

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-cyclohexane-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-I, 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 processes².

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 ¹⁴C 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 pleurisy^{11, 12}.


Comparison 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}.

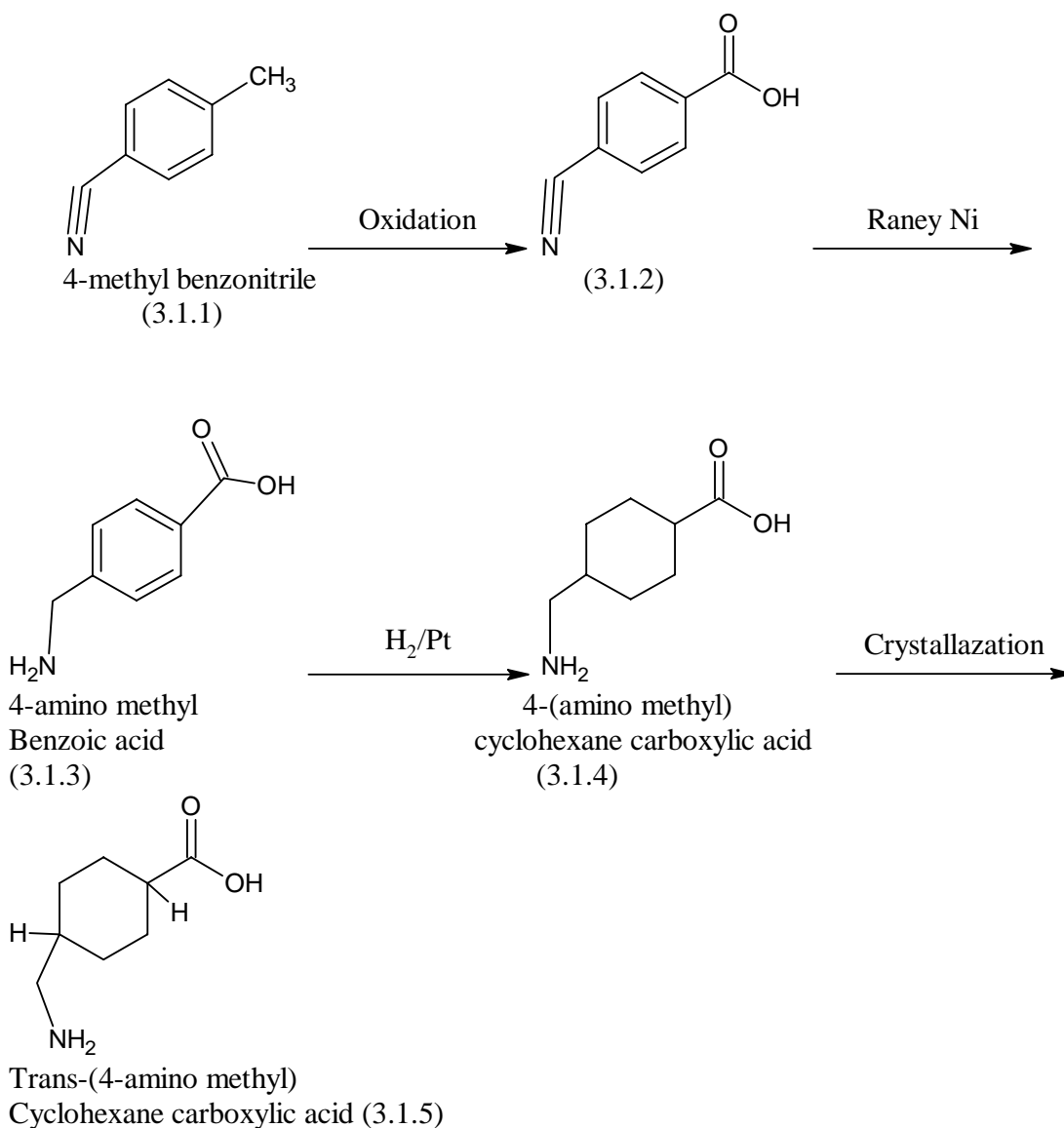
Spectrophotometric analysis of Tranexamic acid

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.

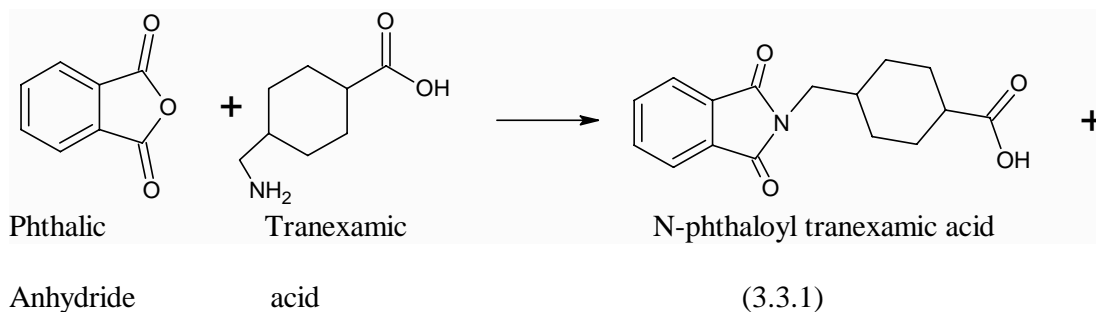
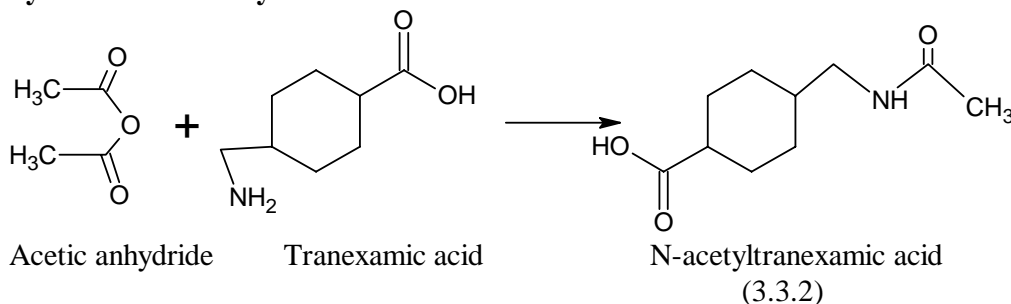
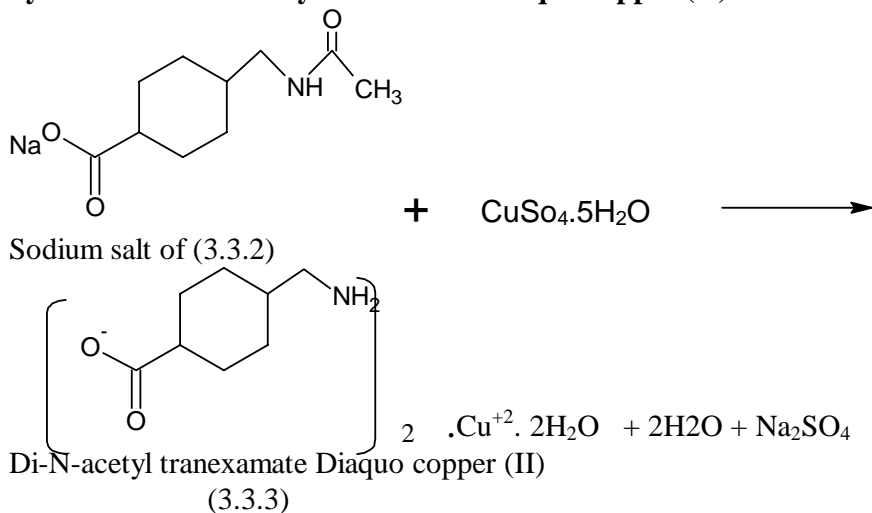
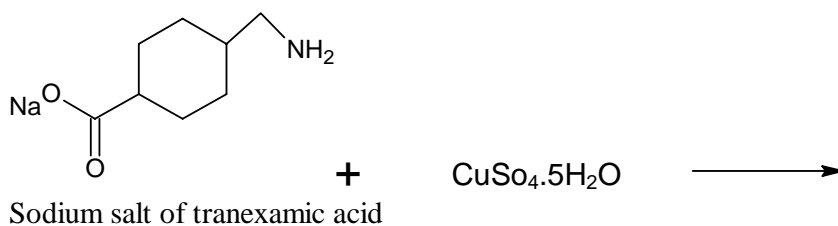
Drug Profile¹⁹:

- | | | |
|-----------------------|---|---|
| 1. Chemical structure | : |  |
| 2. Iupac name | : | Trans-4-(aminomethyl)cyclohexane carboxylic acid |
| 3. Synonyms | : | Ugurol, Cyclocapron, Amacacid, Tranex. |

4. Empirical formula	: $C_8H_{15}NO_2$	11. Category	: aq.solution)
5. Molecular weight	: 157.21	12. Storage	: Antifibrinolytic agent
6. CAS number	: 1197-18-8		: Store in a cool place. Keep container closed when not in use.
7. Appearance	: White crystalline powder	13. Incompatibility	: With strong oxidizing agents.
8. Solubility	: 1g/6ml is soluble in water		
9. Melting point	: > 300°C		
10. PH	: 6.5-8.0(5%)		



Scheme 2.1: Chemical synthesis of Tranexamic acid

Synthesis of N-Phthaloyl tranexamic acid**Synthesis of N-acetyl tranexamic acid****Synthesis of Di-N-acetyl tranexamate Diaquo copper (II)****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 in the joint fluid is about three hours. The concentration of tranexamic acid in a number of other tissues is lower than in blood. Tranexamic acid concentration in cerebrospinal fluid is about one tenth of that of the plasma. The drug passes into the aqueous humor, the concentration being about one tenth of the plasma concentration. Tranexamic acid has been detected in semen where it inhibits fibrinolytic activity but does not influence sperm migration.

7. Pharmacokinetic profile of tranexamic acid²²:

The absorption of tranexamic acid after oral administration in humans is approximately 30% to 50% of the ingested dose and bioavailability is not at all affected by food intake. The plasma protein binding of tranexamic acid is about 3% at therapeutic plasma levels and seems to be fully accounted for

by its binding to plasminogen. It does not bind serum albumin. The initial volume of distribution is 9 to 12 litres. 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 antifibrinolytic 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

1. Text book on Synthesis of essential drugs by Ruben Vardanyan, Victor J. Hruby 332-333.
2. Hiroshi Nishise, Makoto Kurihara and Yoshiki Tani, "Microbial synthesis of Tranexamic acid intermTrans-1,4- dicyano-cyclohexane (t-DCC) through trans-4-cyano-cyclohexane-1-Carboxylic acid (t-MCC)." *Agric. Biol. Chem.*, **51**(9): 2613-2616 (1987).
3. Muhammad Ashfaq and Gul Majid Khan,

- "Synthesis and characterization of some novel tranexamic acid derivatives and their copper(II) Complexes." *J. Medical Sciences*. **5**(1): 327-333 (2001).
4. Jan Loundstrom, Gertrud Westin Sjudahi, N.Ake Jonsson, "synthesis of ¹⁴C labeled tranexamic acid [trans-(¹⁴Cmethyl)-cyclohexane carboxylic acid]" *J. Labelled compounds and Radiopharmaceuticals* **12**(2): 307-310 (2006).
 5. Gohel Mayur, Patel Purvi, Gupta Ashoo, Desai Pankaj "Efficacy of tranexamic acid in decreasing blood loss during and after cesarean section: A randomized case controlled prospective study" *J Obstet Gynecol India* **57**(3): 227-230 (2007).
 6. Fawzy H, Elmistekawy E, Bonneau D, Latter D, Errett L "Can local application of tranexamic acid reduce post coronary bypass surgery blood loss? A randomized controlled trial" *J. Cardiothorac Surg.* **18**(4): 25 (2009).
 7. Abrishami A, Chung F, Wong J."Topical application of antifibrinolytic drugs for on pump cardiac Surgery: a systematic review and meta analysis", *Can J Anaesth.* **56**(3): 202-212 (2009).
 8. Henry DA, Carless PA, Moxey AJ, O. Connell D, Stokes BJ, McClelland B, Laupacis A, Fergusson D, " Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion." *Cochrane Database Syst Rev.* **17** (2007).
 9. Zohar, E., Ellis, M., Ifrach, N., Stern, A., Sapir, O., Fredman, B. "The Postoperative Blood-Sparing Efficacy of Oral versus Intravenous Tranexamic Acid After Total Knee Replacement." *Anesth. Analg.* **99**: 1679-1683 (2004).
 10. Mayer, S. A. "Ultra-Early Hemostatic Therapy for Intracerebral Hemorrhage." *Stroke* **34**: 224-229 (2003).
 11. Astedt B, Mattsson W, Trope C, "Treatment of advanced breast cancer with chemotherapeutics and inhibition of coagulation and fibrinolysis", *Acta Med Scand.* **207**(5): 491-493 (1997).
 12. Seto AH and Dunlap DS, "Tranexamic Acid in Oncology," *Ann Pharmacother.* **30**(7-8): 868-70 (1996).
 13. Casati V, Guzzon D, Oppizzi M, Bellotti F, Franco A, Gerli C, Cossolini M, Torri G, Calori G, Benussi S, Alfieri O "Tranexamic acid compared with high dose aprotinin in Primary elective heart operations: effects on perioperative bleeding and allogenic transfusions." *J. Thorac. Cardiovasc. Surg. Sep.*, **120**(3): 520-527 (2000).
 14. Henry D, Carless P, Fergusson D, Laupacis A. "The safety of aprotinin and lysine derived antifibrinolytic drugs in cardiac surgery: a meta analysis." *CMAJ.* **180**(2): 183-193 (2009).
 15. Nilsson IM, "Clinical Pharmacology of Aminocaproic and Tranexamic Acids," *J Clin Pathol Suppl* **14**: 41-7 (1980).
 16. John Bonnar, Brian L Sheppard, "Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid"
 17. Royston D, "Blood-Sparing Drugs: Aprotinin, Tranexamic Acid, and Epsilon-Aminocaproic Acid," *Int Anesthesiol Clin.* **33**(1): 155-79 (1995).
 18. Hadad Ghada M, El-Gindy Alaa, Mahmoud Waleed M. M, "Optimization and validation of an HPLC-UV method for determination of tranexamic acid in a dosage form and in human urine." *Science lab.com* (2008).
 19. Astedt B, "Clinical Pharmacology of Tranexamic Acid," *Scand J Gastroenterol Suppl.* **137**: 22-5 (1987).
 20. A. Pilbrant, M. Schannong and J. Vessman, "Pharmacokinetics and bioavailability of Tranexamic acid." *European J. Clinical Pharmacology* **20**(1): 323-352 (1981)
 21. www.Rxlist.com
 22. Wright IS "The nomenclature of blood clotting factors." *Can. Med. Assoc. J.*, **86**: 373-374 (1962).
 23. Shapiro SS "Treating thrombosis in the 21st century", *N. Engl. J. Med.* **349**(18): 1762-1764 (2003).