Clinical pharmacology of aminocaproic and tranexamic acids

INGA MARIE NILSSON

From the Coagulation Laboratory, University of Lund, Allmänna Sjukhuset, Malmö, Sweden

In a systematic search for a substance with anti-fibrinolytic properties Okamoto and his group in Japan found that several mercapto- and amino-carbonic acids were active. Of these substances epsilon-aminocaproic acid (EACA) had the strongest antifibrinolytic effect.^{1,2} The Japanese workers described it as a plasmin inhibitor *in vitro* and useful in inhibiting proteolytic enzymes *in vivo*. They gave EACA in a dose of 10-20 g a day by mouth or intravenously to over 100 patients and observed no toxic effects. Their investigation did not include any metabolic studies. EACA has since been widely used and its mode of action and pharmacokinetics intensively studied.

In a continued search for more potent anti-fibrinolytic components p-aminomethyl cyclohexane carboxylic acid (AMCHA) was found to be more potent than EACA.³ This compound contains two stereoisomers. Independently Melander *et al.*⁴ and Okamoto *et al.*⁵ found that only the trans-form was antifibrinolytically active. The antifibrinolytically active form was called tranexamic acid (AMCA). It is 6-10 times stronger than EACA and is now used more widely. Its pharmacokinetics have been the subject of several studies. This paper surveys the pharmacology and toxicology of EACA and AMCA.

Pharmacokinetics

AMINOCAPROIC ACID (EACA)

The absorption, distribution, and excretion of EACA given intravenously and by mouth have been studied in man.⁶⁻⁸ High-voltage electrophoresis and plasma amino-acid chromatography with ion exchange resin loaded paper were used for assaying EACA in plasma, serum, urine, and tissues.⁷⁻⁹ The blood was assayed for fibrinolytic activity by measuring the plasma euglobulin clot lysis time and/or the activity of plasma and of resuspended euglobulin precipitate on unheated and heated fibrin plates. The urokinase activity of urine was assayed by a clot lysis method or by a fibrin plate technique in which the results are expressed in

arbitrary urokinase units by reference to a standard urokinase preparation.^{10,11}

Intravenous administration of 10 g EACA or 100 mg EACA/kg bodyweight produces an initial serum concentration of about 150 mg/100 ml which falls to 3.5 mg/100 ml within 3-4 hours (Fig. 1). The biological half life was calculated to be about 77 minutes. Andersson *et al.*⁸ found that about 70% of the dose given intravenously was excreted in the urine within 24 hours (Fig. 2). McNicol *et al.*⁷ found 80-100% of the given dose in the urine within 4-6 hours. The EACA is thus concentrated

Fig. 1 Concentration of EACA (mg/100 ml) in serum after a dose of 100 mg/kg bodyweight intravenously or by mouth.

Fig. 2 Urinary recovery of EACA in four men volunteers after receiving 100 mg/kg bodyweight intravenously or by mouth.

many times during excretion, urinary levels being 50 to 100 times those found in plasma. McNicol *et al.*⁷ measured the renal clearance rates of EACA in healthy volunteers at a time when their plasma EACA concentrations were stable (that is, they had received repeated doses of EACA). Simultaneously endogenous creatinine clearance rates were also measured. EACA clearances when the plasma concentrations were in the range of 14 to 19 mg/100 ml varied from 65 to 92% of the creatinine clearance. These findings indicated that the kidney handled EACA primarily by filtration.

EACA given by mouth is rapidly absorbed, almost entirely from the gastrointestinal tract. After 100 mg/kg bodyweight by mouth the peak plasma concentration of EACA was 30 mg/100 ml two to three hours after ingestion (Fig. 1). At four hours it was 16 mg/100 ml compared with 3.9 mg/100 ml four hours after intravenous injection. After six hours the concentration was similar to that found after intravenous administration. Renal excretion differed from that found after intravenous injection (Fig. 2). Only 10% of the dose had been excreted within one hour, and 25% within three hours. The 24-hour urinary recovery after the oral administration was 64%. The figure given by McNicol *et al.*⁷ is somewhat higher—namely, 78%.

EACA enters human red cells and various tissues.^{7,8} It appears to move in and out of the cells according to the extracellular concentration. It is quite clear that the major portion of EACA is not metabolised *in vivo*. Since not all of the EACA was recovered in the urine a small portion may be actively metabolised.

In-vitro experiments and clinical experience indicate that a plasma EACA concentration of at least about 13 mg/100 ml is required to control systemic fibrinolytic activity.^{6,7,12} Since EACA is

rapidly excreted in the urine it must be given intravenously at short intervals to maintain a therapeutic level. Nilsson *et al.*^{6,12} recommended a dose of 0.1 g/kg bodyweight every 3-4 hours. McNicol *et al.*⁷ recommended an initial loading dose of 10 g followed by a continuous intravenous infusion of 1 g/hour to keep a steady plasma concentration of about 13 mg/100 ml. With these doses it has also been possible to inhibit the fibrinolytic activity induced by infusion of streptokinase. A therapeutic concentration can also be maintained by giving 0.1 g/kg bodyweight every 4-6 hours.^{6,12}

To inhibit the urokinase activity in the urine EACA has to be present in the urine in a concentration of about 0.1 mol/l—that is, 10 times higher than that needed to inhibit systemic fibrinolysis in plasma. But since the drug is greatly concentrated during excretion, the urinary concentrations being 50 to 100 times those in plasma, effective concentrations of urinary EACA can be achieved by giving smaller doses, which have only a slight systemic effect. Thus a dose of 3 g EACA three times a day is sufficient to inhibit the local fibrinolytic activity in the urinary tract.¹²

TRANEXAMIC ACID (AMCA)

Andersson *et al.*^{8,13} first studied the absorption, distribution, and excretion of AMCA given intravenously and by mouth in man. They measured the acid in serum with a biological method as well as with high-voltage paper electrophoresis. AMCA in urine was measured by high-voltage paper electrophoresis. After intravenous administration of 10 mg AMCA/kg bodyweight the serum concentration was 18, 10, and 5 µg/ml after 1, 3, and 5 hours, respectively (Fig. 3). The biological half life was calculated to be about 80 hours. About 30% was recovered in the urine during the first hour, 55% during the first three hours, and about 90% within 24 hours (Fig. 4).

After AMCA 10 mg/kg bodyweight by mouth the maximum serum concentration was only about 2 µg/ml after three hours. After 100 mg/kg by mouth a plasma concentration of 40 µg/ml was reached within four hours (Fig. 3). Thus AMCA is not absorbed from the gastrointestinal tract so effectively as EACA. About 40% of an oral dose of 10-15 mg/kg was recovered in the urine within 24 hours (Fig. 4). Similar results have been reported by Kaller.¹⁴

More recently Eriksson *et al.*¹⁵ have investigated the pharmacokinetics of AMCA. Two healthy volunteers received 1 g AMCA intravenously. The concentration of AMCA in plasma and urine was measured by a method using high-voltage electrophoresis. The plasma concentration curve (Fig. 5) showed three monoexponential decays. The first was

Fig. 3 Concentration of AMCA ($\mu\text{g/ml}$) in serum after various doses intravenously or by mouth.

Fig. 4 Urinary recovery of AMCA in 10 men volunteers after a single intravenous injection of 10 mg/kg body-weight and in 11 men after a single dose by mouth of 10-15 mg/kg.

Fig. 5 Left. Plasma concentration of AMCA ($\mu\text{g/ml}$) after single intravenous dose of 1 g. Right. Calculated amounts of AMCA after single intravenous dose of 1 g. A. Amount in central compartment. B. Amount in tissue compartment. C. Amount excreted in urine. (●—●) Urinary excretion, experimental points. (From Eriksson *et al.*¹⁵ by permission of the Editor, European Journal of Clinical Pharmacology.)

a very rapid one, the second had a half life of 1.3-2 hours, and the third a half life of 9-18 hours. About half of the dose was recovered unchanged in the urine during the first 3-4 hours, 90-95% within 24 hours, and 95-99% within 48-72 hours.¹⁶ Fig. 5 also shows the calculated amounts of AMCA in the central and tissue compartments at various times and the amounts eliminated. The elimination half life was about one-fourth of the disposition half life.¹⁵ This was owing to the distribution of AMCA in the tissue compartment, which makes it partly unavailable for elimination. The uncorrected plasma clearance rate was 110-115 ml/min, which, corrected for an average plasma protein binding of 15%, approximately equalled the glomerular filtration. This indicates that AMCA is eliminated by glomerular filtration and that neither tubular excretion nor absorption takes place.

Impairment of renal function prolongs the biological half life of AMCA. Thus in patients with serum creatinine concentrations of $>500 \mu\text{mol/l}$ (5.6 mg/100 ml) the half life was 24 to 48 hours.¹⁷ Vessman and Strömberg¹⁸ have developed a rapid gas chromatographic method for measuring AMCA in small biological samples. The lower limit of detection is 40 pg/ml. They studied the plasma concentration of AMCA after giving 0.5 g and 2.0 g by mouth. Peak concentrations of about 5 and 15 $\mu\text{g/ml}$, respectively, were noted within 2-4 hours. After 12 hours the concentration was less than 1 $\mu\text{g/ml}$.

Like EACA, AMCA is widely distributed throughout the extracellular and intracellular compartments. AMCA 1 g given 4-hourly intravenously to patients with subarachnoid haemorrhage enters the cerebrospinal fluid at a concentration of about 2-5 $\mu\text{g/ml}$.¹⁹ Ahlberg *et al.*²⁰ gave 10 mg AMCA/kg bodyweight to patients before knee joint operations. They found that AMCA rapidly diffused into the joint fluid and synovial membranes and reached the same concentration in the joint fluid as in the serum. The biological half life in the joint fluid was about 3 hours. Bramsen²¹ has investigated the aqueous humour concentration of AMCA after oral administration of the drug. On a dose of 25 mg AMCA/kg bodyweight three times a day the concentration within three hours was 1.6 $\mu\text{g/ml}$ compared with a serum concentration of 15 $\mu\text{g/ml}$. The AMCA disappeared slowly from the aqueous humour.

Given by mouth or intravenously AMCA diffuses into semen and inhibits its normally high fibrinolytic activity. AMCA has no effect on the motility of spermatozoa.²² AMCA passes transplacentally to the fetus.²³ After intravenous injection of 10 mg/kg bodyweight the concentration in the fetal serum may be anything between 4 and 31

$\mu\text{g/ml}$. Tranexamic acid can be found in the milk of lactating women given AMCA (Eriksson, personal communication), but the concentration is very low and is about 1/100 of that in the maternal plasma.

AMCA and EACA are distributed among various tissues. The tissues contain plasminogen activators, which the antifibrinolytic drugs inhibit.⁸ Normal tissue activators most probably do not induce but rather sustain bleeding, since they dissolve the small clots sealing opened vessels and essential for the first stage of wound healing. In treating local fibrinolysis due to the action of tissue activators it is important to know which concentrations of the drugs are required and also how long the fibrinolytic inhibitor persists in different tissues. Andersson *et al.*⁸ studied the fibrinolytic activity of various tissue extracts obtained at operation in the presence of increasing concentrations of AMCA and EACA. A 98-100% reduction of the tissue activator activity required the presence of AMCA in a concentration of about 100 $\mu\text{g/ml}$. The corresponding concentration for EACA was 1000 $\mu\text{g/ml}$. An 80% inhibition required 100 $\mu\text{g/ml}$ of EACA or 10 $\mu\text{g/ml}$ of AMCA. Judging from clinical experience an 80% inhibition is sufficient to suppress the activity.

Andersson *et al.*⁸ measured the fibrinolytic activity and the concentration of AMCA and EACA in serum and in pieces of human tissue (colon, kidneys, prostate) obtained at operation. The fibrinolytic activity of homogenates of the tissues was measured on unheated fibrin plates and the concentration of AMCA and EACA with high-voltage electrophoresis. AMCA was given 36-48 hours before the operation in four doses of about 10-20 mg/kg bodyweight each. The corresponding dose of EACA was 100 mg/kg. The last dose was given at various intervals before operation. The results showed that the antifibrinolytically active concentration of AMCA (10 $\mu\text{g/ml}$) persisted longer in the tissues examined than did the corresponding concentration of EACA (100 $\mu\text{g/ml}$). AMCA thus has not only a higher fibrinolytic activity than EACA but it also persists longer in the tissues. After repeated intravenous or oral doses of AMCA (10 mg/kg intravenously 4-5 times a day or 20 mg/kg by mouth 3-4 times a day) an adequate antifibrinolytic activity in tissues can be maintained for up to 17 hours without any further dose. Risberg²⁶ found a retention of AMCA in the lung tissue in rats.

Judging from *in-vitro* experiments and clinical experience control of systemic fibrinolysis requires a plasma AMCA concentration of about 10-15 $\mu\text{g/ml}$. Since the drug is rapidly excreted in the urine it must, like EACA, be given intravenously at

short intervals to maintain a therapeutic level. Andersson *et al.*^{8,13} recommended a dose of 10 mg/kg bodyweight every 3-4 hours. AMCA is not so readily absorbed as EACA and therefore when given by mouth is only three times as active as EACA. An oral dose of about 30-40 mg/kg bodyweight every 4-5 hours should be optimal in treating conditions with generalised fibrinolysis. For inhibiting tissue activators—that is, in the treatment of conditions associated with local fibrinolysis—AMCA has been recommended in a dose of about 20 mg/kg 3-4 times a day.

Inhibition of urokinase activity in the urine requires an AMCA concentration of about 200 $\mu\text{g/ml}$. After AMCA by mouth in a dose of 10 mg/kg bodyweight the fibrinolytic activity of the urine is much reduced (Fig. 6). A dose of 1-2 g two to three times a day is sufficient to inhibit the urokinase activity in the urine.²⁷

Fig. 6 Fibrinolytic activity of urine after AMCA 10 mg/kg bodyweight by mouth.

Toxicology

Both EACA and AMCA are of low acute toxicity.⁴ No fetal abnormalities have been found in teratogenic studies in rats, rabbits, and mice given AMCA in doses of up to 5000 $\mu\text{g/kg}$ a day. Retinal changes have been reported in dogs after receiving AMCA by mouth over a period of one year in doses approximately seven times higher than the maximum recommended daily dose for man. No such changes were seen in dogs given for a year three and a half times the maximal oral dose per kg bodyweight recommended for man, in rats given seven times the maximal human dose for 22 months, or monkeys that had been given 18 times the maximal intravenous dose for 14 days.²⁸ Neither were any retinal changes seen in patients treated with AMCA for months or years (Pandolfi, personal communication). In patients to be treated continuously for several weeks, however, visual acuity, colour perception, the ocular fundi, and fields of vision should be reviewed.

Adenoma and adenocarcinoma of the liver have been reported in rats after 22 months' oral treatment with about 27 times the maximum dose of AMCA/kg bodyweight recommended for man, but not after 12 months' treatment. No such tumours have been seen in rats given six times the maximum daily dose per kg bodyweight recommended for human beings.²⁸

Carroll and Tice²⁹ found that doses of 0.3 to 1.4 g of EACA/kg given intravenously to nephrectomised dogs produced hyperpotassaemia. They believed that EACA is taken up by muscle cells and thereby increases the escape of intracellular K⁺. Muscle pain with increases in the serum enzymes, creatine phosphokinase, and aldolase have been reported in clinical investigations of EACA in patients with hereditary angioneurotic oedema.³⁰ In one case Korsan-Bengtson *et al.*³¹ found Zenker's hyaline degeneration in muscle cells in a muscle biopsy specimen. Wysenbeek *et al.*³² have recently reported a patient who developed an acute delirious state after EACA administration. No residual psychiatric or neurological symptoms were observed. The side effect was thought to be related to the antifibrinolytic effect of the drug since a similar reaction has been reported with another antifibrinolytic drug, Trasylol, which acts completely differently to EACA.

EACA given to dogs and female rats in large doses has resulted in a 50% reduction of fertility but this was reversible.³³ EACA and AMCA, though less often, may cause nausea, diarrhoea, nasal stuffiness, and conjunctival suffusion. Occasionally EACA produces orthostatic symptoms; AMCA does so only rarely. A fall in blood pressure has been reported in a few cases after administration of AMCA.^{34 35}

An important question is whether treatment with EACA or AMCA predisposes to thrombosis and intravascular coagulation. There are isolated reports of arterial or venous thrombosis associated with EACA therapy, but in each case a disease known to predispose to thrombosis has also been present.^{11 36} Furthermore, Rydin and Lundberg³⁷ have reported two patients receiving AMCA to control menorrhagia and Davies and Howell³⁸ one patient treated with AMCA for hereditary angio-oedema who developed intracranial arterial thrombosis. Detailed studies using phlebography³⁹ or ¹²⁵I-fibrinogen uptake⁴⁰ have shown no change in the incidence of venous thrombosis attributable to treatment with EACA after prostatectomy.

In a double-blind multicentre study of 515 patients untreated or treated with EACA the mortality due to pulmonary embolism and myocardial infarction was largely similar in both groups.⁴¹ Hedlund⁴² reported the incidence of thrombosis as detected by the ¹²⁵I fibrinogen uptake test in 201

prostatectomy patients, 100 of whom had taken 1 g AMCA three times a day and 101 a placebo. There was no statistically significant difference in the incidence of thrombosis between the two groups. In tissue cultures of human veins the activator content is unaffected by culture in media containing AMCA (1 mg/ml).⁴³ On the other hand, there is no doubt that EACA and AMCA can perpetuate existing fibrin deposits.^{44 45} Saldeen⁴⁶ found that antifibrinolytic therapy causes persistent fibrin deposits in the lung.

Conclusion

EACA and AMCA are potent antifibrinolytic drugs. AMCA is 7-10 times more potent than EACA by *in-vitro* and *in-vivo* assay. The pharmacokinetics of the drugs are now known and rational dose regimens for treating systemic and local fibrinolysis have been worked out. The drugs have no serious side effects. There is no evidence that they predispose to thrombosis but they may perpetuate existing fibrin deposits.

The following dosages are recommended for various bleeding conditions.

Systemic fibrinolysis This relatively rare clinical condition requires EACA 100 mg/kg intravenously at about 3 hourly intervals. After the first injection EACA can be given by mouth. AMCA 10 mg/kg intravenously 3-4 hourly will give an adequate inhibitory plasma concentration. After an initial intravenous dose about 30-50 mg/kg by mouth may be given 3-4 hourly.

Local fibrinolytic bleedings For inhibiting tissue activators EACA 100 mg/kg intravenously or by mouth should be given three to four times a day. Owing to its sustained tissue activity AMCA 10-20 mg/kg may be given by mouth three to four times daily.

Haematuria Urokinase activity in urine has been effectively inhibited by EACA 50 mg/kg 8 hourly intravenously or by mouth. Judging from urinary excretion studies, AMCA 10 mg/kg intravenously or 20 mg/kg by mouth two to three times a day gives satisfactory results.

This investigation was supported by grants from the Swedish Medical Research Council (B80-19X-00087-16C).

References

- 1 Okamoto S. Ref. to British Patent Specification 1957; 770,693.

- ² Okamoto S, *et al.* A suppressing effect of ϵ -amino-n-caproic acid on the bleeding of dogs, produced with the activation of plasmin in the circulatory blood. *Keio J Med* 1959;**8**:247-66.
- ³ Okamoto S, Okamoto U. Amino-methyl-cyclohexanecarboxylic acid: AMCHA. A new potent inhibitor of the fibrinolysis. *Keio J Med* 1962;**11**:105-15.
- ⁴ Melander B, Gliniecki G, Granstrand B, Hanshoff G. The antifibrinolytically active isomer of AMCHA. *Abstracts of the Xth International Congress of Haematology*, Stockholm, Aug 30-Sept 4 1964:G68.
- ⁵ Okamoto S, *et al.* Behaviour of tissue activators and the action of a series of potent inhibitors on fibrinolysis. *Abstracts of the Xth International Congress of Haematology*, Stockholm, Aug 30-Sept 4 1964: G65.
- ⁶ Nilsson IM, Sjoerdsma A, Waldenström J. Antifibrinolytic activity and metabolism of ϵ -aminocaproic acid in man. *Lancet* 1960;**1**:1322-6.
- ⁷ McNicol GP, Fletcher AP, Alkjaersig N, Sherry S. The absorption, distribution, and excretion of ϵ -aminocaproic acid following oral or intravenous administration to man. *J Lab Clin Med* 1962;**59**:15-24.
- ⁸ Andersson L, Nilsson IM, Collen S, Granstrand B, Melander B. Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. *Ann NY Acad Sci* 1968;**146**:642-58.
- ⁹ Sjoerdsma A, Hansson A. Determination of ϵ -aminocaproic acid in urine by means of high-voltage paper electrophoresis. *Acta Chem Scand* 1969;**13**:2150-1.
- ¹⁰ McNicol GP, Fletcher AP, Alkjaersig N, Sherry S. The use of epsilon aminocaproic acid, a potent inhibitor of fibrinolytic activity, in the management of post-operative hematuria. *J Urol* 1961;**86**:829-37.
- ¹¹ Andersson L. Fibrinolytic states in prostatic disease and their treatment with epsilon-aminocaproic acid. *Acta Chir Scand* 1963;**126**:251-65.
- ¹² Nilsson IM, Andersson L, Björkman SE. Epsilon-aminocaproic acid (E-ACA) as a therapeutic agent. Based on 5 years' clinical experience. *Acta Med Scand (Suppl)* 1966;**448**.
- ¹³ Andersson L, Nilsson IM, Nilén 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* 1965;**2**:230-47.
- ¹⁴ Kaller H. Enterale Resorption, Verteilung und Elimination von 4-Aminomethylcyclohexancarbonsäure (AMCHA) und ϵ -Aminocapronsäure (ACS) beim Menschen. *Naunyn Schmiedbergers Arch Pharmacol* 1967;**256**:160-8.
- ¹⁵ Eriksson O, Kjellman H, Pilbrant Å, Schannong M. Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. *Eur J Clin Pharmacol* 1974;**7**:375-80.
- ¹⁶ Kjellman H. Comments by the manufacturer of cyklokapron. In: Verstraete M, ed. *Haemostatic drugs. A critical appraisal*. The Hague, Martinus Nijhoff Medical Division, 1977:140-1.
- ¹⁷ Andersson L, Eriksson O, Hedlund PO, Kjellman H, Lindqvist B. Special considerations with regard to the dosage of tranexamic acid in patients with chronic renal diseases. *Urol Res* 1978;**6**:83-8.
- ¹⁸ Vessman J, Strömberg S. Determination of tranexamic acid in biological material by electron capture gas chromatography after direct derivatization in an aqueous medium. *Anal Chem* 1977;**49**:369-73.
- ¹⁹ Tovi D, Nilsson IM, Thulin C-A. Fibrinolysis and subarachnoid haemorrhage. Inhibitory effects of tranexamic acid. A clinical study. *Acta Neurol Scand* 1972;**48**:393-402.
- ²⁰ Ahlberg Å, Eriksson O, Kjellman H. Diffusion of tranexamic acid to the joint. *Acta Orthop Scand* 1976;**47**:486-8.
- ²¹ Bramsen T. Effect of tranexamic acid on choroidal melanoma. *Acta Ophthalmol* 1978;**56**:264-9.
- ²² Liedholm P, Åstedt B, Kullander S. Passage of tranexamic acid (AMCA) to semen in man and its effect on the fibrinolytic activity and on migration of spermatozoa. *Fertil Steril* 1973;**24**:517-20.
- ²³ Kullander S, Nilsson IM. Human placental transfer of an antifibrinolytic agent (AMCA). *Acta Obstet Gynec Scand* 1970;**49**:241-2.
- ²⁴ Nilsson IM. Local fibrinolysis as a mechanism for haemorrhage. *Thromb Diathes Haemorrh* 1975;**34**: 623-33.
- ²⁵ Thorsen S. Influence of fibrin on the effect of 6-aminohexanoic acid on fibrinolysis caused by tissue plasminogen activator or urokinase. In: Davidson JF, Rowan RM, Samama MM, Desnoyers PC, eds. *Progress in chemical fibrinolysis and thrombolysis*, vol 3. New York: Raven, 1978:269-83.
- ²⁶ Risberg B. Effect of tranexamic acid on pulmonary tissue fibrinolysis in the rat. *Microvasc Res* 1976;**11**: 307-14.
- ²⁷ Andersson L, Nilsson IM. AMCA (aminomethyl cyclohexane carboxylic acid, Cyklo-kapron) a potent haemostatic agent in urinary tract bleeding. *Scand J Urol Nephrol* 1969;**3**:169-76.
- ²⁸ Kjellman H. Synthetic antifibrinolytics. In: Nilsson IM, ed. *Haemorrhagic and Thrombotic Diseases*. London: John Wiley, 1974:140-5.
- ²⁹ Carroll HJ, Tice D. The effects of epsilon-aminocaproic acid upon potassium metabolism in the dog. *Metabolism* 1966;**15**:449-57.
- ³⁰ Frank MM, Sergeant JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema. *N Engl J Med* 1972;**286**:808-12.
- ³¹ Korsan-Bengtson K, Ysander K, Blohmé G, Tibblin E. Extensive muscle necrosis after long-term treatment with aminocaproic acid (EACA) in a case of hereditary periodic edema. *Acta Med Scand* 1969;**185**: 341-6.
- ³² Wysenbeek AJ, Sella A, Blum I, Yeshurun D. Acute delirious state after ϵ -amino caproic acid administration. *Clin Toxicol* 1979;**14**:93-5.
- ³³ Eneroth G, Grant CA. Epsilon aminocaproic acid and reduction in fertility of male rats. *Acta Pharm Suec* 1966;**3**:115-22.
- ³⁴ Vermeylen J, Verhaegen-Declercq ML, Verstraete M, Fierens F. A double-blind study of the effect of tranexamic acid in essential menorrhagia. *Thromb Diathes Haemorrh* 1968;**20**:583-7.

- ³⁵ Hedlund PO. Antifibrinolytic therapy with cyklokapron in connection with prostatectomy. *Scand J Urol Nephrol* 1969;**3**:177-82.
- ³⁶ Naeye RL. Thrombotic disorders with increased levels of antiplasmin and antiplasminogen. *N Engl J Med* 1961;**265**:867-71.
- ³⁷ Rydin E, Lundberg PO. Tranexamic acid and intracranial thrombosis. *Lancet* 1976;**2**:49.
- ³⁸ Davies D, Howell DA. Tranexamic acid and arterial thrombosis. *Lancet* 1977;**1**:49.
- ³⁹ Becker J, Borgström S. Incidence of thrombosis associated with epsilon-aminocaproic acid administration and with combined epsilon-aminocaproic acid and subcutaneous heparin therapy. *Acta Chir Scand* 1968;**134**:343-9.
- ⁴⁰ Gordon-Smith IC, Hickman JA, El Masri SH. The effect of the fibrinolytic inhibitor epsilon-aminocaproic acid on the incidence of deep-vein thrombosis after prostatectomy. *Br J Surg* 1972;**59**:522-4.
- ⁴¹ Vinnicombe J, Shuttleworth KED. Aminocaproic acid in the control of haemorrhage after prostatectomy: a controlled trial. *Lancet* 1966;**1**:230-4.
- ⁴² Hedlund PO. Postoperative venous thrombosis in benign prostatic disease. A study of 316 patients, using the ¹²⁵I-fibrinogen uptake test. *Scand J Urol Nephrol (Suppl)* 1975;**27**.
- ⁴³ Åstedt B, Pandolfi M, Nilsson IM. Quantitation of fibrinolytic agents released in tissue culture. *Experientia* 1971;**27**:358-9.
- ⁴⁴ Stark SN, White JG, Langer L, Jr, Krivit W. Epsilon-aminocaproic acid therapy as a cause of intrarenal obstruction in haematuria of haemophiliacs. *Scand J Haematol* 1965;**2**:99-107.
- ⁴⁵ Gobbi F. Use and misuse of aminocaproic acid. *Lancet* 1967;**2**:472-3.
- ⁴⁶ Saldeen T. Quantitative determination of intravascular coagulation in the lungs of experimental animals. *Scand J Haematol* 1969;**6**:205-15.