

Data Sheet

CYKLOKAPRON®

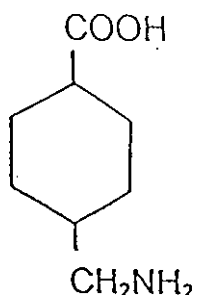
Tranexamic acid

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 noncompetitive 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 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 the 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 three hours.

Indications

1. Haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis. Local fibrinolysis may occur in the following conditions:

- Prostatectomy and bladder surgery
- Menorrhagia
- Epistaxis
- Conisation of the cervix
- Management of dental extraction in patients with coagulopathies
- Ulcerative colitis
- Haematuria
- Gastrointestinal haemorrhage

General fibrinolysis as in prostatic and pancreatic cancer; after thoracic and other major surgery; in obstetrical complications such as abruptio placentae and post-partum haemorrhage; in leukaemia and liver diseases and in connection with thrombolytic therapy with streptokinase.

2. Hereditary angioneurotic oedema.

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 section). 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 Cyklokapron. 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 Cyklokapron only if there is a strong medical indication and under strict medical supervision.

Cyklokapron 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 Cyklokapron until the cause of the irregularity has been established. If menstrual bleeding is not adequately reduced by Cyklokapron, an alternative treatment should be considered.

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

Preclinical safety data

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.

An increased incidence of leukemia in male mice receiving tranexamic acid in food at a concentration of 4.8% (equivalent to doses as high as 5 g/kg/day) may have been related to treatment. Female mice were not included in this experiment.

Hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system have been reported in one strain of rats after dietary administration of doses exceeding the maximum tolerated dose for 22 months. Hyperplastic, but not neoplastic, lesions were reported at lower doses. Subsequent long-term dietary administration studies in a different strain of rat, each with an exposure level equal to the maximum level employed in the earlier experiment, have failed to show such hyperplastic / neoplastic changes in the liver. No mutagenic activity has been demonstrated in several *in vitro* and *in vivo* test systems.

In published, pre-clinical animal studies, epileptic activities were induced by topical application of tranexamic acid to the cortex of anesthetized cats. Similarly, intravenous infusion of high doses (500-600 mg/kg) of tranexamic acid induced seizure-like activity in conscious cats. Severe hind limb spasms developed into generalized convulsions in a rat model following application of tranexamic acid to the lumbar spinal cord. Tranexamic acid within a fibrin sealant similarly induced limb spasms and convulsions in this rat model. Fibrin sealant containing tranexamic acid evoked generalized seizures in rats following application to the cerebral cortex of anesthetized rats. CNS hyperexcitability may be the result of antagonism of γ -aminobutyric acid_A receptors by tranexamic acid.

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 fetus 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 one 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, Cyklokapron 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.

Effects on Fertility

There is no clinical data in humans supporting the impact of tranexamic acid on fertility. Fertility was not affected in male or female rats up to the highest oral dose tested of approximately 900 mg/kg/day

Use in children

Clinical experience with Cyklokapron 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.

Common side effects (1 to < 10%):

Gastrointestinal tract: Nausea, vomiting, diarrhoea.

Uncommon side effects (0.1 to < 1%):

Skin and subcutaneous tissue: Allergic skin reactions

Post-market Reports: The following adverse events have been reported in association with tranexamic acid therapy.

Nervous System Disorders: convulsion, dizziness

Eye Disorders: chromatopsia, visual impairment

Vascular Disorders: embolism, hypotension (after fast injection)

Dosage and Administration

Intravenous administration is necessary only if it is difficult to give adequate doses by mouth.

The recommended standard dose is 2-3 tablets of 0.5g, or 5-10mL by slow intravenous injection at a rate of 1mL/minute, two to three times daily. For the indications listed below the following doses are recommended.

Prostatectomy

5-10mL by slow intravenous injection every eight hours (the first injection being given during the operation) for the first three days after surgery; thereafter 1-1.5g orally three to four times daily until macroscopic haematuria is no longer present.

Menorrhagia

1-1.5g orally three to four times daily for three to four days. CYKLOKAPRON therapy is initiated when bleeding has become profuse.

Epistaxis

1.5g orally three times daily for four to ten days. CYKLOKAPRON solution for injection may be applied topically to the nasal mucosa of patients suffering from epistaxis. This can be done by soaking a gauze strip in the solution, and then packing the nasal cavity.

Haematuria

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

Conisation of the Cervix

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

Dental Surgery in Patients with Coagulopathies

Immediately before surgery, 10mg per kg body-weight should be given intravenously. After surgery, 25mg per kg body-weight are given orally three to four times daily for six to eight days. It may be necessary to administer coagulation factor concentrate. This decision should be made after consulting a specialist on coagulation.

General Fibrinolysis

1.0g (10mL) by slow intravenous injection three to four times daily. With fibrinolysis in conjunction with diagnosed, increased intravascular coagulation i.e. defibrillation syndrome, an anticoagulant such as heparin may be given with caution.

Hereditary Angioneurotic Oedema

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

Renal insufficiency

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

Serum creatinine (micromol/L)	Dose IV	Dose Orally	Dose frequency
120-249	10mg/kg	15mg/kg	twice daily
250-500	10mg/kg	15mg/kg	daily
>500	5mg/kg	7.5mg/kg	daily

Children

Clinical experience with CYKLOKAPRON 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 (eg 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 03 474 7000).

Effects on ability to drive and use machines

Tranexamic acid may cause dizziness and therefore may influence the ability to drive or use machines

Presentation

Tablets: white, capsule shaped, film coated, engraved CY within arcs, dimensions 8.0 mm x 18.0 mm.

Each CYKLOKAPRON tablet contains 500 mg of tranexamic acid as well as the following inactive ingredients: microcrystalline cellulose, purified talc, magnesium stearate, colloidal anhydrous silica, povidone, hydroxypropylcellulose, titanium dioxide, macrogol 8000, vanillin and Eudragit E100.

Solution for injection: sterile, clear and colourless solution, containing 100 mg/mL tranexamic acid.

Each CYKLOKAPRON 5 mL ampoule contains 500 mg of tranexamic acid as well as the following inactive ingredients: water for injections.

Pharmaceutical Precautions

Incompatibilities

CYKLOKAPRON solution for injection should not be mixed with blood for transfusion or infusion solutions containing penicillin.

Shelf-life

Tablets: 36 months

Solution for injection: 36 months

Storage

Tablets: Store below 30°C

Solution for injection: Store at or below 25°C

Medicine Classification

Prescription Medicine.

Package Quantities

Tablets: Bottles of 100

Solution for injection: Ampoules, 10 x 500 mg/5 mL

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