Thrombin *(rINN)*

Factor IIa; Thrombine; Thrombinum; Trombin; Trombina.

Тромбин

CAS — 9002-04-4.
ATC — B02BC06; B02BD30.
ATC Vet — QB02BC06; QB02BD30.

Pharmacopoeias. Many pharmacopoeias have monographs, including *US*.

USP 31 (Thrombin). A sterile, freeze-dried powder derived from bovine plasma containing the protein substance prepared from prothrombin through interaction with added thromboplastin in the presence of calcium. It is capable, without the addition of other substances, of causing the clotting of whole blood, plasma, or a solution of fibrinogen. It should be stored at 2° to 8°. Once reconstituted, solutions should be used within a few hours of preparation. The label should state that the prepared solution should not be injected into or otherwise allowed to enter large blood vessels.

A white to greyish, amorphous substance dried from the frozen state.

Thrombin Alfa *(USAN, rINN)*

Human thrombin (recombinant, glycosylated); Thrombine Alfa; Thrombinum Alfa; Trombina Alfa. Human thrombin (recombinant, glycofrom α).

Тромбин Альфа

CAS — 869858-13-9.

Adverse Effects and Precautions

Hypersensitivity reactions, including anaphylaxis, have occurred rarely. Thrombin solutions must not be injected into blood vessels.

Antibody formation. Exposure to thrombin preparations of bovine origin has led to the development of antibodies to bovine thrombin and factor V with cross-reactivity, in some cases, to human factors. The presence of inhibitors to human factors may produce bleeding abnormalities and interfere with clotting measurements. Platelet infusions, fresh frozen plasma, and activated prothrombin complex concentrates have been used in the management of acute haemorrhagic complications, though often with limited success. Treatments that have been tried, in order to reduce the antibody titre, have included corticosteroids, ciclosporin, antineoplastics, intravenous immunoglobulin, and plasmapheresis.[1,2] Despite the availability of preparations containing virus-inactivated human fibrinogen the use of bovine thrombin is reported to be widespread and cases of acquired factor V inhibitor continue to occur.[3]

1. Ortel TL. Clinical and laboratory manifestations of anti-factor V antibodies. *J Lab Clin Med* 1999; **133:** 326–34.
2. Streiff MB, Ness PM. Acquired FV inhibitors: a needless iatrogenic complication of bovine thrombin exposure. *Transfusion* 2002; **42:** 18–26.
3. Kirkeby KM, Aronowitz P. Acquired factor V inhibitor: a common and avoidable complication of topical bovine thrombin application. *Am J Med* 2005; **118:** 805.

Uses and Administration

Thrombin is a protein substance produced *in vivo* from prothrombin that converts soluble fibrinogen into insoluble fibrin thus producing coagulation.

Thrombin of either human or bovine origin is applied topically to control bleeding from capillaries and small venules. It is applied directly to the bleeding surface either as a solution or dry powder. It may also be used with absorbable gelatin sponge during surgical procedures. Thrombin alfa, a recombinant human thrombin, is used similarly.

Thrombin is a component of fibrin glue (p.1069).

General references. Reviews.

1. Lundblad RL, *et al.* A review of the therapeutic uses of thrombin. *Thromb Haemost* 2004; **91:** 851–60.

Pseudoaneurysm. An acute pseudoaneurysm is an arterial rupture, contained by fibromuscular tissue, that communicates with the artery via a narrow neck. Insertion-site femoral pseudoaneurysm can occur as a result of procedures such as cardiac catheterisation and peripheral angiography. It is usually treated with ultrasound-guided compression, but this time-consuming technique causes discomfort for both the patient and the staff carrying out the procedure, and may be of limited success for large pseudoaneurysms and patients receiving anticoagulation. Surgical repair may be required in some patients. As an alternative to pressure or surgery, thrombin has been given by ultrasound-guided percutaneous injection. In reported series,[1-4] complete thrombosis of the pseudoaneurysm sac occurred in more than 90% of patients with one injection of bovine thrombin. Bovine thrombin has also been used when compression has failed,[4,5] and a comparative study[6] in 30 patients found thrombin to be more successful than compression. Human thrombin has also been used successfully.[7] A retrospective review[8] concluded that bovine and human thrombin were equally effective. The successful use of autologous thrombin in a few patients has also been described.[9]

1. La Perna L, *et al.* Ultrasound-guided thrombin injection for the treatment of postcatheterization pseudoaneurysms. *Circulation* 2000; **102:** 2391–5.
2. Mohler ER, *et al.* Therapeutic thrombin injection of pseudoaneurysms: a multicenter experience. *Vasc Med* 2001; **6:** 241–4.
3. Olsen DM, *et al.* A prospective study of ultrasound scan-guided thrombin injection of femoral pseudoaneurysm: a trend toward minimal medication. *J Vasc Surg* 2002; **36:** 779–82.
4. Stone P, *et al.* Iatrogenic pseudoaneurysms: comparison of treatment modalities, including duplex-guided thrombin injection. *W V Med J* 2003; **99:** 230–2.
5. Lönn L, *et al.* Treatment of femoral pseudoaneurysms: percutaneous US-guided thrombin injection versus US-guided compression. *Acta Radiol* 2002; **43:** 396–400.
6. Lönn L, *et al.* Prospective randomized study comparing ultrasound-guided thrombin injection to compression in the treatment of femoral pseudoaneurysms. *J Endovasc Ther* 2004; **11:** 570–6.
7. Maleux G, *et al.* Percutaneous injection of human thrombin to treat iatrogenic femoral pseudoaneurysms: short- and midterm ultrasound follow-up. *Eur Radiol* 2003; **13:** 209–12.
8. Vázquez V, *et al.* Human thrombin for treatment of pseudoaneurysms: comparison of bovine and human thrombin sonogram-guided injection. *Am J Roentg* 2005; **184:** 1665–71.
9. Quarmby JW, *et al.* Autologous thrombin for treatment of pseudoaneurysms. *Lancet* 2002; **359:** 946–7.

Preparations

Ph. Eur.: Fibrin Sealant Kit;
USP 31: Thrombin.

Proprietary Preparations (details are given in Part 3)
Austral.: Thrombostat†; ***Canad.:*** Thrombostat†; ***NZ:*** Thrombostat; ***Pol.:*** Gastrotrombina; ***S.Afr.:*** Tisseel; ***USA:*** Evithrom; Recothrom; Thrombinar; Thrombogen†; Thrombostat.

Multi-ingredient: ***Arg.:*** Beriplast P; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; TachoComb; TachoSil; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; Tissucol†; ***Canad.:*** Tisseel; ***Chile:*** Beriplast P; ***Cz.:*** TachoComb†; TachoSil; Tissucol; ***Denm.:*** TachoSil; Tisseel Duo Quick; ***Fin.:*** TachoSil; Tisseel Duo Quick; ***Fr.:*** Beriplast; Quixil; TachoSil; Tissucol; ***Ger.:*** Beriplast; Quixil; TachoComb†; TachoSil; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; TachoComb; Tisseel; ***Hung.:*** Beriplast P; TachoComb†; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Quixil; Tisseel; ***Ital.:*** Beriplast; Quixil; TachoSil; Tissucol; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; Quixil; TachoSil; Tissucol; Tissucol Duo; ***Norw.:*** TachoSil; ***Pol.:*** Beriplast; ***Port.:*** Quixil; TachoSil; Tissucol Duo; ***Rus.:*** TachoComb (ТахоКомб); ***Spain:*** Beriplast P Combi; TachoSil; Tissucol Duo; ***Swed.:*** TachoSil; Tisseel Duo Quick; ***Switz.:*** Beriplast P; TachoSil; Tissucol; Tissucol Duo S; ***Thai.:*** Fibrin Glue†; TachoComb†; ***Turk.:*** Beriplast P; Tisseel VH; ***UK:*** TachoSil; Tisseel; ***USA:*** Artiss.

Thrombomodulin Alfa *(rINN)*

ART-123; Thrombomoduline Alfa; Thrombomodulinum Alfa; Trombomodulina alfa. 1–498-Thrombomodulin (human clone TMP26/TMJ1 protein moiety reduced).

Тромбомодулин Альфа

CAS — 120313-91-9.

Profile

Endogenous thrombomodulin is a transmembrane protein found on the surface of endothelial cells, which acts as a thrombin receptor. Thrombomodulin-bound thrombin activates protein C, which then inactivates clotting factors and so limits coagulation.

Thrombomodulin alfa, a recombinant form of thrombomodulin, is under investigation in the prophylaxis of venous thromboembolism and the treatment of disseminated intravascular coagulation.

◊ References.

1. Kearon C, *et al.* Dose-response study of recombinant human soluble thrombomodulin (ART-123) in the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost* 2005; **3:** 962–8.
2. Saito H, *et al.* Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. *J Thromb Haemost* 2007; **5:** 31–41.

Thromboplastin

Cytozyme; Thrombokinase; Tromboplastina; Tromboplastyna.

Profile

Tissue thromboplastin (tissue factor; factor III) is a membrane glycoprotein that is released from damaged tissue and initiates coagulation. The term thromboplastin may also be applied to other related substances with similar activity. Commercial preparations may contain tissue extracts comprising a variety of such substances.

Preparations of thromboplastin have been used as haemostatics.

A preparation of thromboplastin derived from rabbit brain is used in the determination of the prothrombin time for the control of anticoagulant therapy (for further details see Uses and Administration of Warfarin Sodium, p.1432).

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Clauden.

Multi-ingredient: ***Braz.:*** Claudemor; ***Port.:*** Claudemor†; ***Venez.:*** Claudemor†.

Thrombopoietin

Trombopoyetina.

Profile

Thrombopoietin is a naturally occurring colony-stimulating factor that regulates thrombopoiesis (see Haematopoiesis, p.1042). Recombinant thrombopoietin, and a form of recombinant thrombopoietin conjugated with polyethylene glycol (pegacaristim, PEG-megakaryocyte growth and development factor, PEG-rHuMGDF), are under investigation. They have been studied in the management of thrombocytopenia (p.1051) in patients receiving myelosuppressive or myeloablative chemotherapy, and in patients with myelodysplastic syndrome or HIV-associated thrombocytopenia. There is also some interest in the use of recombinant forms of thrombopoietin in stem cell mobilisation regimens and to increase platelet counts in healthy apheresis donors. However, some results have been disappointing and there are reports of neutralising antibody development.

General references. Studies and reviews.

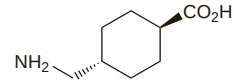
1. Vadhan-Raj S, *et al.* Safety and efficacy of transfusions of autologous cryopreserved platelets derived from recombinant human thrombopoietin to support chemotherapy-associated severe thrombocytopenia: a randomised cross-over study. *Lancet* 2002; **359:** 2145–52.
2. Nomura S, *et al.* Effects of pegylated recombinant human megakaryocyte growth and development factor in patients with idiopathic thrombocytopenic purpura. *Blood* 2002; **100:** 728–30.
3. Schuster MW, *et al.* The effects of pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) on platelet recovery in breast cancer patients undergoing autologous bone marrow transplantation. *Exp Hematol* 2002; **30:** 1044–50.
4. Kuter DJ, Begley CG. Recombinant human thrombopoietin: basic biology and evaluation of clinical studies. *Blood* 2002; **100:** 3457–69.
5. Linker C, *et al.* Recombinant human thrombopoietin augments mobilization of peripheral blood progenitor cells for autologous transplantation. *Biol Blood Marrow Transplant* 2003; **9:** 405–13.
6. Vadhan-Raj S, *et al.* Importance of predosing of recombinant human thrombopoietin to reduce chemotherapy-induced early thrombocytopenia. *J Clin Oncol* 2003; **21:** 3158–67.
7. Geissler K, *et al.* Prior and concurrent administration of recombinant human megakaryocyte growth and development factor in patients receiving consolidation chemotherapy for de novo acute myeloid leukemia—a randomized, placebo-controlled, double-blind safety and efficacy study. *Ann Hematol* 2003; **82:** 677–83.

Tranexamic Acid *(BAN, USAN, rINN)*

Acide tranexamique; Ácido tranexámico; Acidum tranexamicum; AMCA; *trans*-AMCHA; CL-65336; Kyselina tranexamová; Traneksaamihappo; Traneksamik Asit; Traneksamo rūgštis; Tranexámsav; Tranexamsyra. *trans*-4-(Aminomethyl)cyclohexanecarboxylic acid.

Транексамовая Кислота

$C_8H_{15}NO_2$ = 157.2.
CAS — 1197-18-8.
ATC — B02AA02.
ATC Vet — QB02AA02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Tranexamic Acid). A white or almost white, crystalline powder. Freely soluble in water and in glacial acetic acid; practically insoluble in alcohol and in acetone. A 5% solution in water has a pH of 7.0 to 8.0.

Incompatibility. Solutions of tranexamic acid are incompatible with benzylpenicillin.

Adverse Effects

Tranexamic acid appears to be well tolerated. It can produce dose-related gastrointestinal disturbances. Hypotension has occurred, particularly after rapid intravenous dosage. Thrombotic complications have been reported in patients receiving tranexamic acid, but these are usually a consequence of its inappropriate use (see Precautions, below). There have been a few instances of transient disturbance of colour vision associated with use of tranexamic acid; in such cases the drug should be stopped. Hypersensitivity skin reactions have also been reported.

Effects on the eyes. Tranexamic acid has been associated with retinopathy[1] and visual impairment.[2] A haemodialysis patient developed almost total loss of vision within 2 weeks of starting daily tranexamic acid injections after emergency surgery for a bleeding peptic ulcer. Vision was largely restored within a few days of stopping tranexamic acid,[2] although some impairment persisted in conditions of poor light. The patient had experienced visual impairment previously when given tranexamic acid. The authors noted that doses of tranexamic acid should be reduced in patients with renal impairment undergoing dialysis.

A patient undergoing regular peritoneal dialysis for Epstein's syndrome developed ligneous conjunctivitis, gingival hyperpla-

sia, and peritoneal protein loss associated with the use of tranexamic acid.[3]

1. Snir M, *et al.* Central venous stasis retinopathy following the use of tranexamic acid. *Retina* 1990; **10:** 181–4.
2. Kitamura H, *et al.* Tranexamic acid-induced visual impairment in a hemodialysis patient. *Clin Exp Nephrol* 2003; **7:** 311–14.
3. Diamond JP, *et al.* Tranexamic acid-associated ligneous conjunctivitis with gingival and peritoneal lesions. *Br J Ophthalmol* 1991; **75**: 753–4.

Effects on the skin. A widespread, patchy rash with associated blisters, considered on skin biopsy to be a fixed-drug eruption, occurred in a 33-year-old woman.[1] Tranexamic acid, which she had taken for 8 years and which had been well tolerated, was identified as the cause. Desensitisation was unsuccessful. Tranexamic acid was also suspected as being the cause of a fixed-drug eruption in a 36-year-old woman.[2] Pruritic, vesicle-bullous lesions appeared within a few hours of starting tranexamic acid and the lesions resolved completely 3 days after stopping therapy even though other drug treatment was continued.

1. Kavanagh GM, *et al.* Tranexamic acid (Cyklokapron)-induced fixed-drug eruption. *Br J Dermatol* 1993; **128:** 229–30.
2. Carrión-Carrión C, *et al.* Bullous eruption induced by tranexamic acid. *Ann Pharmacother* 1994; **28:** 1305–6.

Precautions

Tranexamic acid should not be used in patients with active intravascular clotting because of the risk of thrombosis. Patients with a predisposition to thrombosis are also at risk if given antifibrinolytic therapy. Haemorrhage due to disseminated intravascular coagulation should therefore not be treated with antifibrinolytic compounds unless the condition is predominantly due to disturbances in fibrinolytic mechanisms; tranexamic acid has been used when the latter conditions are met, but with careful monitoring and anticoagulant cover.

Lysis of existing extravascular clots may be inhibited in patients receiving tranexamic acid. Clots in the renal system can lead to intrarenal obstruction, so caution is required in patients with haematuria. Doses of tranexamic acid should be reduced in patients with renal impairment. Licensed product information recommends that regular eye examinations and liver function tests should be performed if tranexamic acid is used long term.

Some studies have suggested that tranexamic acid when given to patients after a subarachnoid haemorrhage increases the incidence of cerebral ischaemic complications (see Haemorrhagic Disorders under Uses, below).

Rapid intravenous dosage may be associated with adverse effects (see above).

Interactions

Drugs with actions on haemostasis should be given with caution to patients on antifibrinolytic therapy. The potential for thrombus formation may be increased by oestrogens, for example, or the action of the antifibrinolytic antagonised by compounds such as thrombolytics.

Retinoids. Antifibrinolytics should be used with caution in patients receiving oral *tretinoin* as thrombotic events have been reported in patients being treated with tranexamic acid and tretinoin (see Antifibrinolytics, p.1619).

Pharmacokinetics

Tranexamic acid is absorbed from the gastrointestinal tract with peak plasma concentrations occurring after about 3 hours. Bioavailability is about 30 to 50%. Tranexamic acid is widely distributed throughout the body and has very low protein binding. It diffuses across the placenta and is distributed into breast milk. Tranexamic acid has a plasma elimination half-life of about 2 hours. It is excreted in the urine mainly as unchanged drug.

◊ References.

1. Andersson L, *et al.* Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. *Ann N Y Acad Sci* 1968; **146:** 642–56.
2. Kullander S, Nilsson IM. Human placental transfer of an antifibrinolytic agent (AMCA). *Acta Obstet Gynecol Scand* 1970; **49:** 241–2.
3. Pilbrant Å, *et al.* Pharmacokinetics and bioavailability of tranexamic acid. *Eur J Clin Pharmacol* 1981; **20:** 65–72.

Uses and Administration

Tranexamic acid is an antifibrinolytic drug that inhibits breakdown of fibrin clots. It acts primarily by blocking the binding of plasminogen and plasmin to fibrin; direct inhibition of plasmin occurs only to a limited degree. Tranexamic acid is used in the treatment and prophylaxis of haemorrhage associated with excessive fibrinolysis. It is also used in the prophylaxis of hereditary angioedema.

Tranexamic acid is given by mouth and by slow intravenous injection or continuous infusion. Parenteral dosage is usually changed to oral after a few days. Alternatively, an initial intravenous injection may be followed by continuous infusion.

For short-term use in **haemorrhage**, oral doses are 1 to 1.5 g (or 15 to 25 mg/kg) 2 to 4 times daily. When given by slow intravenous injection doses are 0.5 to 1 g (or 10 mg/kg) 3 times daily. Tranexamic acid is given by continuous infusion at a rate of 25 to 50 mg/kg daily.

Tranexamic acid is given for prolonged periods in **hereditary angioedema** in doses of 1 to 1.5 g by mouth 2 or 3 times daily.

Children may be given doses of 25 mg/kg orally or 10 mg/kg intravenously, usually 2 or 3 times daily, depending on the indication.

Reduced doses are recommended for patients with renal impairment (see below).

Solutions of tranexamic acid have been applied topically, for example as a bladder irrigation or mouthwash.

Administration in renal impairment. Licensed drug information recommends reduced doses of tranexamic acid for patients with renal impairment, based on the serum-creatinine concentration (SCC):

- SCC 120 to 250 micromoles/litre: 15 mg/kg twice daily orally, or 10 mg/kg twice daily intravenously
- SCC 250 to 500 micromoles/litre: 15 mg/kg once daily orally, or 10 mg/kg once daily intravenously
- SCC higher than 500 micromoles/litre: 7.5 mg/kg once daily or 15 mg/kg once every 48 hours orally, or 5 mg/kg once daily or 10 mg/kg once every 48 hours intravenously (some products contra-indicate use in severe renal impairment)

Haemorrhagic disorders. Tranexamic acid and aminocaproic acid are structurally related synthetic antifibrinolytic drugs that block the binding of plasminogen and plasmin to fibrin, thereby preventing dissolution of the haemostatic plug.[1,2] A plasma concentration of tranexamic acid of 5 to 10 micrograms/mL has been considered necessary for effective inhibition of fibrinolysis.[2]

Antifibrinolytics are used to control haemorrhage that is considered to be caused by excessive fibrinolysis. Antifibrinolytic therapy may also be indicated in the prevention of rebleeding in some haemorrhagic conditions, the rationale being to retard dissolution of the haemostatic plug formed in response to vascular injury.

In haemorrhage caused by a congenital or acquired deficiency of blood coagulation factors, haemostatic drugs have a secondary role and may be useful in reducing requirements of factor concentrates. In patients with haemophilias (p.1048) antifibrinolytics may be added to coagulation factor replacement before dental surgery, and used in the prevention and treatment of mucosal bleeding after the procedure. The route depends on the severity of the coagulation factor deficiency and the procedure to be undertaken; for example, tooth extraction will probably require more prophylactic cover than dental scaling. Regimens therefore vary,[3-7] but an initial oral or intravenous dose of tranexamic acid may be followed by oral use, or topical 5% mouthwash continued for up to 7 days after dental procedures. Tranexamic acid has been used similarly in patients with von Willebrand's disease[4] (p.1051). An approach using tranexamic acid mouthwashes has also been used to reduce the risk of bleeding after oral surgery in patients on anticoagulant therapy.[8,9] Tranexamic acid may prove beneficial in patients with other congenital bleeding disorders such as α_2-antiplasmin deficiency.[10] Aminocaproic acid has been tried in a few patients with hereditary haemorrhagic telangiectasia with mixed results.[11] Tranexamic acid has been reported to be effective in the control of epistaxis in these patients; reports generally describe oral use,[12,13] but tranexamic acid has also been applied directly as nasal drops.[14]

Tranexamic acid and aminocaproic acid have each been used in an attempt to prevent rebleeding in patients with subarachnoid haemorrhage (see Stroke, p.1185), particularly if surgery is to be delayed. However, while rebleeding may be reduced, there can be an increase in the incidence of cerebral ischaemic complications resulting in little overall improvement in outcome.[15] Paradoxically, rebleeding has been noted in patients given high doses of aminocaproic acid after subarachnoid haemorrhage (see Effects on the Blood under Aminocaproic Acid, p.1053).

Tranexamic acid has been used to control gastrointestinal haemorrhage, e.g. due to peptic ulcer disease (p.1702) or oesophageal varices (see Variceal Haemorrhage under Monoethanolamine, p.2346). In a meta-analysis[16] of 6 studies, involving a total of 1267 patients given tranexamic acid for acute upper gastrointestinal haemorrhage, treatment with tranexamic acid was associated with a 20 to 30% decrease in the rate of rebleeding, a 30 to 40% decrease in the need for surgery, and a 40% decrease in mortality. However, the validity of one study included in the analysis has been disputed,[17,18] and it is not the usual treatment in these patients.

Tranexamic acid or aminocaproic acid have been suggested to control bleeding in many other conditions. These include haemorrhage after surgical or other procedures including prostatectomy, bladder surgery, and cervical conisation. They may be used to reduce perioperative blood loss and allogeneic transfusion requirements.[19-23] They may also be effective in other conditions associated with excessive fibrinolysis such as menorrhagia (see below), epistaxis, and placental abruption.

1. Mannucci PM. Hemostatic drugs. *N Engl J Med* 1998; **339:** 245–53.
2. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. *Drugs* 1999; **57:** 1005–32.
3. Zanon E, *et al.* Proposal of a standard approach to dental extraction in haemophilia patients: a case-control study with good results. *Haemophilia* 2000; **6:** 533–6.
4. Stubbs M, Lloyd J. A protocol for the dental management of von Willebrand's disease, haemophilia A and haemophilia B. *Aust Dent J* 2001; **46:** 37–40.
5. Villar A, *et al.* The use of haemostatic drugs in haemophilia: desmopressin and antifibrinolytic agents. *Haemophilia* 2002; **8:** 189–93.
6. Scully C, *et al.* Oral care for people with hemophilia or a hereditary bleeding tendency (World Federation of Hemophilia, Treatment of Hemophilia series, October 2002, No 27). Available at: http://www.wfh.org/2/docs/Publications/Dental_Care/TOH-27_English_Oral_Care.pdf (accessed 25/10/05)
7. Lee APH, *et al.* Effectiveness in controlling haemorrhage after dental scaling in people with haemophilia by using tranexamic acid mouthwash. *Br Dent J* 2005; **198:** 33–8.
8. Carter G, Goss A. Tranexamic acid mouthwash—a prospective randomized study of a 2-day regimen vs 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions. *Int J Oral Maxillofac Surg* 2003; **32:** 504–7.
9. Carter G, *et al.* Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. *J Oral Maxillofac Surg* 2003; **61:** 1432–5.
10. Favier R, *et al.* Congenital α -plasmin inhibitor deficiencies: a review. *Br J Haematol* 2001; **114:** 4–10.
11. Annichino-Bizzacchi JM, *et al.* Hereditary hemorrhagic telangiectasia response to aminocaproic acid treatment. *Thromb Res* 1999; **96:** 73–6.
12. Sabbà C, *et al.* Efficacy of unusually high doses of tranexamic acid for the treatment of epistaxis in hereditary hemorrhagic telangiectasia. *N Engl J Med* 2001; **345:** 926.
13. Sabbà C, *et al.* Rendu-Osler-Weber disease: experience with 56 patients. *Ann Ital Med Int* 2002; **17:** 173–9.
14. Klepfish A, *et al.* Intranasal tranexamic acid treatment for severe epistaxis in hereditary hemorrhagic telangiectasia. *Arch Intern Med* 2001; **161:** 767.
15. Roos YBWEM, *et al.* Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 27/10/05).
16. Henry DA, O'Connell DL. Effects of fibrinolytic inhibitors on mortality from upper gastrointestinal haemorrhage. *BMJ* 1989; **298:** 1142–6.
17. Brown C, Rees WDW. Drug treatment for acute upper gastrointestinal bleeding. *BMJ* 1992; **304**: 135–6.
18. Barer D. Drug treatment for acute upper gastrointestinal bleeding. *BMJ* 1992; **304**: 383.
19. Levi M, *et al.* Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999; **354:** 1940–7.
20. Schmarts. Antifibrinolytics. *Acta Anaesthesiol Belg* 2003; **54:** 319–22.
21. Ho KM, Ismail H. Use of intravenous tranexamic acid to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis. *Anaesth Intensive Care* 2003; **31:** 529–37.
22. Brown JR, *et al.* Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007; **115:** 2801–13.
23. Henry DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 27/06/08).

Hereditary angioedema. Hereditary angioedema, formerly known as hereditary angioneurotic oedema, is a rare autosomal dominant disease caused by either a deficiency of complement C1 esterase inhibitor or, more rarely, a lack of functioning inhibitor.[1-6] The disease presents as episodic attacks of oedema, usually of the extremities and face, and often involving the gastrointestinal mucosa producing abdominal pain. A non-pruritic rash may also occur. A few patients develop life-threatening laryngeal oedema. Attacks generally last about 1 to 3 days and may occur as frequently as weekly or there may be years between attacks. The first attack may occur at any age although initial presentation in childhood is most common. Trauma, especially dental surgery, illness, and emotional stress may provoke an attack although often there is no precipitating factor.

Treatment of the acute attack is essentially supportive. If laryngeal oedema is present adrenaline, antihistamines, and corticosteroids may be given (as for Anaphylaxis, p.1205) even though patients with hereditary angioedema often fail to respond ade-

quately to them. The mainstay of treatment of an acute attack is replacement therapy with complement C1 esterase inhibitor. Fresh frozen plasma has been used although there is a risk of initially exacerbating the oedema due to the presence of other complements in the plasma. Tracheostomy or tracheal intubation may be necessary.

Once the acute attack has subsided most patients will not require further treatment, but those who experience life-threatening attacks, repeated episodes of swelling around the face or neck, or incapacitating attacks require long-term **prophylactic therapy**. A synthetic androgen (danazol or stanozolol) or an antifibrinolytic (aminocaproic acid or tranexamic acid) is effective for long-term prophylaxis.[1,2,4,6] Danazol and stanozolol raise serum concentrations of C1 esterase inhibitor possibly by enhancing its synthesis in the liver.[2,6] Aminocaproic acid and tranexamic acid may act by inhibiting plasmin activation.[7] A synthetic androgen is often preferred because these seem to be more effective than antifibrinolytics. In children, however, androgens are generally avoided because of their adverse effects. Nevertheless, they have been used in children, with close monitoring, when antifibrinolytics have been ineffective.[3] In exceptional circumstances, long-term prophylaxis with twice weekly C1 esterase inhibitor may be indicated for adults when antifibrinolytics and androgens are ineffective, not tolerated, or contra-indicated.[6]

Short-term prophylaxis may be used in situations expected to provoke an attack, such as surgery or dental work. Complement C1 esterase inhibitor is given within 24 hours before the procedure, or fresh frozen plasma may be used if this is not available. Alternatively, a synthetic androgen or antifibrinolytic may be used, but these must be started several days before the procedure and continued for 2 days after.

Investigational therapies for the management of hereditary angioedema include a recombinant complement C1 esterase inhibitor, icatibant acetate (a bradykinin receptor antagonist), and ecallantide (an inhibitor of human plasma kallikrein).

1. Nzeako UC, *et al.* Hereditary angioedema: a broad review for clinicians. *Arch Intern Med* 2001; **161:** 2417–29.
2. Fay A, Abinun M. Current management of hereditary angio-oedema (C'1 esterase inhibitor deficiency). *J Clin Pathol* 2002; **55:** 266–70.
3. Farkas H, *et al.* Clinical management of hereditary angio-oedema in children. *Pediatr Allergy Immunol* 2002; **13:** 153–61.
4. Bowen T, *et al.* Canadian 2003 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *J Allergy Clin Immunol* 2004; **114:** 629–37.
5. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol* 2005; **114:** 10–16.
6. Gompels MM, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139:** 379–94. Correction. *ibid.*; **141:** 189–90. [dose]
7. Ritchie BC. Protease inhibitors in the treatment of hereditary angioedema. *Transfus Apheresis Sci* 2003; **29:** 259–67.

Menorrhagia. Tranexamic acid is used in women with menorrhagia (p.2126) who do not require contraception or hormonal therapy. It reduces uterine blood loss in such women when used during menstruation.[1-3] A comparative trial[1] found tranexamic acid 1 g by mouth every 6 hours to be more effective than the NSAID mefenamic acid, a commonly used treatment for the condition, and etamsylate. It is also more effective than cyclical norethisterone[2] (although less so than a progesterone-releasing intra-uterine device[3]). A review,[4] which included these and some other studies, reported that tranexamic acid reduces menstrual blood loss by about 34 to 59% over 2 to 3 cycles.

1. Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *BMJ* 1996; **313:** 579–82.
2. Preston JT, *et al.* Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. *Br J Obstet Gynaecol* 1995; **102:** 401–406.
3. Milsom I, *et al.* A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Am J Obstet Gynecol* 1991; **164:** 879–83.
4. Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. *Drugs* 2003; **63:** 1417–33.

Preparations

BP 2008: Tranexamic Acid Injection; Tranexamic Acid Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Cyklokapron; ***Austria:*** Cyklokapron; ***Belg.:*** Exacyl; ***Braz.:*** Hemoblock; Transamin; ***Canad.:*** Cyklokapron; ***Chile:*** Espercil; ***Cz.:*** Cyklokapron†; Exacyl; ***Denm.:*** Cyklokapron; ***Fin.:*** Caprilon; Cyklokapron; ***Fr.:*** Exacyl; Spotof; ***Ger.:*** Anvitoff†; Cyklokapron; ***Gr.:*** Transamin; ***Hong Kong:*** CP-Tran; Cyklokapron; Qualixamin; Transamin; ***Hung.:*** Exacyl; ***India:*** Tranarest; Tranfib; Traxamic†; ***Indon.:*** Asamnex; Clonex; Ditranex; Intermic; Kalnex; Lunex; Nexa; Plasminex; Pytramic; Ronex; Theranex; Tranexid; Transamin; ***Irl.:*** Cyklokapron; ***Israel:*** Hexakapron; ***Ital.:*** Tranex; Ugurol; ***Jpn:*** Transamin; ***Malaysia:*** Transamin; Tren; ***Neth.:*** Cyklokapron; ***Norw.:*** Cyklokapron; ***NZ:*** Cyklokapron; ***Philipp.:*** Cyclotrax; Cyklokapron; Dostan; Fibrinon; Fimoplas; Hemoclot; Hemostan; Hemotrex; Micranex; Proklot; Trenaxin; ***Pol.:*** Exacyl; ***S.Afr.:*** Cyklokapron; ***Singapore:*** Cyklokapron; ***Spain:*** Amchafibrin; ***Swed.:*** Cyklo-F; Cyklokapron; Tranon; ***Switz.:*** Anvitoff†; Cyklokapron; ***Thai.:*** Tramic; Transamin; ***Turk.:*** Transamine; ***UK:*** Cyklokapron; ***USA:*** Cyklokapron; ***Venez.:*** Ciclokapron.

Multi-ingredient: ***Fr.:*** Quixil; ***Ger.:*** Quixil; ***India:*** Tranfib MF; ***Ital.:*** Quixil; ***Jpn:*** Sin Colgen Kowa Kaze; ***Neth.:*** Quixil; ***Port.:*** Quixil.

von Willebrand Factor

Facteur Willebrand humain (human von Willebrand factor); Factor humanus von Willebrandi (human von Willebrand factor); Factor VIII-related Antigen; vWF.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Human von Willebrand Factor). A preparation of a plasma protein fraction that contains the glycoprotein von Willebrand factor with varying amounts of coagulation factor VIII, depending on the method of preparation. It is prepared from human plasma obtained from blood from healthy donors: the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus.

When reconstituted as stated on the label, the potency is not less than 20 international units of von Willebrand factor per mL. It is a white or pale yellow, hygroscopic powder or friable solid. Store in airtight containers. Protect from light.

Profile

von Willebrand factor is used in the treatment and prophylaxis of bleeding in von Willebrand's disease (p.1051), usually when desmopressin is ineffective or contra-indicated. It is generally contained in plasma concentrate preparations with factor VIII, but highly purified preparations that contain very little factor VIII are also available in some countries. Dosage depends on the extent and source of bleeding. Hypersensitivity reactions may occur rarely, and as for other plasma-derived preparations, the risk of transmission of infective agents cannot be totally excluded.

◊ References.

1. Smith MP, *et al.* Continuous infusion therapy with very high purity von Willebrand factor concentrate in patients with severe von Willebrand disease. *Blood Coag Fibrinol* 1997; **8:** 6–12.
2. Goudemand J, *et al.* Clinical management of patients with von Willebrand's disease with a VHP vWF concentrate: the French experience. *Haemophilia* 1998; **4** (suppl 3): 48–52.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Wilfactin; Wilstart; ***Gr.:*** Wilfactin.