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Tranexamic Acid

A Review of its Use in Surgery and Other Indications

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Data Selection

Sources: Medical literature published in any language since 1966 on tranexamic acid, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'tranexamic acid' and 'haemorrhage'. Medline and EMBASE search terms were 'tranexamic acid', 'pharmacokinetics', 'pharmacology' and 'therapeutic use'. Searches were last updated 30 Apr 1999.

Selection: Studies in patients undergoing surgery and those with haemorrhagic disorders who received tranexamic acid. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: tranexamic acid, surgery, cardiac, hepatic, orthopaedic, urinary tract, gastrointestinal, haemophilia, gynaecology, haemorrhage, hereditary angioneurotic oedema, hyphaema, subarachnoid, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability, dosage and administration.

Contents

Summary

Abstract

Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules.

Intravenously administered tranexamic acid (most commonly 10 mg/kg followed by infusion of 1 mg/kg/hour) caused reductions relative to placebo of 29 to 54% in postoperative blood losses in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), with statistically significant reductions in transfusion requirements in some studies. Tranexamic acid had similar efficacy to aprotinin 2×10^6 kallikrein inhibitory units (KIU) and was superior to dipyridamole in the reduction of postoperative blood losses. Transfusion requirements were reduced significantly by 43% with tranexamic acid and by 60% with aprotinin in 1 study. Meta-analysis of 60 trials showed tranexamic acid and aprotinin, unlike ε-aminocaproic acid (EACA) and desmopressin, to reduce significantly the number of patients requiring allogeneic blood transfusions after cardiac surgery with CPB.

Tranexamic acid was associated with reductions relative to placebo in mortality of 5 to 54% in patients with upper gastrointestinal bleeding. Meta-analysis indicated a reduction of 40%.

Reductions of 34 to 57.9% versus placebo or control in mean menstrual blood loss occurred during tranexamic acid therapy in women with menorrhagia; the drug has also been used to good effect in placental bleeding, postpartum haemorrhage and conisation of the cervix. Tranexamic acid significantly reduced mean blood losses after oral surgery in patients with haemophilia and was effective as a mouthwash in dental patients receiving oral anticoagulants.

Reductions in blood loss were also obtained with the use of the drug in patients undergoing orthotopic liver transplantation or transurethral prostatic surgery, and rates of rebleeding were reduced in patients with traumatic hyphaema. Clinical benefit has also been reported with tranexamic acid in patients with hereditary angioneurotic oedema.

Tranexamic acid is well tolerated; nausea and diarrhoea are the most common adverse events. Increased risk of thrombosis with the drug has not been demonstrated in clinical trials.

Conclusions: Tranexamic acid is useful in a wide range of haemorrhagic conditions. The drug reduces postoperative blood losses and transfusion requirements in a number of types of surgery, with potential cost and tolerability advantages over aprotinin, and appears to reduce rates of mortality and urgent surgery in patients with upper gastrointestinal haemorrhage. Tranexamic acid reduces menstrual blood loss and is a possible alternative to surgery in menorrhagia, and has been used successfully to control bleeding in pregnancy.

Pharmacodynamic Properties

Tranexamic acid exerts its antifibrinolytic effect by blocking lysine binding sites on plasminogen molecules and thereby inhibiting the interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin. Although plasmin can still be formed under these circumstances, it is unable to bind to and degrade fibrin.

Tranexamic acid is 6 to 10 times more potent in terms of binding to plasminogen/plasmin than the other synthetic antifibrinolytic agent ε-aminocaproic acid (EACA). Suppression of fibrinolysis by tranexamic acid is manifested in surgical patients by reductions in blood levels of D-dimer, but the drug has no effect on blood coagulation parameters. Concurrent administration of heparin does not influence the activity of tranexamic acid.

Pharmacokinetic Properties

Maximum plasma concentrations of tranexamic acid are attained within 3 hours of an oral dose; the presence of food in the gastrointestinal tract has no effect on the pharmacokinetic parameters of the drug. Elimination after intravenous administration is triexponential, and over 95% of each dose is eliminated as unchanged drug in the urine. The total cumulative excretion after an intravenous dose is approximately 90% after 24 hours.

Of the total amount of circulating tranexamic acid, 3% is bound to plasminogen. The drug crosses the blood-brain barrier and the placenta, but excretion into breast milk is minimal. Tranexamic acid is not detectable in saliva after systemic (oral) administration, and mouthwashing with 5% w/v aqueous solutions of the drug results in plasma drug concentrations below 2 mg/L.

Therapeutic Use

Cardiac Surgery. Perioperative treatment with tranexamic acid (most commonly as an intravenous loading dose of 10 mg/kg followed by an infusion of 1 mg/kg/hour) resulted in significant reductions in postoperative blood losses (mostly measured over 12 to 24 hours) in randomised, double-blind comparisons with placebo in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Losses via mediastinal drains were reduced by 29 to 54% relative to placebo, and statistically significant reductions in red blood cell transfusion requirements were reported in some but not all studies. Inconsistency in results with respect to reduction or elimination of transfusions may have been caused in part by variation between institutions in transfusion criteria.

The protease inhibitor aprotinin has been the most frequently used comparator in randomised but nonblind studies of tranexamic acid in patients undergoing cardiac surgery with CPB. Postoperative blood losses (over 6 hours) were reduced to a similar extent by tranexamic acid 10 mg/kg intravenously followed by infusion of 1 mg/kg/hour and aprotinin 2×10^6 kallikrein inhibitory units (KIU) intravenously in 1 study, with both treatments being superior to dipyridamole. Similar effects on postoperative blood losses with the 2 drugs were reported in 2 further studies. Both agents significantly reduced postoperative transfusion requirements in one of these trials (by 43 and 60% with tranexamic acid and aprotinin, respectively; both $p < 0.05$ *vs* control group). Other studies have shown greater reductions in 24-hour blood losses with aprotinin or EACA than with tranexamic acid, but definitive conclusions cannot be drawn from these trials because of inconsistent transfusion data and small patient numbers.

A meta-analysis of 60 randomised clinical trials of haemostatic agents in cardiac surgery with CPB showed tranexamic acid to be associated with a significant decrease (relative to placebo or no treatment) in the proportion of patients requir-

ing allogeneic blood transfusions. A similar effect was found with aprotinin but not with EACA or desmopressin.

Acute Upper Gastrointestinal Bleeding. Reduction of blood transfusion requirements with tranexamic acid therapy in patients with upper gastrointestinal bleeding was first described in 1973. In randomised double-blind studies, predominantly in patients with peptic ulceration or erosion, reductions relative to placebo in mortality rates have ranged from 5 to 54% with tranexamic acid (4.5 to 6g daily for 5 to 7 days in most studies); statistical significance between tranexamic acid and placebo was obtained in the largest published trial.

Meta-analysis of studies of tranexamic acid in patients with upper gastrointestinal haemorrhage showed the drug to be associated with reductions relative to placebo of 20 to 30% in rates of rebleeding, 30 to 40% in the need for surgery and 40% in mortality rates.

Oral Surgery. Proportions of patients with postoperative bleeding complications ranged from 0 to 6.7% when mouthwashes of tranexamic acid were used after oral surgery in patients receiving oral anticoagulant therapy. The corresponding range in patients who received placebo was 13.3 to 40%. In patients with haemophilia, 5 days' treatment with tranexamic acid 1g 3 times daily orally resulted in a mean blood loss after oral surgery of 61.2ml, compared with an 84.1ml loss with placebo, and reduced consumption of clotting factors (14.3 *vs* 78.6% of patients).

Other Surgery. Substantial and statistically significant reductions relative to placebo in mean postoperative blood losses (57 and 65.9%) were reported in 2 trials after perioperative tranexamic acid therapy in patients undergoing total knee arthroplasty, with significant reductions in transfusion requirements. Clinical benefit relative to placebo was obtained after intravenous infusion of tranexamic acid 40 mg/kg/hour in 1 study in patients undergoing orthotopic liver transplantation, with no episodes of hepatic artery or portal vein thrombosis occurring within 1 month of surgery.

Four-week incidences of haemorrhage after transurethral prostatic surgery in a randomised study in 100 men were 24% after treatment with tranexamic acid (1g 3 times daily orally) and 56% in patients who received no antifibrinolytic therapy.

Gynaecology. Reductions of 34 to 57.9% versus placebo or control in mean menstrual blood loss were reported in women with menorrhagia receiving 2 to 3 cycles of treatment with tranexamic acid. The drug was at least as effective as nonsteroidal anti-inflammatory therapy and more effective than etamsylate (ethamsylate) or norethisterone. Efficacy of tranexamic acid in the control of bleeding has also been reported in individual patients with placental abruption or postpartum haemorrhage. A mean 71% reduction in postoperative blood loss was noted in a double-blind study in patients who received tranexamic acid 1.5g daily orally for 12 days after conisation of the cervix. In another double-blind study, 1 of 38 patients who received tranexamic acid and 4 of 37 who received placebo experienced late bleeding after cervical conisation with suturing; the difference between groups was not statistically significant.

Other Indications. An oral dosage of tranexamic acid 1g 3 times daily significantly reduced the frequency of secondary ocular haemorrhage after traumatic hyphaema in controlled trials; further data from a case series of 340 children

showed rates of rebleeding of 1.1% and 9.6% in patients who received tranexamic acid and no antifibrinolytic therapy, respectively.

Reductions versus placebo in number and severity of attacks of oedema in patients with hereditary angioneurotic oedema were reported in 2 randomised, double-blind studies of tranexamic acid, and clinical benefit was obtained with the drug (1.5g orally 3 times daily) in 6 of 7 patients described in a case series.

There was a significant reduction (from 24% with placebo to 9% with tranexamic acid therapy for up to 4 weeks) in the rate of rebleeding in a randomised double blind placebo-controlled study in 479 patients with subarachnoid haemorrhage. However, overall outcome was not improved with tranexamic acid after 3 months; this was attributed to an increase in incidence of cerebral ischaemia.

Tolerability

Tranexamic acid is well tolerated. Adverse events are uncommon and usually manifest as nausea or diarrhoea, or occasionally as orthostatic reactions. Results of controlled clinical studies have not confirmed concerns over the possibility of an increased thrombotic tendency in patients treated with inhibitors of fibrinolysis. No increases in incidence of thrombotic events were reported with tranexamic acid in studies of patients undergoing cardiac surgery with CPB or in a retrospective case analysis of 256 women with bleeding disorders in pregnancy. No mutagenic activity or harmful fetal effects of tranexamic acid have been reported.

Retinal changes seen in dogs after very high dosages of tranexamic acid for 1 year have not been reported in humans receiving the drug at therapeutic dosages. However, disturbances in colour vision have been documented, and patients who develop this symptom should discontinue therapy.

Dosage and Administration

Tranexamic acid is presented in a variety of formulations for oral (tablets and syrup) or intravenous use. A dosage of 500mg to 1g by slow intravenous injection 3 times daily or 1 to 1.5g 2 to 3 times daily orally is recommended for local fibrinolysis. For general fibrinolysis, a single dose of 1g or 10 mg/kg by slow intravenous injection is recommended.

Patients undergoing cardiac surgery have most commonly received tranexamic acid intravenously as a 10 mg/kg dose before CPB and an infusion of 1 mg/kg/hour thereafter. A daily dosage of 4.5 to 6g daily (divided into 3 to 6 doses) for 5 to 7 days (intravenous followed by oral therapy) has been used most frequently in patients with upper gastrointestinal bleeding.

Patients with haemophilia who are about to undergo oral surgery require 1 to 1.5g orally every 8 hours, and a 4.8 to 5% mouthwash, used for 2 minutes 4 times daily for 7 days, has shown good efficacy in dental patients receiving anticoagulant therapy.

Intravenous infusion of 10 mg/kg before release of tourniquet may be used in patients undergoing knee arthroplasty, and treatment with oral tranexamic acid 6 to 12g daily for 4 days has been used in patients undergoing transurethral prostate surgery. Intravenous infusion of 40 mg/kg/hour has been used to good effect in patients undergoing orthotopic liver transplantation.

Women with menorrhagia should receive tranexamic acid 1 to 1.5g 3 to 4 times daily orally for 3 to 4 days. Dosages of 1.5g or 1 to 1.5g orally 3 times daily are recommended for conisation of the cervix or traumatic hyphaema, respectively, and oral treatment with 1.5g 3 times daily is recommended for the management of hereditary angioneurotic oedema.

Tranexamic acid is contraindicated in patients with a history of thromboem-

bolic disease, and dosage reductions are recommended in patients with renal insufficiency.

1. Blood Coagulation and the Fibrinolytic System

The blood coagulation cascade is the second key element in the formation of the haemostatic seal at sites of tissue injury, the first being the aggregation and deposition of platelets. This cascade consists of a sequence of reactions that leads to the cleavage of prothrombin into 2 fragments, one of which is the enzyme thrombin. Thrombin in turn cleaves small peptides from fibrinogen to produce fibrin monomer which then polymerises to form insoluble fibrin. Thrombin also activates factor XIII, an enzyme that catalyses the formation of covalent bonds between fibrin molecules to form a clot resistant to dissolution.[1]

The fibrinolytic system is activated by the deposition of fibrin and assists in the maintenance of an open lumen in damaged blood vessels. A balance between the formation and lysis of fibrin is required to maintain and remould the haemostatic seal during the several days in which the injured vessel wall is repaired.[1] Fibrinolysis is mediated through the activation of plasminogen, the plasma precursor of the proteolytic enzyme plasmin. Plasminogen binds to lysine residues on the surface of fibrin and is converted to plasmin by an activator released from endothelial cells [tissue plasminogen activator (t-PA)] that simultaneously binds to fibrin. Plasmin then degrades fibrin into large fragments known as X and Y; these are subsequently broken down into soluble fibrin degradation products.[1] Excessive fibrinolysis is prevented by the greater affinity of plasminogen for fibrin than for fibrinogen and the increased ability of t-PA to activate plasminogen when it is bound to fibrin. In addition, plasma contains a protease inhibitor called α_2-antiplasmin that rapidly inactivates any plasmin that escapes from a fibrin clot.[1]

Defective formation or excessively rapid dissolution of fibrin results in excessive or recurrent bleeding. The unwanted dissolution of haemostatic fibrin can be prevented by antifibrinolytic drugs that stabilise fibrin structures. Two synthetic derivatives of the amino acid lysine, tranexamic acid [4-(aminomethyl)cyclohexanecarboxylic acid] (fig. 1) and ε-aminocaproic acid (EACA; 6-aminohexanoic acid) have antifibrinolytic activity in humans. The activity of the *trans*-isomer of tranexamic acid was first described in 1964,[2] since which time the drug has been used in a variety of clinical settings. This review examines the status of the drug in the management of surgical and other conditions in which antifibrinolytic therapy is appropriate.

2. Overview of Pharmacodynamic Properties

The antifibrinolytic effect of tranexamic acid results from the formation of a reversible complex of the drug with plasminogen. Human plasminogen contains lysine binding sites that are important for interactions not only with synthetic antifibrinolytic amino acid derivatives but also with α_2-antiplasmin and fibrin.[3] One of these binding sites has a high affinity for tranexamic acid [dissociation constant (K_d) = 1.1 μmol/L]; the others have low affinity only (K_d = 750 μmol/L). Tranexamic acid almost completely blocks the interaction of plasminogen and the heavy chain of plasmin with the lysine residues of fibrin monomer, primarily through its binding to the high affinity lysine binding site of plasminogen.[4] Saturation of this site with tranexamic acid prevents binding of plasminogen to the surface of fibrin (fig. 2). This process

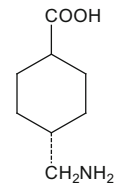

Fig. 1. Structural formula of tranexamic acid.

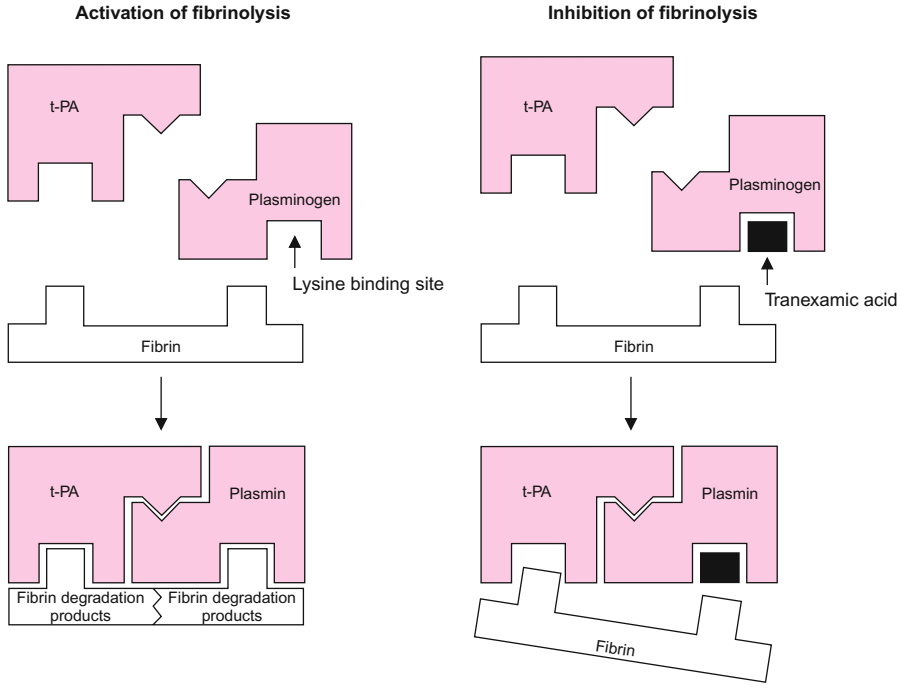

Fig. 2. Antifibrinolytic action of tranexamic acid. Normally, plasminogen binds to fibrin at a lysine binding site and is converted in the presence of tissue plasminogen activator (t-PA) to plasmin. Tranexamic acid blocks the lysine binding site and prevents access of plasminogen to the fibrin molecule.

retards fibrinolysis because, although plasmin is still formed, it is unable to bind to fibrinogen or fibrin monomer. Conversely, when the binding site of plasmin is blocked by tranexamic acid, inactivation by α_2-antiplasmin cannot proceed.

Comparisons of the binding potencies of tranexamic acid and EACA in fibrinolytic test systems have shown tranexamic acid to be more potent by a factor of between 6 and 10.[2,5-7] Tranexamic acid competitively inhibits the activation of trypsinogen by enterokinase and, at concentrations 4 times greater, noncompetitively inhibits the proteolytic action of trypsin.[8] The drug also weakly inhibits thrombin.[5]

The noncovalent interactions between plasminogen/plasmin and other macromolecules such as fibrin are mediated by a series of 5 triple disulphide-bonded plasmin(ogen) domains called kringles, each of which has a single binding site for lysine analogues.[9,10] Recent data indicate that both tranexamic acid and EACA interact with kringle 5.[11]

The pharmacodynamic effects of tranexamic acid vary according to the indication in which the drug is being used; observations from patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), women with menorrhagia, patients undergoing total knee arthroplasty and recipients of orthotopic liver transplants are summarised in table I. In these studies, suppression of fibrinolysis by tranexamic acid was manifested by reductions in blood levels of D-dimer (a breakdown product of cross-linked fibrin) relative to those in untreated patients, and the drug had no effect overall on blood coagulation parameters (e.g. platelet counts, activated partial thromboplastin times and prothrombin times). These observations are to be expected in view of the mechanism of action of tranexamic acid. Improved platelet function was indicated by

Table I. Pharmacodynamic properties of tranexamic acid in patients. Effects described are relative to those seen in untreated control or placebo groups

Patients undergoing cardiac surgery with CPB
Suppression of increase in blood D-dimer levels after surgery[12-14]
No effect on blood antiplasmin activity[14]
No effect on blood fibrinogen levels[12,13]
Reduction in blood levels of fibrinogen split products[a][15]
Reduction in platelet glycoprotein-1b receptor expression after CPB[16]
Blockade of plasmin-induced partial platelet activation during CPB[17]
No effect on aPTT, PT or platelet counts[12,13]
Women with menorrhagia
Reduced t-PA and plasmin activity in menstrual and peripheral blood[18]
Patients undergoing total knee arthroplasty
Reduced levels of D-dimer in wound blood[19]
No effect on α_2-antiplasmin, t-PA or PAI-1 levels in peripheral venous or wound blood[19]
No effect on levels of prothrombin fragments 1 and 2 or platelet counts in peripheral venous or wound blood[19]
Patients undergoing orthotopic liver transplantation
No effect on blood levels of fibrinogen or factors V, VII or VIII[20]
Patients with subarachnoid haemorrhage
Reduced plasminogen activity in blood and CSF[21]
No effect on levels of fibrin degradation products in CSF[21]

a Noted after initial dose of tranexamic acid before start of CPB. No significant difference from placebo after CPB.

aPTT = activated partial thromboplastin time; **CPB** = cardiopulmonary bypass; **PAI-1** = plasminogen activator inhibitor 1; **PT** = prothrombin time; **t-PA** = tissue plasminogen activator.

thromboelastogram results in 1 study,[15] but these findings were contradicted by those of another that showed no significant effect of tranexamic acid on this parameter.[13] Concurrent administration of heparin does not interfere with the antifibrinolytic activity of tranexamic acid.[22]

3. Overview of Pharmacokinetic Properties

Data from healthy volunteers showed maximum plasma concentrations of tranexamic acid to be reached within 3 hours of oral administration.[23] The presence of food had no effect on gastrointestinal absorption or other pharmacokinetic characteristics of the drug (table II). After intravenous administration of tranexamic acid (single dose of 1g), elimination followed 3 exponential phases, with over 95% of the dose being excreted unchanged in the urine. Total clearance (CL) ranged from 6.6 to 7 L/h (110 to 116 ml/min) in the 3 individuals who participated in this study. Mean total urinary excretion in terms of quantity of drug administered was 959 mg/g.[23] Other data have shown that approximately 30% of an intravenous dose of 10 mg/kg is recovered in the urine during the first hour after administration; the total excretion rises to 45% after 3 hours, and to approximately 90% after 24 hours.[5,6]

At therapeutic plasma concentrations (5 to 10 mg/L), tranexamic acid is weakly (approximately 3%) bound to plasma protein: this appears to be fully accounted for by binding to plasminogen.[24] The drug crosses the blood-brain barrier[25] and diffuses rapidly into joint fluid and synovial membranes.[26] Excretion in breast milk is low: the concentration of tranexamic acid in breast milk of lactating women 1 hour after the last dose of 2 days' treatment was approximately 1% of the peak serum concentration.[27] The drug also passes through the placenta.[28,29]

Tranexamic acid could not be detected in the saliva of healthy volunteers who had received

Table II. Pharmacokinetics of tranexamic acid. Single oral doses of 2g of tranexamic acid were given to 3 healthy volunteers. Each volunteer received 1 dose while fasting and another after a standard meal[23]

Parameter (mean value)	Fasting	After food
C_{max} (mg/L)	14.4	14.8
t_{max} (h)	2.8	2.9
AUC_{6h} (mg/L • h)	59.5	61.3
AUC_{∞} (mg/L • h)	147.7[a]	
F (%)	33.4	34.9
CL_R (L/h)	8.2	7.9
Ae_{24h} (mg)	639	669

a Overall mean result (fasting and non-fasting).

Ae_{24h} = amount excreted in urine in 24 hours; **AUC_{6h}** = area under the plasma drug concentration versus time curve from zero to 6 hours; **AUC_{∞}** = area under the plasma drug concentration versus time curve from zero to infinity; **C_{max}** = peak plasma drug concentration; **CL_R** = renal clearance; **F** = systemic bioavailability; **t_{max}** = time to C_{max}.

single oral doses of 1g.[30] However, very high drug concentrations (mean 200 mg/L) were attained in saliva 30 minutes after mouth rinsing for 2 minutes with a 5% aqueous solution of tranexamic acid, while plasma concentrations remained below 2 mg/L. This formulation has been investigated in patients undergoing oral surgery (section 4.4).

4. Therapeutic Use

4.1 Use in Cardiac Surgery With Cardiopulmonary Bypass

Excessive bleeding after surgery involving CPB is attributable to the size of the surgical wound required for these procedures and by the activation of both coagulation and fibrinolysis by the passage of blood through the CPB circuit. This stimulation of the formation and dissolution of clots results in excessive consumption of coagulation factors and predisposes patients to prolonged and excessive bleeding.[31]

The problem is exacerbated by loss of platelets and impairment of their adhesion and aggregation because of enzymatic and mechanical injury in the extracorporeal oxygenator. Transfused blood products are used extensively in patients undergoing cardiac surgery, but recent concern over the availability and safety of these products has prompted much interest in methods of minimising perioperative transfusion requirements.[32-34] These include autologous blood donation, intra- and postoperative cell salvage, normovolaemic haemodilution and pharmacological methods.[35] As drug therapy is easy to use and allows the complex and time-consuming measures associated with autologous blood transfusion to be avoided,[34] prophylactic administration of antifibrinolytic drugs in patients undergoing CPB has been investigated extensively since the late 1970s.

The most important outcome in studies of the efficacy of antifibrinolytic therapy in patients who undergo cardiac surgery is reduction in use of allogeneic blood products. However, many groups of investigators have measured intermediate outcomes (e.g. postoperative bleeding, coagulation profiles and platelet counts) on the assumption that any beneficial effects on these parameters will result in reduced transfusion requirements.[36]

Appropriate analysis of data is also important if results are to be interpreted in a clinically relevant manner: ideally, the percentage of patients who received allogeneic blood and the median number of units used should be reported (since most blood products are administered in predetermined units). Nonparametric statistical methods are also desirable in most analyses because blood product usage does not follow a normal distribution: many patients will require few or no transfusions, whereas a small number will require large quantities of red cells and haemostatic products.[36]

The efficacy of tranexamic acid in the reduction of blood loss and transfusion requirements in patients undergoing cardiac surgery with CPB has been assessed in comparisons with no antifibrinolytic therapy, with the other synthetic lysine derivative EACA, with aprotinin (a protease inhibitor derived from bovine lung tissue) and with desmopressin (a synthetic polypeptide related to antidiuretic hormone that shortens bleeding time by inducing factor VIII:von Willebrand factor release). In this review, emphasis will be given to randomised studies with untreated or placebo control groups in which proportions of patients who received at least 1 unit of allogeneic red blood cells after surgery were reported. Most of the studies were conducted in a double-blind manner; others did not include administration of placebo infusions to patients in the control group, however. Studies are summarised in tables III and IV.

In most of the studies listed, patients underwent coronary artery bypass graft (CABG) surgery, valve replacement or both. Some investigators included only patients undergoing repeat surgery;[13,38] this is noteworthy because such procedures are associated with longer coronary bypass times, more extensive tissue dissection and more severe perioperative bleeding than primary cardiac surgery.[13] Initial loading doses were typically given 20 to 30 minutes before surgery, with further drug being infused during the procedure. However, a

Table III. Efficacy of tranexamic acid (TRA) in cardiac surgery. Results of randomised, double-blind placebo (PL)-controlled studies in which postoperative blood losses and transfusion requirements were measured in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Results are means ± standard errors and all drugs were given intravenously unless stated otherwise

Reference	No. of patients evaluated	Treatment	Postoperative blood loss	Proportion of patients transfused (%)	Red blood cells transfused	Relative efficacy
Brown et al.[15]	30	TRA 15 mg/kg before CPB, then 1 mg/kg/h × 5h	710ml[a]**	27*	NS between groups (figures NA)	TRA before/during surgery > TRA after > PL
	30	TRA 15 mg/kg after CPB, then 1 mg/kg/h × 5h	1020ml[a]	33*		
	30	PL	1202ml[a]	66		
Coffey et al.[37]	16	TRA 10mg/kg, then 1 mg/kg/h × 12h	711 ± 96ml*	56	356ml	TRA > PL
	14	PL	1160 ± 168ml	57	528ml	
Dryden et al.[38]	22	TRA 10g	538ml[a]**	NA	480ml[a]**	TRA > PL
	19	PL	1170ml[a]	NA	1500ml[a]	
Hardy et al.[39]	43	TRA 10g, then PL infusion during surgery	438ml[a]**	67	2U[a]	TRA ≡ EACA > PL
	46	EACA 15g, then 1 g/h during surgery	538ml[ab]	50	2U[a]	
	45	PL	700ml[a]	61	2U[a]	
Horrow et al.[40]	18	TRA 10 mg/kg, then 1 mg/kg/h × 10h	496 ± 228ml[c]**	NA	275 ± 241ml[c]	TRA > PL
	20	PL	750 ± 314ml[c]	NA	227 ± 324ml[c]	
Horrow et al.[41]	37	TRA 10 mg/kg, then 1 mg/kg/h × 12h	328g***	11	NA	TRA > DES ≡ PL
	38	DES 0.3 μg/kg after heparin reversal	443g	24	NA	
	40	TRA + DES (dosages as above)	310g***	5	NA	
	44	PL	462g	18	NA	
Horrow et al.[12]	24	TRA 2.5 mg/kg, then 0.25 mg/kg/h × 12h	504g	21	NS between groups	TRA 10 mg/kg + 1.0 mg/kg/h > PL. No additional benefit with larger doses
	22	TRA 5.0 mg/kg, then 0.5 mg/kg/h × 12h	386g	14		
	21	TRA 10 mg/kg, then 1 mg/kg/h × 12h	365g*	19		
	27	TRA 20 mg/kg, then 2 mg/kg/h × 12h	344g*	15		
	27	TRA 40 mg/kg, then 4 mg/kg/h × 12h	369g*	15		
	27	PL	552g	15		
Katsaros et al.[42]	104	TRA 10g infused over 20min after anaesthesia induction	474 ± 24ml***	12*	89 ± 18ml***	TRA > PL
	106	PL	906 ± 51ml	25	273 ± 34ml	
Shore-Lesserson et al.[13]	17	TRA 20 mg/kg, then 2 mg/kg/h during surgery	649 ± 391ml[c]**	59*	500ml[a]	TRA > PL
	13	PL	923 ± 496ml[c]	92	750ml[a]	

a Median.

b Borderline statistical significance (p = 0.05 *vs* placebo).

c Mean ± standard deviation.

DES = desmopressin; **EACA** = ε-aminocaproic acid; **NA** = information not available; **NS** = no statistically significant difference; **U** = units; * p < 0.05, ** p < 0.01, *** p < 0.001 *vs* placebo; **>** indicates greater efficacy; ≡ indicates equivalent efficacy.

Table IV. Efficacy of tranexamic acid (TRA) in cardiac surgery. Results of randomised (unless stated otherwise) studies [use of placebo (PL) in control group not stated] in which postoperative blood losses and transfusion requirements were measured in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Results are means ± standard errors and all drugs were given intravenously unless stated otherwise

Reference	No. of patients evaluated	Treatment	Postoperative blood loss	Proportion of patients transfused (%)	Red blood cells transfused	Relative efficacy
Blauhut et al.[14]	15	TRA 10 mg/kg, then 1 mg/kg/h × 10h	403 ± 52ml	47*	0.80 ± 0.28U	APR > TRA ≥ no treatment
	14	APR 2×10^6 KIU, then 0.5×10^6 KIU/h + 1×10^6 KIU in CPB circuit	269 ± 38ml*	21*	0.36 ± 0.20U*	
	14	No antifibrinolytic therapy	453 ± 52ml	64	1.57 ± 0.40U	
Corbeau et al.[43]	41	TRA 15 mg/kg after heparinisation + 15 mg/kg after heparin reversal	1015 ± 409ml[a]*	37	0.8 ± 1.1U[a]	TRA ≡ APR > no treatment
	43	APR 2×10^6 KIU, then 0.5×10^6 KIU/h + 2×10^6 KIU in CPB circuit	834 ± 448ml[a]*	35	0.8 ± 1.4U[a]	
	20	No antifibrinolytic therapy	1416 ± 559ml[a]	60	1.7 ± 1.8[a]	
Menichetti et al.[44]	24	TRA 10 mg/kg, then 3 mg/kg/h + 10 mg/kg in CPB circuit	737 ± 400ml*	50*	NA	APR ≥ EACA > TRA > no treatment
	24	APR 2×10^6 KIU, then 0.5×10^6 KIU/h + 2×10^6 KIU in CPB circuit	298 ± 140ml*	8*	NA	
	24	EACA 80 mg/kg, then 30 mg/kg/h + 80mg in CPB circuit	512 ± 250ml*	17*	NA	
	24	No antifibrinolytic treatment	811 ± 600ml	75	NA	
Penta de Peppo et al.[45]	15	TRA 10 mg/kg, then 1 mg/kg/h × 10h	534 ± 288ml[a]	7	NA	APR ≥ EACA ≥ TRA ≡ no treatment
	15	APR 2×10^6 KIU, then 0.5×10^6 KIU/h during surgery + 2×10^6 KIU in CPB circuit	344 ± 106ml[a]***	0	NA	
	15	EACA 10g, then 2 g/h × 5h	509 ± 148ml[a]*	20	NA	
	15	No antifibrinolytic treatment	724 ± 280ml[a]	20	NA	
Pugh & Wielogorski[46]	22	TRA 2.5g + 2.5g in CPB circuit	375ml[b]*	NA	600ml[b]	TRA ≡ APR > no treatment
	21	APR 1×10^6 KIU + 1×10^6 KIU in CPB circuit	230ml[b]*	NA	420ml[b]	
	23	No antifibrinolytic treatment	615ml[b]	NA	1050ml[b]	
Rousou et al.[47][c]	206	TRA 2g, then 8g infused during CPB	803.7 ± 44.13ml***	35**	0.69U***	TRA > no treatment
	209	No antifibrinolytic treatment	1114.1 ± 44.66ml	51	1.27U	
Speekenbrink et al.[48]	15	TRA 10 mg/kg, then 1 mg/kg/h to total dose of 1g	352 ± 150ml[a]*	87	2.9 ± 1.9U[a]	TRA ≡ APR > DIP ≥ no treatment
	15	APR 2×10^6 KIU to CPB circuit	270 ± 174ml[a]**	80	2.3 ± 2.1U[a]	
	15	DIP 100mg qid orally from 36h before surgery, then 0.24 mg/kg/h × 24h	523 ± 275ml[a]	93	2.3 ± 1.7U[a]	
	15	No antifibrinolytic treatment	674 ± 411ml[a]	73	3.1 ± 3.3U[a]	

a Mean ± standard deviation.

b Median.

c Nonrandomised study. Patients were recruited during 2 consecutive 6-month periods.

APR = aprotinin; **DIP** = dipyridamole; **EACA** = epsilon-aminocaproic acid; **KIU** = kallikrein inhibitory units; **NA** = information not available; **qid** = 4 times daily; **U** = units; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* placebo; **>** indicates greater efficacy; ≥ indicates tendency to greater efficacy; ≡ indicates equivalent efficacy.

single pre-operative dose was used alone in some studies.[38,39,42,46] In addition, Corbeau and colleagues[43] gave a second dose of tranexamic acid after heparin reversal at the end of surgery, and some investigators added additional drug to the CPB circuit.[44,46] Antifibrinolytic treatment was most commonly given for 10 to 12 hours. Appropriate nonparametric statistical methods were used in most cases [or parametric analysis of variance (ANOVA) after logarithmic transformation of data], although some investigators reported use of t-tests only (with no further details of data handling).[37,45] Blood losses were recorded most commonly over 12 to 24 hours, although some authors reported 6-[48] or 48-hour[43] losses.

4.1.1 Comparisons With Placebo

Overall, tranexamic acid was shown to be statistically and clinically superior to placebo in terms of reduction of blood loss in the double-blind studies summarised in table III. The most common regimen consisted of a loading dose of 10 mg/kg followed by an infusion of 1 mg/kg/hour (higher dosages were shown to confer no additional benefit[12]). Mediastinal drain losses in patients receiving the drug ranged in these studies from 29 to 54% of those seen with placebo, with reductions of around one-third being most frequent. In addition, Karski et al. reported reductions in 24-hour blood losses of 35 and 37% relative to placebo ($p = 0.0001$) after total perioperative tranexamic acid doses of 10 and 20g, respectively, in their double-blind study in 147 patients.[49] There was no statistically significant difference between the active treatment groups.

Statistically significant reductions in proportions of patients who required transfusions of allogeneic red blood cells were also reported,[13,15,42] although these data are less consistent (table III). Coffey et al.[37] and Hardy et al.[39] showed transfusion requirements to be similar between groups. The reasons for these findings are not clear, although limited sizes of patient groups (especially in the study of Coffey et al.[37]) and the inclusion of patients undergoing primary surgery only by Hardy et al.[39] may have contributed to this effect. Furthermore, transfusion criteria vary between different institutions and were not uniform across the studies. Horrow et al.[12] found no differences between groups in transfusion requirements in their comparison of 5 dosages of tranexamic acid with placebo, and suggested that their strict criteria for transfusion (including haematocrit ≤21%) might have accounted for this. Tranexamic acid was associated with a significant ($p = 0.01$) reduction in median overall exposure to allogeneic blood products in the study of Hardy et al., however.[39]

Karski et al.[49] noted no overall difference in red blood cell transfusion requirements between treatment and placebo groups, but did report a 93% increase in transfusion volume in 11 patients with excessive bleeding (6-hour blood loss >750ml), 9 of whom received placebo.

4.1.2 Comparisons With Other Agents

Comparisons of tranexamic acid with other agents have been carried out mainly in randomised nonblind studies, although comparable efficacy to EACA and superiority over desmopressin have been shown in placebo-controlled studies[39,41] (table III). Initial data analysis in one of these trials suggested similar efficacy for tranexamic acid 1 mg/kg/hour (after a loading dose of 10 mg/kg) and desmopressin 0.3 μg/kg (before and after surgery) in terms of proportions of patients who received blood transfusions.[41] However, subsequent 2×2 analysis indicated that 8% of all patients who received tranexamic acid alone or tranexamic acid with desmopressin and 21% of those receiving desmopressin alone or placebo required transfusions ($p = 0.024$).

Other comparisons have been carried out in a nonblind fashion in small numbers of patients. Aprotinin has been the most common comparator, administered intravenously usually as a loading dose of 2.0×10^6 kallikrein inhibitory units (KIU) with an infusion during surgery of 0.5×10^6 KIU. In most studies, aprotinin was added to the CPB circuit, usually in addition to a loading dose and infusion (table IV). Speekenbrink et al.[48] showed tranexamic acid (10 mg/kg loading dose + 1 mg/kg/hour) to be equivalent in efficacy to aprotinin

(2×10^6 KIU) in terms of postoperative blood loss, with both treatments being superior to the platelet aggregation inhibitor dipyridamole. However, proportions of patients receiving allogeneic blood transfusions were similar in all groups; in addition, data were recorded for only 6 hours after surgery.

Tranexamic acid and aprotinin were associated with similar reductions in postoperative blood loss (relative to untreated control patients) in 2 studies.[43,46] In one of these, reductions in transfusion requirements of 43 and 60% for tranexamic acid and aprotinin, respectively, were reported ($p < 0.05$ *vs* control group for both agents) [table IV].[46] Corbeau et al.[43] stated that the greater reduction in 48-hour postoperative bleeding with aprotinin seen in their study was accounted for by blood losses in patients undergoing CABG (n = 55), with no significant difference in patients undergoing aortic valve replacement (n = 49). Similar reductions in proportions of patients who needed blood transfusions (38 to 42% *vs* control group) and mean numbers of units transfused (53% *vs* control group) were seen in both active treatment groups, although statistical significance versus control was not attained. Other reports showed greater reductions in 24-hour postoperative blood losses with aprotinin or EACA than with tranexamic acid.[14,44,45] However, in terms of statistical significance between groups, transfusion data did not match these findings in 2 studies,[14,45] and patient numbers were too small for definitive conclusions to be drawn in all three.

A meta-analysis of 60 randomised controlled trials in patients undergoing cardiac surgery, of which 12 assessed tranexamic acid (882 patients; median sample size 47), 45 assessed aprotinin (5808 patients), 12 assessed desmopressin (793 patients) and 3 assessed EACA (118 patients), showed tranexamic acid to be associated with a significant decrease versus placebo or no treatment in the overall proportion of patients who required transfusion of allogeneic blood [odds ratio (OR) 0.50; 95% confidence interval (CI) 0.34–0.76; $p = 0.0009$], as was aprotinin (OR 0.31; 95% CI 0.25–0.39; $p < 0.0001$).[35] Neither EACA nor desmopressin had a statistically significant effect on the proportion of patients who received transfusions, although only a small number of EACA recipients were included in this analysis.

4.2 Use in Acute Upper Gastrointestinal Bleeding

The rationale for the use of antifibrinolytic drugs in the management of bleeding from gastrointestinal lesions is based on observations of high local levels of fibrinolytic enzymes in the gastrointestinal tract.[50] Common causes of such bleeding include duodenal ulceration, gastric or duodenal erosion, varices, gastric ulceration, Mallory-Weiss lesions, erosive oesophagitis and angioma.[1] Despite improvements in diagnostic techniques, the overall mortality rate from upper gastrointestinal bleeding has changed little over past decades: an investigation carried out in the early 1990s indicated that, of 2217 patients with haematemesis and malaena, 8.5% died and 11% experienced rebleeding after initial treatment.[51] Death was associated with rebleeding, age over 60 years and the finding of blood in the stomach at endoscopy.

Drugs used in patients with upper gastrointestinal bleeding include antacids, histamine-H_2 receptor antagonists and antifibrinolytic agents. Survival is the most important measure of success with any treatment in this condition: most deaths are reported within 1 or 2 weeks of the initial bleed, and benefit of therapy will therefore be apparent after only short courses of treatment.[52]

Reduction by tranexamic acid of blood transfusion requirements in patients with haemorrhage of the stomach or duodenum was first reported in 1973,[53] and a small number of additional studies has been conducted since that time (table V).

Peptic ulceration or erosion was the predominant cause of bleeding, and diagnoses were made with radiography and/or endoscopy. Treatment regimens varied, but patients received tranexamic acid 4.5 to 6g daily for 5 to 7 days in most studies. Sex and age distributions were similar across the studies, all of which were randomised and double-blind.

Table V. Efficacy of tranexamic acid (TRA) in upper gastrointestinal bleeding. Effect on clinical end-points in randomised, double-blind placebo (PL)-controlled studies

Reference	No. patients of evaluated [mean age (y)]	Treatment regimens	Deaths	No. patients with rebleeding	No. of patients needing surgery
Barer et al.[54]	256 [60.4]	TRA 1g IV q6h × 2d, then 1g PO q6h × 5d	16 (6.3%)**	58 (22.7%)	47 (18.4%)
	259 [60.8]	CIM 400mg IV q6h × 2d, then 400mg PO q6h × 5d	20 (7.7%)*	50 (19.3%)	36 (13.9%)
	260 [62.9]	PL	35 (13.5%)	51 (19.6%)	40 (15.4%)
Bergqvist et al.[55]	21 [60.8]	TRA 2g PO q4h × 2d	3 (14.3%)	NA	7 (33.3%)
	22 [57.6]	PL	5 (22.7%)	NA	7 (31.8%)
Biggs et al.[56]	103[a]	TRA 1g IV + 1g PO q8h × 2d, then 1g PO q8h × 3d	2 (1.9%)	7 (6.8%)	7 (6.8%)**
	97[a]	PL	4 (4.1%)	19 (19.6%)	21 (21.6%)
Cormack et al. [53]	76[b]	TRA 1.5g PO q8h × 7d	3 (3.9%)	8 (10.5%)[c]	NA
	74[b]	PL	3 (4.1%)	11 (14.9%)[c]	NA
Engqvist et al.[57]	76 [58.8]	TRA 1g IV q4h × ≤3d, then 1.5g PO qid ≤4d	11 (14.5%)	23 (30.3%)	10 (13.2%)
	73 [56.4]	PL	12 (16.4%)	29 (39.7%)	18 (24.7%)
Staël von Holstein et al.[58]	72 [62.4]	TRA 1g IV q4h × 3d, then 1.5g PO q6h × 3d	2 (2.8%)	10 (13.9%)	3 (4.2%)*
	82 [65.4]	PL	4 (4.9%)	19 (23.2%)	15 (18.3%)

a Majority of patients aged ≥50y (numbers not given).

b 59% of patients aged >60y.

c No. of patients who required transfusions.

CIM = cimetidine; **IV** = intravenously; **NA** = data not available; **PO** = orally; **q4h** = every 4 hours; **q6h** = every 6 hours; **q8h** = every 8 hours; **qid** = 4 times daily; * $p < 0.05$, ** $p < 0.01$ *vs* placebo.

Reductions relative to placebo in rates of mortality after treatment with tranexamic acid ranged from 5 to 54%, although most investigators had randomised too few patients for definitive conclusions to be drawn. Statistical significance in favour of tranexamic acid was attained in the largest study, however (6.3 *vs* 13.5%; $p = 0.0092$); a similar effect was noted for cimetidine (7.7 *vs* 13.5% with placebo; $p = 0.045$).[54]

Rates of rebleeding (or continued bleeding) after treatment were reduced substantially relative to placebo in 2 studies (by 65%[56] and 40%[58]), but statistical significance was not attained in either case. In one of these trials,[56] rebleeding was analysed only if it was severe enough to warrant surgery; in others, rebleeding was defined as a fresh haemorrhage or fall in haemoglobin levels after admission.[54,58] Tranexamic acid was associated with statistically significant reductions in numbers of patients requiring surgery in 2 studies,[56,58] and with a nonsignificant reduction relative to placebo of 47% in one other.[57] Patients who received tranexamic acid appeared the most likely to undergo surgery in the study of Barer et al.;[54] however, the differences between treatment groups were not statistically significant, and these patients were the least likely to die after surgery (their postoperative mortality rate was 31% of that in the placebo group). It should be noted that criteria for surgery were not clearly specified by most investigators, but that the majority of operations were in patients with severe continued or recurrent haemorrhage. Patients randomised to tranexamic acid in the study of Staël von Holstein et al.[58] required statistically significantly fewer units of transfused blood than those randomised to placebo, and a substantial but statistically nonsignificant reduction in the total number of units transfused was reported by Cormack et al.[53] (fig. 3).

Meta-analysis of the above 6 studies showed treatment with tranexamic acid to be associated with a 20 to 30% reduction versus no treatment in the rate of rebleeding, a 30 to 40% reduction in the need for surgery and a 40% reduction in mortal-

ity.[52] The pooled odds ratio relative to placebo of 0.60 for mortality rates achieved statistical significance ($p < 0.05$) with each of 2 meta-analytical methods (95% CIs 0.40–0.89 and 0.39–0.90).

4.3 Use in Oral Surgery

Bleeding after oral surgical procedures can be excessive, and is potentially hazardous in patients with haemophilia and in those requiring long term anticoagulant therapy, not least because the oral mucosa and saliva are rich in plasminogen activators.[59] Conventional prophylaxis and treatment of excessive haemorrhage in dental patients with haemophilia involves replacement therapy with plasma concentrates of factor VIII or factor IX.[60]

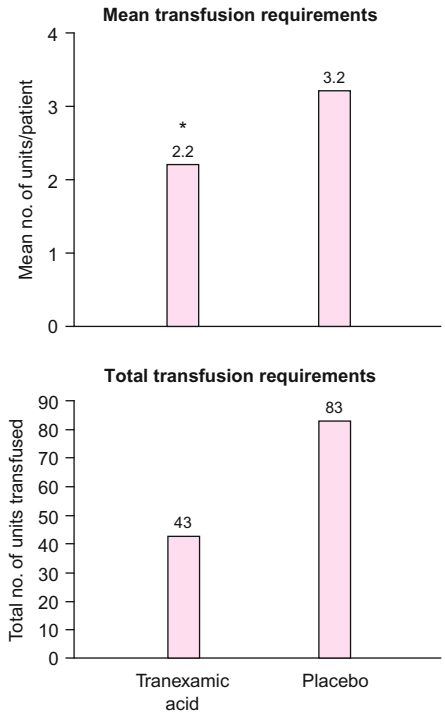

Fig. 3. Effect of tranexamic acid on transfusion requirements in patients with acute upper GI bleeding. Mean number of units of blood transfused per patient after 6 days' (3 days' intravenous and 3 days' oral) treatment with tranexamic acid 6 g/day (n = 72) or placebo (n = 82)[58] and total number of units of blood transfused after 7 days' treatment with tranexamic acid 4.5 g/day (n = 76) or placebo (n = 74).[53] * p = 0.018 *vs* placebo.

Patients taking anticoagulant medication (most commonly for cardiac conditions) have their anticoagulant dosages reduced or discontinued (with attendant increases in the risk of thromboembolic complications) before oral surgery.[61] Interest in the use of antifibrinolytic therapy in these groups of patients has been stimulated by the potential of such treatment to reduce or eliminate the need for transfused coagulation factors and to render unnecessary alterations in oral anticoagulant regimens, particularly in the light of early data showing reductions in clotting factor concentrate requirements and days spent in hospital after tranexamic acid and antibiotic therapy were added to treatment schedules.[62]

4.3.1 Patients Receiving Anticoagulant Therapy

Three randomised, double-blind placebo-controlled studies have been carried out to assess the effect of tranexamic acid on bleeding complications after oral surgery in patients with cardiac conditions being managed with long term oral anticoagulation therapy (table VI). Two-minute mouthwashes were used in preference to conventional oral therapy in all studies because systemic administration of tranexamic acid does not result in therapeutic drug concentrations in saliva[30] (section 3) and because plasma drug concentrations are not clinically significant after mouthwash therapy.[30] Whereas no attempt was made to adjust anticoagulant dosages or clotting times in 2 of these studies,[64,65] anticoagulant therapy was stopped and the international normalised ratio (INR) reduced from 3.0 to 4.5 to between 1.5 and 2.5 in patients randomised to placebo in the other (with blinding maintained for the operating oral surgeon).[63] Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) were not allowed for at least 2 weeks before surgery in 2 studies;[64,65] however, these drugs were stated to have been excluded for 1 week after surgery only in the third.[63]

Overall, proportions of patients with postoperative bleeding complications ranged from 0 to 6.7% with tranexamic acid and from 13.3 to 40% with placebo. Additional data from a nonblind study in 92 patients receiving various oral anticoagulant

Table VI. Antifibrinolytic efficacy of tranexamic acid mouthwash (TRA) in oral surgery. Results of randomised, double-blind placebo (PL)-controlled studies in patients receiving oral anticoagulant therapy for cardiac indications

Reference	Procedures	No. of patients evaluated (INR range)	Treatment regimen	Percentage of patients with postoperative bleeding complications	Comments
Borea et al.[63]	Extraction with or without mucosal flap raising/suturing	15 (3.0–4.5)	TRA 4.8% w/v for 2 min qid × 7d after surgery	6.7[a]	Bleeding complication = bleeding for >20 min
		15 (1.5–2.5)	PL	13.3[a]	
Ramström et al.[64]	Extraction, removal of retained teeth or endodontic surgery	44 (2.1–4.0)	TRA 5.0% w/v for 2 min qid × 7d after surgery	0**	Bleeding complication = bleeding for >20 min not controlled by compression with gauze
		45 (2.1–4.0)	PL	22.2	
Sindet-Pedersen et al.[65]	Extraction with or without mucosal flap raising/suturing. Bone removal in 10 PL and 6 TRA patients	19 (2.5–4.8)	TRA 4.8% w/v for 2 min qid × 7d after surgery	5.3*	Bleeding complication = bleeding for >20 min not controlled by compression with gauze
		20 (2.5–4.8)	PL	40.0	

a Anticoagulant therapy was withdrawn in patients randomised to placebo.

INR = international normalised ratio; **qid** = 4 times daily; * $p < 0.05$, ** $p < 0.01$ *vs* placebo.

regimens suggest that adjustment of anticoagulant dosages and addition of heparin are unnecessary in patients receiving tranexamic acid mouthwash after oral surgery.[61]

4.3.2 Patients With Haemophilia

Five days' treatment with tranexamic acid at an oral dosage of 1g 3 times daily from 2 hours before surgery (n = 14) was associated with a mean postoperative blood loss of 61.2ml in an early study in patients with haemophilia.[66] This was statistically significantly lower ($p < 0.025$) than the mean loss of 84.1ml recorded in 14 patients who received placebo. Plasma concentrates of factors VIII and IX equivalent to 1L of human plasma were given to all patients 1 hour before dental extraction; the decision to transfuse additional factor VIII or IX was based on the clinician's subjective assessment of clinical need and not on specified criteria. Tranexamic acid mouthwash was associated with a substantial decrease in the use of additional clotting factors (14.3 *vs* 78.6% of patients who received placebo), although statistical significance was not stated.

Statistically significant reductions with tranexamic acid mouthwash in rates of bleeding complications and clotting factor requirements were also reported in a nonblind study in 40 patients divided into 3 treatment groups.[60] Two groups received high doses of factor concentrate (groups A and B) and the third (group C) received low doses only (to bring plasma clotting factor levels to approximately 10% of normal values). All patients also received systemic therapy with tranexamic acid (37 to 103 mg/kg/day), but mouthwash (5% w/v 4 times daily) was also used in groups B and C only. There were no bleeding complications after oral surgery in group B ($p < 0.05$ *vs* group A), and the mean quantity of clotting factor concentrates needed in group C was lower than that required for group A or B ($p < 0.01$).

4.4 Use in Other Types of Surgery

Clinical benefit of tranexamic acid in terms of reduction of perioperative blood loss and transfusion requirements has been assessed in numerous studies in patients undergoing surgery associated with high levels of perioperative bleeding. Of particular interest are orthopaedic surgery, liver transplantation and procedures involving the urinary tract.

4.4.1 Orthopaedic Surgery

The use of a pneumatic tourniquet to produce a dry surgical field in joint replacement surgery is associated with enhancement of local fibrinolytic

activity and subsequent increases in postoperative blood loss.[67] Table VII shows details and results of 2 well designed clinical studies in patients undergoing total knee arthroplasty, both of which showed substantial and statistically significant reductions (57 and 65.9%) versus placebo in mean postoperative blood loss after perioperative tranexamic acid therapy. Significant reductions in transfusion requirements were also recorded (table VII). These results confirmed earlier observations in 29 patients undergoing total knee arthroplasty.[70] In one of the studies,[69] 15 patients in the placebo group were given tranexamic acid in an attempt to control heavy bleeding after surgery. Subsequent reductions in blood loss were minimal, however, and the authors concluded that the drug has little effect when used under these circumstances.

4.4.2 Orthotopic Liver Transplantation

Patients undergoing orthotopic liver transplantation experience extensive bleeding, the surgical causes of which include portal hypertension, transection of the numerous collateral channels, fragility of the tissues involved and the complexity and duration of this major vascular procedure.[71] In addition, the coagulation system undergoes profound changes, including dilutional coagulopathy before removal of the liver and further deterioration (caused by the absence of the normal hepatic synthetic and clearance mechanisms) during the anhepatic phase, during this type of surgery.[71]

One randomised, double-blind and placebo-controlled study has shown clinical benefit with tranexamic acid (intravenous infusion of 40 mg/kg/hour to a maximum dose of 20g) in patients undergoing primary isolated orthotopic liver transplantation (fig. 4).[72] Exclusion criteria included primary biliary cirrhosis and primary sclerosing cholangitis (both of which carry increased risk of major surgical blood loss) and Budd-Chiari syndrome (because of its association with increased rates of thrombosis). Veno-venous bypass was used in 40% of patients on tranexamic acid and 35% of those who received placebo, and all patients received dipyridamole and heparin for 24 hours after completion of hepatic arterial anastomosis. No episodes of hepatic artery or portal vein thrombosis were reported within 1 month of surgery, and there were no significant differences be-

Table VII. Efficacy of tranexamic acid (TRA) in orthopaedic surgery. Effects on postoperative blood loss and transfusion requirements in patients undergoing total knee arthroplasty. Studies were randomised, double-blind and placebo (PL)-controlled and involved patients receiving cemented or uncemented prostheses. All patients received thromboprophylaxis with low molecular weight heparin, and blood losses from intra-articular and subcutaneous drains were measured

Reference	No. of patients evaluated [mean age (y)]	Regimen	Mean postoperative blood loss (ml) ± SD	Proportion of patients transfused (%)	Total no. of red blood cell units transfused in each group	Comments
Benoni & Fredin[68]	43 [76]	TRA 10 mg/kg IV infusion (maximum dose 1g) before release of tourniquet and after 3h	520 ± 230**	18.6***	12**	Blood losses recorded until drain removal (24–33h)
	43 [74]	PL	1210 ± 480	55.8	40	
Hiippala et al.[69]	39 [70]	TRA 15 mg/kg IV infusion before release of tourniquet, then 10 mg/kg after 3–4h and 6–7h	128 ± 76† (recovery) + 278 ± 170† (surgical ward)	43.6†	38	Blood losses recorded until drain removal. Blood transfusion when Hb < 6.2 mmol/L
	38 [69]	PL	641 ± 320 (recovery) + 550 ± 349 (surgical ward)	89.5	117	

Hb = haemoglobin level; **IV** = intravenous; **NA** = data not available; **SD** = standard deviation; ** $p < 0.01$, *** $p < 0.001$, † $p < 0.0001$ *vs* placebo.

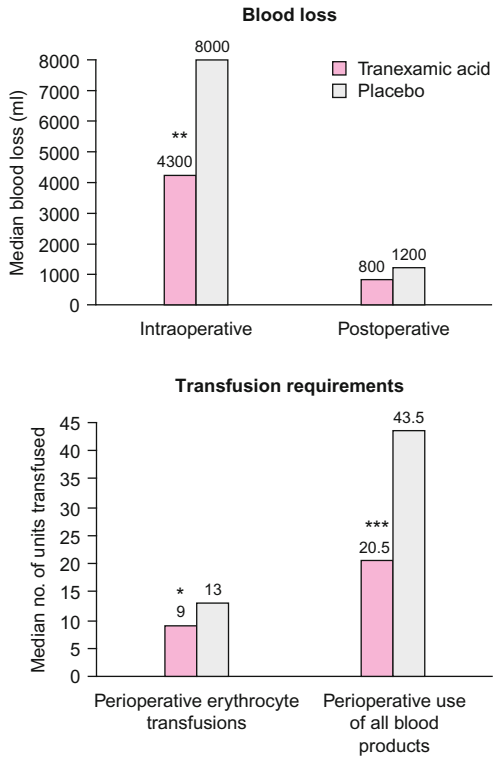

Fig. 4. Effect of tranexamic acid on median blood loss and transfusion requirements in patients undergoing orthotopic liver transplantation.[72] Patients were randomised in a double-blind fashion to treatment with tranexamic acid 40 mg/kg/h (maximum dose 20g) by intravenous infusion (n = 25) or placebo (n = 20) during surgery. All end-points were measured for the first 24 hours in intensive care. * p = 0.03, ** p = 0.006, *** p = 0.003 *vs* placebo.

tween tranexamic acid and placebo groups in rates of death or repeat surgery.

Tranexamic acid was found not to have any significant beneficial effect in another double-blind placebo-controlled study.[73] However, in this trial in 32 patients, a much lower dosage of the drug (2 mg/kg/hour) than that used in the previously described study[72] was given. In addition, results from a nonblind study in 20 patients showed intravenous tranexamic acid (10 mg/kg at the anhepatic stage of surgery and 3 mg/kg/hour thereafter until transfer to the intensive care unit) to be associated with a decrease in mean (± standard deviation) intraoperative blood loss (from 12 594 ± 11 911ml in the control group to 6042 ± 3949ml with active treatment; $p < 0.05$).[74]

4.4.3 Urinary Tract Surgery

Urine and the mucosa of the urinary tract are rich in plasminogen activators which facilitate the lysis of blood clots. In particular, urine dissolves clots in the prostatic cavity of patients who have undergone prostatectomy; this results in haematuria and sometimes in anaemia.[59] Early randomised double-blind studies in men undergoing prostatectomy showed significant reductions in urinary blood loss when tranexamic acid 1.5 to 3g daily was given for 3 days after surgery.[75,76]

A randomised study in 100 men, 92 of whom underwent transurethral resection of the prostate gland (TURP) and 8 of whom underwent endoscopic prostatic tumour resection, showed the 4-week incidence of secondary haemorrhage to be 24% in patients treated with tranexamic acid (1g 3 times daily orally for 3 weeks after surgery) and 56% in patients who received no antifibrinolytic therapy ($p < 0.01$ between groups). None of the patients who received tranexamic acid and 4 of those who did not receive the drug were readmitted to hospital for treatment of bleeding complications, although this difference between groups was not statistically significant. An earlier study appeared to show no significant effect of tranexamic acid (1g by intravenous infusion plus 1g orally 3 times daily for 7 days) on postoperative bleeding in patients who underwent transvesical prostatic adenomectomy.[77] However, only 10 patients received the drug in this 7-day trial (in which the antifibrinolytic efficacy of tranexamic acid was compared with that of *Bothrops jararaca* venom).

4.5 Use in Gynaecology

4.5.1 Menorrhagia

Menorrhagia, or excessive menstrual bleeding, is a common condition among women, approximately 19% of whom consider their menstruation to be heavy (reviewed by Liddell[78]). Although it is a subjective complaint (women who present with this condition can base their assessment only on their own experience and perception of a 'normal'

period), the condition is distressing and potentially disabling. The term 'menorrhagia' encompasses both heavy bleeding associated with uterine disorders and dysfunctional uterine bleeding with no apparent underlying pelvic disease.

Analysis of population studies has indicated that the median volume of blood lost during a normal period is approximately 30ml, with menorrhagia being diagnosed when the total loss is in excess of 80ml (reviewed by Higham and Shaw[79]). Menstrual blood losses of 50 to 60ml are associated with negative iron balance, and iron deficiency anaemia is diagnosed in 67% of women who lose in excess of 80ml. In addition, 60 to 70% of women with menorrhagia also present with dysmenorrhoea; women so affected experience a particularly debilitating combination of symptoms.[78]

Menorrhagia can be acute or chronic, and in 80% of cases is associated with the ovulatory cycle. Treatment options fall into 3 categories: medical therapy, transcervical endometrial resection or hysterectomy. As surgery carries a significant risk of morbidity, various medical treatments have been advocated as potentially desirable and effective alternatives. These include antifibrinolytic agents, prostaglandin synthetase inhibitors, oral contraceptives and intra-uterine progestogens.[80] The preferred clinical end-point in the assessment of these treatments is reduction in menstrual blood volume, measured objectively with an accurate procedure such as the alkaline haematin method of Hallberg and Nilsson.[81]

Clinical studies of tranexamic acid therapy in women with menorrhagia have involved only small numbers of patients and have been of variable design, but results to date have been consistent (table VIII). Women with idiopathic menorrhagia were selected after gynaecological examination in all 5 studies, and mean menstrual blood loss at baseline was stated to be in excess of 80 ml/cycle in four.[80,82,84,85] The alkaline haematin method was used to estimate menstrual losses in all trials except one,[83] in which the Oxford total body counter method was used.

Reductions of 34 to 57.9% versus placebo or control groups in mean menstrual blood loss were achieved over 2 to 3 cycles of oral treatment with tranexamic acid 2 to 4.5 g/day in the studies summarised in table VIII. In addition, the drug was shown to be at least as effective as NSAID therapy[80,82] and more effective than the haemostatic agent etamsylate[82] or cyclical administration of norethisterone[85] in the treatment of ovulatory menorrhagia. In the double-blind study of Preston et al.,[85] 56% of patients who received tranexamic acid achieved a menstrual blood loss of less than 80 ml/cycle after 2 months' treatment (despite mean pre-treatment losses of 175 ml/cycle), whereas only 9.5% of those who received norethisterone did so (mean pre-treatment loss of 173 ml/cycle). In addition, Bonnar and Sheppard[82] stated that 19, 13 and 4%, respectively, of patients who received tranexamic acid, mefenamic acid or etamsylate reported concurrent improvements in symptoms of dysmenorrhoea. Of the 27 patients who received etamsylate, 67% expressed a desire to stop treatment after the trial, whereas 77% of patients receiving tranexamic acid and 74% of those receiving mefenamic acid wished to continue. Very large reductions in menstrual blood loss were achieved with intra-uterine administration of levonorgestrel in 1 study (of the 3 treatment groups, this was the only one in which the mean menstrual loss was reduced to <80 ml/cycle); however, 7 of the 16 women so treated developed amenorrhoea after up to 12 months' treatment.[80]

4.5.2 Bleeding Associated With Pregnancy

Bleeding during pregnancy is associated with a 3- to 4-fold increase in perinatal mortality.[86] Fibrin is known to be an important structural component of uteroplacental blood vessels, and fibrinolytic activity is inhibited in the vicinity of trophoblast cells in the terminal sections of the spiral arteries.[87,88] Placental bleeding appears to result from structural weakness of and vascular defects in placental blood vessels. Placental abruption (abruptio placentae) is characterised by activation of the fibrinolytic system,[89] and tranexamic acid has been used to secure local haemostasis and to reduce

Table VIII. Efficacy of tranexamic acid (TRA) in menorrhagia. All treatments were given orally

Reference	Study design	No. of patients evaluated	Treatment regimens	Effect on mean menstrual blood loss	Effect on mean duration of menses	Effect on number of sanitary towels used	Comments
Bonnar & Sheppard[82]	r, nb	26	TRA 1g q6h days 1–5	↓54.3% *vs* C***	↔	↓13.0% *vs* C**	3 cycles of no treatment (C), then 3 treatment cycles
		23	MEF 500mg q8h days 1–5	↓20.4% *vs* C***	↔	↓8.0% *vs* C*	
		27	ET 500mg q6h days 1–5	↔	↔	↔	
Callender et al.[83]	r, db, co, pc	16	TRA 1g qid days 1–4	↓34.0% *vs* PL*	↔	↓20.3% *vs* PL**	3 cycles of no treatment, then 3 cycles each of TRA and PL
Gleeson et al.[84]	nb	15	TRA 1g q6h days 1–5	↓57.9% *vs* C*	NA	NA	3 cycles of no treatment (C), then 3 treatment cycles
Milsom et al.[80]	nb	16	IUD releasing LEV 20 μg/day	↓83.3, 87.7 and 95.6% *vs* C after 3, 6 and 12mo***	NA	NA	2 cycles of no treatment (C), then drug treatment × 2 cycles or IUD × 12mo
	r, db, co	15	TRA 1.5g tid days 1–3, then 1g bid days 4–7	↓47.5% *vs* C**	↔	NA	
			FLU 100mg bid days 1–5	↓24.0% *vs* C*	↔	NA	
Preston et al.[85]	r, db, pc	25	TRA 1g qid days 1–4	↓44.6% *vs* PL†	NA	↔	PL run-in × 2 cycles, then 2 treatment cycles
		21	NOR 5mg bid d19–26	↔	NA	↔	

C = control; **bid** = twice daily; **co** = crossover; **db** = double-blind; **ET** = ethamsylate; **FLU** = flurbiprofen; **IUD** = intra-uterine device; **LEV** = levonorgestrel; **MEF** = mefenamic acid; **NA** = data not available; **nb** = nonblind; **NOR** = norethisterone; **qid** = 4 times daily; **q6h** = every 6 hours; **q8h** = every 8 hours; **pc** = placebo-controlled; **PL** = placebo; **r** = randomised; **tid** = 3 times daily; ↓ indicates a statistically significant reduction; ↑ indicates a statistically significant increase; ↔ indicates no statistically significant change; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, † $p < 0.0001$ *vs* comparator.

the risk of premature labour as the drug is known to cross the placental barrier (section 3).

Seventy three consecutive patients with placental abruption were treated with tranexamic acid before caesarian section.[89] Of these, 67 received 1g of the drug intravenously immediately before delivery and 6 in early pregnancy with less pronounced symptoms received oral treatment with 4g daily until delivery. Perinatal mortality in this series of women was 8%, and there were no cases of haemorrhagic diathesis or thrombosis and no maternal deaths.

Twelve live births (8 by normal vaginal delivery) were reported in a series of 12 women with vaginal bleeding in the second half of pregnancy who received tranexamic acid at an oral dosage of 1g 3 times daily orally for 7 days.[29] Tranexamic acid was also used to good effect in a woman with central placenta praevia who presented as an obstetric emergency with very heavy vaginal bleeding.[90] After transection of the placenta to deliver a live infant, bleeding was controlled with a total intravenous dose of tranexamic acid of 3g infused over a 24-hour period. The authors suggested that intravenous therapy with tranexamic acid should be considered before surgical options in patients with persistent postpartum haemorrhage.

4.5.3 Conisation of the Cervix

This procedure is used in the management of noninvasive cancer of the cervix. Postoperative bleeding requiring additional treatment is seen in approximately 14% of patients when open surgery without suturing is used.[91] The use of antifibrinolytic agents is logical in these patients because cervical tissue contains high levels of plasminogen activator. Results of a double-blind,

placebo-controlled study with open surgical technique in 45 patients showed a significant (mean 71%; $p < 0.05$) reduction in postoperative blood loss in those who received tranexamic acid at an oral dosage of 1.5g 3 times daily for 12 days after surgery.[92] In another double-blind study, 1 of 38 women who received tranexamic acid 4.5 g/day orally and 4 of 37 who received placebo for 13 days after cervical conisation with suturing experienced late bleeding.[93] The difference between groups was not statistically significant.

4.6 Other Indications

4.6.1 Ocular Trauma

The iris and choroid carry high endothelial levels of plasminogen tissue activator, whereas the aqueous humour in the anterior segment of the eye has a diluent effect on blood after intraocular haemorrhage. Intraocular blood usually coagulates, and dissolution of the clot is necessary for its reabsorption. However, intraocular fibrinolysis may dissolve fibrin clots sealing damaged blood vessels and thus cause secondary bleeding (reviewed by Verstraete[86]). This, the most serious complication of traumatic hyphaema, is usually observed 2 to 7 days after ocular injury and may cause impaired vision or blindness.

Results from 2 controlled trials showed that tranexamic acid 1g or 25 mg/kg 3 times daily orally significantly reduces the frequency of secondary ocular haemorrhage.[94,95] More recently, clinical benefit of tranexamic acid was reported in a case series of 340 children with nonperforating traumatic hyphaema, 121 of whom received the drug (dosage not specified).[96] There was no rebleeding in 26 patients who were confined to bed, and only 1 episode (1.1%) in 95 who were allowed free ambulation in hospital; this was statistically significant ($p < 0.01$) compared with the 9.6% rate of secondary haemorrhage in children treated with bed rest and no antifibrinolytic therapy.[96] Furthermore, in a randomised nonblind study in patients aged 6 to 47 years with nonperforating traumatic hyphaema, tranexamic acid 25 mg/kg/day orally for 6 days was associated with a 3.6% rate of secondary haemorrhage in 28 individuals.[97] This was statistically significantly better ($p < 0.01$) than the rate of 33.3% seen in 27 patients who received conservative treatment only.

4.6.2 Hereditary Angioneurotic Oedema

This condition is characterised by recurrent, circumscribed and non-pitting subepithelial oedema that can involve any part of the body. The skin and mucosa of the gastrointestinal and upper respiratory tracts may be affected, with resultant acute attacks of abdominal pain and risk of asphyxiation. Hereditary angioneurotic oedema is carried in an autosomal dominant fashion, and symptoms are caused by a deficiency of C1-esterase inhibitor that leads to uncontrolled activation of the complement system and overproduction of fragments, many of which have vasoactive properties. In addition, C1-esterase inhibitor impedes the action of kallikrein on kininogen conversion and neutralises plasmin (reviewed by Verstraete[86] and Sim and Grant[98]).

The rationale behind the use of antifibrinolytic agents in hereditary angioneurotic oedema lies in the counteracting effect of these drugs on the continuous activation of contact and fibrinolytic systems.[99] Results of 2 randomised, double-blind crossover trials carried out in the early 1970s showed a reduction in the number and severity of attacks of oedema in patients treated with tranexamic acid, although benefit was not obtained in all patients who received the drug.[100,101] The reasons for this remain unclear. Further data from a case series of 7 Finnish patients showed clinical benefit in 6 of these individuals after oral treatment with tranexamic acid 1.5g 3 times daily.[102] Greatest efficacy was reported when the drug was taken at the onset of an attack, and 2 of 3 patients who received continuous therapy (1g 2 to 3 times daily) remained almost symptom-free for the duration of treatment.

4.6.3 Subarachnoid Haemorrhage

Rupture of an intracranial aneurysm results principally in bleeding into the subarachnoid space and subsequent brain damage due to destruction of brain parenchyma, increased intracranial pressure, brain shift and herniation, and hydrocephalus.

Around 15% of patients die instantly; those who survive have a 20% risk of rebleeding and developing delayed ischaemic cerebral deficits.[86,103] Rebleeding has been attributed to fibrinolysis of the blood clot around the fundus of the aneurysm, and antifibrinolytic therapy has been used to increase the durability of this clot.

A randomised, placebo-controlled, double-blind study in 479 patients with subarachnoid haemorrhage showed a significant ($p < 0.001$) reduction in the rate of rebleeding (from 24% in placebo-treated patients to 9% in those who received intravenous tranexamic acid 6 g/day for the first week and 4 g/day thereafter for up to 4 weeks, with some patients receiving oral therapy at a dosage of 6 g/day for the third and fourth weeks).[104] Treatment was started within 72 hours of haemorrhage in all patients. Overall outcome was not improved after 3 months, however, because of an increase in the incidence of cerebral ischaemia (15% in the placebo-treated group *vs* 24% in patients who received active treatment). Findings of other studies published during the 1970s and early 1980s[105-112] have been inconsistent in terms of clinical benefit of tranexamic acid in these patients.

In an analysis of 672 patients participating in the International Cooperative Study on the Timing of Aneurysm Surgery, in which patients who received antifibrinolytic therapy (tranexamic acid or EACA) and those who did not were compared, inhibition of fibrinolysis was associated with a significant reduction in the rate of rebleeding (11.7 *vs* 19.4%; $p = 0.01$).[113] However, significant increases in rates of ischaemic deficit (32.4 *vs* 22.7%; $p = 0.01$) and hydrocephalus (13.5 *vs* 6.8%; $p = 0.02$) were also reported.

5. Tolerability

Adverse events with tranexamic acid therapy are uncommon; nausea or diarrhoea and, occasionally, orthostatic reactions are most often reported.[86] There is a theoretical risk of increased thrombotic tendency during treatment with inhibitors of fibrinolysis, and there have been isolated case reports of cerebral thrombosis,[114,115] arterial thrombosis,[116] acute renal failure[117,118] and coronary graft occlusion[119] in patients receiving tranexamic acid. However, these observations have not been confirmed by the results of controlled clinical studies; indeed, several randomised studies in patients undergoing cardiac surgery with CPB have shown no excess incidence of thrombotic events in patients receiving the drug.[12,37,41,48] Furthermore, similar rates of thromboembolic complications were reported for placebo and tranexamic acid in both trials conducted in patients undergoing total knee arthroplasty.[68,69] However, the incidence of cerebral ischaemia was higher in patients with subarachnoid haemorrhage given tranexamic acid than in placebo recipients (section 4.6.3).

No thrombogenic effect of tranexamic acid was detected in a retrospective analysis of case records of 256 women with bleeding disorders in pregnancy, 168 of whom underwent caesarian section.[120] These findings are particularly significant because pregnant women have low fibrinolytic capacity and an increased risk of thrombosis (especially after caesarian section).

Although atrophy of the retinal rod and cone layers has been reported after 1 year's oral administration of tranexamic acid in dogs, the dosages used were of the order of 7 times those recommended in humans.[121] Moreover, no retinal changes were found in patients who received the drug at therapeutic dosages for periods ranging from 15 months to 8 years.[122] As instances of disturbance in colour vision have been reported, it is nevertheless recommended that treatment with tranexamic acid should be withdrawn from any patients who develop this symptom.[123]

No mutagenic activity of tranexamic acid has been detected in *in vitro* and *in vivo* test systems,[121,124] and no fetal abnormalities were identified in early dysmorphology and reproductive studies in animals.[125,126]

6. Dosage and Administration

Although tranexamic acid has been studied in a number of clinical settings, the uses for which the drug is approved vary between countries. The fol-

lowing recommendations therefore include dosages recommended by the manufacturer and regimens most frequently used by clinical investigators. Tranexamic acid is available in 500 mg/5ml ampoules for intravenous use, and as a syrup containing 500mg in 5ml and 500mg tablets for oral administration. For local fibrinolysis the recommended dosage is 500mg to 1g by slow intravenous injection 3 times daily or 1 to 1.5g orally 2 to 3 times daily.[123] In general fibrinolysis, a single dose of 1g or 10 mg/kg by slow intravenous injection is recommended.[123] Dosages in children should be calculated according to bodyweight at 25 mg/kg/dose.[123] Other dosages for specific indications are as follows:

Cardiac surgery with CPB: Although there is no officially recommended regimen for this indication, an initial intravenous dose of 10 mg/kg given over 20 to 30 minutes before surgery and followed by an infusion of 1 mg/kg/hour during CPB has been used most frequently in clinical studies. Additional benefit does not appear to be obtained with higher dosages[12] (see section 4.1.1).

Upper gastrointestinal bleeding: A daily dosage of 4.5 to 6g daily, divided into 3 to 6 doses, for 5 to 7 days has been most commonly used in these patients. Tranexamic acid was administered intravenously for the first 2 to 3 days in the majority of clinical studies summarised in section 4.2, with oral therapy being used thereafter.

Oral surgery: 1 to 1.5g orally every 8 hours in patients with haemophilia (dosage based on 25 mg/kg 3 times daily). A 4.8 to 5% w/v mouthwash for 2 minutes 4 times daily for 7 days after surgery has been most frequently used in patients receiving oral anticoagulants (section 4.3.1).

Other surgery: 10 to 15 mg/kg by intravenous infusion before release of tourniquet, with 1 or 2 further doses at 3-hour intervals if necessary, may be used in knee arthroplasty. Intravenous infusion of 40 mg/kg/hour to a maximum dose of 20g has been used in patients undergoing orthotopic liver transplantation (section 4.4.2). Perioperative therapy with 500mg to 1g 3 times daily intravenously, then oral treatment with 1g 3 to 4 times daily, may be used in patients undergoing prostatectomy. Patients undergoing transurethral surgery have received 6 or 12g daily for 4 days around the time of surgery (section 4.4.3).

Gynaecological indications: 1 to 1.5g 3 to 4 times daily orally for 3 to 4 days is recommended in menorrhagia. Patients undergoing conisation of the cervix may be managed with 1.5g orally 3 times daily.

Other indications: 1 to 1.5g orally 3 times daily may be used in patients with traumatic hyphaema. Oral therapy with 1.5g 3 times daily is recommended in patients with hereditary angioneurotic oedema.

Tranexamic acid is contraindicated in patients with a history of thromboembolic disease, and dosage reductions are recommended in patients with renal insufficiency.[123] Haemorrhage due to disseminated intravascular coagulation should not be treated with any antifibrinolytic agent unless both bleeding tendency and systemic fibrinogenolysis are present;[127] in such cases, careful monitoring and anticoagulant cover are also required.[128]

7. Place of Tranexamic Acid in Surgery and Other Indications

Since its introduction into clinical practice over 30 years ago, tranexamic acid has been used for a wide variety of clinical conditions in which antifibrinolytic therapy has been deemed potentially beneficial. The use of the drug is made more attractive in many patients by its ability to inhibit fibrinolysis while having no apparent effect on blood clotting parameters.

Much recently published literature on tranexamic acid and other antifibrinolytic agents has dealt with the use of these drugs in patients undergoing cardiac surgery with CPB, and clinical opinion on the relative merits of these drugs is divided.[31,36,129] Tranexamic acid has greater antifibrinolytic activity than EACA[86] and is at least as effective. Results of 1 study only showed greater efficacy of EACA:[45] this conclusion was based on a statistical analysis that showed patients who received EACA, but not those who received tran-

examic acid, to have lost significantly less blood after 24 hours than those who received no antifibrinolytic therapy. However, as mean blood losses were 534 and 509ml with tranexamic acid and EACA, respectively, the clinical significance of this finding is questionable (particularly as a smaller proportion of tranexamic acid than EACA patients required postoperative transfusions).

Several commentators have expressed a preference for aprotinin over tranexamic acid on the basis of extensive clinical experience and consistent clinical benefit with the former.[36,86,129] However, other reviewers[31,33] have pointed out that clinical studies have failed to show any consistent superiority of aprotinin over tranexamic acid, and that both drugs reduce blood loss after cardiac surgery.

Other factors that influence outcomes in studies of patients undergoing cardiac surgery with CPB include the expertise of the surgeon, the use of normothermic CPB and variation of and adherence to transfusion criteria.[34] Such considerations are likely to affect the extent of use of antifibrinolytic therapy in different institutions. However, cost-benefit analysis of pharmacological haemostasis has indicated that the use of such therapy results in indirect cost savings from reductions in operating theatre time and reduced lengths of stay in intensive care units and surgical wards.[130] Although no such analysis of patients receiving tranexamic acid specifically has been carried out, several authors have pointed out that the acquisition cost of the drug is considerably lower than that of aprotinin, and that its use circumvents any risk of allergic reactions or sensitisation.[31,33,46]

The use of antifibrinolytic drugs is of interest in patients with upper gastrointestinal bleeding because these agents tend to be inexpensive, are usually well tolerated and could potentially be given to the majority of patients (including the many who are not cared for by specialist physicians).[52] Despite its apparent efficacy in these patients, tranexamic acid is not used widely to treat patients with upper gastrointestinal bleeding because of the efficacy of other medical and endoscopic treatments.[59] Nevertheless, clinical benefit (including reductions in mortality rates) of tranexamic acid has been shown in patients with upper gastrointestinal bleeding, and controlled comparisons with other antifibrinolytic drugs and medical interventions are now necessary to clarify the overall place of the drug in the management of this condition.

The demonstration of increased uterine fibrinolytic activity in menorrhagia underlines the potential utility of antifibrinolytic therapy in this condition.[18] Tranexamic acid is superior in terms of reduction of menstrual blood loss to etamsylate or cyclical therapy with norethisterone, and is at least as effective as NSAIDs. Endometrial suppression with a progestogen introduced into the uterus via an intrauterine device is highly effective in the management of menorrhagia, and is likely to be preferable to hysterectomy in many patients. However, there is a risk of pelvic inflammation associated with intrauterine devices, and some women develop amenorrhoea with this treatment.[131,132] Combined oral contraceptives are also effective in the management of menorrhagia, and they offer the additional advantage of providing reliable contraception to those who require it. However, 30 to 40% of patients experience adverse effects that include headaches, weight change, breast tenderness, nausea, vomiting, mood changes, hypertension and thromboses.[79] Clinical studies comparing the efficacy and tolerability of combined oral contraception and tranexamic acid in women with menorrhagia have not been carried out to date.

Although results from controlled clinical trials are not available, case series and reports indicate that tranexamic acid can be used successfully to control bleeding in patients with placental abruption or postpartum haemorrhage. Tranexamic acid therapy has also been shown to reduce excessive blood loss after conisation of the cervix.

Inhibition of fibrinolysis is effective in the prevention of excessive bleeding after oral surgery in patients with haemophilia and those receiving oral anticoagulant therapy. In particular, data from well designed studies have shown clearly the efficacy of mouthwash formulations of tranexamic acid in dental patients being treated with oral anticoagu-

lants for cardiac indications. A major advantage of this treatment is that it eliminates the need for adjustment or discontinuation of anticoagulant treatment around the time of dental treatment.

Significant reductions after tranexamic acid therapy in postoperative blood losses and transfusion requirements have also been observed in patients undergoing total knee arthroplasty, although the need for transfusions was not eliminated. Limited evidence to date suggests that early and aggressive treatment of fibrinolysis is beneficial in patients undergoing orthotopic liver transplantation, and that reductions in perioperative blood loss and transfusion requirements are obtained when tranexamic acid is used in these patients. However, current opinion states that antifibrinolytic agents should be given in orthotopic liver transplantation only when fibrinolysis is demonstrated objectively (preferably by thromboelastography).[71] Tranexamic acid also reduces blood losses in patients undergoing prostatic surgery and reduces the incidence of secondary bleeding after traumatic hyphaema, although only small numbers of studies, or data from case series only, are available for these indications.

The place of tranexamic acid and fibrinolytic agents in general in patients with subarachnoid haemorrhage is questionable. Prevention of rebleeding with early surgery has been stated to be the most effective treatment option, and antifibrinolytic therapy is unlikely to be useful in patients with subarachnoid haemorrhage until means of minimising ischaemic complications have been developed.[103]

In conclusion, tranexamic acid has been shown during its long clinical history to be useful in patients with a broad range of haemorrhagic conditions, particularly when bleeding from mucosal sites is involved, and to have a good tolerability profile. Its efficacy in reducing postoperative blood losses and transfusion requirements make tranexamic acid a useful adjunct to a number of types of surgery, and the drug appears to reduce rates of mortality and the need for urgent surgery in patients with upper gastrointestinal haemorrhage. Tranexamic acid may also have cost and tolerability advantages over aprotinin in patients undergoing cardiac surgery with CPB. Tranexamic acid reduces menstrual blood loss and may provide an alternative to surgery in women with menorrhagia, and case series and individual reports indicate utility of the drug in the management of bleeding in pregnancy.

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