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A Risk-Benefit Assessment of Aprotinin in Cardiac Surgical Procedures

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Summary

Aprotinin, a naturally occurring serine protease inhibitor, has found widespread application during cardiac surgical procedures as a consequence of its ability to decrease blood loss and transfusion requirements. While its efficacy in a variety of clinical situations associated with increased risk of blood loss has been well established, at the same time, various complications including anaphylaxis, renal insufficiency, graft closure and arterial thromboses have been reported in association with aprotinin administration.

In order to more fully evaluate the risks and benefits associated with aprotinin usage, this review first of all examines the hazards associated with transfusion of blood and blood products. Consideration is then given to various alternatives to allogeneic transfusion, including autologous predonation, acute normovolemic hemodilution, perioperative cell salvage and intraoperative plasma sequestration.

A critique of other available pharmacological therapies, specifically desmopressin, aminocaproic acid and tranexamic acid, reviewing their modes of action, efficacy and associated complications, is then made. The role of aprotinin in cardiac surgery is then discussed and its pharmacology, including consideration of its antifibrinolytic, platelet preserving and anti-inflammatory effects is reviewed. Finally, an analysis of potential complications associated with aprotinin administration is undertaken. Issues involving its influence on specific measures of anticoagulation, namely partial thromboplastin time and activated clotting time, and issues relating to graft patency, hypothermic circulatory arrest, renal function, and allergic reactions are analysed and interpreted.

In summary, this review concludes that most of the risks associated with aprotinin administration primarily involve inadequate anticoagulation and those of developing an allergic reaction, particularly upon aproptinin re-exposure. The benefits of aproptinin to decrease blood loss and transfusion requirements are confirmed, and there is evidence pointing to the intriguing possibility of a potential salutary effect on perioperative central nervous system complications.

In order to evaluate the risks and benefits associated with aprotinin when given to decrease blood loss and transfusion requirements in surgical procedures, it is necessary to first consider the risks of transfusion in general, then to discuss the role of possible alternative therapies before finally considering the relative merits of aprotinin administration. To facilitate this, we have undertaken a systematic literature review based on a computerised MEDLINE search of clinically related material from 1990 to 1996 in cardiac surgery, the major surgical field in which the use of aprotinin has been most common. This was supplemented using manual bibliography reviews to search for relevant material.

1. Transfusion Risk

The complications associated with excessive blood loss and transfusion, which may accompany certain surgical procedures or result from complex acquired coagulopathy, are of significant concern to anaesthesiologists and surgeons.[1] The risks of transfusion of homologous blood and blood products are well recognised, and include ABO/Rhesus incompatibility, sepsis, febrile reactions, immunosuppression and viral transmission.[2-7]

1.1 ABO/Rhesus Incompatibility

The incidence of ABO/Rhesus incompatibility, which may lead to life-threatening complications, varies from 1 in 2000 to 6000 units transfused, and is mainly attributable to incompatible blood being administered because of a clerical error.[3,7]

1.2 Sepsis

Overwhelming sepsis, largely caused by contamination with *Yersinia* or *Pseudomonas*, which can both replicate at 4°C, and *Staphylococcus* or *Salmonella*, which are most often associated with platelet contamination, is estimated to occur with 1 in 100 000 units transfused.[6] Alloimmunisation, representing development of antibodies to antigens in homologous blood products (e.g. antibodies to antigens on platelet and leucocyte membranes) or in plasma [e.g. immunoglobulin (Ig) A], may result in an acute haemolytic reaction or the development of a delayed reaction, manifest as diminished duration of survival of transfused red blood cells (RBC) and mild jaundice.[8]

1.3 Immunological Effects

Immunosuppression, leading to impaired host-defence mechanisms, is also increasingly recognised as being caused by transfusion of allogeneic blood. In a retrospective review of 376 patients un-

dergoing spinal, knee or hip surgery, an overall infection rate of 6.1% was noted, and the use of homologous whole blood, as well as several variables not related to transfusion, were significant predictors of postoperative infection.[5] In a review of 145 trauma patients, the requirement for a larger number of units of blood or blood products, along with age, number of injured organs, and necessity for colostomy, were identified as a significant risk for infection.[9] A study of 169 patients undergoing bowel resection for Crohn's disease identified blood transfusion as being strongly correlated with the development of sepsis, and prolonged postoperative stay was significantly correlated with transfusion of 2 or more units of blood.[10] A similar relationship between transfusion rates and infection was demonstrated in a review of 594 patients with thermal injuries;[11] in this study, the number of transfusions was significantly related to the development of infectious complications, independent of patient age or burn size.

Allogeneic blood transfusions also have significant immunological effects in patients undergoing organ transplantation. There is concern that graft rejection may be enhanced through sensitisation of the patient to human leukocyte (HLA) antigens, as a consequence of previous allogeneic blood exposure. In one study of liver transplant recipients,[12] those with positive lymphocytotoxic crossmatches against their donor had a 1-year survival rate of 56%, compared with 82% in control patients having negative crossmatches. Similarly, in patients undergoing heart transplantation, HLA antibodies against the donor increase the risk of rejection and have been shown to significantly decrease graft survival.[13]

1.4 Viral Transmission

Viral transmission is one of the most frequently cited risks of allogeneic blood and blood product transfusions; the highest public awareness is related to the risk of transmission of HIV through blood transfusion. While relatively low, the risk of seroconversion after receiving infectious blood given during an infective window is estimated to be 1 in 493 000 transfusions [95% confidence interval (CI), 202 000 to 2 778 000] for HIV, and 1 in 641 000 (95% CI 256 000 to 2 000 000) for human T-cell lymphotropic virus (HTLV).[2] The risk of transmitting hepatitis B virus (HBV) or hepatitis C virus (HCV) is higher. Blood contamination with hepatitis B resulting in seroconversion occurs with a reported frequency of 1 in 63 000 (95% CI 31 000 to 147 000); for hepatitis C, the risk of seroconversion is 1 in 103 000 (95% CI 28 000 to 288 000).[2]

The aggregate risk of viral seroconversion after receiving infective blood is estimated at 1 in 34 000, of which HBV and HCV account for 88% of the risk. It is estimated that these risks will decrease significantly (by 27% to 72%) with the use of newer screening tests that shorten the window periods for these 4 viruses.

Despite the declining risk of post-transfusion hepatitis, now estimated at about 3 per 10 000 units transfused,[14] about 10% of patients infected with hepatitis B or C develop chronic active hepatitis, and 10% will develop cirrhosis, which may require either a liver transplantation or long term supportive care.[2,15]

1.5 Coagulopathy

Patients exposed to massive transfusion are at risk of developing a clinically significant coagulopathy, which further contributes to increased morbidity and mortality.[16] Two main mechanisms are believed to trigger such coagulopathies. The first is simple dilution of platelets and soluble clotting factors, resulting in thrombocytopenia and dilutional coagulopathy. The second is more complex and results from disseminated intravascular coagulation; it involves consumption of platelets and clotting factors as a result of activation of tissue factor and tissue plasminogen activator (tPA) from ischaemic or traumatised tissues.

2. Alternatives to Allogeneic Transfusion

Autologous blood predonation, blood salvage and sequestration, along with a better understanding of the physiology of haemostasis, have triggered changes in the clinical use of blood and

blood component transfusions over last few years. Predonation of autologous blood before elective surgery has become more widespread, particularly in orthopaedics and cardiac surgery, and has been shown to significantly reduce the need for allogeneic transfusion.[17,18] Unfortunately, this technique has limitations, including the expense and the need for a sufficient preoperative collection interval, but it is increasingly perceived by the public as an important initiative to enhance the safety of blood volume restoration.

Acute normovolaemic haemodilution (NHD), employing intraoperative phlebotomy with sequestration of one or more units of whole blood, combined with simultaneous colloid and crystalloid administration to maintain circulating blood volume, is increasingly being employed in elective surgical procedures during which significant blood loss is anticipated.[19,20] In a clinical study of NHD resulting in a nadir haemoglobin of 2.8 g/dl in 8 healthy adolescents undergoing surgical correction of idiopathic scoliosis, and a concomitant laboratory study employing a pig model of stepwise NHD until death, it was determined that abnormal haemostasis measurably develops before compromise of global tissue oxygenation.[21] Abnormal microvascular bleeding with absence of observable clot, unaccompanied by quantitative thrombocytopenia and without any evidence of compromised tissue oxygenation, was seen in all patients. Overall, the coagulopathy observed in both patients and animals was not caused by thrombocytopenia (unlike that seen after massive transfusion), and the authors of that study recommended replacement therapy with fresh frozen plasma, as it contains all soluble procoagulants.

The use of intraoperative and postoperative cell salvage has been variably employed in cardiac and orthopaedic surgery, and its use has generally been limited. Intraoperative cell salvage requires specific equipment for heparinising, collecting, washing, haemoconcentrating and reinfusing shed blood.[22] As such, it is a relatively expensive undertaking for routine use, requiring specific equipment, disposables and a dedicated technician for its operation. In addition, processing of the salvaged blood results in loss of plasma components, giving rise to the risk of a dilutional coagulopathy. Postoperative cell salvage generally employs a more simple system, involving only the collection and reinfusion of blood lost through wound drains. However, the potential for microbial contamination of blood and the risk of coagulopathy, associated with reinfusion of various kallikreins and fibrinolytic mediators, limit its utility.[23,24]

Intraoperative plasma sequestration, using differential centrifugation to collect platelet rich plasma has also been of value in decreasing autologous blood use in cardiac surgery, probably by helping to avoid cardiopulmonary bypass (CPB)-related platelet damage.[25] Unfortunately, this technique also involves significant expense because of associated personnel and equipment costs, and clinical results vary from positive results – less bleeding, reduced use of allogeneic blood, and improved coagulation – to negative reports that have been unable to document any beneficial effects.[26] The current utility of this technique remains unclear.

3. Antiproteases, Antifibrinolytics and Platelet Agonists

Pharmacological methods to decrease blood loss and allogeneic transfusion are being put under increased scrutiny. Currently, the 4 drugs that have been most intensively investigated are desmopressin (1-D-deamino-arginine vasopressin; DDAVP), tranexamic acid, aminocaproic acid and aprotinin. As the main subject of this review, and because of its increasingly widespread utilisation, the risks and benefits of aprotinin will be considered in section 4.

3.1 Pharmacology

3.1.1 Desmopressin

Desmopressin, a vasopressin analogue, exerts a potent and long-lasting antidiuretic effect, having a plasma half-life of 2.5 to 4 hours.[27] Its potential role in acquired bleeding diatheses during cardiac surgery is predicated on its ability to release vari-

ous procoagulant mediators from the endothelium. Levels of the procoagulant and platelet-enhancing factors VIII and XII, and von Willebrand factor (vWF), as well as the profibrinolytic activity of tPA and platelet-inhibiting prostacyclin, all peak within 60 to 90 minutes of administration of desmopressin 0.3 μg/kg.

Despite an initial report of a significant haemostatic effect during cardiac surgery,[28] prophylactic desmopressin administration has not subsequently been shown to be efficacious, even when combined with tranexamic acid antifibrinolytic therapy, which is designed to counter the increase in tPA release.[29,30] However, in the presence of postoperative platelet dysfunction, directed desmopressin therapy has been shown to decrease transfusion requirements in patients undergoing cardiac surgery.[31]

3.1.2 Aminocaproic Acid and Tranexamic Acid

Tranexamic acid and aminocaproic acid are low–molecular-weight (157 daltons and 131 daltons, respectively) synthetic antifibrinolytics of the aminocarboxylic acid class. Analogues of the amino acid lysine, they exert their primary effect by saturating the lysine binding sites (kringles) of plasminogen (and tPA), thus displacing it from the fibrin surface and inhibiting the proteolytic action of the serine-histidine enzyme site of plasminogen/plasmin. On a molar basis, tranexamic acid is at least 7 times more potent than aminocaproic acid. This is a function of the more rigid quaternary structure of tranexamic acid, which fixes the distance between its amino and carboxylic groups, the components that comprise the plasminogen binding-site substrate analogue for this class of antifibrinolytics.[32] The plasma half-life of tranexamic acid and aminocaproic acid are both approximately 80 to 120 minutes.

Both tranexamic acid and aminocaproic acid are effective in decreasing blood loss and transfusion requirements during cardiac operations;[30,33,34] and tranexamic acid has also demonstrated an ability to decrease bleeding and transfusion requirements in patients undergoing total knee arthroplasty.[35,36]

3.2 Risks and Benefits in Major Surgery

In a meta-analysis of all randomised clinical trials published in English-language peer-reviewed journals between 1980 and 1993, the efficacy of tranexamic acid, aminocaproic acid, desmopressin and aprotinin was assessed by Fremes et al.[34] These authors concluded that the literature supports the prophylactic use of tranexamic acid or aminocaproic acid, and more strongly supports administration of aprotinin for the reduction of postoperative bleeding associated with open-heart surgery and the limitation of homologous blood use where indicated. They also concluded that evidence of benefit for the prophylactic administration of desmopressin was negligible.

The efficacy of aminocaproic acid and tranexamic acid to decrease transfusion requirements has also been evaluated during orthotopic liver transplantation (OLT).[37,38] Administration of aminocaproic acid during OLT has been shown to reduce markers of fibrinolysis, although no measure of efficacy regarding blood loss or transfusion requirements was made.[39]

In a prospective, randomised clinical trial, investigators compared groups of patients who had received either aprotinin or aminocaproic acid during OLT, with those who had received neither.[38] In this study, aprotinin significantly reduced the number of red blood cell and component transfusions compared with aminocaproic acid, which was no different from placebo. Administration of tranexamic acid during OLT has also been shown to reduce transfusion requirements,[38] although no direct comparisons have been made with aprotinin.

Unlike aprotinin, there are currently no overall tolerability data for tranexamic acid or aminocaproic acid, nor are there published studies evaluating the effects of tranexamic acid or aminocaproic acid on graft patency in patients after coronary artery bypass surgery. One study in such patients suggested a possible increase in the rate of myocardial infarction (MI) in those receiving tranexamic acid; a numerical, but not statistically significant, increase in MI was found.[40] Of some concern is the cumulative literature over the years

demonstrating an association between treatment with tranexamic acid or aminocaproic acid and the development of thrombotic complications in a variety of conditions.[41-51] Because of their mechanism of action, the lysine analogues, unlike aprotinin, are exclusively antifibrinolytic in action, apparently without significant effects on inflammatory mediators or on the intrinsic coagulation cascade.[32]

4. Aprotinin

4.1 Pharmacology

Aprotinin is one of a series of naturally occurring serine protease inhibitors. Independently discovered by 2 research groups in 1930 and in 1936, aprotinin was identified as a trypsin-kallikrein inactivator isolated from bovine lung tissue.[32] It has a molecular weight of 6512 daltons and consists of 58 amino acid residues. A strongly basic protein, the effect of aprotinin results from the formation of aprotinin-protease complexes between the reactive Lys-15–Ala-16 site of the aprotinin molecule, and the active serine site of the enzyme.[52]

The concentration of commercially prepared aprotinin is usually given in kallikrein inactivator units (KIU), where one KIU is defined as the amount of aprotinin that decreases the activity of 2 biological kallikrein units by 50%.[52] 100 000 KIU are equivalent to 14mg of pure polypeptide or 2.15 μmol/L aprotinin.[32] By clinical convention, 'high-dose' aprotinin is derived from data from the Hammersmith Hospital, London, UK,[53] wherein 2 mKIU are administered as a loading dose followed by a continuous infusion of 0.5 mKIU/h intraoperatively, and a further 2 mKIU into the pump prime if CPB is used.[53] This regimen results in plasma concentrations ranging between 1.3 to 5.8 μmol/L (60 to 269 KIU/ml),[54] and is generally referred to as the 'high-dose', 'full-dose', or 'Hammersmith' regimen.[53] Subsequent dose-finding studies have employed 50% of the 'Hammersmith' dose, generally called 'half-dose', while 'pump-only' dose is considered as 2 mKIU into the CPB circuit only.

At clinically relevant dosages, aprotinin has been shown to inhibit human trypsin, plasmin, plasma kallikrein, and tissue kallikreins in a dose-dependent manner by forming reversible stoichiometric enzyme-inhibitor complexes (table I).[52] These enzymes play important roles in the kallikrein-kininogen-kinin system, the complement system, the coagulation system, and the fibrinolytic system, where plasmin and plasma kallikrein occupy functionally important positions. In reviewing the literature regarding aprotinin, it is important to recognise that different regimens of aprotinin will have variable effects in influencing inflammatory, fibrinolytic and coagulation cascades, depending upon the plasma aprotinin concentration at various times.

Aprotinin has been investigated for over 40 years in a variety of different clinical scenarios. Its clinical use was first reported in 1953 for treatment of acute pancreatitis and later for shock syndromes and hyperfibrinolytic haemorrhage.[32] The most extensive clinical investigations have been conducted in patients undergoing cardiac operations, liver transplantation or vascular procedures.[53-60] More recently, clinical studies in orthopaedic patients have being undertaken;[61,62] these have demonstrated the benefit of high-dose aprotinin administration in decreasing blood loss and transfusion requirements, and have also shown a strong trend toward reduced development of deep venous thrombosis after primary and revision hip arthroplasty procedures.

Despite a large volume of *in vitro* research and clinical studies, the mechanism of action of aprotinin in preventing coagulopathy and blood loss during cardiopulmonary bypass and other proce-

Table I. Enzyme-aprotinin dissociation constants (K_i)[52]

Serine protease	K_i (μmol/L)
Trypsin	6×10^{-8}
Plasmin	2.3×10^{-4}
Kallikrein	
plasma	3.0×10^{-2}
urine	0.9×10^{-4}
Elastase	3.5

dures remains unclear. Numerous clinical studies in a wide variety of surgical procedures have demonstrated the effects of aprotinin in reducing blood loss and there is evidence for several possible mechanisms. These are probably inter-related and, to some extent, dosage specific. Inhibition of the contact-coagulation system via kallikrein inhibition,[52] inhibition of protein C (a natural anticoagulant and a primary modulator of the extrinsic coagulation pathway via inactivation of Va),[63,64] attenuation of plasmin-induced fibrinolysis,[52] and platelet receptor preservation,[65] all interact and summate to produce the clinical effect, and have been shown *in vitro* and *in vivo* to operate during aprotinin therapy.

4.1.1 Antifibrinolytic Effects

As a nonspecific serine protease inhibitor, aprotinin can exert both a direct effect to inactivate plasmin,[32,52] as well as an indirect effect to suppress the enzymatic activators of various inflammatory feedback loops that serve to amplify plasmin activation. tPA and factor XIIa are both activators of plasminogen, converting it to plasmin – the ultimate mediator of fibrinolysis – and are formed and consumed in quantity during cardiopulmonary bypass.[58,66]

As a potential, though weak, inhibitor of kallikrein (which independently stimulates factor XII activation) aprotinin inhibits the formation of factor XIIa, both indirectly through kallikrein inactivation and by direct inhibition of factor XIIa activity.[67] Aprotinin also significantly reduces the production of bradykinin, a potent stimulator of tPA and fibrinolysis.[32]

In various studies, the antifibrinolytic activity of aprotinin has been shown to reduce the formation of fibrin degradation products,[58,68] increase α2-antiplasmin activity, and enhance plasminogen activator inhibitor (PAI) activity.[69] Much evidence exists for the major antifibrinolytic effects of aprotinin being manifest as a direct inhibition of plasmin-mediated fibrinolysis, while there are also data showing that aprotinin suppresses kallikrein activity in a dose-related manner.[32,52]

4.1.2 Platelet Preservation

Aprotinin has been shown to prevent the prolongation of bleeding time that occurs after CPB, and to reduce thromboxane A_2 (TxA_2) release from platelets during CPB, indicating suppression of nonspecific platelet activation.[70] The mechanism of this action on platelet function has not been fully elucidated, but electron microscopy has shown significant preservation of platelet aggregation on extracellular matrix after CPB with aprotinin administration.[71] There is also evidence that platelet glycoprotein (GP) Ib receptor activity, responsible for the initiation of haemostasis by mediating platelet adherence to subendothelial surfaces of blood vessels via endothelium-bound vWF, is preserved during aprotinin administration.[72] Cleavage of membrane-bound GPIb by plasmin,[73] and plasmin-induced translocation of GPIb from plasma membrane surface and receptor internalisation without degradation, have been demonstrated, and are believed[74] to be primarily responsible for acquired platelet dysfunction after CPB.

Aprotinin restores normal platelet membrane GPIb functionality and overall platelet adhesive function through neutralisation of plasmin.[72] In addition, in up to one-third of patients, heparin prevents binding of vWF to platelet GPIb receptors, an effect that has been shown to be prevented by aprotinin administration.[74,75]

Platelet activation and adhesion at the site of vascular injury can occur by several independent, but related, mechanisms: through activation of the platelet thrombin receptor, by cleavage of its membrane-bound extracellular terminal amino group; via adenosine diphosphate (ADP) release from activated platelets to initiate GPIIb/IIIa fibrinogen receptor activation; and by activation of GPIIb/IIIa receptors by TxA_2. In addition, it is now recognised that increased shear-stress, as found at bleeding sites, can independently induce platelet aggregation.[76] In the presence of high shear stress, release of platelet-stored vWF, which binds to GPIb receptor, induces opening of transmembrane calcium channels and leads to a functional change

in GPIIb/IIIa receptor, resulting in binding to fibrin.[76]

Therefore, in platelets, despite blockade of TxA_2 generation by systemic aspirin administration, the aspirin-independent thrombin pathway still functions to produce haemostatic plug formation after tissue injury.[77] Further platelet disruption, however, as may occur during CPB, results in loss of platelet GPIb adhesive receptors, and compounds the functional loss of the TxA_2 pathway resulting from aspirin treatment, thus accounting for the increased blood loss found in patients maintained on aspirin and undergoing CPB.[78] High-dose aprotinin, in part by preserving platelet receptor function, has been shown to significantly decrease blood loss and transfusion requirements in aspirin-pretreated patients undergoing cardiac surgery.[79,80]

4.1.3 Anti-Inflammatory Effects and the CNS

Since Kirklin and colleagues[81] first coined the term 'whole body inflammatory response' to characterise the changes in vascular permeability and diffuse derangements of various organ systems found after CPB, it is now recognised that the complement system is but one of a number of potentially detrimental humoral cascades activated by the process of extracorporeal circulation.[82] In addition to the complement system, the kallikrein-bradykinin cascade, the coagulation cascade, the fibrinolytic cascade the and arachidonic acid pathway are all stimulated, and interact with formed blood elements to release inflammatory mediators, cytokines and various proteolytic enzymes.[83] Subtle or serious organ-system dysfunction is therefore often readily detectable in the majority of patients after CPB.[84]

With the demonstration of early postoperative cerebral oedema in 6 of 6 patients undergoing cardiac surgery,[85] it became apparent that alterations in blood-brain barrier permeability, or other such alteration in vascular integrity, is the rule rather than the exception after CPB. In animal models, bradykinin has been shown to be intimately linked to the development of cerebral oedema.[86] In a pig model of hypothermic circulatory arrest, aprotinin administration was shown to significantly decrease the extent of cerebral oedema formation, and to result in better preservation of high energy phosphates and normalisation of endothelium-mediated vasoreactivity, in comparison with untreated controls.[87] As yet there have been no randomised clinical trials in which the efficacy of aprotinin in decreasing postoperative brain dysfunction (manifest as subtle impairments of neuropsychological performance[84,87]) or stroke, has been prospectively assessed.

In several of the clinical series that have been reported to date, however, there is some indication that aprotinin may exert a salutary effect on CNS injury. In a recent multicentre dose-ranging trial of aprotinin in repeat coronary revascularisation surgery,[88] a significantly lower postoperative stroke rate was seen in aprotinin-treated patients: while the overall stroke rate was 2.1% (6/287), of which 5 of 6 strokes occurred in placebo-treated patients, there was 1 stroke in patients treated with pump-only aprotinin and none in patients receiving aprotinin. In a single-centre study of aprotinin therapy in aspirin-treated patients undergoing coronary and valve surgery,[80] a trend toward decreased stroke rate was observed in aprotinin recipients; postoperative strokes were reported in 3.4% (1/29) of aprotinin-treated patients and 16% (4/25) of placebo recipients.

In an unpeer-reviewed report assessing efficacy of pump-only dose aprotinin versus control, i.e. standard, therapy in over 1400 patients undergoing cardiac surgery, there was a computed tomography–verified 2.1% incidence of ischaemic cerebrovascular accident (CVA) in aprotinin-treated patients overall, with 1.6% recovery from CVA on discharge, and a 0.45% incidence of chronic CNS sequelae; in contrast there was an overall incidence of CVA of 3.1% in control patients, of whom there was a 2.3% recovery from CVA at discharge, and a 0.78% incidence of chronic sequelae.[89]

In a pooled analysis of data from 4 published US trials of aprotinin in coronary artery bypass surgery, combined with unpublished data from 2 other trials obtained from the manufacturer of aprotinin,

the incidence of outcomes such as MI, stroke, renal failure and death was assessed.[90] Issues were raised concerning use of aprotinin in dosages other than the high-dose (Hammersmith) regimen, but with respect to aprotinin administration in patients undergoing coronary artery bypass surgery, the authors[90] confirmed that high-dose aprotinin was well tolerated and effective for indicated patients at risk of bleeding complications. In this much larger analysis, Smith and Muhlbaier et al.,[90] were also able to confirm the intriguing reduction in stroke rate initially reported by Levy et al.,[88] demonstrating a 1.0% versus 2.4% incidence of stroke ($p = 0.027$) in recipients of high-dose aprotinin compared with placebo recipients.

While not conclusive, these data are certainly intriguing and suggests that some of the anti-inflammatory properties of aprotinin, especially its inhibition of bradykinin, may be of clinical significance in decreasing the CNS sequelae of CPB. A related compound, nafamostat mesilate (a synthetic antiprotease with a similar profile of activity to that of aprotinin), has been shown in a rabbit model to significantly decrease cerebral vasospasm after subarachnoid haemorrhage (SAH).[91] In a clinical trial of patients presenting with SAH, lower incidences of cerebral vasospasm and better clinical outcomes were seen in those treated with nafamostat in comparison with historical controls.[92]

4.2 Role in Cardiac Surgery

The original seminal report by Royston and colleagues[93] demonstrated the efficacy of high-dose aprotinin in patients undergoing repeat cardiac operations. Subsequent evaluation by the US Food and Drug Administration (FDA) assessing both safety and efficacy of several further prospective, randomised clinical trials in cardiac surgical patients, resulted in specific FDA approval of aprotinin administration for patients at high risk of bleeding during reoperative coronary artery bypass surgery or primary coronary artery bypass surgery with impaired coagulation.

A meta-analysis of all randomised clinical trials published in peer-reviewed English-language journals from January 1980 to June 1993, assessing efficacy of prophylactic drug treatment for the prevention of postoperative bleeding in open heart surgery, considered 32 trials eligible for analysis.[34] Of these, 13 involved desmopressin,[28,30,94-104] 2 assessed aminocaproic acid,[105,106] 2 examined tranexamic acid,[30,107] and 16 investigated aprotinin use.[54,66,70,79,108-118] The results of this analysis indicated that therapy with aminocaproic acid or aprotinin was associated with a greater reduction in chest-tube drainage and a significantly reduced volume of postoperative red blood cell transfusion than that seen after desmopressin or placebo administration. They also showed that only in aprotinin-treated patients was there a reduction in the proportion of patients receiving transfusions.[34]

Several further randomised clinical trials have confirmed and extended these results. The efficacy of high-dose aprotinin to decrease blood loss, transfusion requirements and exposure to allogeneic blood products was confirmed in a single-centre study of patients receiving aspirin within 48 hours of primary coronary artery bypass surgery.[80] In a comparison of high-dose aprotinin with tranexamic acid 20 mg/kg or placebo in patients undergoing primary coronary artery bypass surgery, aprotinin was shown to significantly decrease blood loss, transfusion volumes and number of patients requiring transfusion, whereas tranexamic acid treatment did not differ from placebo for any of these outcomes.[58] In another single-centre study, 149 patients undergoing cardiac surgery were randomised to receive either high-dose aprotinin, desmopressin 0.3 to 0.4 μg/kg, or placebo; significant reductions in blood loss and the number of patients requiring transfusion were observed in the aprotinin-treated compared with the desmopressin- or placebo-treated groups.[59] Of note, desmopressin administration did not increase levels of factor VIII coagulant activity or vWF antigen in comparison with aprotinin or placebo, analogous to earlier results.[29]

Four large multicentre US clinical trials in patients undergoing cardiac surgery have been reported.[88,119-121]

In a 5-centre study of 216 patients undergoing primary or repeat coronary artery bypass surgery, and randomised to high-dose aprotinin or placebo,[119] significant reductions in percentages of patients requiring donor red blood cells, platelets, fresh frozen plasma and cryoprecipitate were demonstrated in aprotinin-treated patients undergoing either primary or repeat surgery. As discussed in section 4.4, the rates of graft patency, mortality and MI did not differ significantly between groups.

In a dose-finding study of 287 patients undergoing repeat coronary artery bypass surgery at 11 institutions,[88] patients were randomised to receive either placebo, or high-dose, half-dose or pump-only aprotinin. Significantly fewer patients required donor transfusions in the full- and half-dose groups compared with the placebo and pump-only groups, while all aprotinin-treated groups required significantly fewer units of donor red blood cells compared with the placebo group. There were no significant differences among treatment groups with respect to the incidence of perioperative MI.[88]

In a further study of primary coronary artery bypass surgery at 21 US hospitals, 740 patients were similarly randomised to receive placebo, or high-dose, half-dose or pump-only aprotinin.[120] The mean number of red blood cell units transfused was reduced by approximately 50% in all 3 aprotinin groups, relative to placebo recipients, and the mean number of blood product exposures was approximately 2.5 times greater in the placebo group than in any of the aprotinin-treated groups. There were no differences in mortality between groups. The incidences of raised serum creatinine level of more than 0.5 mg/dl over preoperative levels were not significantly difference between the groups (10% high-dose, 7% half-dose, 8% pump-only and 8% in placebo). However, there was a significant ($p = 0.045$) increase in the percentage of patients diagnosed as definite, probable or possible MI between the pump-only group and the placebo-treated group. This diagnosis was made in 11% of high-dose, 13% of half-dose, and 16% of pump-only patients, in comparison with 9% of placebo-treated patients.[120]

In a 5-centre trial of 212 patients undergoing primary valve surgery, patients were randomised to placebo, or high-dose or half-dose aprotinin.[121] In this study, aprotinin treatment was associated with a reduction in volume of shed mediastinal blood, but did not decrease the percentage of patients receiving transfusions, compared with placebo. As discussed in section 4.6, in this study there was also a significantly higher number of aprotinin-treated patients with postoperative renal dysfunction.[121]

Alternative strategies have also been investigated by various European groups. One single-centre study of 115 patients undergoing primary coronary artery bypass surgery randomised patients to placebo, or to high-dose or pump-only aprotinin.[57] They demonstrated significant decreases in blood loss in both aprotinin-treated groups, but were unable to show significant decreases in red blood cell transfusions between treatment groups or placebo.

Rather than prophylactic intraoperative administration, one single-centre study randomised patients undergoing primary coronary artery bypass or cardiac valve surgery to postoperative administration of 2 mKIU aprotinin or placebo, commencing on arrival in the postoperative care unit.[122] Significant decreases in chest tube drainage and use of autologous blood products were reported for the aprotinin-treated group. However, administration of other than high-dose aprotinin has not been subjected to the same degree of rigorous tolerability analysis, and is not currently recommended, nor is administration of aprotinin recommended in general, other than to patients clearly defined as being at increased risk of blood loss.

4.3 Potential Complications

The overall incidence of adverse effects after administration of aprotinin has been very low, despite its usage worldwide. In a review of the initial

usage of aprotinin in 671 cardiac patients in 41 centres in the UK, Bidstrup et al.[123] reported that adverse events were reported in only 20 patients (3%).

In general, the types of problems to be considered with aprotinin therapy can be grouped into those associated with management of anticoagulation during CPB, issues involving graft patency after coronary bypass surgery, circulatory arrest, concerns regarding renal dysfunction, and allergic reactions. The one area in which biological derivatives such as aprotinin (and the more widely used albumin) present an unquantifiable risk, is in the potential, if any, for transmission of prion-like entities and risk of slow virus disease. The ready availability of synthetic aprotinin derivatives based on recombinant technology offers the promise of more specific targeting of effect to enhance the anti-inflammatory potentialities of aprotinin, while essentially eliminating possible risk of biological transmission.

4.3.1 Monitoring of Celite versus Kaolin Activated Clotting Time

It has been shown that aprotinin inhibits the contact activation phase of coagulation.[53,124] As mentioned in section 4.1.1, aprotinin in clinically relevant concentrations *in vitro* inhibits factor XIIa activity (by about 20%), while producing an almost 50% inactivation of factor IXa.[67] This is manifest clinically as a prolongation of the partial thromboplastin time (PTT), as reported in patients during total hip arthroplasty in the presence, but not the absence, of aprotinin therapy.[61] As a consequence, other measures of contact activation, specifically the activated clotting time (ACT) – widely employed during cardiac and other surgical procedures – are also variably influenced by aprotinin administration.[80,125,126]

To measure ACT, automated systems employ tubes containing specific amounts of activator, most commonly celite or diatomaceous earth. Another commonly used activator is kaolin, or porcelain clay. Dietrich and Jochum[127] have shown that the positively charged aprotinin molecule is adsorbed by the highly negatively charged kaolin. However, aprotinin does not appreciably bind to celite. The implications of this are that in the presence of aprotinin, celite-based ACT (cACT) will be variably prolonged after heparin administration as a consequence of the combined effects of aprotinin and heparin to inhibit contact activation and result in a prolongation of the ACT. A system using kaolin-based ACT (kACT), however, will only be prolonged in proportion to the heparin added to the system because of adsorption of aprotinin by the kaolin in the tube.[125-127]

Despite the conclusions of some clinical studies,[128] however, these data should not be taken to reflect a 'heparin-sparing' effect of aprotinin. The degree of inhibition of factor VIIa–tissue factor complex by aprotinin in clinically relevant dosages is uncertain,[67,129] whereas there is definite evidence for extrinsic activation of coagulation – which can only be inhibited by heparin – occurring during CPB.[130] Accordingly, there is general agreement that heparin dosage should not be decreased during aprotinin administration,[126,131] and that if using cACT, values should be kept in excess of 750 seconds.[132] In discussing the trend toward a higher incidence of MI seen in 1 study in repeat coronary revascularisation patients receiving aprotinin,[40] it has been speculated by Cosgrove et al.[117] that prolonged cACT with aprotinin may lead to reduced heparin administration, resulting in inadequate anticoagulation. Furthermore, the significantly prolonged cACT found with aprotinin may also lead to excessive administration of protamine after CPB, causing difficulties during attempted reheparinisation, and being misinterpreted as aprotinin-induced heparin resistance.[133]

4.4 Graft Patency in Cardiac Surgery

In part, one measure of the clinical recognition of the remarkable efficacy of aprotinin to decrease blood loss and transfusion requirements during cardiac surgical procedures has been the development of the reciprocal concern, that of producing a postoperative hypercoagulable state, particularly

in light of the prothrombotic sequelae associated with lysine-analogue antifibrinolytics.[41-51]

One of the most serious complications of coronary revascularisation surgery is the development of coronary graft occlusion. Canine studies have demonstrated that thrombosis, resulting from endothelial damage, is the primary mechanism of early graft closure.[134] Because of the complex and inter-related nature of the coagulation/fibrinolytic cascades, predicting the dominant influence that intraoperative aprotinin administration will exert on postoperative coagulation and thrombosis is problematic. Not only is the degree of enzymatic inhibition of the various inflammatory serine proteases by aprotinin highly dose-dependent, but the magnitude of the role each of these diverse mediators subsequently plays in inciting thrombosis also varies in relation to its site concentration in relation to various other mediators.

One aspect of the haemostatic system that plays an important role in the regulation of thrombin formation is that of activated protein C (aPC). The protein C system is activated by binding of thrombin to the thrombomodulin receptor on the endothelial surface. In conjunction with protein S and platelet phospholipid membrane, activated protein C inactivates factors Va and VIIIa to inhibit further prothrombin conversion and thus limits thrombin formation. aPC additionally inhibits plasminogen activator inhibitor (PAI-1), to stimulate fibrinolysis. As such, interference with aPC formation could theoretically enhance thrombin formation and promote thrombosis. In therapeutic dosages, aprotinin has been shown to inhibit protein C activation,[135] and concern has been expressed about the potential for this to increase clot formation after heparin reversal.[57]

Several studies have examined the influence of aprotinin on coagulation and fibrinolysis after cardiac surgery.[69,136] During the first postoperative day, levels of fibrin degradation products (FDP), which were significantly elevated intraoperatively only in control patients, fell to similar levels in both aprotinin and control patients. Levels of FDP then rose steadily from day 2 to day 9 in both groups, in an identical manner. Concomitant with this, a significant increase in tPA and PAI-1 occurred in the immediate postoperative period. This was followed over the ensuing week by a slow decline in tPA levels, independent of intraoperative aprotinin administration. In contrast, PAI-1 levels were significantly higher at postoperative day 1 in untreated control patients, compared with those receiving intraoperative aprotinin, in whom levels of PAI-1 were less than 50% those of the untreated group.[69]

Whether higher PAI-1 levels imply increased thrombotic risk is unclear, but if so, this does suggest that by decreasing postoperative PAI-1 levels, aprotinin may further help to decrease postoperative thrombotic risk.[69] Conversely, others[136] have interpreted evidence of decreased postoperative PAI levels, in the presence of lower plasminogen activity in aprotinin-treated patients and despite similar levels of thrombin-antithrombin (TAT) complexes, as indicative of a postoperative hypercoagulable phase. However, these authors[136] stated that the identification of hypercoagulability after aprotinin treatment was opined on the basis of other apparently unreported evidence of postoperative increases in TxA_2 levels in aprotinin-treated patients.[136] In the clinical setting, whether the inhibition of PAI-1 activity (with the potential to decrease thrombus formation) or the inhibition of aPC (with the potential to enhance thrombus formation) is the dominant effect of aprotinin administration remains unresolved.

Specific concern regarding aprotinin administration and graft occlusion after coronary revascularisation surgery is focused on the study by Cosgrove et al.,[117] involving 169 patients undergoing reoperative myocardial revascularisation, who were randomised to high-dose or half-dose aprotinin, or to placebo. Although significant reductions in blood loss were shown for all doses of aprotinin, the incidence of Q-wave myocardial infarction (MI) was reported as 17.5%, 14.3% and 8.9%, respectively (a nonsignificant difference), and there was also a trend toward increased serum creatinine levels in patients receiving high-dose

aprotinin. *Post mortem* examinations in 7 of the 13 patients who died during the study demonstrated patency of all arterial conduits, but thrombi in 6 of 12 vein grafts in the 9 patients who received aprotinin; all 5 vein grafts in the 4 placebo-treated patients were patent. Although these differences in rates of MI and graft occlusion did not achieve statistical significance, they did suggest that increased risk may be associated with aprotinin administration.

On discussion of Cosgrove et al.'s study,[117] however, it was acknowledged that the increases in activated clotting time seen with aprotinin administration may have led to inadequate anticoagulation in some patients; as discussed in section 4.3.1, this could well result in activation of tissue factor–dependent coagulation and graft thrombosis.[130] Subsequently, several studies have been conducted to specifically assess graft patency after aprotinin administration.

In one of the first reports assessing postoperative graft patency after aprotinin treatment, 52 patients undergoing primary myocardial revascularisation exclusively with arterial grafts, and receiving aprotinin in a dosage equivalent to 75% of high-dose therapy (470 ± 70mg), underwent angiography 8 to 21 days postoperatively. These demonstrated a patency rate of 99% (142/143), and only one Q-wave MI was noted.[137] Using noninvasive magnetic resonance imaging to assess graft patency in 43 high-dose aprotinin recipients, compared with 47 placebo-treated control patients, undergoing primary coronary bypass surgery, Bidstrup et al.[138] reported a patency rate for all grafts in 88.4% of aprotinin patients and 91.5% of placebo patients. Overall, 126 of 131 grafts in the aprotinin recipients and 134 of 138 grafts in the placebo recipients were patent. Neither difference was statistically significant.

Using noninvasive ultrafast computed tomography, Lemmer et al.[119] assessed early graft patency in 216 patients undergoing primary (n = 151) or repeat coronary artery bypass grafting, who were randomised to receive either high-dose aprotinin or placebo at 5 different centres. Early graft patency rates were 92.0% in the aprotinin group and 95.1% in the placebo group, while clinical MI rates were 8.9% *vs* 5.6% in primary and 10.3% *vs* 8.3% in repeat operations for aprotinin *vs* placebo, respectively. None of these comparisons was statistically significant, but significant reductions in total blood product exposures and in transfusion requirements were shown for the aprotinin-treated patients compared with placebo.

Havel et al.[139] randomised 45 patients undergoing primary myocardial revascularisation to high-dose or pump-only aprotinin, or to placebo. All patients underwent coronary angiography on the seventh to twelfth postoperative day, and no difference was found in graft patency rates (93.8%, 94.5% and 93.3% in the high-dose, pump-only and placebo groups, respectively). In one further study,[140] 110 patients undergoing primary coronary revascularisation were randomised to high-dose aprotinin or placebo and underwent angiography 18 to 35 days postoperatively. Again there was no significant difference in overall graft patency rates, being 89.5% (111/124) in the aprotinin group and 87.2% (89/102) in the placebo group, while all grafts were patent in 72.7% (32/44) and 71.4% (25/35) of patients, respectively. Vein grafts were occluded in 16% (7/44) of aprotinin patients compared with 29% (10/35) of placebo-treated patients (a non significant difference), while arterial grafts were occluded in 5/27 and 0/27 patients, respectively (a near significant difference, $p = 0.0511$).

Overall, it can be stated that despite several studies specifically designed to detect increased graft occlusion after aprotinin therapy, there is no evidence for any statistically detectable effect. Whether this was a result of inadequate power based on the relatively large sample size required to detect events occurring with low incidence remains at issue. An analysis of low-incidence outcomes such as myocardial infarction (MI), stroke, renal failure and death, based on pooled data from 4 published trials of aprotinin in coronary artery bypass surgery and combined with unpublished data from 2 other clinical trials, was reported in an

editorial.[90] In analysing the results of half-dose aprotinin studies involving 636 coronary artery bypass recipients, it was indicated that the nonsignificant difference in mortality, 3.8% *vs* 5.3% for placebo and half-dose aprotinin, respectively, would require 3160 patients per group to achieve statistical significance. The similar mortality of placebo *vs* high-dose aprotinin, 2.7% *vs* 2.8% respectively, based on analysis of 1721 coronary artery bypass patients, would require 422 000 patients to detect such a small difference. These authors[90] concluded that high-dose aprotinin is 'safe' and effective for use as indicated in reoperative coronary artery bypass, primary coronary artery bypass with impaired coagulation systems, and patients refusing blood and blood products for personal reasons. They also concluded that more information is required in order to consider half-dose aprotinin to be 'safe' for any patient.[90]

4.5 Hypothermic Circulatory Arrest

The demonstrated efficacy of aprotinin in decreasing blood loss and transfusion in various cardiac surgical procedures has led to its use in a variety of high-risk patients undergoing hypothermic circulatory arrest (HCA) with untoward results being reported in some of these cases.

Sundt et al.[141] used high-dose aprotinin in 20 patients undergoing primary or repeat operations on the thoracic or thoracoabdominal aorta using CPB and HCA. They reported that 7 patients died in hospital, of whom 5 underwent *post mortem* examinations. These disclosed platelet-fibrin thrombi in the coronary arteries of 4 patients, in the pulmonary arteries of 2 patients, in the renal arteries of 4 patients and in the brains of 2 patients. Additionally, renal dysfunction occurred in 13 of the 20 patients in the study, 5 of whom required dialysis. These 20 patients were contrasted with 20 age-matched historical control patients undergoing similar operations without aprotinin. Of these patients, 18 had a relatively uneventful postoperative course; however, there was 1 death and 1 case of renal dysfunction not requiring dialysis. Of note is the observation that while it was intended that ACT was to be maintained at >480 sec, the lowest ACT recorded in the aprotinin group during CPB was 353, and the total dose of heparin administered was 30% less than in the comparator group (27 850 ± 439 U/kg *vs* 40 250 ± 552 U/kg). In another retrospective report of aprotinin usage in 53 patients undergoing deep hypothermic CPB with or without HCA, and contrasted with 27 historical control patients, a higher incidence of bleeding and thrombosis-related deaths was observed in the aprotinin-treated patients.[142] It is considered that in both of these reports inadequate heparinisation, probably caused by the (then relatively unrecognised) influence of aprotinin in prolonging cACT (section 4.3.1), was the most likely aetiology.[143]

In contrast, several investigators have offered their experiences with aprotinin during HCA in both adults and paediatric patients undergoing cardiac surgery.[144,145] In a retrospective comparison of high-dose aprotinin administration in 24 adult patients undergoing complex aortic procedures with 24 age-matched controls undergoing similar procedures without aprotinin, no significant difference in neurological events, or MI rate was found, while there was a trend toward reduced in-hospital mortality in aprotinin-treated patients.[144] Of note, cACT was maintained at >750 seconds and kACT was maintained at >500 seconds during aprotinin administration, and aprotinin recipients received significantly more heparin than the comparator group (total dose 40 187U *vs* 31 771U). Elevated serum creatinine level was 3.5 times more common with aprotinin administration, but temporary postoperative dialysis was required with equal frequency in both groups and no patient required permanent haemodialysis.

In a study by Mossinger et al.[145] of 60 paediatric patients undergoing CPB and randomised to high-dose or half-dose aprotinin or placebo, 37 patients underwent HCA. No adverse effects attributable to aprotinin were observed, and plasma levels of fibrin split products were significantly reduced in the aprotinin-treated groups in a dose-related fashion. In a clinical commentary, Dietrich[146] further noted that during the previous 5 years, HCA

with aprotinin had been used in about 500 children without evidence of harmful effects.

4.6 Renal Function in Cardiac Surgery

Because its primary mode of elimination is through uptake into brush border epithelial cells of the proximal tubules of the kidney,[147] less than 2% of a 1 mKIU dose of aprotinin appears in urine. In animal studies, administration of aprotinin has been shown to decrease glomerular filtration rate (GFR), creatinine clearance and urine volume, suggesting a role for the kallikrein-kinin system in regulating renal function.[52] In animal studies, administration of large doses of aprotinin was reported to result in kidneys becoming pale and swollen.[148] In canine studies, aprotinin increased sodium excretion and decreased potassium excretion, but no effects were observed on GFR or renal blood flow.[149] Results of clinical studies differ in the magnitude of the effects of aprotinin on renal function, but, with the exception of patients undergoing HCA, there has been no significant association with postoperative renal insufficiency or failure.

In a study of 13 patients undergoing coronary revascularisation surgery with CPB receiving high-dose aprotinin, osmolar clearance and fractional sodium excretion were higher in the aprotinin group than in the group of 13 control patients shortly after CPB, with no significant differences between groups at 24 hours postoperatively.[150] In a prospective study of 902 adult cardiac surgical patients treated with high-dose aprotinin at one centre and compared with 882 untreated controls, no differences in serum creatinine level were found between the groups on the first or second postoperative days.[114] Increased serum creatinine was found to be significantly associated with age and duration of surgery, but not with aprotinin treatment. There was also no significant difference in the incidence of postoperative haemodialysis, which was required in 2.2% of control group and 2.3% of aprotinin-treated patients.

In an 11-centre placebo-controlled North American trial of high-dose, half-dose and pump-prime–only aprotinin therapy, 8.8% (19/215) of aprotinin recipients and 8.3% (6/72) of placebo recipients were reported to experience renal failure, acute renal failure, or abnormal renal function in the postoperative period.[88] In all treatment groups there was a transient decrease in creatinine levels in the immediate postoperative period after which creatinine levels increased above baseline and then subsequently normalised. There were no significant differences between aprotinin-treated or placebo-treated groups in the incidences of patients with peak increases in postoperative creatinine levels >0.5 mg/dl or >2.0 mg/dl above baseline.

A recent report of high-dose aprotinin administration in 7 patients undergoing cardiac surgery who had chronic renal failure (CRF) and who were maintained on dialysis indicated that aprotinin was associated with reductions in bleeding and blood transfusions, compared with a group of 9 patients with CRF undergoing similar procedures without aprotinin.[151] Two recent studies in patients undergoing total hip arthroplasty found no significant differences between patients treated with high-dose aprotinin and those receiving placebo with respect to serum urea and creatinine levels during the perioperative period.[61,62]

In the study of Cosgrove et al.,[117] nonsignificant increases in serum creatinine level of >0.5 mg/dl from baseline were found in 25%, 20% and 18% of patients treated with high-dose or half-dose aprotinin, or placebo, respectively. In a recent 5-centre placebo-controlled trial of high-dose or half-dose aprotinin, 212 patients undergoing primary sternotomy for valve replacement or repair were assessed for perioperative blood loss, transfusion requirements and renal function.[121] While aprotinin was associated with a decrease in volume of shed mediastinal blood, it did not decrease the percentage of patients receiving transfusions. Although overall adverse event rates were similar among all groups, there was a significantly ($p = 0.008$) higher incidence of renal dysfunction between the groups, being 11% in high-dose, 7% in half-dose and 0% in placebo-treated patients. A significantly greater number of aprotinin-treated

patients also had increases in serum creatinine level >0.5 mg/dl; 30% of high-dose, 14% of half-dose and 8% of placebo recipients showed such elevations (p = 0.003). These authors[121] also found an association between diabetes mellitus and high-dose aprotinin in relation to the development of renal failure. Although only 18 of 212 patients has diabetes mellitus, all 3 who had developed renal failure were in the high-dose group; renal failure did not develop in diabetic patients in half-dose or placebo groups.

The influence of high-dose aprotinin on renal function was specifically assessed in a prospective 5-centre trial of 260 patients undergoing primary or repeat coronary revascularisation with use of CPB.[152] Timed urine collections were used to assess urine volume and for calculation of creatinine clearance. There was a nonsignificant trend toward increases in serum creatinine level to occur more frequently and to a greater extent in aprotinin treated patients in comparison with placebo-treated patients. There was no difference in timed urine output or development of abnormal creatinine clearances between groups at any time postoperatively. While not statistically significant, 23.5% (8/34) of patients with diabetes mellitus treated with aprotinin had postoperative increases in serum creatinine level of 0.5 mg/dl or greater in comparison with 13.3% (4/30) of placebo-treated patients with diabetes mellitus.

It has been speculated that as the proximal tubular epithelial cells take up small proteins such as aprotinin and insulin, with large protein loads associated with high-dose aprotinin therapy, this system might be overwhelmed, producing swelling of proximal tubular cells and detrimental mechanical effects on filtrate flow, leading to increases in serum creatinine levels.[121] Whether patients with diabetes mellitus are at greater risk of this remains speculative, but the trend toward increases in serum creatinine level in such patients observed in 2 studies[121,152] does call for caution in the administration of high-dose aprotinin to patients with diabetes mellitus until more data are available. Overall, however, despite the potential for transient increases in serum creatinine level, it does not appear that aprotinin produces any clinically significant detrimental effects on renal function.

4.7 Allergic Reactions

In a report of 86 patients re-exposed to aprotinin for cardiac surgical procedures, suspected anaphylactic reactions occurred in 5.8% (5/86).[153] However, no immunological studies were performed to confirm these clinical impressions. Anti-aprotinin IgG and IgM antibodies have been documented in some,[154-156] but not all,[157,158] patients after treatment with aprotinin.

In their comprehensive review of the risk of aprotinin allergy, Leskiw and Levy[153] report that based on a review of postmarketing studies from outside the US, and other controlled and open studies, the risk of anaphylactic reactions to aprotinin can be estimated at <0.5%, with patients previously treated with the drug being at increased risk.

In addition to the potential for these immunologically mediated reactions, it should also be borne in mind that as a highly basic molecule, rapid intravenous administration of aprotinin can lead to an anaphylactoid reaction, resulting in hypotension, flushing and tachycardia, as a result of direct release of histamine from mast cells.[52] Accordingly, it is advised that in all patients, an intravenous test dose of aprotinin 1ml be administered prior to receiving the full loading dose. Furthermore, in patients with known or suspected previous exposure to aprotinin, some form of testing for sensitisation, e.g. a skin-prick test, even before the administration of the test dose should be carried out.[53,153]

5. Conclusion

In this review we have tried to assess the role of aprotinin therapy in a variety of clinical situations, attempting to balance the risks of blood loss and attendant transfusion, with other options designed to limit homologous blood use. It is clear that antifibrinolytic therapy using the synthetic lysine analogues aminocaproic acid and tranexamic acid does have significant potential for clinical efficacy.

Whether their clinical benefit in any given situation outweighs the risks remains currently unknown because of the complete absence of any large-scale clinical trials documenting safety as well as efficacy. Their role is a matter for judicious consideration.

In all, the risks of high-dose aprotinin administration appear to primarily consist of those associated with inadequate anticoagulation, generally a consequence of misunderstanding the complex interactions of aprotinin with differing ACT activators, and those of developing an allergic reaction. Against this, the consistent and well documented efficacy and safety of high-dose aprotinin in reliably decreasing blood loss and transfusion requirements in a variety of cardiac and noncardiac surgical procedures must be considered. Whether salutary effects on other organ systems, particularly the brain, are realised as a consequence of the potential anti-inflammatory effects of aprotinin is a matter for further study.

Thus, consistent with that most fundamental tenet of clinical medicine, *primum non nocerem*, the risk of excessive blood loss in each patient must be considered against the costs of pre-emptive aprotinin administration. To paraphrase David Royston,[159] perhaps the one individual most responsible for initiating the dramatic, yet serendipitous, observations of the remarkable efficacy of high-dose aprotinin to decrease blood loss in a wide spectrum of high-risk cardiac surgical procedures, 'Serine protease inhibitors, if correctly investigated and used, have the potential to revolutionise future pharmacological approaches to many medical problems, not just bleeding'.[159]

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