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TRANEXAMIC ACID (TXA)- AND MEFENAMIC ACID: An Overview

D.Nagavalli*[1], P.Nanthagopal[2]

[1*]M.Pharm, Ph.D., Professor & H.O.D,Department of Pharmaceutical Chemistry,

Adhiparasakthi College of Pharmacy,Melmaruvathur,Tamil Nadu,India.

[2,]Department of Pharmaceutical Chemistry, Adhiparasakthi College of Pharmacy,Melmaruvathur, Kancheepuram Distric, The Tamilnadu Dr.M.G.R Medical university Chennai-28,Melmaruvathur-603319,Tamil Nadu,India.

Abstract:

The entire world has come major problem is facing on puberty womens for entier life cycle,involved in Common causes for Heay bleeding (periods) is termed is called-**Menorrhagia** , grappling with a common enemy in womens Menstrual cycles. The Heavy or prolonged vaginal bleeding.(HMB-Heavy Menstrual Bleeding) has menstrual period with excessively heavy blood flow.Abnormal utrine bleeding can be caused by strctural abnormalities in reproductive tract, anovulation, bleeding disorders, hormonal issues (hypothyroidism) or cancer of the reproductive tract.Tougher challenge leading to millions of cases and a staggering number of patients is affected in Anemic condition. Tranexamic Acid and Mefenamic Acid is an FDA-approved and sold under the oral administration for (NSAIDS and Antifibrinolytics) drug for use in Puberty womens for during heavy bleeding in menstrual cycle. Tranexamic Acid is a prevents the breakdown of blood clots to control excessive bleeding during periods. Mefenamic acid is also blocks the production of certain chemical messengers that cause pain and inflammation, Tranexamic acid blocks the activity one of the specific for preventing fibrin degradation , Tranexamic acid has a eight times the antifibrinolytic activity of an older analogue, aminocarproic acid. It is together Tranexamic Acid and Mefenamic acid is used for treatement of heavy menstrual bleeding and acute pain that occurs with menstrual disorders. According to the study conducted, it was found that when was given alone in the patient suffering from HMB with acute pain symptoms, the mean recovery was 87.3% and mortality rate was 69.34% Trapic-MF significantly reduces the heay and mortality and shows more safety,efficacy and reduced serious adverse effects by absolute 8% and no significant Grade 3 or 4 adverse effects were reported. When Tranexamic Acid was given in combination with Mefenamic acid was superior to Tranexamic acid alone in reducing recovery (65.5%) and accelerating improvement in clinical status among patients with heavy bleeding and pain, notably among those receiving problems. The mortality rate for Mefenamic acid in combination with Tranexamic acid , a relative reduction of 35%. Adverse events and serious adverse events were reported in 41% and 15% of patients treated with Mefenamic acid in combination with Tranexamic acid, respectively, vs. 48% and 20% in patients treated with Tranexamic acid.

Keywords: HMB, Tranexamic Acid, Mefenamic Acid,Antifibrolytic agent.

Introduction:

Tranexamic acid was first made in 1962 by Japanese researchers Shosuke and Utako Okamoto. It is on the World Health Organization's List of Essential Medicines.Tranexamic acid is available as a generic drug. Tranexamic acid is frequently used following major trauma.Tranexamic acid is used to prevent and treat blood loss in a variety of situations, such as dental procedures, heavy menstrual bleeding, and surgeries with high risk of blood loss.The U.S. Food and Drug Administration (FDA) approved tranexamic acid oral tablets for treatment of heavy menstrual bleeding on 13 November 2009. Mefenamic acid is an analgesic that is U.S FDA approved of the treatment of dysmenorrhea, low back pain,pain.Mefenamic acid is a member of the anthranilic acid derivatives (or fenamate) class of nonsteroidal anti-inflammatory drugs (NSAIDs), and is used to treat mild to moderate pain. Today, the entire world major problem younger to adult womens facing has come to a standstill, grappling with a common enemy,for heay bleeding menstrual cycle. It is main reason for Hermonal imbalance and cancer for uterus or cervix, Certain type of birth control (IUD) and some life style modifications.Heavy bleeding time undoubtedly proven to be a tougher challenge leading to millions of cases a staggering number of Anemic patients. An outbrs through various studies will give us an opportunity to hopefully mitigate the severity of this crisis.HMB is a mainly for leads to result on many other reproductive system problems such as PCOS,Uterus bulkiness, irrugular periods, cervix infection. Clinically significant bleeding can occurs as a consequence of surgery,trauma, obstetric complications.Anticogulation, using for various disorders of hemostasis. Tranexamic acid(TXA) most commonly used for antifibrinolytic agents: it is a role in postpartum hemorrhage, menorrhagia,trauma-hemorrhage.Mefenamic acid is used for the short-term relif of mild to moderate pain from various condition such as headache,**Menstrual cramps**, muscle aches. This also effective for decrease swelling,pain,fever. Association with Tranexamic acid-Mefenamic acid-treatement of Heavy menstrual bleeding,arthritis,hemorrhagic complicatios.Clinical use of TXA-across a broad spectrum of bleeding disorders. Hemoptysis is a common complication of cystic fibrosis (CF),malignancies.Tranexaic acid may act as a competitive inhibitor of the CNS neurotransmitter GABA cause Cerebral vasoconstriction and ischaemia.

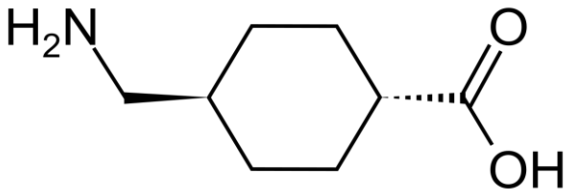


Fig.No:1 Tranexamic acid

Tranexamic acid - Physico-chemical Properties:

Chemical Name:	**4-aminomethyl cyclohexanicarboxylic acid**
Molecular Formula	C8H15NO2
Molar Mass	157.21g/mol
Density	1.0806 (rough estimate)
Melting Point	>300 °C (lit.)

Boling Point	281.88°C (rough estimate
Flash Point	135- 357°C
Water Solubility	1g/6ml
Solubility	Freely soluble in water and in glacial acetic acid, practically insoluble in acetone and in ethanol (96 %).
Appearance	Yellow-like crystals Color White.
pKa	pKa 4.3 (Uncertain);10.6 (Uncertain)
Storage Condition	2-8°C
Stability	Hygroscopic
Refractive Index	1.4186 (estimate)

Use: Hemostatic drugs, traumatic bleeding effect is remarkable, preoperative preventive medication can reduce surgical bleeding

Action: Antifibrinolytic agent.

Receptor: Competitive inhibitor of plasminogen activation to plasmin

Dosing Availabilit: Ampule of 1 gm in 10 mL.

Formulations: IV and PO; can use IV as topical

Indication: **1)** Postpartum bleeding

2) Periprocedural hemorrhage in hemophiliacs.

Storage:

Tablet dosage form Store at room temperature away from light and moisture. Keep all medications away from children and pets. Store at 25°C.

Pharmacodynamics:

Tranexamic acid is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin. At much higher concentrations it behaves as a noncompetitive inhibitor of plasmin similar to aminocaproic acid, a similar antifibrinolytic which is 10-fold less potent. 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 compounds. In patients with hereditary angioedema, inhibition of the formation and activity of plasmin by tranexamic acid may prevent attacks of angioedema by decreasing plasmin-induced activation of the first complement protein (C1).Thereby inhibiting the dissolution of fibirin clots. Plasmin then digests fibrin.Tranexamic acid bind reversibly in plasminogen at the lysine binding site. Binding potency of the plasminogen is 6 to 10 fold higher as compared to other antifibrinolytic drugs.

Off-target antagonism of GABA(A) receptors may be associated with the development of convulsions and hyperexcitability following tranexamic acid administration1 - the risk appears higher with improper administration or administration during cardiovascular surgery.6 Consider EEG monitoring of patients with a history of seizure.

Mechanism of action:

Tranexamic acid competitively and reversibly inhibits the activation of plasminogen via binding at several distinct sites, including four or five low-affinity sites and one high-affinity site, the latter of which is involved in its binding to fibrin. The binding of plasminogen to fibrin induces fibrinolysis - by occupying the necessary binding sites tranexamic acid prevents this dissolution of fibrin, thereby stabilizing the clot and preventing hemorrhage.

Pharmacological Action:

Tranexamic acid (tranexamic acid) is a synthetic amino acid antifibrinolytic drug, which can competitively inhibit the binding of fibrin lysine and fibrinolytic enzyme, thereby inhibiting the cleavage of fibrin clots and producing hemostasis. It is mainly used clinically for various bleeding caused by hyperfibrinolysis. Tranexamic acid is a synthetic lysine analog, which can competitively bind plasminogen to lysine binding site on plasminogen and plasmin, thus competitively inhibit the degradation of fibrin, reduce fibrinolytic activity and play a role in promoting coagulation. Theoretically, the use of tranexamic acid can lead to insufficient fibrinolytic activity, which may increase the risk of postoperative thrombotic events.

Mode of Action: Tranexamic acid is a synthetic analog of the amino acid lysine. It serves as an antifibrinolytic by reversibly binding four to five lysine receptor sites on plasminogen. This decreases the conversion of plasminogen to plasmin, preventing fibrin degradation and preserving the framework of fibrin's matrix structure.[5] Tranexamic acid has roughly eight times the antifibrinolytic activity of an older analogue, ε-aminocaproic acid.[citation needed] Tranexamic acid also directly inhibits the activity of plasmin with weak potency (IC50 = 87 mM),[6] and it can block the active-site of urokinase plasminogen activator (uPA) with high specificity (Ki = 2 mM), one of the highest among all the serine proteases.

Side effects are rare.Some include changes in color vision, blood clots, and allergic reactions. Greater caution is recommended in people with kidney disease. Tranexamic acid appears to be safe for use during pregnancy and breastfeeding.Tranexamic acid is an antifibrinolytic medication

Pharmacokinetic: It is given parenterally (iv mostly),orally and topically.Effect on therapeutic plasma concentration is 5 to 10mg/mL for inhibiting fibrinolysis.**After i**.m & oral rote max.plasma concentration is obtained after 0.5 & 2-3 hrs respectively.Bioavailability is 33% of oral drug.Not related with meals.3% of the drug bound to plasma proteins. It cross placenta, B-B barrier & eyes.

Absorption:

The bioavailability of tranexamic acid after oral administration in humans is approximately 30 to 50% of the ingested dose and is not affected by food intake.5 The Cmax and Tmax following multiple oral doses (1300 mg three times daily x 5 days) were 16.41 mcg/mL and 2.5 h, respectively.

Volume of distribution:

The initial volume of distribution of tranexamic acid is 0.18 L/kg and its steady-state volume of distribution is 0.39 L/kg.5 Tranexamic acid distributes into cerebrospinal fluid and the aqueous humor of the eye at concentrations approximately 1/10th of typical plasma concentrations. Tranexamic acid is also able to cross the placenta, found in cord blood at concentrations equivalent to maternal plasma concentrations.

Protein binding:

Tranexamic acid is approximately 3% protein-bound in plasma at therapeutic concentrations. As it does not bind to serum albumin, it is likely that this protein binding is accounted for by tranexamic acid's binding to serum plasminogen.

Metabolism:

Tranexamic acid metabolism is poorly characterized but does not appear to be a significant means of drug elimination. According to prescribing information, approximately 1% and 0.5% of an orally administered dose are excreted as a dicarboxylic acid and acetylated metabolite, respectively.

Route of elimination : Urinary excretion is the primary means of tranexamic acid elimination, with >95% of an administered dose excreted in the urine as unchanged parent drug.5 The rate of excretion is dependent on the route of administration - approximately 90% of an intravenously administered dose is excreted within 24 hours whereas only 39% of an orally administered dose is excreted within the same time frame.

Half-life: Following intravenous administration, the apparent elimination half-life is approximately 2 hours and the mean terminal half-life is approximately 11 hours.

Clearance:

The plasma clearance of tranexamic acid is 110-116 mL/min.

Toxicity:

Reported symptoms of tranexamic acid overdose include severe gastrointestinal symptoms, hypotension, thromboembolism, visual impairment, convulsions, mental status changes, and rash.

Tranexamic acid (TXA) is a medication used to treat or prevent excessive blood loss from major trauma, postpartum bleeding, surgery, tooth removal, nosebleeds, and heavy menstruation. It is also used for hereditary angioedema.It is taken either orally or by injection into a vein.

CLINICAL APPLICATION:

Tranexamic acid has been found to decrease the risk of death due to any cause in people who have significant bleeding due to trauma.It is most effective if taken within the first three hours following major trauma.It also decreases the risk of death if given within the first three hours of brain injury. Tranexamic acid is used in dentistry in the form of a 5% mouth rinse after extractions or surgery in patients with prolonged bleeding time; e.g., from acquired or inherited disorders.

Menstrual bleeding:

Tranexamic acid is sometimes used to treat heavy menstrual bleeding. When taken by mouth it both safely and effectively treats regularly occurring heavy menstrual bleeding and improves quality of life. Another study demonstrated that the dose does not need to be adjusted in females who are between ages 12 and 16.

Childbirth:

Tranexamic acid is sometimes used (often in conjunction with oxytocin) to reduce bleeding after childbirth.Death due to postpartum bleeding is reduced in women receiving tranexamic acid.

Surgery: Tranexamic acid is sometimes used in orthopedic surgery to reduce blood loss, to the extent of reducing or altogether abolishing the need for perioperative blood transfusion. It is of proven value in clearing the field of surgery and reducing blood loss when given before or after surgery. Drain and number of transfusions are reduced.

In surgical corrections of craniosynostosis in children it reduces the need for blood transfusions.

In spinal surgery (e.g., scoliosis), correction with posterior spinal fusion using instrumentation, to prevent excessive blood loss. In cardiac surgery, both with and without cardiopulmonary bypass (e.g., coronary artery bypass surgery), it is used to prevent excessive blood loss. Tranexamic acid is used for a short period of time before and after the surgery to prevent major blood loss and decrease the need for blood transfusions.

Dentistry:

In the United States, tranexamic acid is FDA approved for short-term use in people with severe bleeding disorders who are about to have dental surgery.

UNSAFE:

Avoid consumption of alcohol while taking Tranexamic acid and Mefenamic acid Tablet's as it may cause increased drowsiness. It can also increase the risk of stomach bleeding.

Hematology:

There is not enough evidence to support the routine use of tranexamic acid to prevent bleeding in people with blood cancers. However, there are several trials that are currently assessing this use of tranexamic acid.For people with inherited bleeding disorders (e.g. von Willebrand's disease), tranexamic acid is often given.It has also been recommended for people with acquired bleeding disorders (e.g., directly acting oral anticoagulants (DOACs)) to treat serious bleeding.

Nose bleeds:

The use of tranexamic acid, applied directly to the area that is bleeding or taken by mouth, appears useful to treat nose bleeding compared to packing the nose with cotton pledgets alone.It decreases the risk of rebleeding within 10 days.

Other uses:

Tentative evidence supports the use of tranexamic acid in hemoptysis. In hereditary angioedema

In hereditary hemorrhagic telangiectasia - Tranexamic acid has been shown to reduce frequency of epistaxis in patients with severe and frequent nosebleed episodes from hereditary hemorrhagic telangiectasia.

In melasma - tranexamic acid is sometimes used in skin whitening as a topical agent, injected into a lesion, or taken by mouth, both alone and as an adjunct to laser therapy; as of 2017 its safety seemed reasonable but its efficacy for this purpose was uncertain because there had been no large scale randomized controlled studies nor long term follow-up studies.It is allowed as a quasi-drug for skin whitening in Japan. In hyphema - Tranexamic acid has been shown to be effective in reducing risk of secondary hemorrhage outcomes in people with traumatic hyphema

Clinical Use:

clinically, tranexamic acid has significant effects on insect bite, eczema dermatitis, simple purpura, chronic urticaria, artificial urticaria, toxic eruption and drug eruption, and has certain effects on erythroderma, scleroderma, SLE, erythema multiforme, herpes zoster and alopecia areata, as well as hereditary angioedema. The treatment of chloasma is generally effective for about 3 weeks, markedly effective for 5 weeks, and a course of treatment for 60 days. Oral administration of 0.25~0.5g each time, 3~4 times a day. A few patients may have side effects such as nausea, fatigue, itching, abdominal discomfort and diarrhea, and the symptoms disappear after drug withdrawal.

Experimental use:

Tranexamic acid might alleviate neuroinflammation in some experimental settings.Tranexamic acid can be used in case of postpartum hemorrhage; it can decrease the risk of death due to bleeding by one third according to the WHO.

Contraindications:

Allergic to tranexamic acid

History of seizures

History of venous or arterial thromboembolism or active thromboembolic disease

Severe kidney impairment due to accumulation of the medication, dose adjustment is required in mild or moderate kidney impairment.

Adverse effects:

Side effects are rare. Some reported adverse events include changes in color vision, blood clots, and allergic reactions such as anaphylaxis.[Whether the risk of venous thromboembolism (blood clots) is actually increased is a matter of debate. The risk is mentioned in the product literature, and they were reported in post marketing experience. Despite this, and the inhibitory effect of tranexamic acid on blood clot breakdown, large studies of the use of tranexamic acid have not shown an increase in the risk of venous or arterial thrombosis, even in people who had previously experienced thrombosis under other circumstances. The adverse reactions of taking tranexamic acid are less than those of aminocaproic acid. **Headache, dizziness, nausea, diarrhea, vomiting, chest tightness, drowsiness and other symptoms may occur, which can gradually disappear after stopping the drug**. Occasionally, intracranial thrombosis and bleeding caused by drug overdose, and less commonly**, menstrual discomfort (caused by blood coagulation during menstruation).** Since this product can enter the cerebrospinal fluid, it may have central nervous system symptoms such as blurred vision, headache, dizziness, fatigue, etc. after injection, especially related to the injection speed, but it is rare. If this product must be used continuously for a long time, it should be monitored for ophthalmic examination (such as vision test, vision, visual field and fundus). For thrombogenic tendencies (such as acute myocardial infarction), it should be used with caution; renal insufficiency, postoperative hematuria should be used with caution; secondary hyperfibrinolytic state caused by disseminated intravascular coagulation, before heparinization, Use this product with caution; if it is combined with other coagulation factors (such as factor IX), you should be alert to thrombosis. Tranexamic acid is contraindicated with thrombolytic agents such as penicillin or urokinase; oral contraceptives, estrogen or prothrombin complex concentrates are combined with this product to increase the risk of thrombosis

Special populations:

Tranexamic acid is categorized as pregnancy category -B.

Small amounts appear in breast milk if taken during lactation. If it is required for other reasons, breastfeeding may be continued.

In kidney impairment, tranexamic acid is not well studied. However, due to the fact that it is 95% excreted unchanged in the urine, it should be dose adjusted in patients with renal impairment. In liver impairment, dose change is not needed as only a small amount of the drug is metabolized through the liver.

RECENT ADVANCE:

Tranexamic acid has recently received widespread attention due to its addition in **Yunnan Baiyao toothpaste**. this medicine is a good medicine widely used in clinic, and its important role is to stop bleeding. it is even considered as a hemostatic medicine, which is mainly used for hemostasis after major surgery and postpartum. Of course, hemostasis is probably the minimum reason why many toothpastes are added to hope to have an effect.

Topical Tranexamic acid allows for a direct delivery of Tranexamic acid to the skin and is a good alternative option for people who cannot tolerate oral Tranexamic acid or those who do not wish to take oral medication for melasma. Tranexamic acid 5% and 2% are most commonly prescribed. Several studies have been done comparing topical Tranexamic acid to traditional topical treatment.

Microneedling with Tranexamic acid

TXA- Tranexamic acid.

Technique:

Microneedling creates micro-wounds in the skin at a typical depth of 1.5 mm that allows topical formulations to penetrate deeper into the skin while also stimulating collagen production and the release of growth factors. Microneedling can be done with several different devices. Dermapens allow needles to puncture the epidermis just at the location of the device, whereas dermarollers allow for the device to roll across the skin without removing the device. Clinicians generally roll over the entire face several times in different directions. Microneedling with TXA often is done with 4 mg/ml TXA. Microneedling allows for deeper penetration of topical TXA into the dermis in an even manner. Benefits to this method include a relatively quick and noninvasive method for introducing TXA into the skin.

Safety and side effects(Microneedling)

Microneedling with TXA can cause pain, itching, and erythema, which lasts about 1–2 days for most patients.

Tranexamic acid Treatement of (Melasma)-

Hyperpigmentation of womens (brown patchesappear on the face)- Hormonal changes (Sun-exposure/pregnancy)

Melasma is a common, difficult-to-treat skin condition with high recurrence rates. TXA is a drug used off-label to combat refractory melasma and comes in topical, intralesional, and oral formulations. Oral therapy is an effective and safe treatment for melasma with proper screening. While patients may be hesitant to start an oral therapy, intralesional injections and microneedling with topical TXA both have similar efficacy to oral therapy while minimizing systemic side effects. Both methods are effective at reducing the appearance of melasma with similar efficacies and limited adverse reactions. Microneedling is minimally invasive and relatively painless but may be associated with more itching and irritation and requires purchase of a specific tool. On the contrary, intralesional injections use more universal equipment but require skilled injectors and may be associated with more pain than microneedling and possible hypopigmentation. Topical TXA therapy was the least effective treatment of TXA. However, this treatment method has minimal side effects and can be combined with other cosmeceuticals for the treatment of melasma. Clinicians should consider prescribing topical TXA in patients who may not tolerate HQ. Intralesional TXA injections or oral TXA can be utilized as a second-line treatment for refractory or severe melasma or as an alternative to laser/light therapy.

Clinical studies:

TXA- Tranexamic acid.

Evidence : In a nonrandomized split-face control trial, 60 patients with moderate to severe melasma were injected on one side of their face with 4 mg/ml TXA and the other side with normal saline every 2 weeks for 12 weeks (insulin syringe). At the 12-week follow-up, the Hemi-mMASI score was significantly lower for the TXA side of the face compared with the normal saline side, and this result continued at 24-week follow-up. Ninety percent of patients showed good to excellent response on the TXA side.

One study investigated the recurrence of melasma after intralesional injections. Researchers performed 4 mg/ml TXA injections on five participants every 2 weeks for seven sessions and with follow-up for 48 weeks (30-gauge (G) needle). A significant decrease in mMASI score was seen in week 16. However, there was no statistically significant improvement in mMASI score at week 48 with a 60% recurrence rate. Patient satisfaction scores also decreased from week 16 to week 48. While this is a small study, melasma has a high recurrence rate and this study highlights the short-term efficacy of TXA injections.

DOSE ADMINISTRATION:

3-4gm/day in three divided doses for upto 4 or 5 days per cycle in mennorrhagia.

0.5-1gm i.v, during surgery or 0.5 -2.5 gm by i.v. infusion each time as required.

Missed Dose

If you miss a dose, take it as soon as you remember. If it is near the time of the next dose, skip the missed dose. Take your next dose at the regular time. Do not double the dose to catch up.

Drug-Food Interactions: No interactions found/established.

Drug-Disease Interactions: Inform your doctor if you have deep vein thrombosis, pulmonary embolism (blockage of blood vessels in the lungs), coagulopathy (formation of blood clots), epilepsy, peptic ulcers, asthma, glaucoma, gastrointestinal toxicity, high blood pressure, or heart problems.

DRUG-DRUG INTERACTION:

Blood-thinners: Anticoagulants – Warfarin, heparin.
Estrogens,Tretinoin,Tibolone,IBUPROFEN, CELECOXIB, DULOXETINE, FLUOXETINE ,SERTRALINE.

UNSAFE: Avoid consumption of alcohol while taking Tranexamic acid it may cause increased drowsiness. It can also increase the risk of stomach bleeding.

OTHER COMBINATIONS:(Oral –Route)-Tablet.

Tranexamic acid + Mefenamic acid
Etamsylate + Tranexamic acid
Tranexamic acid + Dicolfenac

MEFENAMIC ACID:

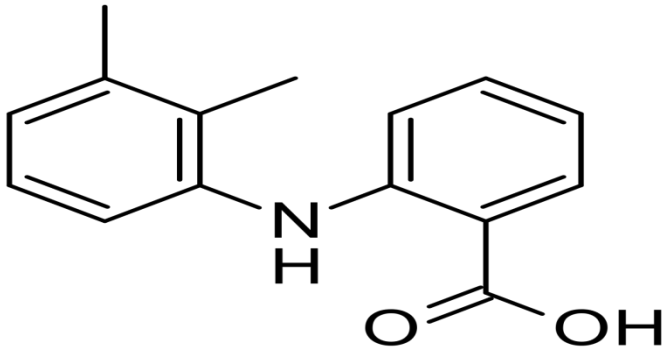


Fig.No:2 Mefenamic acid

Chemical Name:	N-2,3-xylylanthranilic acid
Molecular Formula	$C_{15}H15NO2$
Molar Mass	241.28g/mol
Density	1.0324 (rough estimate)
Melting Point	230-232°C
Boling Point	384.38°C (rough estimate)
Flash Point	140- 293°C
Water Solubility	20mg/L (at 30°C)
Solubility	Practically insoluble in water and dissolve in dilute solution of alkali hydroxide, slightly soluble in acetone and in ethanol (96 %).
Appearance	White to pale Yellow - crystals Color White.
pKa	4.2(at 25°C)
Storage Condition	2-8°C
Stability	Hygroscopic
Refractive Index	1.5200 (estimate)

Use: NSAIDS, Migraines, Dental pain, Rheumatoid Arthritis.

Action : Inhibition of Prostaglandin synthesis.

Receptor : COX-I and COX-II- inhibitors

Dosing Availabilit: Oral- route:500mg/day;

Formulations: IV and PO; can use IV as topical.

Storage:

Tablet dosage form Store at room temperature away from light and moisture. Keep all medications away from children and pets. Store at 25°C.

Pharmacodynamics:

Mefenamic acid, an anthranilic acid derivative, is a member of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs). It exhibits anti-inflammatory, analgesic, and antipyretic activities. Similar to other NSAIDs, mefenamic acid inhibits prostaglandin synthetase.

Mechanism of action:

Mefenamic acid binds the prostaglandin synthetase receptors COX-1 and COX-2, inhibiting the action of prostaglandin synthetase. As these receptors have a role as a major mediator of inflammation and/or a role for prostanoid signaling in activity-dependent plasticity, the symptoms of pain are temporarily reduced.

Nonsteroidal anti-inflammatory drug Mechanism of action .Like other members of the anthranilic acid derivatives (or fenamate) class of NSAIDs, it inhibits both isoforms of the enzyme cyclooxygenase (COX-1 and COX-2). This prevents formation of prostaglandins,[10][14] which play a role in pain sensitivity, inflammation and fever, but also in hemostasis, kidney function, sustaining of pregnancy, and protection of the gastric mucosa.

Pharmacokinetic : It is given Orally and topically.Effect on therapeutic plasma concentration is 10 to 25 mg/mL for inhibiting COX-1 and COX-2 .After oral rote max.plasma concentration is obtained after 0.5 & 1-3 hrs respectively.Bioavailability is 29% of oral drug.Not related with meals.3% of the drug bound to plasma proteins. It cross placenta, skin & eyes.

Absorption:

Mefenamic acid is rapidly absorbed from the gut and reaches highest concentrations in the blood plasma after one to four hours. When in the bloodstream, over 90% of the substance are bound to plasma proteins. It probably crosses the placenta, and is found in the breast milk in small amounts.

Volume of distribution- 1.06 L/kg [Normal Healthy Adults (18-45 yr)]

Protein binding- 90%

Metabolism:

It is metabolized by the liver enzyme CYP2C9 to the only weakly active 3'-hydroxymethylmefenamic acid. 3'-carboxymefenamic acid has also been identified as a metabolite, as well as carboxy glucuronides of all three substances. Mefenamic acid and its metabolites are excreted via the urine (52–67%) and the faeces (20–25%, or less than 20% following another source). The parent substance has a biological half-life of two hours; the half-life of its metabolites may be longer.

Half-life-2 hours.

Route of elimination: The fecal route of elimination accounts for up to 20% of the dose, mainly in the form of unconjugated 3-carboxymefenamic acid.3 The elimination half-life of mefenamic acid is approximately two hours. Mefenamic acid, its metabolites and conjugates are primarily excreted by the kidneys. Both renal and hepatic excretion are significant pathways of elimination.

Clearance

Oral cl=21.23 L/hr [Healthy adults (18-45 yrs)]

RECENT ADVANCE:

While studies have been conducted to see if mefenamic acid can improve behavior in transgenic mouse models of Alzheimer's disease there is little evidence that mefenamic acid or other NSAIDs can treat or prevent Alzheimer's in humans; clinical trials of NSAIDs other than mefenamic acid for treatment of Alzheimer's have found more harm than benefit.[24][25][26]A small controlled study of 28 human subjects showed improved cognitive impairment using mefenamic acid non-steroidal anti-inflammatory therapy

Clinical Studies:(MEFENAMIC ACID)

In controlled, double-blind,clinical trails, Mefenamic acid was evaluated for the treatement of primary spasmodic dysmenorrhea,. The parameters used in determine efficacy included pain assessment by both patient and investigator; the need for concurrent analgesic medication ; and evaluation of change in frequency and severity of symptoms characteristic of spasmodic dysmenorrhea. Patients received either Mefenamic acid , 500mg (2 capsules) as an intial dose of 250mg every 6 hours, or placebo at onset of bleeding or of pain , whichever began first. After three menstrual cycles, patients were crossed over to the alternate treatement for an additional three cycles. Mefenamic acid was significantly superior to placebo in all parameters, and both treatment(drug and placebo) were equally.

Mefenamic Acid may cause serious side effects including:

nausea, tiredness, itching, yellowing of your skin or eyes (jaundice) ,Abdominal pain , Vomiting

Diarrhoea ,Indigestion, Heartburn

Drug Interactions:

Drug-Drug Interactions: MEFENAMIC ACID may interact with pain killers (aspirin, ibuprofen, celecoxib, diclofenac, naproxen), anti-gout (probenecid), immunosuppressants (cyclosporine, tacrolimus), anticoagulants (warfarin, heparin), anti-rheumatoid (methotrexate), anti-HIV (zidovudine), anti-depressant (duloxetine, lithium, fluoxetine, sertraline), and steroid medication (mifepristone).

Drug-Food Interactions: No interactions found/established.

Drug-Disease Interactions: Inform your doctor if you have peptic ulcers, bleeding disorders, asthma, fluid retention, gastrointestinal toxicity, rash, renal toxicity, thrombosis, anaemia, heart failure, liver toxicity, high blood pressure, platelet aggregation inhibition, or hyperkalemia (high potassium levels).

In-Depth Precautions and Warning:

Do not take MEFENAMIC ACID if you are allergic to any of its components, if you have severe heart, kidney or liver failure, suffered bleeding problems such as bleeding from the stomach or bowels while taking any pain killers or have peptic ulcers or inflammatory bowel disease. Inform your doctor if you have high blood pressure, heart problems, high cholesterol, dehydration, asthma, liver and kidney problems. Consult your doctor if you are pregnant or breastfeeding. MEFENAMIC ACID may cause drowsiness and dizziness, so drive only if you are alert. MEFENAMIC ACID should not be given to children as safety has not been established. Stop taking MEFENAMIC ACID and consult your doctor immediately if you have stomach pain or any signs of bleeding in the intestine or stomach such as blood in stools.

Usage:

To treat Mild and Moderated pain.

Menstrual Cramps.

Precautions:

Aspirin, Ibuprofen, Naproxen- Allergic to Mefenamic acid.

OVERDOSE: Breathing-difficulty, extrem drowsiness, stomach pain.

OTHER COMBINATIONS:(Oral –Route)-Tablet.

Tranexamic acid + Mefenamic acid
Mefenamic acid + Paracetamol
Mefenamic acid + Dicyclomine

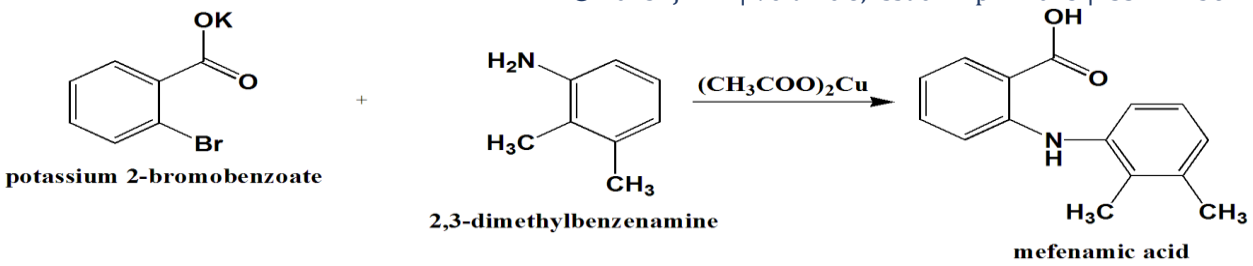
Chemistry of Mefenamic acid:

Structure Activity Relationship:((Mefenamic acid))

1) General SAR for anthranylic acid derivatives can be using different activity
2) Activity decreases when substitution on anthranilic acid ring.
3) Activities due to substitution on the N-aryl ring follows the general order m > o > p.
4) For disubstitution products, activity was found to be maximum when o and m positions are substituted near to each other on the N-aryl ring.
5) Substitutions on the N-aryl ring with such groups which leads the ring to be noncoplanar with the anthranilic acid ring increases the binding of the drug and hence, increases the activity (meclofenamic acid being more active than flufenamic acid).
6) NH-moiety of the anthranilic ring is important for the activity of the drug, and replacement of NH-moiety with O, CH3, S, SO2, N-CH3 or N-COCH3 groups decreases the activity of drug.
7) Position of the acidic function is important for the activity and not the nature of acidic function.
8) Replacement of carboxylic acid function with isosteric tetrazole function has no significant effect on the activity of compound

Method of Synthesis:

Potassium salt of 2-bromobenzoic acid is reacted with , 3-dimethylaniline in the presnce of copper(ll) acetate to give a Mefenamic acid.



PRODUCT DETAIL:

About Tranexamic acid and Mefenamic acid

Tranexamic acid and Mefenamic acid Tablet is a combination medicine used to treat dysmenorrhea (period pain) and menorrhagia (heavy menstrual bleeding). Besides this, Tranexamic acid and Mefenamic acid Tablets is also used to treat severe blood loss, swelling in various body parts, fever, inflammation, and migraine headache. Menstrual cramps, also known as dysmenorrhea, are characterized by cramps and pain during menstruation. Menorrhagia is a condition with abnormally heavy or prolonged bleeding during menstruation/periods.

Trnexamic acid and Mefenamic acid Tablets is a combination of two drugs: Tranexamic acid (anti-fibrinolytic) and Mefenamic acid (NSAID). Tranexamic acid helps the body's natural blood clot process by preventing fibrin's breakdown, this stops fibrinolysis, a process that stops blood clot formation. Mefenamic acid works by blocking the effect of chemical messengers that cause pain.(prostaglandins)

CONCLUSION

Tranexamic acid and Mefenamic acid is a combination of drugs which (HMB) with pain treatement. Antifibrinolytic with COX-I and COX-II inhibitor condition Tranexamic acid and Mefenamic acid is usually superior. This means that Tranexamic acid with Mefenamic acid provides more potent with a degree of (HMB)with pain, menstrual cramp treatement that physicians feel worthwhile.

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REFERENCE

1. Okamoto S, Sato S, Takada Y, et al. An active stereo isomer (trans-form) of AMCHA and its fibrinolytic (antiplasminic) action in vitro and in vivo. Keio J Med 1964; 13: 177–85

2. Tall AR, Mistilits SP: Studies on Ponstan (mefenamic acid): I. Gastro-intestinal blood loss; II. Absorption and excretion of a new formulation. J Int Med Res (UK). 1975, 3 (3) p176-82.

3. Winder CV, Kaump DH, Glazko et al: Experimental observations of flufenamic, mefenamic, and meclofenamic acids. AnnPhys Med (Eng), Suppl p7-49.1967.

4. Glazko AJ: Experimental observations of flufenamic, mefenamic, and meclofenamic acids. Part III. Metabolic disposition, in Fenamates in Medicine. A Symposium, London, 1966. Annals of Physical Medicine, Supplement, pp 23-36, 1967.

6. Budoff PW: Use of mefenamic acid in the treatment of primary dysmenorrhea. JAMA. 241: 2713-2716, 1979.

7. Buchanan RA, et al. The breast milk excretion of mefenamic acid. Curr Ther Res. 10:592, 1968.

8. Corby DG, Decker WJ: Management of acute poisoning with activated charcoal. Pediatrics. 54:324,1974.

9. Champion GD, Graham GG: Pharmacokinetics of non-steroidal anti-inflammatory agents. Aust NZ J Med. 8 (Supp 1): 94-100, Jun 1978.

10.McGurk KA, Remmel RP, Hosagrahara VP, Tosh D, Burchell B: Reactivity of mefenamic acid 1-o- acyl glucuronide with proteins in vitro and ex vivo. Drug Metab Dispos. Aug 1996, 24 (8) p842-9.

11.Ito K, Niida Y, Sato J et al: Pharmacokinetics of mefenamic acid in preterm infants with patent ductus arteriosus. Acta Paediatr JPN. 36 (4): 387-91, 1994.

12. Berkow R, Fletcher AJ, editors. The Merck manual of diagnosis and therapy. 15th ed. Rahway (NJ): Merck & Co., 1987

13) Anonick PK, Vasudevan J, Gonias SL. Antifibrinolytic activities of α-N-acetyl-L-lysine methyl ester, ε-aminocaproic acid, and tranexamic acid; importance of kringle interactions and active site inhibition. Arterioscler Thromb 1992 Jun; 12(6): 708–16.

14) Hoylaerts M, Lijnen HR, Collen D. Studies on the mechanism of the antifibrinolytic action of tranexamic acid. Biochim Biophys Acta 1981 Feb 18; 673(1): 75–85.

15) Blauhut B, Harringer W, Bettelheim P, et al. Comparison of the effects of aprotinin and tranexamic acid on blood loss and related variables after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1994 Dec; 108(6): 1083–91.

16) Colferai MMT, Miquelin GM, Steiner D. Evaluation of oral tranexamic acid in the treatment of melasma.[published online ahead of print, 2018 Dec 9]. J Cosmet Dermatol. 2018; 18: 1495- 1501. doi:10.1111/jocd.12830.

17) Zhu CY, Li Y, Sun QN, Takada A, Kawada A. Analysis of the effect of different doses of oral tranexamic acid on melasma: a multicentre prospective study. Eur J Dermatol. 2019; 29(1): 55- 58. doi:10.1684/ejd.2018.3494.

18) Kim KM, Lim HW. The uses of tranexamic acid in dermatology: a review. [published online ahead of print, 2022 Mar 24]. Int J Dermatol. 2022. doi:10.1111/ijd.16160.

19) John M. Chauncey; Jerald S. Wieters. Tranexamic acid - statpearls - NCBI bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK532909/. Accessed August 18, 2022.