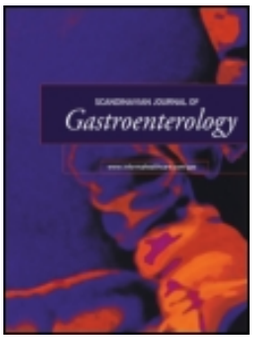

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B. Åstedt

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Clinical Pharmacology of Tranexamic Acid

B. ÅSTEDT
Dept. of Gynaecology and Obstetrics,
University Hospital of Lund, Lund, Sweden

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Tranexamic acid (AMCA) is a potent antifibrinolytic drug occurring in two isomeric forms; the antifibrinolytic potency resides in the transisomeric form. The main action of AMCA is blocking of the lysine-binding sites of the plasminogen molecule, which are of importance for the binding to fibrin. This prevents activation of plasminogen by plasminogen activator also absorbed to fibrin. AMCA can be administered perorally or intravenously and is excreted into the urine. It enters tissues and fluids in various concentrations and crosses the placenta. There is no evidence of a thrombogenic effect of AMCA, but in accordance with its action, it prolongs dissolution of fibrin deposits already formed. AMCA is a drug of high clinical value for the treatment of bleedings due to both systemic and local fibrinolysis.

Key words: AMCA; fibrinolytic inhibitor; tranexamic acid

Prof. Birger Åstedt, M.D., Kvinnokliniken, Lasarettet i Lund, S-221 85 Lund, Sweden

CHEMISTRY

The discovery of the effect of epsilon-aminocaproic acid (EACA) on fibrinolytic bleeding was published by Okamoto et al. in 1959 (1). EACA was rapidly introduced in several countries as an important drug for the treatment of fibrinolytic bleeding and haemorrhage. Clinical experience was first reported by Nilsson et al. (2).

Large amounts of EACA had to be administered to give a sufficient effect, however; the search for a more potent antifibrinolytic drug was therefore continued. This was found in 4-aminomethylcyclohexanecarboxylic acid (3). This antifibrinolytic compound occurs in two isomeric forms, the antifibrinolytic potency residing in the transisomeric form (4, 5).

The structure of tranexamic acid is shown in Fig. 1. The compound is soluble in water but not in alcohol or ether. The antifibrinolytic activity is dependent on a distance of 7 Å between the amino and carboxy groups. AMCA is 7–10 times more potent than EACA (6–8). This great potency has been ascribed to the more stable and rigid molecular structure compared with that of EACA (8).

There are mainly two methods in use for the determination of AMCA. In serum it can be measured by separation of the amino acids by high-voltage electrophoresis with exposure to a ninhydrine reagent and photometric assay of the ninhydrine complex (9). In biological material it can be determined by electron capture gas chromatography (10).

ACTION OF AMCA

AMCA induces structural changes in the plasminogen molecule (11, 12), which facilitates the activation of plasminogen into plasmin (13, 14). Thus, paradoxically, this involves activation of

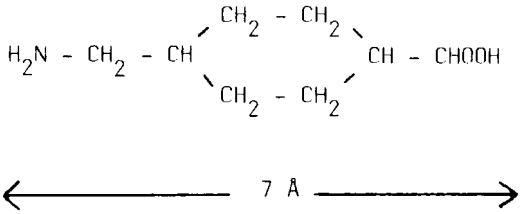

Fig. 1. Trans-4-aminomethyl cyclohexane carboxylic acid (tranexamic acid (AMCA)).

the fibrinolytic system, but in vivo this mechanism is less important. The influence of the conversion of plasminogen into plasmin in the presence of fibrin is more important. AMCA blocks the lysine-binding sites of the plasminogen molecule, which are essential for its binding to fibrin. This prevents activation by plasminogen activator, which is also absorbed to fibrin (15, 16). A second important antifibrinolytic effect of AMCA is blocking of the lysine-binding sites of free plasmin already formed. This prevents (17, 18) the binding to fibrin, and the AMCA–plasmin complex is rapidly inactivated by α_2-antiplasmin and α_2-macroglobulin. This mechanism is illustrated in Fig. 2.

PHARMACOKINETICS

AMCA is not so readily absorbed as EACA (19). Food intake does not influence the absorption of AMCA (20). The biological half-life is 2–3 h. Besides the binding to plasminogen, the protein binding is negligible (21). The absorption of AMCA and its distribution and excretion were studied by Andersson et al. (8, 9) and Kaller (19).

After intravenous administration of 10 mg AMCA/kg body weight the concentration in plasma was 18, 10, and 5 mg/ml after 1, 3, and 5 h. When a similar dose of AMCA of 10 mg/kg body weight was given orally, the maximum concentration in plasma was about 2 mg/l.

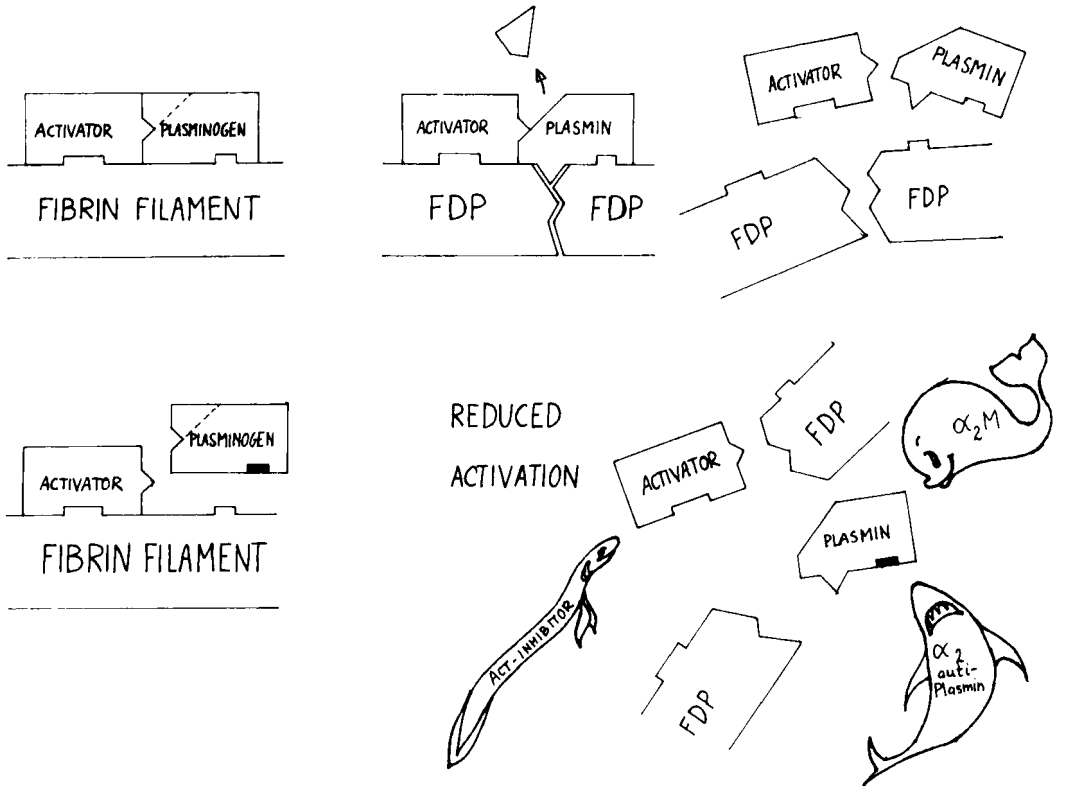

Fig. 2. Antifibrinolytic effect of AMCA. Top: In the absence of AMCA the activation of plasminogen into plasmin by the plasminogen activator takes place on the fibrin filament. Plasmin degrades fibrin into fibrin degradation products (FDP). Activator and plasmin molecules are liberated and are able to generate further enzymatic activity. Bottom: AMCA (indicated by ■) blocks the lysine-binding sites of plasminogen, which are essential for the adsorption to fibrin, and thereby prevents activation by the activator also adsorbed to fibrin. This results in reduced activation with a reduced capacity to degrade fibrin. Small amounts of plasmin are formed, however, and the free AMCA plasmin complex is rapidly inactivated by α_2-antiplasmin and, to a lesser degree, by α_2-macroglobulin. Free activator molecules are inhibited by fast-acting specific activator inhibitors.

Table I. Concentration of AMCA (% of plasma concentration)

Cerebrospinal fluid	10–30%
Aqueous humour	10%
Joints	90–100%
Seminal fluid	10–100%
Cord blood	40–100%
Milk	1–2%

Increasing the doses 10-fold, to 100 mg/kg body weight, gave a concentration in plasma of 40 mg/l after 4 h. Administration of 1 g of AMCA to an adult of normal body weight results in a plasma concentration of 8–10 mg/l, which is a therapeutic level. A concentration of 10 mg/l is required for an 80% inhibition of tissue activator activity (9).

AMCA is excreted into the urine by glomerular filtration. After intravenous administration the 24-h recovery from urine is about 90%. When given by mouth the recovery is about 40%, which indicates a prolonged and persistent uptake in tissues. The excretion is prolonged in patients with impaired renal function and in oliguria. After intravenous administration the drug can be determined in plasma 24 h later in such patients.

The distribution of AMCA in some fluids is shown in the Table I. It crosses the placenta (22, 23), but secretion in breast milk is low (24). It has no influence on the migration of sperm cells (25). No data are available concerning the concentration in gastric juice, but the clinical effect of AMCA on gastrointestinal haemorrhage has been clearly demonstrated (26, 27).

TOXICOLOGY AND SIDE EFFECTS

Nausea and diarrhoea may occur but seldom necessitate withdrawal of the drug. When given intravenously, infusion should be given slowly to prevent the vomiting reflex.

The toxicity of AMCA is low. Retinal atrophy was observed in dogs receiving large amounts of the drug, about seven times that recommended for man, and given for 12 months. Such changes have not been found after normal doses in dogs (28, 29), nor have any changes been observed in patients treated for many years for hereditary angioneurotic oedema (30). There is no evidence of any teratogenic or carcinogenic effect of AMCA.

An important question is whether depression of the fibrinolytic defence system might be hazardous. However, an evaluation of the clinical literature produced no evidence of such a risk (31). It has also been shown that the plasminogen activators, which activate the fibrinolytic system and are present in the vascular endothelium, are not affected by AMCA (32). But there is also no doubt that AMCA prolongs the dissolution of previously formed fibrin deposits.

To sum up, AMCA is a potent antifibrinolytic drug with no serious side effects. There is no evidence of a thrombogenic effect of the drug, but by virtue of its mode of action it prolongs dissolution of previously formed fibrin deposits. To inhibit systemic fibrinolysis, AMCA should be administered intravenously in a dose of 10 mg/kg body weight, the dose being repeated after 3–4 h. For the inhibition of local fibrinolysis the same doses should be given initially, followed by 20 mg/kg orally three to four times a day.

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