Tranexamic acid: A proven antifibrinolytic agent (A review)

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ABSTRACT

According to the present statistics in an year around 5% of women aged 30-49 years visit their general practitioners with menorrhagia. Every year in the United Kingdom around 45,000 hysterectomies and a further 10,000 endometrial ablations are performed for menorrhagia. Of the many antifibrinolytic drugs tranexamic acid is majorly used to treat excessive bleeding. It is of proven value in clearing the field of surgery and reducing pre and postoperative blood loss. Unlike other antifibrinolytic drugs, the side effects of tranexamic acid are uncommon. Prolonged treatment may heighten the risk of an increased thrombotic tendency, such as deep vein thrombosis, yet it is used in obstetrics, dentistry, cardiac surgery, orthopedic surgery, hemophilia, angioedema. It is a structural analog of lysine. It is 6-10 times more effective than aminocaproic acid. Present article on tranexamic acid gives a review on the pharmacological and analytical profile, synthesis, development, and utility of this drug in wide variety of fields.

Key words: Antifibrinolytic agent, Tranexamic acid, bleeding.

INTRODUCTION

Tranexamic acid is used as firstline nonhormonal treatment of dysfunctional uterine bleeding, and heavy bleeding associated with uterine fibroids. It is used for bleeding, or risk of bleeding increased upon fibrinolysis, neoplasms, gastrointestinal bleeding, hematuria, postoperative bleeding. It has the advantage of causing lesser side effects when compared to other antifibrinolytic drugs.

Synthesis

Chemical Synthesis

Tranexamic acid (Trans-4-(aminomethyl)cyclohexane carboxylic acid) (3.1.5) is synthesized from 4-methylbenzonitrile (3.1.1). Oxidation of the methyl groups gives the mononitrile of terephthalic acid (3.1.2). The cyano group in this compound is reduced by hydrogen using raney nickel as a catalyst. The benzene ring of the resulting 4-aminomethylbenzoic acid (3.1.3) is reduced to a cyclohexane moiety by hydrogen and a platinum catalyst, which forms an isomeric mixture of 4-aminomethylcyclohexane carboxylic acids (3.1.4) and the desired trans isomer (3.1.5) is isolated by crystallization of the mixture of its sodium salts1.

Microbial Synthesis

Trans-4-Cyano-cyclobexane-1-carboxylic acid (MCC), an intermediate in the synthesis of tranexamic acid, was found to be accumulated in the culture broth of Acremonium sp. D9K, when grown on mms-l, 4-dicyanocyclohexane (t-DCC) as
a nitrogen source. The addition of an organic nitrogen source was effective for the growth of the strain, the accumulation of f-MCC and the activity of the conversion of the dinitrile by resting cells. Tranexamic acid (transmononitrile was -4-aminomethylcyclohexane-1-carboxylic acid) is synthesized via a sequence of chemical processes.

Synthesis of the derivatives of tranexamic acid

N-Phthaloyltranexamic Acid (3.3.1), N-Acetyltranexamic Acid (3.3.2), Di-Tranexamate Diaquo Copper (II) (3.3.4), Di-N-Phthaloyltranexamate Diaquo Copper (II) (3.3.5) and Di-N-Acetyltranexamate Diaquo Copper (II) (3.3.3) were synthesized, using novel and reproducible procedures. (3.3.5) showed unidentate bonding of carboxylic group to copper (II) while (3.3.3) and (3.3.4) indicated bidentate bonding of carboxylate group to copper (II)3.

Radio labeled compounds

Synthesis of 14 C labeled tranexamic acid [Trans-amino-(14C-methyl)-cyclohexane carboxylic acid] was done and the activity was found to be retained4.

Detailed report on Tranexamic acid

Tranexamic acid significantly reduces the amount of blood loss during and after the lower segment cesarean section (LSCS) and its use was not associated with any side effects5. Topical application of tranexamic acid in patients undergoing primary coronary artery bypass grafting led to a significant reduction in postoperative blood loss without adding extra risk to the patient6. Topical application of antifibrinolytics can reduce postoperative bleeding and transfusion requirements in patients undergoing on-pump cardiac surgery7. Anti-fibrinolytic drugs provide worthwhile reductions in blood loss and the need for allogeneic red cell transfusion8. Because oral drug administration is simple and does not require specific infusion equipment, the authors suggest that oral TA is a superior blood-sparing strategy compared with IV drug administration9. Ultra-early hemostatic therapy, given within 3 to 4 hours of onset, may potentially arrest ongoing bleeding and minimize hematoma growth after ICH. Given the current lack of effective therapy for ICH, clinical trials testing this treatment approach are justified10. A case of advanced breast cancer with cerebral metastasis and pleurisy is reported in which irradiation and cytosis had failed to retard progressive growth and spread of the tumour. Adjuvant therapy with heparin combined with the fibrinolytic inhibitor tranexamic acid was followed by regression of the cerebral metastasis as well as the pleurisy11, 12.

Comparision of tranexamic acid with other fibrinolytics

Tranexamic acid and aprotinin show similar clinical effects on bleeding and allogeneic transfusion in patients undergoing primary elective heart operations13. The risk of death tended to be consistently higher with use of aprotinin than with use of lysine analogues. Aprotinin had no clear advantages to offset these harms. Either tranexamic acid or α-aminoacaproic acid14 should be recommended to prevent bleeding after cardiac surgery15. Ethamsylate did not reduce mean menstrual blood loss whereas mefenamic acid reduced blood loss by 20% and tranexamic acid reduced blood loss by 54%16, 17.

Spectrophotometric analysis of Tranexamic acid

A simple and reliable high-performance liquid chromatographic method with UV detection at 245 nm has been developed and validated for determination of tranexamic acid in a dosage form and in human urine. Before injection samples were derivatized with phenyl isothiocyanate (PITC). The reaction temperature, reaction time, and concentration of PITC used for derivatization were optimized. Chromatographic separation was on a C18 column with a 65:35 (v/v) mixture of 10 mM phosphate buffer, pH 3.6, and acetonitrile as mobile phase18.

Drug Profile:

1. Chemical structure : Trans-4-(aminomethyl)cyclohexane carboxylic acid
2. Iupac name : Tranex
4. Emperical formula : C₈H₁₅NO₂
5. Molecular weight : 157.21
6. CAS number : 1197-18-8
7. Appearance : White crystalline powder
8. Solubility : 1g/6ml is soluble in water
9. Melting point : > 300°C
10. PH : 6.5-8.0 (5% aq. solution)
11. Category : Antifibrinolytic agent

Scheme 2.1: Chemical synthesis of Tranexamic acid
Synthesis of N-Phthaloyl tranexamic acid

\[
\text{Phthalic anhydride + Tranexamic acid} \rightarrow \text{N-phthaloyl tranexamic acid}
\]  
(3.3.1)

Synthesis of N-acetyl tranexamic acid

\[
\text{Acetic anhydride + Tranexamic acid} \rightarrow \text{N-acetyltranexamic acid}
\]  
(3.3.2)

Synthesis of Di-N-acetyl tranexamate Diaquo copper (II)

\[
\left[\text{Di-N-acetyl tranexamate Diaquo copper (II)}\right] + \text{CuSO}_4\cdot5\text{H}_2\text{O} \rightarrow \text{Sodium salt of tranexamic acid} + 2\text{Cu}^{2+} \cdot 2\text{H}_2\text{O} + 2\text{H}_2\text{O} + \text{Na}_2\text{SO}_4
\]  
(3.3.3)

2.3.4: Synthesis of Di-tranexamate Diaquo copper (II):
Mechanism of action
Tranexamic acid is a synthetic derivative of the amino acid lysine. It exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules. It inhibits endometrial plasminogen activator and thus prevents fibrinolysis and the breakdown of clot20.

Clinical Pharmacology
Tranexamic acid binds more strongly than aminocaproic acid to both the strong and weak receptor sites of the plasminogen molecule in a ratio corresponding to the difference in potency between the compounds21. Tranexamic acid passes through the placenta. The concentration in cord blood after an intravenous injection of 10 mg per kg to pregnant women is about 30 mg per L, as high as in the maternal blood. In breast milk the concentration is about one hundredth of the serum peak concentration. Tranexamic acid diffuses rapidly into joint fluid and the synovial membrane. In the joint fluid the same concentration is obtained as in the serum. The biological half-life of tranexamic acid is about three hours. The concentration of tranexamic acid remains in different tissues for about 17 hours and in serum, up to seven or eight hours. Biotransformation is limited to a small fraction of the drug i.e., less than 5%. The biological half life in the joint fluid is about 3 hours. This drug is known to be substantially excreted by the kidney. The main route of elimination is through urine. The overall renal clearance is equal to overall plasma clearance about 110 to 116 mL/min. 95% of the dose is excreted in urine as the unchanged drug.

Side effects, Drug interactions, Precautions and contraindications
Nausea, vomiting, diarrhea may occur but disappear when the dosage is reduced. Giddiness, hypotension, thromboembolic events have been reported occasionally23. Chlorpromazine may increase cerebral vasospasm and ischemia. Tranexamic acid should not be administered concomitantly with Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates, as the risk of thrombosis may be increased. Caution should be exercised when tranexamic acid is administered to lactating mother and patient with renal insufficiency. Tranexamic acid Injection is contraindicated in patients with acquired defective color vision, in patients with subarachnoid hemorrhage, in patients with active intravascular clotting.

CONCLUSION
Thus, unlike other antifibrilolytic agents, tranexamic acid proved to be the better drug under this class for various purposes, as well as proved to be the safest with minimum side effects.

REFERENCES
3. Muhammad Ashfag and Gul Majid Khan,


