Drug Therapy

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HEMOSTATIC DRUGS

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WHEN bleeding is the consequence of a specific defect of hemostasis, the goal of treatment is to correct the defect. A typical example is the replacement of factor VIII by transfusion in patients with hemophilia. Specific treatment may be impossible, however, because bleeding may result from multiple defects or because no cause can be identified. In such situations, nontransfusional drugs that help to stop bleeding are indicated.[1] These drugs may also be indicated for patients who refuse blood transfusion or for those who undergo surgical procedures associated with large blood losses necessitating many transfusions of donated blood. Many nontransfusional hemostatic drugs have been evaluated, but only a few have proven clinical efficacy. This article will review antifibrinolytic amino acids (aminocaproic acid and tranexamic acid), aprotinin, desmopressin, and conjugated estrogens.

ANTIFIBRINOLYTIC AMINO ACIDS

Two synthetic derivatives of the amino acid lysine, 6-aminohexanoic acid (aminocaproic acid) and 4-(aminomethyl)cyclohexanecarboxylic acid (tranexamic acid), have antifibrinolytic activity in humans.[2,3] Both drugs bind reversibly to plasminogen and thereby block the binding of plasminogen to fibrin and its activation and transformation to plasmin (Fig. 1).[4,5] Aminocaproic acid and tranexamic acid (which is about 10 times more potent than aminocaproic acid and has a longer half-life) are effective even when bleeding is not associated with laboratory signs of excessive fibrinolysis.[6] Since both drugs enter the extravascular space and accumulate in tissues,[7] the basis for their efficacy is thought to be the inhibition of tissue fibrinolysis and the consequent stabilization of clots.

Primary Menorrhagia

Excessive menstrual bleeding is the most frequent cause of iron-deficiency anemia in women of reproductive age. Tranexamic acid reduces blood loss by 40 to 50 percent, as documented in a randomized controlled trial in 76 women.[8] The drug is thought to act by inhibiting plasminogen activator, which is present in high concentrations in the endometrium.[8] Its use is recommended only when the presence of organic lesions in the uterus has been ruled out and when combined estrogen–progestogen preparations, which control dysmenorrhea and menstrual irregularity more effectively, are unacceptable or contraindicated. The recommended oral dose of tranexamic acid is 10 to 15 mg per kilogram of body weight every eight hours, from the onset of menstrual bleeding until it is arrested.

Gastrointestinal Bleeding

The use of antifibrinolytic drugs in patients with gastrointestinal lesions that cause bleeding is rational, because the local concentration of fibrinolytic enzymes is high in the digestive tract.[9] Clinical trials of tranexamic acid in patients with upper gastrointestinal bleeding have had conflicting results.[1,6] A meta-analysis of results in 1267 patients with peptic ulcers, mucosal erosions, or other causes of bleeding found reductions of 20 to 30 percent in recurrent bleeding, 30 to 40 percent in the need for surgery, and 40 percent in mortality.[10] Despite these results, tranexamic acid is not widely used to treat patients with bleeding from the upper digestive tract because of the efficacy of other medical and endoscopic treatments.

Bleeding in the Urinary Tract

The urine and the urinary tract mucosa are very rich in plasminogen activators, which facilitate the lysis of clots.[7] After prostatectomy, urine dissolves clots in the prostatic cavity, resulting in hematuria and sometimes anemia. In clinical trials involving patients who had undergone prostatectomy, aminocaproic acid or tranexamic acid reduced blood loss by approximately 50 percent, as compared with placebo.[11-13] The recommended dosage of tranexamic acid is 10 to 15 mg per kilogram every eight hours intravenously, starting immediately after surgery, followed by 20 mg per kilogram orally every eight hours until macroscopic hematuria stops. The corresponding dosage of aminocaproic acid is 50 to 60 mg per kilogram intravenously six times per day, followed by the oral administration of the same dose. The drugs are not known to reduce the need for transfusion or to decrease mortality after prostatectomy, however, and they are therefore not given routinely. These drugs are contraindicated in patients with bleeding from the upper urinary tract because of the risk that clots will be retained in the ureter and the bladder.

Oral Bleeding in Congenital and Acquired Coagulation Disorders

Antifibrinolytic drugs are useful for the control of bleeding after dental extractions in patients with he-

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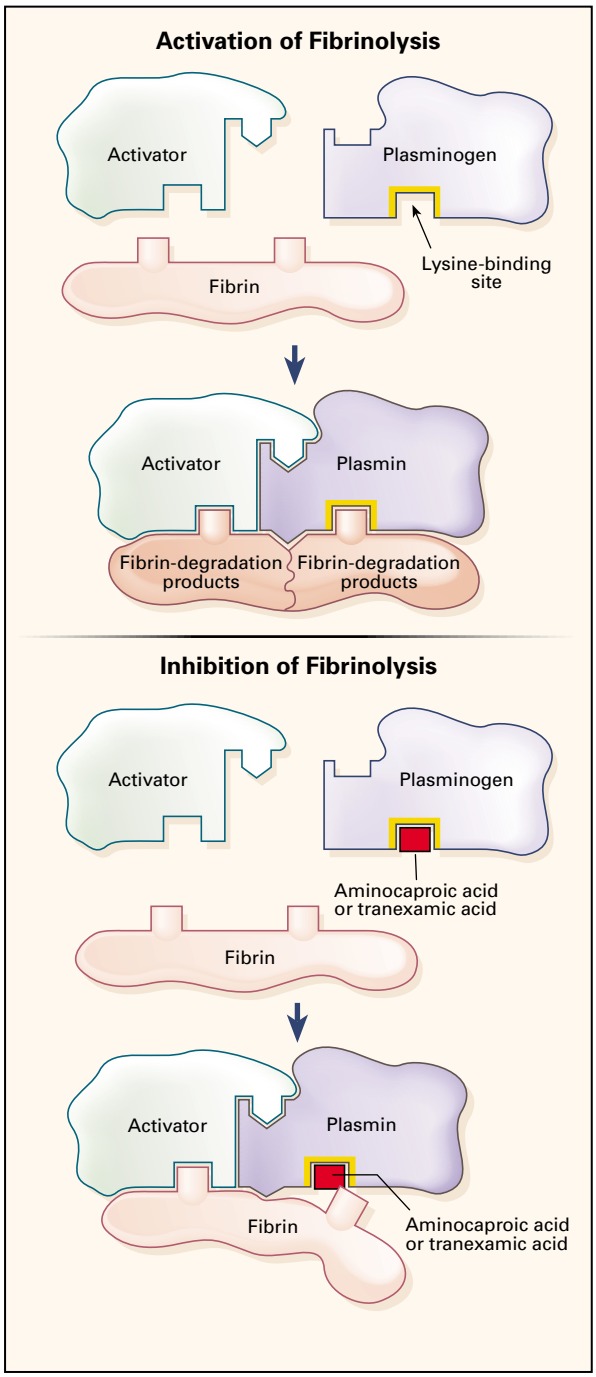

Figure 1. Antifibrinolytic Action of Aminocaproic Acid and Tranexamic Acid.

The upper diagram shows the activation of plasminogen on the fibrin surface. Plasminogen binds to fibrin at a lysine-binding site and is changed to plasmin, its activated form. Plasmin degrades fibrin into fibrin-degradation products. In the lower diagram, aminocaproic acid or tranexamic acid blocks the lysine-binding site on plasminogen, which is essential for binding to fibrin, and thereby prevents the activation of plasminogen on the surface of fibrin, although plasmin generation does occur.

mophilia, because the oral mucosa and saliva are rich in plasminogen activators.[14] In two small clinical trials, aminocaproic acid or tranexamic acid reduced recurrent bleeding and the amount of clotting-factor–replacement therapy needed.[15,16] In adults, the recommended oral dose is 50 to 60 mg of aminocaproic acid per kilogram every four hours or 20 to 25 mg of tranexamic acid per kilogram every eight hours until the dental sockets are completely healed. Mouthwashes containing tranexamic acid (1 g every six hours) are effective for the prevention of oral bleeding in patients with hemophilia[17] and in patients who require dental extraction while receiving long-term oral anticoagulant therapy.[18] Extraction can be performed without stopping or reducing the dose of the anticoagulant agent, which may increase the risk of thrombosis in patients with atrial fibrillation or artificial heart valves.[18]

Bleeding in Patients with Thrombocytopenia

In two uncontrolled studies of 30 patients with amegakaryocytic or megakaryocytic thrombocytopenia, aminocaproic acid was effective in stopping mucosal bleeding (in the nose, uterus, or gastrointestinal tract) and bleeding associated with dental extraction, without affecting platelet counts.[19,20] Transfusion requirements may not be reduced by the use of these drugs, however.

Bleeding after Thrombolytic Treatment

Thrombolytic therapy in patients with acute myocardial infarction may be complicated by bleeding due to hyperfibrinolysis.[21] There is little evidence, however, that antifibrinolytic drugs (lysine derivatives and aprotinin, discussed below) are useful when bleeding complications develop during or shortly after thrombolytic treatment.

Reducing Blood Loss during Cardiac Surgery

Cardiac surgery is the prototypical operation in which the adoption of blood-saving measures is warranted. Factors contributing to the relatively large blood losses in cardiac surgery include the size of the surgical wound, the exposure of blood to artificial surfaces in the extracorporeal oxygenator, enzymatic and mechanical injury to platelets and coagulation factors, and hyperfibrinolysis during and after cardiopulmonary bypass. The results of clinical trials involving at least 1000 patients who were treated with tranexamic acid or aminocaproic acid have consistently demonstrated that either drug reduces blood loss by 30 to 40 percent, as compared with placebo.[22-27]

The following regimens were the most effective: for aminocaproic acid, a bolus intravenous dose of 150 mg per kilogram before the operation, followed by an infusion of 15 mg per kilogram per hour during the operation,[24] and for tranexamic acid, 10 mg

per kilogram given intravenously before the operation, followed by 1 mg per kilogram per hour during the operation.[27] In these studies, however, the amount of blood products given, the most important measure of the efficacy of prophylactic therapy, was either not measured or not reduced by antifibrinolytic drugs,[22-27] and none of the studies were of sufficient size to determine whether the incidence of serious side effects was increased by the treatment. Other nontransfusional hemostatic drugs, such as aprotinin and desmopressin, have also been used; they are discussed below.

Joint Replacement

In a randomized, controlled study of 86 patients undergoing knee replacement, the patients given a single dose of 10 mg of tranexamic acid per kilogram before the tourniquet was released lost less blood than those given placebo (mean blood loss, 730 vs. 1410 ml) and needed fewer transfusions.[28] These findings were confirmed by a similar study involving 76 patients.[29] Despite these results, antifibrinolytic drugs and hemostatic drugs in general cannot be recommended for routine prophylaxis during joint replacement, since the two to three units of blood needed by most patients can easily be supplied through a program of storing autologous blood for transfusion.[30] The use of drugs to reduce bleeding should therefore be considered only for patients in whom large blood losses are predicted, such as those undergoing double joint replacement or repeated operations.

Orthotopic Liver Transplantation

Patients undergoing orthotopic liver transplantation lose large amounts of blood, in part because of preexisting coagulopathy and intraoperative fibrinolysis. In a clinical study of 45 patients given high-dose tranexamic acid (20 to 30 mg per kilogram) or placebo during surgery, treated patients had about 50 percent less intraoperative blood loss and required fewer transfusions.[31] These preliminary results need confirmation.

The therapeutic indications for antifibrinolytic amino acids and the corresponding evidence of their efficacy are summarized in Table 1. Aminocaproic acid or tranexamic acid has been used in patients with other hemorrhagic conditions (such as epistaxis, bleeding after tonsillectomy, and secondary bleeding after traumatic hyphema), but the available data are insufficient to establish indications for the treatment of these conditions. The drugs are contraindicated in patients with subarachnoid bleeding, because they may induce vasospasm and ischemic stroke.[32-34]

Side Effects

The side effects of tranexamic acid and aminocaproic acid are dose-dependent and usually involve the gastrointestinal tract (nausea, vomiting, abdominal pain, and diarrhea). The main risk entailed by these drugs is that thrombotic complications will result from the inhibition of fibrinolysis, which is a natural mechanism of defense against the formation of thrombus. There are at least 10 case reports describing the formation of thrombi in association with the use of these drugs. On the other hand, no striking increase in the risk of thrombosis has been observed when the drugs have been used during operations that are often complicated by venous and arterial thromboembolism, such as cardiac surgery[22-26] and knee replacement.[28,29] However, these studies were not designed to evaluate thrombotic complications, and most were too small to detect differences in outcomes with relatively low incidence, such as stroke, myocardial infarction, and coronary-bypass graft occlusion.

TABLE 1. INDICATIONS FOR THE USE OF THE ANTIFIBRINOLYTIC DRUGS TRANEXAMIC ACID AND AMINOCAPROIC ACID IN THE TREATMENT OF EXCESSIVE BLEEDING.

CLINICAL SITUATION	STUDY	GRADE OF EVIDENCE*
Primary menorrhagia	Bonnar and Sheppard[8]	A
Upper gastrointestinal bleeding	Henry and O'Connell[10]	A
Dental extraction in patients with coagulation disorders	Walsh et al.[15] Forbes et al.[16] Sindet-Pedersen et al.[18]	A
Bleeding associated with thrombocytopenia	Gardner and Helmer[19] Bartholomew et al.[20]	B

*The evidence has been graded as A, B, or C as follows: A denotes that the therapeutic value of tranexamic acid or aminocaproic acid has been demonstrated by clinical trials evaluating its safety and efficacy, B that safety and efficacy have been demonstrated by well-conducted studies but no clinical trials, and C that safety and efficacy have been demonstrated by case studies or reports but no well-conducted studies.

APROTININ

Aprotinin, a polypeptide with a molecular weight of 6512, is extracted from bovine lung. It inhibits the action of several serine proteases (such as trypsin, chymotrypsin, plasmin, and tissue and plasma kallikrein) through the formation of reversible enzyme–inhibitor complexes.[35,36] By inhibiting kallikrein, aprotinin indirectly inhibits the formation of activated factor XII, a biochemical reaction normally amplified by kallikrein by means of a positive-feedback mechanism[37] (Fig. 2). Hence, aprotinin inhibits the initiation of both coagulation and fibrinolysis induced by the contact of blood with a foreign surface. Aprotinin does not affect platelet function.[38-40]

Aprotinin is inactive when given orally. It is administered intravenously in an initial loading dose, followed by a continuous infusion. The enzymatic

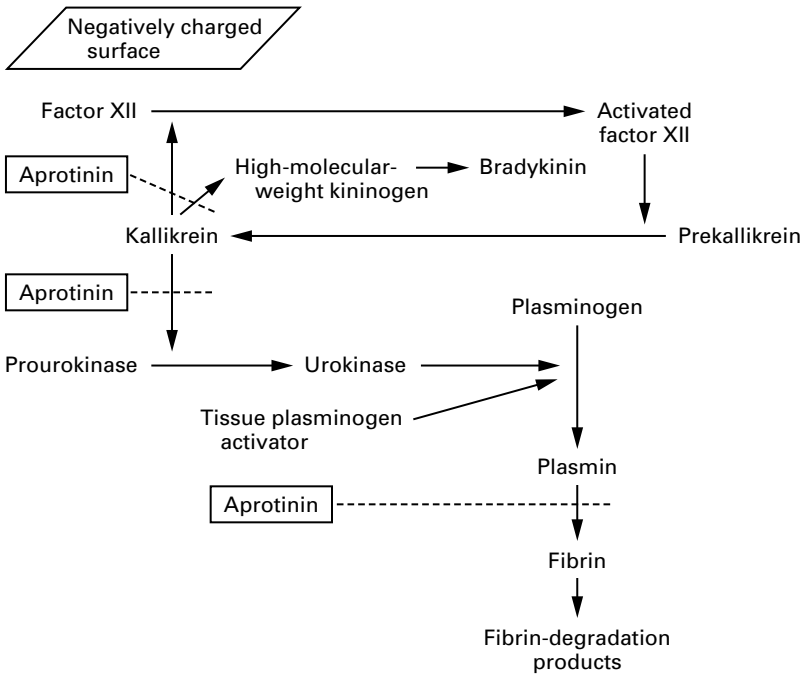

Figure 2. Inhibition of the Contact System and of Fibrinolysis by Aprotinin.

The arrows indicate activation or release. The broken lines indicate inhibition. Activation of the contact system is initiated by the binding of plasma factor XII to a negatively charged surface, where autoactivation of factor XII occurs, converting it to activated factor XII. The presence of small amounts of activated factor XII converts prekallikrein to kallikrein, which in turn activates factor XII, cleaves high-molecular-weight kininogen, generating the vasoactive peptide bradykinin, and converts prourokinase to urokinase. Fibrinolysis consists of the activation of plasminogen, which is converted to the enzyme plasmin, which in turn digests fibrin, generating fibrin-degradation products. Plasminogen is activated by urokinase and by tissue plasminogen activator. Aprotinin acts as an inhibitor of kallikrein and plasmin.

activity of the compound is expressed in kallikrein inactivation units (KIU). Plasma concentrations of 125 KIU per milliliter are necessary to inhibit plasmin, and concentrations of 300 to 500 KIU per milliliter are needed to inhibit kallikrein.[36]

Cardiac Surgery

The broad antiproteolytic action of aprotinin prompted its use in reducing blood loss in patients undergoing cardiac surgery, during which there is increased plasma proteolysis. In an open-label, randomized study of 22 patients undergoing repeated cardiac surgery, blood loss in the patients who were treated with aprotinin (2 million KIU before surgery and a continuous infusion of 0.5 million KIU during surgery) was 80 percent less and transfusion requirements were 60 percent lower than in the control group.[41] Subsequently, double-blind studies involving more than 500 patients demonstrated the effectiveness of aprotinin in patients undergoing common operations such as valve replacement and coronary-artery bypass grafting.[42-47] It is also effective in operations characterized by particularly large blood losses, such as those in patients taking aspirin,[48] in patients with endocarditis,[49] and in patients undergoing heart transplantation.[50]

Lower-dose regimens have subsequently been proposed — for example, 3 million to 4 million KIU, or 2 million KIU added to the oxygenator.[51-53] The regimen of 3 million to 4 million KIU of aprotinin is as effective hemostatically as the full-dose aprotinin regimen, but the oxygenator-only regimen may not be.[51] Aprotinin is less effective when given postoperatively than when given prophylactically.[54] The criteria for choosing between aprotinin and other hemostatic drugs for patients undergoing cardiac surgery are discussed below.

Orthotopic Liver Transplantation

A relatively low dose of aprotinin (2 million KIU) resulted in a reduction of approximately 35 percent in blood loss and a 50 percent reduction in transfusion requirements, as compared with no treatment, in a total of 20 patients undergoing orthotopic liver transplantation.[55] In a subsequent study of a larger dose (2 million KIU after the induction of anesthe-

sia, followed by an infusion of 0.5 million KIU per hour during the operation) in a total of 24 patients, transfusion requirements in the treated patients were less than a third of those in the control patients.[56] These studies were neither randomized nor controlled. In one small, randomized study of a total of 20 patients, aprotinin was not more effective than placebo.[57]

Side Effects

Aprotinin is a heterologous polypeptide, and therefore it can cause hypersensitivity reactions, particularly after repeated exposure. In one study of 240 patients given aprotinin two or more times, 7 had hypersensitivity reactions (ranging from skin flushing to severe circulatory depression). Most reactions occurred when aprotinin was administered a second time within six months after the first exposure and were not severe.[58]

Aprotinin can cause venous and arterial thrombosis and thus the occlusion of coronary-bypass grafts and other vascular grafts. In controlled studies with coronary angiography, however, aprotinin did not lead to an increased rate of early occlusion of saphenous-vein or internal-mammary-artery grafts.[47,59-61] Similarly, in a small study, there was no increased risk of venous thromboembolism after hip replacement in patients treated with aprotinin.[62] In prospective, placebo-controlled, randomized studies of aprotinin-treated patients who had undergone coronary-artery bypass surgery, there was no increase in the occurrence of myocardial infarction or death.[51] Pooled analysis of data from six studies of coronary-artery bypass surgery, which evaluated a total of 861 patients assigned to receive aprotinin or placebo,[63] found a lower prevalence of stroke among the patients treated with aprotinin.

Recently, concern that aprotinin, which is extracted from bovine lungs, might transmit the agent responsible for bovine spongiform encephalopathy and new-variant Creutzfeldt–Jakob disease has led to the withdrawal of the drug in Italy. No other country, in Europe or elsewhere, has taken this step so far. The manufacturers of aprotinin state that the bovine lungs used to extract aprotinin have been collected in geographic areas in which no cases of transmissible spongiform encephalopathy have been recorded, and there is no evidence that any patients with the disorder have received aprotinin.

DESMOPRESSIN

Plasma concentrations of factor VIII, the clotting factor that is deficient or defective in patients with hemophilia A, and von Willebrand factor, the adhesive protein that is deficient or defective in patients with von Willebrand's disease, can be increased for a short time by the administration of 1-deamino-8-D-arginine vasopressin (desmopressin), an analogue of arginine vasopressin.[64] These effects, which mimic replacement therapy with blood products, form the rationale for the use of desmopressin in the treatment of patients with hemophilia A or von Willebrand's disease, both of which are congenital bleeding disorders.[65-67] The evidence of efficacy is so clear that no controlled clinical trials have been judged necessary.

Desmopressin has also been used in patients with other congenital and acquired bleeding disorders.[66,68,69] In such patients, the effect of desmopressin may be mediated by the attainment of supranormal plasma concentrations of von Willebrand factor and the appearance of ultralarge multimers of this factor,[70] which support platelet adhesion to the vascular subendothelium more actively than multimers of normal size.[71] Increased hemostasis may also be mediated by high plasma concentrations of factor VIII, a rate-accelerating factor in the process of fibrin formation.[72]

Congenital Bleeding Disorders

The optimal intravenous or subcutaneous dose of desmopressin in patients with congenital bleeding disorders is 0.3 μg per kilogram, and the optimal intranasal dose is 300 μg in adults and 150 μg in children.[73,74] Plasma concentrations of factor VIII and von Willebrand factor are approximately doubled or quadrupled by the administration of desmopressin, reaching a peak 30 to 60 minutes after intravenous infusion and 60 to 90 minutes after subcutaneous or intranasal administration.[73,74] These doses can be repeated as clinically necessary at intervals of 12 to 24 hours, but tachyphylaxis may occur after three or four doses.[75]

Most patients with low plasma concentrations of normal von Willebrand factor (that is, those with type I von Willebrand's disease) respond to desmopressin with increases in factor VIII concentrations that are similar to or even greater than those in patients with mild hemophilia,[75] and their bleeding time becomes normal.[70,75] However, the bleeding time in patients with severe von Willebrand factor deficiency (type III von Willebrand's disease)[76] or those with dysfunctional von Willebrand factor (type II disease)[70] is usually not shortened.

Desmopressin is the treatment of choice for patients with mild hemophilia A or type I von Willebrand's disease who have spontaneous bleeding or who are scheduled to undergo surgery. It shortens or normalizes the bleeding time in some patients with congenital defects of platelet function.[77] Although the effect of desmopressin on a laboratory measure such as the bleeding time may not correspond to a hemostatic effect in patients, the results in a few well-studied cases suggest that desmopressin may be an alternative to blood products during or after surgery or childbirth in such patients.[78]

Acquired Bleeding Disorders

Desmopressin has also been used in patients with uremia, who have complex abnormalities of hemostasis, reflected in part by a prolonged bleeding time.[79] In a group of these patients who were given an intravenous infusion of desmopressin, the prolonged bleeding time became normal for four to six hours in about 75 percent.[68] Desmopressin given before invasive procedures (such as biopsies and major surgery) seems to prevent bleeding,[68] but controlled studies of this effect are lacking. Currently, the clinical use of desmopressin in patients with uremia is based on the link between the degree of prolongation of the bleeding time and the patient's tendency toward excessive bleeding.[79] Conjugated estrogens are an alternative to desmopressin for patients with uremia who have bleeding problems.

Cirrhosis

In spite of the fact that patients with cirrhosis have high plasma concentrations of factor VIII and von Willebrand factor, they have prolonged bleeding times that are shortened by intravenous desmopressin.[69,80] Hence, the drug might be used as a prophylactic treatment for patients who need invasive diagnostic procedures and have a prolonged bleeding time. It is not effective, however, in controlling acute gastrointestinal bleeding in patients with cirrhosis.[81]

Reducing Blood Loss during Surgery

In a single study of 70 patients undergoing complex cardiac surgery, desmopressin given at the time of chest closure reduced blood loss and transfusion requirements by about 30 percent.[82] In three studies of a total of 330 patients who were undergoing simpler cardiac operations, however, there were no significant differences between desmopressin and placebo.[83-85] In a meta-analysis of 17 clinical trials, which included a total of 1171 patients, desmopressin significantly reduced postoperative blood loss (by 9 percent, a value of little clinical importance).[86] Perhaps the low efficacy of desmopressin in cardiac surgery is due to its fibrinolytic activity,[64] an unfavorable property in treating a condition accompanied by hyperfibrinolysis. The main therapeutic indications for the use of desmopressin and the corresponding evidence are summarized in Table 2.

Side Effects

Common side effects include mild facial flushing and headache. Because of its potent antidiuretic effect, desmopressin can cause water retention and hyponatremia.[87] In patients given more than one dose, plasma sodium and body weight should be measured daily and excessive administration of fluids avoided. Arterial thrombosis (sometimes causing fatal stroke or myocardial infarction) has occurred in a few patients treated with desmopressin.[88] In patients at high risk for thrombosis (such as those undergoing coronary-artery bypass grafting), there was no excess rate of thrombotic complications among those given desmopressin.[89]

TABLE 2. INDICATIONS FOR THE USE OF DESMOPRESSIN IN THE TREATMENT OF EXCESSIVE BLEEDING.

CLINICAL SITUATION	STUDY	GRADE OF EVIDENCE*
Mild hemophilia A or type I von Willebrand's disease	Mannucci et al.[65] Kobrinsky et al.[66] de la Fuente et al.[67]	B
Congenital defects of platelet function	Rao et al.[77] DiMichele and Hathaway[78]	C
Uremia	Mannucci et al.[68]	C
Cirrhosis	Mannucci et al.[69] Burroughs et al.[80]	C
Drug-induced bleeding (aspirin, ticlopidine)	Kobrinsky et al.[66] Mannucci et al.[69]	C

*The evidence has been graded as A, B, or C as follows: A denotes that the therapeutic value of desmopressin has been demonstrated by clinical trials evaluating its safety and efficacy, B that safety and efficacy have been demonstrated by well-conducted studies but no clinical trials, and C that safety and efficacy have been demonstrated by case studies or reports but no well-conducted studies.

HEMOSTATIC DRUGS AS PROPHYLAXIS IN PATIENTS UNDERGOING CARDIAC SURGERY

Aminocaproic acid, tranexamic acid, desmopressin, and aprotinin have all been evaluated in patients undergoing cardiac surgery. On the basis of direct comparisons[90-92] and a meta-analysis,[93] all four agents reduce operative blood loss. Aprotinin is most effective in reducing blood loss, followed in descending order by tranexamic acid, aminocaproic acid, and desmopressin[93]; their order with respect to cost at the most commonly recommended dose is the same. In terms of reducing blood-transfusion requirements, the most important criterion for efficacy, the results also favor aprotinin. In terms of safety, firm data from clinical trials demonstrating that the frequency of graft occlusion does not increase with use of the drug are available only for aprotinin.

The cumulative evidence leads to the choice of aprotinin, but it should be reserved for patients who are likely to need transfusion of donated blood, notably those undergoing second operations, those who have preexisting hemostatic defects or are taking antiplatelet drugs, and those with sepsis; preoperative testing of hemostasis is not useful. The prophylactic use of aprotinin in all patients is not recommended, because many cardiac surgical procedures are not usually associated with the need for donated blood and because hypersensitivity reactions can occur on second exposure to the drug.

TABLE 3. NONTRANSFUSIONAL TREATMENT OF BLEEDING IN PATIENTS WITH UREMIA.

COMPOUND	ONSET OF EFFECT	DURATION OF EFFECT	INDICATIONS*
Desmopressin	Immediate	6–8 hr	Acute bleeding Before biopsy or emergency surgery
Conjugated estrogens	Delayed	10–15 days	Chronic, recurrent bleeding Before elective surgery
Erythropoietin	Delayed	Sustained	Prevention of bleeding

*The safety and efficacy of the drugs in question for all indications are supported by case studies or reports but no well-conducted studies (grade C).[68,94,95,97]

CONJUGATED ESTROGENS

Conjugated estrogens shorten prolonged bleeding times and reduce or stop bleeding in patients with uremia.[94,95] The mechanism of conjugated estrogens' effect on the bleeding time in these patients is unknown, nor is it known whether other estrogen preparations have this effect. Conjugated estrogens can be given intravenously or orally. In patients with uremia, a single daily infusion of 0.6 mg per kilogram, repeated for four to five days, shortened the bleeding time by approximately 50 percent for at least two weeks.[95] A daily oral dose of 50 mg shortened the bleeding time after an average of seven days of treatment.[96]

The clinical use of conjugated estrogens in patients with uremia (like the use of desmopressin) is based on data indicating that the tendency of these patients to have bleeding is directly related to the degree of prolongation of the bleeding time.[79] The chief advantage of conjugated estrogens over desmopressin is the longer duration of their effect on the bleeding time (10 to 15 days, as compared with 6 to 8 hours). Hence, conjugated estrogens should be given when long-lasting hemostasis is required — for example, to prevent bleeding during elective surgical procedures or to treat recurrent episodes of gastrointestinal or nasal bleeding (Table 3). On the other hand, desmopressin should be given when an immediate effect on hemostasis is required — for instance, to stop acute bleeding or to prevent bleeding at the time of emergency surgery. The two products can be given concurrently, thus exploiting the different timing of their maximal effects.

In patients with chronic renal insufficiency, recombinant erythropoietin causes a dose-dependent increase in the hematocrit and eliminates the need for blood transfusions.[98] The progressive increases in the hematocrit are paralleled by a pronounced shortening of the bleeding time and the improvement of platelet adhesion.[97] Because most patients with chronic renal insufficiency are now regularly treated with erythropoietin, short-acting hemostatic drugs such as desmopressin and conjugated estrogens are recommended only for patients with acute or subacute renal failure.

Conjugated estrogens are well tolerated, and side effects are negligible or absent. Since no more than five to seven daily doses are recommended, adverse effects due to estrogenic hormonal activity are usually avoided.

CONCLUSIONS

The antifibrinolytic drugs aminocaproic acid and tranexamic acid are useful in patients with a broad range of hemorrhagic conditions, particularly when there is excessive bleeding from mucosal sites. Desmopressin is the treatment of choice for patients with mild hemophilia or type I von Willebrand's disease. It has also been used successfully to treat or prevent bleeding in patients with other hemorrhagic disorders, including congenital defects of platelet function, chronic liver disease, and hemostatic defects induced by the therapeutic use of antithrombotic drugs such as aspirin and ticlopidine.[66,69] There have been no well-conducted clinical trials demonstrating the efficacy of desmopressin.

In cardiac surgery, antifibrinolytic drugs (lysine derivatives and aprotinin) are more effective than desmopressin; aprotinin is preferred because its efficacy and safety have been more extensively evaluated. However, aprotinin should be used prophylactically only when the patient is expected to need transfusions of donated blood or when the patient refuses transfusion for religious or other reasons.

Hemostatic agents for topical use, the so-called fibrin tissue adhesives, have not been considered in this review, because objective data on their efficacy and safety are limited.[99] Much effort will undoubtedly be directed toward developing and evaluating newer topical agents. In addition, efforts are being made to replace plasma-derived coagulation factors with the corresponding recombinant products. Recombinant factor VIII, factor IX, and activated factor VII are already licensed (the last only in Europe); clinical studies of recombinant von Willebrand factor will soon begin.

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