sheffer et al., 1972).

In most cases the cause of the disease is probably an inborn error in the biosynthesis of a serum-α_2-globulin, whose function is to inhibit the enzymatic activity of complement factor C1. In rarer instances the disease is due to an abnormal C1 inhibitor molecule which is available in normal quantities in the serum but is not capable of normal activity. There is much evidence that the periodic activation of C1 is related to the attacks of oedema; therefore, inhibition of this activity should counteract the development of oedema. Besides activation by the antigen-antibody interaction, C1 is also activated by plasmin. This implies that it should be possible to reduce C1 activity, and thereby alleviate attacks of HANO, with the aid of plasmin inhibitors.

Blohmé, G: Treatment of hereditary angioneurotic eodema with tranexamic acid. Acta Med Scand 192 (1972) p. 293.

No. of patients: 5.

Diagnosis: HANO.

Blohmé has treated five HANO 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 in the continuously treated patients was 1.5–4.5 g tranexamic acid daily 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.

Lundh, B: Tranexamic acid in hereditary angioneurotic oedema. A progress report. New Engl J Med 288 (1973) p. 53.

No. of patients: 1.

Diagnosis: HANO.

A patient has been treated continuously with tranexamic acid since June 1967. Up to July 1972 he had received more than 12,000 g in doses of 1.5 g six times daily (9 g daily). Before treatment was started the patient had several HANO attacks a month, 11 of which, involving laryngeal oedema, were life-threatening. No servere attacks occurred after the initiation of tranexamic acid therapy.

Ohela, K: Treatment of hereditary angioneurotic oedema with tranexamic acid and cinnarizine. Acta Dermatovenerol (Stockholm) 56 (1976) p 61.

No. of patients: 7.

Diagnosis: Hereditary angioneurotic oedema.

Tranexamic acid was given to all the patients during attacks. The dosage used was 1—1.5 g b.i.d. or t.i.d. In addition, three patients were treated continuously with doses of 0.5—1.5 g t.i.d. The result was fewer and milder attacks in six out of seven cases. The best effect was obtained when tranexamic acid was given immediately before an attack. Only one patient had to discontinue treatment owing to tiredness, dizziness and nausea.

Sheffer, A L, Austen, K F & Rosen, F S: Tranexamic acid therapy in hereditary angioneurotic oedema. New Engl J Med 287 (1972) p. 452.

No. of patients: 18.

Diagnosis: HANO.

Eleven females and seven males with HANO were admitted to a trial employing a double-blind cross-over technique. They were given 1 g tranexamic acid thrice daily or placebo and were instructed to record any gastrointestinal disorders, subcutaneous and oropharyngeal oedema or hoarse-

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

ness. Renal and hepatic functions were checked regularly. The therapeutic results were assessed each month.

In seven patients the frequency of attacks fell to zero, or nearly zero, during tranexamic acid therapy but remained unchanged during the placebo periods. Four patients responded to therapy with only a slightly reduced frequency of attacks but with a marked reduction in the severity of their oedema. In one case tranexamic acid was ineffective. The remaining patients completed only one phase in the cross-over trial. The difference in attack rate between the placebo and tranexamic acid groups was statistically significant: $t = 4.9$, $P < 0.005$. The side effects of the drug were insignificant. One patient complained of perianal pruritus and four of mild abdominal discomfort and diarrhoea. Renal and hepatic function tests revealed no abnormalities.

Sheffer, A L et al: Tranexamic acid: preoperative prophylactic therapy for patients with hereditary angioneurotic edema. J Allergy Clin Immunol 60 (1977) p 38.

No. of patients: 14.

Diagnosis: Hereditary angioneurotic oedema.

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. Sheffer treated them 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.

Zacharlae, H et al: Tranexamic acid (Cyklokapron®) in hereditary angioneurotic oedema. Ugeskr Laeg 137 (1975) p 1106.

No. of patients: 8.

Diagnosis: Hereditary angioneurotic oedema.

Tranexamic acid was given by mouth to eight patients with hereditary angioneurotic oedema. The duration of treatment was 1—4 years. The daily dosages ranged between 1.5 g and 6 g. The effect was evident: both the frequency and severity of the attacks were reduced.

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.

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.
Women with menorrhagia may be divided into 2 groups.
Women with a demonstrable organic cause of menorrhagia (e.g. myoma, polyps of the corpus, adenomyosis). Cyklokapron is a suitable agent for the treatment of older women near the menopause. Surgical treatment is preferable for younger or middle-aged women. As an exception, such patients may also be given Cyklokapron for shorter periods.
Women without a demonstrable organic cause of menorrhagia. Younger women whose fertility is to be maintained should be treated with either oral contraceptives or Cyklokapron. Some women in this group will thus be treated with Cyklokapron for a fairly lengthy period; this is especially true in the case of women for whom treatment with oral contraceptives is contraindicated. Women in middle age with severe menorrhagia who no longer wish to remain fertile should be treated surgically. An alternative is oral contraceptives. Treatment with Cyklokapron is suitable for older women near the menopause.
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.

Adverse effects Gastrointenstinal symptoms (nausea, vomiting, diarrhoea) occur but disappear when the dose is reduced. Isolated cases of dizziness or reduced blood pressure have been reported.
To be observed by reason of experimental findings in animals. In the dog, retina changes have been observed after long-term administration of large doses of tranexamic acid, and in the cat after intravenous injection of 250 mg per kg body weight and day for 14 days. Such changes have not been obtained in the rat where the maximum tolerated dose has been administered. No retina changes have been reported or observed at ophthalmic checkups of patients treated with Cyklokapron for several weeks or months. For patients who are to be treated for several weeks an ophthalmic checkup is advisable (sharpness of vision, colour vision, fundus, field of vision, etc.) if possible before treatment is initiated and regularly during treatment.
In one colony of rats, biliary, duct hyperplasia and two or three cases of adenocarcinoma of the liver have been reported after 22 months of oral administration of the maximum tolerated dose. In another colony of rats, no tumours have been obtained after long-term administration. All mutagenic investigations have been negative.

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 *Tablets 0.5 g* (white, round, flat, stamped CY within arcs diam. 13 mm): 50 and 100. *Mixture 0.1 g/ml:* 250 ml. *Ampoules 0.1 g/ml:* 6 × 5 ml, 6 × 10 ml.

Notes

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