Clinical pharmacology of aminocaproic and tranexamic acids

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In a systematic search for a substance with antifibrinolytic properties Okamoto and his group in Japan found that several mercapto- and amino-carboxylic acids were active. Of these substances epsilon-aminocaproic acid (EACA) had the strongest antifibrinolytic effect.\(^\text{1,2}\) 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 antifibrinolytic components p-aminomethyl cyclohexane carboxylic acid (AMCHA) was found to be more potent than EACA.\(^\text{3}\) This compound contains two stereoisomers. Independently Melander et al.\(^\text{4}\) and Okamoto et al.\(^\text{5}\) 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.\(^\text{6-8}\) 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.\(^\text{7-9}\) 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.\(^\text{10,11}\)

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.\(^\text{8}\) found that about 70% of the dose given intravenously was excreted in the urine within 24 hours (Fig. 2). McNicol et al.\(^\text{7}\) 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.
many times during excretion, urinary levels being 50 to 100 times those found in plasma. McNicol et al. 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 endogeneous 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. is somewhat higher—namely, 78%.

EACA enters human red cells and various tissues. 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. Since EACA is rapidly excreted in the urine it must be given intravenously at short intervals to maintain a therapeutic level. Nilsson et al. recommended a dose of 0-1 g/kg bodyweight every 3-4 hours. McNicol et al. 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.

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.

TRANEXAMIC ACID (AMCA)

Andersson et al. 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.

More recently Eriksson et al. 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
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**Fig. 3** Concentration of AMCA (μg/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 bodyweight and in 11 men after a single dose by mouth of 10-15 mg/kg.

**Fig. 5** Left. Plasma concentration of AMCA (μg/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. (From Eriksson et al., 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. 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. 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 μmol/l (5.6 mg/100 ml) the half life was 24 to 48 hours. Vessman and Strömberg 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 μg/ml, respectively, were noted within 2-4 hours. After 12 hours the concentration was less than 1 μg/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 μg/ml. Ahlberg et al. 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. Bramsen 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 μg/ml compared with a serum concentration of 15 μg/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. AMCA passes transplacently to the fetus. After intravenous injection of 10 mg/kg bodyweight the concentration in the fetal serum may be anything between 4 and 31
μg/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. Normal tissue activators probably do not induce but rather sustain bleeding, since they dissolve the small clots sealing opened vessels and are 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. 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 μg/ml. The corresponding concentration for EACA was 1000 μg/ml. An 80% inhibition required 100 μg/ml of EACA or 10 μg/ml of AMCA. Judging from clinical experience an 80% inhibition is sufficient to suppress the activity.

Andersson et al. 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 μg/ml) persisted longer in the tissues examined than did the corresponding concentration of EACA (100 μg/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. Risberg 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 μg/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. 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 μg/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.

![Fig. 6 Fibrinolytic activity of urine after AMCA 10 mg/kg bodyweight by mouth.](http://jcp.bmj.com/)

**Toxicology**

Both EACA and AMCA are of low acute toxicity. No fetal abnormalities have been found in teratogenic studies in rats, rabbits, and mice given AMCA in doses of up to 5000 μg/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. 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 Tice\(^29\) 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, creatinine phosphokinase, and aldolase have been reported in clinical investigations of EACA in patients with hereditary angioneurotic oedema.\(^30\) In one case Korsan-Bengtsen 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.\(^3\)\(^6\)\(^1\)\(^1\)\(^2\)\(^6\) Furthermore, Rydin and Lundberg\(^37\) have reported two patients receiving AMCA to control menorrhagia and Davies and Howell\(^38\) one patient treated with AMCA for hereditary angio-oedema who developed intracranial arterial thrombosis. Detailed studies using phlebography\(^39\) or \(^125\)I-fibrinogen uptake\(^40\) 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.\(^41\) Hedlund\(^42\) reported the incidence of thrombosis as detected by the \(^125\)I 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.\(^44\)\(^45\) Saldeen\(^46\) 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.

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**References**

2 Okamoto S, et al. A suppressing effect of \(\varepsilon\)-amino- 

acapric acid on the bleeding of dogs, produced with the 

activation of plasmin in the circulating blood. 


3 Okamoto S, Okamoto U. \(\varepsilon\)-amino-methyl-cyclohexane-

carboxylic acid: AMCHA. A new potent inhibitor of the 

fibrinolysis. 


4 Melander B, Gliniecki G, Granstrand B, Hanshoff G. 

The antifibrinolytically active isomer of AMCHA. 

*Abstracts of the Xth International Congress of 


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. Anti-

fibrinolytic activity and metabolism of \(\varepsilon\)-amino-

capric acid in man. 


7 McNicol GP, Fletcher AP, Alkaerisig N, Sherry S. The 

absorption, distribution, and excretion of \(\varepsilon\)-amino-

capric acid following oral or intravenous administra-

tion to man. 


8 Andersson L, Nilsson IM, Collen S, Granstrand B, 

Melander B. Role of uroukinase 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 \(\varepsilon\)-amino-

capric acid in urine by means of high-voltage paper 

electrophoresis. 


10 McNicol GP, Fletcher AP, Alkaerisig N, Sherry S. The 

use of epsilon aminocaproic acid, a potent inhibitor 

of fibrinolytic activity, in the management of post-

operative hematuria. 


11 Andersson L. Fibrinolytic states in prostatic disease 

and their treatment with epsilon-aaminocaproic acid. 


12 Nilsson IM, Andersson L, Björkman SE. Epsilon-

aminocaproic acid (E-ACA) as a therapeutic agent. 

Based on 5 years' clinical experience. 


13 Andersson L, Nilsson IM, Niléhn J-E, Hedner U, 

Granstrand B, Melander B. Experimental and 

clinical studies on AMCA, the antifibrinolytically 

active isomer of \(p\)-aminomethyl cyclohexane 

carboxylic acid. 


14 Kaller H. Enterale Resorption, Verteilung und 

Elimination von \(4\)-Aminomethylcyclohexan-carbonsäure 

(AMCHA) und \(\varepsilon\)-Aminocaproinsäure (ACS) 

beim Menschen. 

*Naunyn Schmiedersch Arch Pharmacol* 


15 Eriksson O, Kjellman H, Pilbrant Å, Schannong M. 

Pharmakokinetics of tranexamic acid after intra-

venous administration to normal volunteers. 


16 Kjellman H. Comments by the manufacturer of 


*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. 


18 Vessman J, Strömberg S. Determination of tranexamic 

cacid in biological material by electron capture gas 

cromatography after direct derivatization in an 

aqueous medium. 


19 Tovi D, Nilsson IM, Thulin CA. Fibrinolysis and sub-

arachnoid haemorrhage. Inhibitory effects of tran-

examic acid. A clinical study. 


20 Ahlberg Å, Eriksson O, Kjellman H. Diffusion of 

tranexamic acid to the joint. 


21 Bramsén T. Effect of tranexamic acid on choroidal 

melanoma. 


22 Liedholm P, Åstedt B, Kullander S. Passage of tran-

examic acid (AMCA) to semen in man and its effect 

on the fibrinolytic activity and on migration of 

spermatozoa. 


23 Kullander S, Nilsson IM. Human placental transfer 

of an antifibrinolytic agent (AMCA). 


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-

amino-

hexanoic 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. 


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. 


28 Kjellman H. Synthetic antifibrinolitics. In: *Nilsson 

IM*, ed. 

*Haemorrhagic and Thrombotic Diseases*. 


29 Carroll HJ, Tice D. The effects of epsilon-amino-

acapric acid upon potassium metabolism in the dog. 


30 Frank MM, Sergent JS, Kane MA, Alling DW. 

Epsilon aminocaproic acid therapy of hereditary 

gangioneuritic edema. 


31 Korsan-Bengtsen K, Ysander K, Blohmé G, Tibblin E. 

Extensive muscle necrosis after long-term treatment 

with aminocaproic acid (EACA) in a case of hered-

itary periodic edema. 

*Acta Med Scand* 1969;185: 

341-6.

32 Wyseenbeek AJ, Sella A, Blum I, Yeshurun D. Acute 

delirious state after \(\varepsilon\)-amino caproic acid adminis-

traion. 

*Clin Toxicol* 1979;14:93-5.

33 Eneroth G, Grant CA. Epsilon aminocaproic acid and 

reduction in fertility of male rats. 


34 Vermylen J, Verhaegen-Declercq ML, Verstraete M, 

Fierens F. A double-blind study of the effect of 

tranexamic acid in essential menorrhagia. 

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