Journal of Cardiothoracic and Vascular Anesthesia 31 (2017) 2183–2205

Contents lists available at ScienceDirect

ScienceDirect

journal homepage: www.jcvaonline.com

Review Article

Antifibrinolytic Agents in Cardiac and Noncardiac Surgery: A Comprehensive Overview and Update

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Key Words: antifibrinolytic; tranexamic acid; aminocaproic acid; aprotinin; coagulation; surgical bleeding; antifibrinolytic agents; blood transfusion; cardiac surgical procedures; cardiopulmonary bypass; multiple trauma; postoperative hemorrhage; serine proteinase inhibitors

USING STRATEGIES TO mitigate blood loss and the need for transfusion is a fundamental component of caring for surgical patients. Antifibrinolytic use is standard practice for complex cardiac surgery and cardiac surgery involving cardiopulmonary bypass (CPB). The most recent Society of Thoracic Surgeons (STS) and Society of Cardiovascular Anesthesiologists (SCA) Blood Conservation Clinical Practice Guidelines give their highest recommendation (IA) for the use of antifibrinolytics in cardiac surgery.[1] Outside the context of cardiac surgery, the use of antifibrinolytics in the perioperative period to reduce blood loss and minimize allogeneic transfusion requirements has burgeoned in the past decade.[2] Antifibrinolytic agent use is now included in the 2015 World Health Organization list of "essential medicines,"[3] multiple trauma management protocols,[4,5] postpartum hemorrhage (PPH) prevention and treatment,[6,7] and in a broad range of other surgical specialties (hepatobiliary,[8,9] orthopedic,[10] neurologic,[11] obstetric/gynecologic,[12] urologic,[13] vascular,[14] pediatric).[15] As the use of antifibrinolytics has increased in both noncardiac and cardiac surgery, concerns have been raised regarding the potential serious adverse effects of these hemostatic agents and their safe clinical use.

Antifibrinolytics comprise a group of pharmacologic agents that includes epsilon-aminocaproic acid (EACA), tranexamic acid (TXA), and aprotinin. This review and update focuses on the background, uses in cardiac and major noncardiac surgery (particularly for EACA and TXA), costs, and precautions and concerns associated with each antifibrinolytic agent.

Epsilon Aminocaproic Acid

EACA (Amicar; Clover Pharmaceuticals, Marietta, GA) is a highly water-soluble, colorless crystal that is 1 of 2 currently available synthetic lysine analogs. Both lysine analogs (EACA and TXA) act to block plasminogen's conversion to plasmin, leading to a resultant inhibition in fibrinolysis. See Fig 1 for EACA's chemical structure and Fig 2 for a detailed description and schematic of its mechanism of action.

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http://dx.doi.org/10.1053/j.jvca.2017.02.029

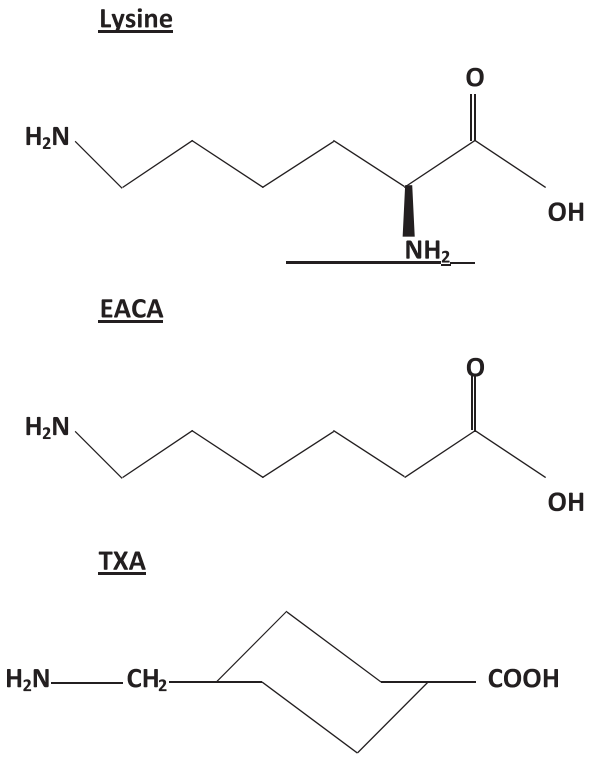

Fig 1. Lysine, epsilon aminocaproic acid, and tranexamic acid molecular structures. Note the structural similarity to the amino acid lysine from which they are derived.

History and Development

EACA was first studied in the laboratory setting as far back as 1914, but research in humans increased in the late 1950s when Japanese researchers tested its use for the treatment of various ailments (dysmenorrhea, emesis gravidarum, toxemia of pregnancy) for which EACA was efficacious with minimal side effects.[16] Fibrinolytic activity was not measured at that time, but subsequent studies showed that EACA acted as a potent inhibitor of plasminogen activation, and investigators quickly recognized the potential of EACA for controlling bleeding in different clinical scenarios, including surgery.[17] In the 1960s, EACA was first used in prostatectomy surgery based on research done by Sack et al,[18] which showed a clinically significant reduction in blood loss in 18 patients treated with a continuous EACA infusion compared with 18 patients who received placebo. EACA was approved by the US Food and Drug Administration (FDA) in 1964.

Mechanism of Action and Pharmacokinetics

Typically, the proteolytic serum enzyme plasmin hydrolyzes polymerized fibrin, resulting in fibrinolysis and dissolution of fibrin clot. EACA modulates the fibrinolytic pathway in the intravascular space by reversibly binding to the lysine-binding sites of plasminogen (the zymogen precursor of plasmin). Due to EACA's structural similarity to lysine (see Fig 1), it is able to bind competitively to the tissue plasminogen activator (TPA)/plasminogen/plasmin complex, inhibiting the binding of this complex molecule onto fibrin. EACA's binding inhibition prevents plasmin release and inhibits fibrinolysis, thereby enhancing hemostasis.[19]

EACA's volume of distribution is 30 L with intravenous (IV) administration, with peak serum concentrations reached in approximately 10 minutes.[20] After prolonged administration, EACA distributes throughout both intravascular and extravascular compartments and penetrates red blood cells and other tissue cells. It is unknown whether EACA crosses the placenta or is distributed in breast milk,[8] but there is evidence that it does cross the blood-brain barrier.[21] EACA primarily is excreted via the kidneys, with 65% of the unchanged drug present in urine. Renal clearance approximates creatinine clearance (116 mL/min), with a terminal elimination half-life of 2 hours. Total body clearance is decreased markedly in patients with renal failure and there is evidence it is only partially removed (25%) by hemodialysis and peritoneal dialysis.[22] Of note, EACA clearance is reduced in neonates compared with older children and adults.[23,24]

Use in Cardiac Surgery

EACA has been shown to be effective in reducing bleeding and transfusion needs associated with cardiac surgery involving CPB in adults.[25,26] In the observational study by Mangano et al[25] of 4,374 patients undergoing myocardial revascularization, the 3 antifibrinolytics (aprotinin, EACA, TXA) were assessed prospectively with regard to drug efficacy and serious adverse outcomes. All agents were effective in reducing perioperative blood loss, and the authors concluded that EACA and TXA were safe alternatives to aprotinin.[25] A 2007 meta-analysis comparing all 3 antifibrinolytic agents during cardiac surgery demonstrated that EACA was effective in reducing blood loss and transfusion needs when used prophylactically without increased adverse effects.[27] In 2008, the Blood conservation using Antifibrinolytics: Randomized Trial (BART) was published, which at the time was the largest randomized multicenter blinded trial comparing aprotinin, TXA, and EACA.[28] BART was a blinded, multicenter, randomized controlled trial (RCT) comparing the 3 agents in high-risk cardiac surgery patients (procedures with an average risk of death at least twice that expected for isolated primary coronary artery bypass grafting [CABG]). BART assigned 2,331 high-risk cardiac surgical patients undergoing CPB to 1 of 3 groups: 781 received aprotinin, 770 received TXA, and 780 received EACA. The primary outcome was postoperative bleeding, with a secondary outcome of 30-day mortality. Results demonstrated that all 3 agents decreased postoperative bleeding, with the trial terminated early due to a higher rate of death in the aprotinin group (relative risk [RR] 1.53; 95% confidence interval [CI] 1.06-2.22).[28] Using BART-derived data, Raghunathan et al[29] compared TXA and EACA using a "clinical value" analysis to include clinical outcomes, costs, satisfaction with care, and functional status; there were no significant differences in overall safety and efficacy between the 2 drugs.[29]