

DATA SHEET

TRANEXAMIC ACID TABLETS

Tranexamic acid 500 mg

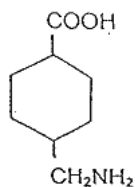
Description

Tranexamic acid (CAS 1197-18-8).

Chemical name: trans-4-aminomethylcyclohexane-carboxylic acid.

The empirical formula of tranexamic acid is $C_8H_{15}NO_2$ and its molecular weight is 157.2.

The chemical structure of tranexamic acid is:



Tranexamic acid is a white crystalline powder that is odourless or almost odourless. It is freely soluble in water and in glacial acetic acid, practically insoluble in methanol, ethanol, acetone, diethyl ether and benzene. Taste of amino-acids.

pKa: 4.3 and 10.6

Pharmacology

Tranexamic acid is a competitive inhibitor of plasminogen activation and at much higher concentrations a non-competitive inhibitor of plasmin, thus implying that tranexamic acid interferes with the fibrinolytic process in the same way as aminocaproic acid. Tranexamic acid is about 10 times more potent *in vitro* than aminocaproic acid.

Tranexamic acid binds considerably more strongly than aminocaproic acid to both the strong and weak sites of the plasminogen molecule in a ratio corresponding to the difference in potency between the compounds.

Tranexamic acid in a concentration of 1 mg/mL does not aggregate platelets *in vitro*. Tranexamic acid in concentrations up to 10 mg/mL blood has no influence on the platelet count, the coagulation time or various coagulation factors in whole blood or citrated blood in normal subjects. On the other hand tranexamic acid in concentrations of 10 mg/mL and 1 mg/mL blood prolongs the thrombin time.

Tranexamic acid does not bind to serum albumin. The plasma protein binding is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen.

Three hours after a single oral dose of 25 mg/kg, the peak serum level was 15.4 g/L and the aqueous humour level was 1.6 g/L.

The total amount of metabolites excreted in urine during 72 hours is less than 5%. Possible routes of biotransformation are acetylation or deamination followed by oxidation or reduction. After oral administration approximately 50% of the parent compound, 2% of the deaminated dicarboxylic acid and 0.5% of the acetylated product are excreted.

Tranexamic acid is eliminated by glomerular filtration, excretion being about 90% at 24 hours after intravenous administration of 10 mg/kg bodyweight. After oral administration of 10 to 15 mg/kg body weight the urinary excretion at 24 hours is 39% and at 48 hours is 41%.

The plasma peak level after 1 g orally is 8 mg/L and after 2 g, 15 mg/L, both obtained three hours after dosing.

A parallel intake of food has no influence on the bioavailability of the drug.

When administered 36 to 48 hours before surgery in 4 doses of 10 to 20 mg/kg, an antifibrinolytically active concentration (10 µg/mL) of tranexamic acid remains in different tissues for about 17 hours and in the serum for up to seven or eight hours.

Tranexamic acid passes through to the placenta. The concentration in cord blood after an intravenous injection of 10 mg/kg to pregnant women could be fairly high, about 30 µg/mL of foetal serum.

The concentration in breast milk is about one hundredth of the serum peak concentration obtained.

Tranexamic acid passes to semen and inhibits its fibrinolytic activity but does not influence sperm migration.

Tranexamic acid crosses the blood-brain barrier.

The drug passes into the aqueous humour, the concentration being about one tenth of the plasma concentration.

Tranexamic acid diffuses rapidly to the joint fluid and the synovial membrane, and in the joint fluid the same concentration is obtained as in the serum. The biological half-life in the joint fluid is about 3 hours.

Indications

1. Haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis. Local fibrinolysis may occur in the following conditions:
 - Menorrhagia
 - Epistaxis
 - Conisation of the cervix
 - Management of dental extraction in patients with coagulopathies
 - Ulcerative colitis
 - Haematuria
 - Gastrointestinal haemorrhage
 2. Hereditary angioneurotic oedema
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Contraindications

Patients with a history or risk of thrombosis should not be given tranexamic acid, unless at the same time it is possible to give treatment with anticoagulants.

Active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis.

The preparation should not be given to patients with acquired disturbances of colour vision. If disturbances of colour vision arise during the course of treatment the administration of the preparation should be discontinued.

Patients with subarachnoid haemorrhage should not be given tranexamic acid as anecdotal experience indicates that cerebral oedema and cerebral infarction may be caused in such cases.

Hypersensitivity to tranexamic acid or any of its ingredients.

Precautions

The dose of tranexamic acid should be reduced in patients with renal impairment because of the risk of accumulation (see Dosage and Administration). Isolated cases of obstruction of the urinary tract due to blood clots have been observed when tranexamic acid has been used to treat severe bleeding from the upper urinary tract.

Tranexamic acid therapy is not indicated in haematuria caused by diseases of the renal parenchyma. Intravascular precipitation of fibrin frequently occurs in these conditions and may aggravate the disease. In addition, in cases of massive renal haemorrhage of any cause, antifibrinolytic therapy carries the risk of clot retention in the renal pelvis.

Although clinical evidence shows no significant increase in thrombosis, possible risk of thrombotic complications cannot be ruled out. Venous and arterial thrombosis or thromboembolism has been reported in patients treated with tranexamic acid. In addition, cases of central retinal artery and central retinal vein obstruction have been reported. A few patients have developed intracranial thrombosis with tranexamic acid but further observation is needed to assess the significance of this potential hazard. There are no data on the use of tranexamic acid in women taking oral contraceptive agents.

Patients with a high risk for thrombosis (a previous thromboembolic event and a family history of thromboembolic disease) should use tranexamic acid only if there is a strong medical indication and under strict medical supervision.

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.

Blood in body cavities such as pleural space, joint spaces and urinary tract (e.g. renal pelvis, bladder) may develop 'indissoluble clots' in these cavities due to extravascular blood clots which may be resistant to physiological fibrinolysis.

Patients with irregular menstrual bleeding should not use tranexamic acid until the cause of the irregularity has been established. If menstrual bleeding is not adequately reduced by tranexamic acid an alternative treatment should be considered.

Patients with disseminated intravascular coagulation (DIC) who require treatment with tranexamic acid must be under the strict supervision of a physician experienced in treating this disorder.

Focal areas of retinal degeneration have developed in cats, dogs and rats following oral or intravenous tranexamic acid at doses between 250 to 1600 mg/kg/day (6 to 40 times the recommended usual human dose) from 6 days to 1 year. The incidence of such lesions has varied from 25% to 100% of animals treated and was dose related. At lower doses some lesions have appeared to be reversible.

Limited data in cats and rabbits showed retinal changes in some animals with doses as low as 126 mg/kg/day (only about 3 times the recommended human dose) administered for several days to two weeks.

No retinal changes have been reported or noted in eye examinations in patients treated with tranexamic acid for weeks to months in clinical trials. However, visual abnormalities, often poorly characterised, represent the most frequently reported postmarketing adverse event in Sweden. For patients who are to be treated continually for longer than several days, an ophthalmological examination, including visual acuity, colour vision, eye-ground and visual fields, is advised before commencing and at regular intervals during the course of treatment. Tranexamic acid should be discontinued if changes in examination results are found.

Use in pregnancy

Australian Pregnancy Categorisation B1.

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Reproduction studies performed in mice, rats and rabbits have not revealed any evidence of impaired fertility or adverse effects on the foetus due to tranexamic acid.

The long-term clinical experience is limited to 21 pregnant women, treated for 1 to 18 weeks, in most cases to prevent further haemorrhage in connection with ablatio placentae. All women delivered alive and normal children except for prematurity. The short-term experience comprises 67 women with abruptio placentae treated with a single dose just before delivery by caesarean section. All deliveries went well and were not further complicated by haemorrhage.

There are no adequate and well-controlled studies in pregnant women. However, tranexamic acid is known to cross the placenta and appears in cord blood at concentrations approximately equal to maternal concentration. Because animal reproduction studies are not always predictive of human response, tranexamic acid should be used during pregnancy only if clearly needed.

Use in lactation

Tranexamic acid is secreted in the mother's milk at a concentration of about a hundredth of the corresponding serum levels but is not likely to influence the child at therapeutic doses.

Use in children

Clinical experience with tranexamic acid in menorrhagic females under 15 years of age is not available.

Interactions with other drugs

Clinically important interactions have not been observed with tranexamic acid tablets. Because of the absence of interaction studies, simultaneous treatment with anticoagulants must take place under the strict supervision of a physician experienced in this field.

Adverse Effects

Gastrointestinal discomfort occurs in more than 30% of patients after oral administration of 6 g/day. The discomfort disappears when the dose is reduced. Hypotension may occur after fast injection.

Common side effects (> 1/100): GI: Nausea, vomiting, diarrhoea.

Less common side effects: Skin: Allergic skin reactions.

Rare side effects (< 1/1000): Thromboembolic events, impaired colour vision and other visual disturbances. Exceptional cases of giddiness have been reported.

Dosage and Administration

The product is for oral administration only.

The recommended standard dose is 2 to 3 500 mg tablets, 2 to 3 times daily. For the indications listed below, the following doses are recommended:

Menorrhagia

1 - 1.5 g orally 3 to 4 times daily for 3 to 4 days. Tranexamic acid therapy is initiated when bleeding has become profuse.

Epistaxis

1.5 g orally 3 times daily for 4 to 10 days.

Haematuria

1 - 1.5 g orally 2 to 3 times daily until macroscopic haematuria is no longer present.

Conisation of the cervix

1.5 g orally 3 times a day for 12 to 14 days post-operatively.

Dental surgery in patients with coagulopathies (oral post-surgery administration only)

After surgery, 25 mg per kg body weight are given orally 3 to 4 times daily for 6 to 8 days. Coagulation factor concentrate might be necessary to administrate.

Hereditary angioneurotic oedema

1 - 1.5 g orally 2 to 3 times daily as intermittent or continuous treatment, depending on whether the patient has prodromal symptoms or not.

Ulcerative colitis

1 - 1.5 g (i.e. 2 to 3 tablets), 2 to 3 times daily.

Renal insufficiency

For patients with impaired renal function, the following dosages are recommended:

Serum creatinine (micromol/L)	Dose orally	Dose frequency
120 - 249	15 mg/kg	twice daily
250 - 500	15 mg/kg	daily
> 500	7.5 mg/kg	daily

Children

Clinical experience with tranexamic acid in menorrhagic children under 15 years of age is not available.

Overdosage

Overdose data are limited. There is one report of overdosage in which a seventeen-year-old ingested 37 g of tranexamic acid and after receiving treatment with gastric lavage, mild intoxication was reported.

Symptoms of overdose may include dizziness, headache, nausea, vomiting, diarrhoea, orthostatic symptoms and hypotension.

There is no known antidote for tranexamic acid overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures should be instituted as required.

Activated charcoal may reduce absorption of tranexamic acid if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube once the airway is protected.

In addition to this, monitor vital signs to detect a possible hypotensive episode. Monitor fluid and electrolyte status in patients with severe vomiting or diarrhoea and administer IV fluids and replace electrolytes as necessary. Monitor urine output and maintain adequate diuresis. Monitor for clinical evidence of thromboembolic complications (e.g. chest pain, shortness of breath, flank pain, extremity pain). Because there is a risk of thrombosis in predisposed individuals; anticoagulant therapy should be considered in these patients.

In symptomatic patients, support respiratory and cardiac function. Monitor blood count, renal function, pulse oximetry and/or blood gases and obtain a chest x-ray. Obtain an ECG and institute continuous cardiac monitoring.

Contact the National Poisons Information Centre for advice on the management of an overdose (telephone 0800 764 766).

Presentation

Tablets: white, film-coated, oblong tablets, marked on one side with FW291, with a break-line on the reverse.

Each tranexamic acid tablet contains 500 mg of tranexamic acid as well as the following inactive ingredients: microcrystalline cellulose, povidone, croscarmellose sodium, colloidal anhydrous silica, talc, magnesium stearate, titanium dioxide, macrogol 8000, vanillin and methacrylate polymers.

Pharmaceutical Precautions

Shelf-life

24 months

Storage

Store below 25°C.

Medicine Classification

Prescription Medicine.

Package Quantities

Tablets: 60 tablets per carton

Name and Address of the Sponsor

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