Review Article

Natural and synthetic antifibrinolytics in cardiac surgery

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In an effort to reduce morbidity associated with transfusion of blood products, the use of antifibrinolytics to decrease bleeding and transfusions after cardiopulmonary bypass (CPB) is receiving widespread attention. The predominant haemostatic defect induced by CPB and, therefore, the mechanisms by which natural (aprotinin) or synthetic antifibrinolytics (Σ-aminocaproic acid, tranexamic acid) exert their effects have been difficult to define. Nonetheless, all three substances appear to be effective in the treatment or in the prevention of excessive bleeding associated with cardiac surgery. However, the administration of these drugs should not attempt to replace meticulous surgical and anaesthetic care. In particular, the importance of an appropriate transfusion practice cannot be overemphasized. The efficient use of these, sometimes expensive, drugs must take into account not only the initial cost, but also the short- and long-term economic consequences for the health care provider of using, or not using, a given medication. Unfortunately, the comprehensive data on which authoritative conclusions may be reached are not yet available. Pending availability of these data, the present use of antifibrinolytics at the Montreal Heart Institute is the following: (1) patients undergoing elective primary myocardial revascularization or valve surgery do not receive prophylactic antifibrinolytics; (2) patients undergoing repeat myocardial revascularization, repeat valve surgery, or primary or repeat combined procedures, receive prophylactic Σ-aminocaproic acid; (3) Σ-aminocaproic acid may be used to treat excessive chest drainage in the postoperative period; (4) the prophylactic and the therapeutic uses of low doses of aprotinin are currently under investigation.

Afin de réduire morbidité associée aux transfusion sanguines, les anesthésistes et les chirurgiens cardiaques utilisent de plus en plus les antifibrinolytiques dans le but de diminuer le saignement et les besoins transfusionnels secondaires à la circulation extracorporelle (CEC). Les modifications de l'hémostase induites par la CEC et, par voie de conséquence, les mécanismes d'action des antifibrinolytiques naturels (l'aprotinine) ou de synthèse (l'acide Σ-aminocaproique et l'acide tranexamique), sont mal connus. Néanmoins, l'efficacité des ces trois médicaments pour prévenir ou traiter le saignement secondaire à la CEC ne semble plus de doute. Toutefois, ces médicaments ne peuvent remplacer les soins attentifs des anesthésistes et des chirurgiens et, tout particulièrement, une pratique transfusionnelle adéquate. Afin de parvenir à une utilisation efficient de ces médicaments parfois coûteux, le dispensateur de soins devra tenir compte non seulement de leur coût d'achat, mais également des conséquences à court et à long terme de leur utilisation ou de leur non-utilisation. Malheureusement, toutes les données nécessaires à cette analyse coût/bénéfice ne sont pas encore disponibles. En attendant les résultats de ces études, le protocole en vigueur à l'Institut de Cardiologie de Motréal peut se résumer ainsi : 1) les patients subissant une chirurgie élective et de première intention pour revascularisation du myocarde ou remplacement valvulaire ne recoivent pas d'antifibrinolytiques de façon prophylactique ; 2) les patients réopérés pour revascularisation du myocarde ou remplacement valvulaire, ou subissant toute chirurgie combinée (primaire ou de réintervention) recoivent de l'acide Σ-aminocaproique en prophylaxie ; 3) l'acide Σ-animocaproique peut être utilisé dans le traitement d'un saignement médiastinal excessif dans la période post-opératoire ; 4) concurremment, nous sommes à étudier l'efficacité de faibles doses d'aprotinine en chirurgie cardiaque de l'adulte.

Key words
ANAESTHESIA: cardiac;
BLOOD: coagulation; antifibrinolytics, aprotinin, 6-aminocaproic acid, tranexamic acid;
SURGERY: cardiovascular, cardiopulmonary bypass.

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Contents

Excessive bleeding associated with cardiopulmonary bypass (CPB) has always been a major concern to cardiac anaesthetists and surgeons. In an effort to reduce morbidity associated with transfusion of blood products (transmitted infectious diseases, transfusion reactions, etc.) and to answer concerns that the demand for blood and blood products may exceed the supply, many strategies have been explored to diminish the need for transfusion both during and after CPB. Pharmacological reduction of bleeding associated with CPB has received much attention recently. It has the main advantage of being readily available and easy to administer, of avoiding the use of costly equipment, and that it may be used prophylactically rather than therapeutically. Antifibrinolytics are some of those drugs which have been used either to treat or to prevent excessive bleeding associated with cardiac surgery.

Epsilon-aminocaproic acid (EACA) and tranexamic acid (TA), two synthetic antifibrinolytics, and aprotinin (A), an antifibrinolytic and proteinase inhibitor derived from bovine lung, have been used with varying success and enthusiasm in open heart surgery. An appreciation of the haemostatic defects induced by CPB, of the possible mechanisms by which antifibrinolytics may prevent or correct these defects, and of the efficacy and efficiency of antifibrinolytics is essential for the optimal use of these drugs in cardiac surgical patients.

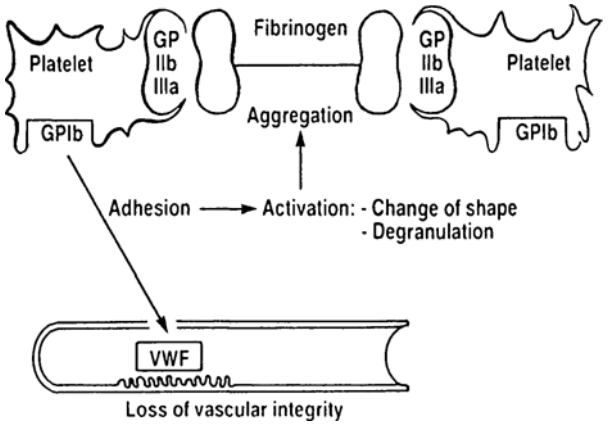

FIGURE 1 Primary haemostasis. Platelet adhesion is mediated via von Willebrand factor (VWF) and platelet receptor GPIb. Subsequent aggregation is mediated via GPIIb and GPIIIa receptors.

Haemostasis and cardiopulmonary bypass (CPB)

The normal process of haemostasis will be reviewed briefly to understand better the changes in haemostasis associated with CPB and the mechanism of action of antifibrinolytics in this setting.[1]

The first stage of haemostasis is primary haemostasis in which platelets play a major role. Von Willebrand factor anchors platelets to damaged vessels via the GPIb platelet receptors. Platelet adhesion is followed by activation: a change in platelet shape and subsequent degranulation. Substances liberated from the platelet granules stimulate platelet aggregation by way of their receptors GPIIb-IIIa (Figure 1).

Stimuli leading to platelet adhesion also activate the contact phase of coagulation. Activation of factor XII converts prekallikrein into kallikrein and activates the intrinsic pathway of coagulation that leads to the generation of thrombin. Kallikrein plays a pivotal role in coagulation: it amplifies the activation of factor XII via a positive feedback mechanism, and converts plasminogen into plasmin.

Initiation of the coagulation process leads to simultaneous activation of the fibrinolytic system, thus generating plasmin. Plasmin, apart from its well-known action in the cleavage of fibrin, is also believed to reduce the number of platelet receptors GPIb, causing a decrease in the capacity of platelets to adhere (Figure 2).[2]

Many articles have been written on the complex subject of haemostasis and CPB. Despite several opposing views, a trend in the pathogenesis of bleeding following CPB seems to emerge. Before 1970, it was generally held that nonsurgical, post-CPB bleeding was due to fibrinolysis.[3] An acquired platelet defect is now recognized as the most common cause of nonsurgical, post-CPB bleeding.[3,4-9]

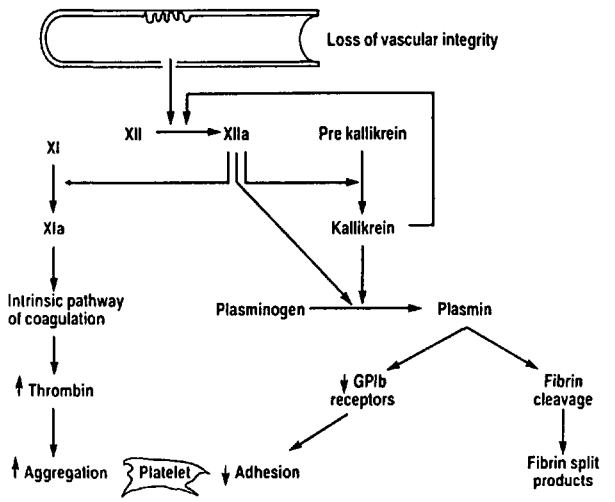

FIGURE 2 Contact phase of coagulation. Activation of factor XII (Hageman factor) stimulates the intrinsic pathway of coagulation while simultaneously initiating fibrinolysis. Kallikrein plays a major amplifying role.

Haemodilution secondary to initiation of CPB leads to thrombocytopenia but the platelet count usually remains above $100{,}000 \cdot \mu l^{-1}$ and cannot explain the bleeding tendency following CPB.[3,8,9] Platelet adhesion to the CPB circuit also contributes to thrombocytopenia. Contrary to normal haemostasis, platelet adhesion to the CPB circuit is mediated by the interaction of GPIIb-IIIa with the fibrinogen adsorbed to the artificial surfaces.[10]

Platelet dysfunction associated with CPB is manifested by a rapid rise in the bleeding time and a decrease in the capacity of the platelets to aggregate *in vitro*. The bleeding time usually returns to normal within two to four hours following CPB, except in a subgroup of patients where the platelet defect persists. The exact mechanism of this dysfunction is unknown but a transient depletion of a functional platelet component or a reversible membrane abnormality are possible causes.[5] The platelet membrane abnormality may be explained by a decrease in the number of GPIb receptors secondary to mechanical trauma by CPB or to the action of plasmin.[8,11] The degree of platelet dysfunction is related to the duration and to the degree of hypothermia during CPB.[4,5] Recently, CPB has been shown to cause also the prolonged circulation of activated, "spent" platelets which may not be able to contribute normally to the platelet aggregate, potentially rendering it more vulnerable to disaggregation by proteases.[12]

Synthetic antifibrinolytics: general considerations

Chemical structure and activity

Three synthetic antifibrinolytic drugs have been used in humans and their clinical application has been reviewed extensively by Verstraete in 1985.[13] They are epsilon-aminocaproic acid (EACA), tranexamic acid (TA), and p-aminomethylbenzoic acid (PAMBA). The therapeutic use of PAMBA is anecdotal, and since this drug has not been used in cardiac surgery, it will not be discussed further.

The potential use of EACA as a therapeutic agent was first described in 1959, and the antifibrinolytic activity of the trans-isomer of TA was clarified in 1964. Both EACA and TA are small molecules, with molecular weights of 131 and 157 daltons respectively, and have similar properties. Their antifibrinolytic effect is related to a reversible complex formation with plasminogen and with the active protease plasmin. Saturation of the lysine binding site of plasminogen (the precursor of plasmin) with these drugs displaces plasminogen from the surface of fibrin. Even if plasminogen is transformed into active plasmin, plasmin cannot bind to fibrin and its proteolytic action is inhibited.[13] Also, the displacement of plasminogen from the surface of fibrin prevents its activation into plasmin by fibrin-bound tissue activator.[14] Thus, EACA and TA are thought to act by preventing the premature dissolution of the normal fibrin clot. It follows that these drugs cannot prevent bleeding unless clotting has occurred.

Pharmacokinetic behaviour and side effects

It is generally accepted that TA is approximately ten times more potent than EACA. Both drugs have an elimination half-life between one and two hours, and are rapidly excreted in the urine in an active form. Due to this short half-life, in cardiac surgical patients, EACA and TA are administered as a bolus dose followed by an infusion. An intravenous loading dose of 100–150 $mg \cdot kg^{-1}$ followed by an infusion of 10–15 $mg \cdot kg^{-1} \cdot hr^{-1}$ of EACA produces the desired blood concentrations in adults. The usual bolus dose of TA is 10 $mg \cdot kg^{-1}$, followed by an infusion of 1 $mg \cdot kg^{-1} \cdot hr^{-1}$. Tranexamic acid has been shown to display a higher and more sustained antifibrinolytic activity than EACA in renal, intestinal and prostatic tissue.[15] However, the relative activity of these drugs in cardiac and surrounding tissues is unknown.

Treatment with fibrinolytic inhibitors is associated with a theoretical risk of an increased thrombotic tendency. The reader is referred to the review article by Verstraete for a discussion of thrombosis (intracranial or in other vascular areas) associated with the use of EACA or TA. The author concludes that this association may be fortuitous and that further observations are needed to assess the reality of this potential hazard.[13] Controlled trials of the prophylactic administration of EACA or TA to cardiac surgical patients have not been associated with an increased incidence of venous, coronary or cerebrovascular thrombosis.[16–18] How-ever, all these studies used a limited number of

patients and the incidence of thrombosis is likely to be a small one. Thus, the power of these studies is probably too small to provide definitive data with respect to the increase, or lack thereof, of thrombosis following the use of EACA or TA.

Epsilon-aminocaproic acid and TA effectively reduce bleeding associated with lower urinary tract surgery, but they should be administered cautiously to patients bleeding in the kidneys or ureters to avoid thrombosis of the upper urinary tract.[13,19] This is very different from the acute renal failure secondary to glomerular capillary thrombosis reported by Gralnick *et al.* in a patient treated with EACA for postoperative bleeding after total correction of tetralogy of Fallot, who continued to receive high doses of EACA despite evidence of disseminated intravascular coagulation.[20] The risk of using EACA in disseminated intravascular coagulation is well substantiated by animal experiments.[21] Should the use of herapin and EACA in this context be contemplated, consultation with a haematologist is strongly recommended.[22]

Noncardiac uses of EACA and TA

The value of EACA and TA in the management of various haemorrhagic and nonhaemorrhagic disorders remains controversial.[13,14,19] It is well established for the prevention of bleeding after dental extraction in haemophiliacs and in the treatment of hereditary angioneurotic oedema. These drugs may also help to reduce the bleeding associated with tonsillectomy, prostatic surgery, cervical conisation, recurrent epistaxis, menorrhagia, abruptio placentae, and liver transplantation. They may also be of use to reduce gastric and intestinal bleeding, and prevent recurrence of bleeding after traumatic hyphaema and subarachnoid haemorrhage. Unfortunately, increased cerebral ischaemic complications appear to negate the initial beneficial effect of antifibrinolytic drugs on rebleeding after subarachnoid haemorrhage.

EACA and TA in cardiac surgery

Historically, the administration of synthetic antifibrinolytics to cardiac surgical patients can be divided into two periods. From 1964 to the mid-seventies, EACA was used to control or to prevent bleeding in patients undergoing surgery for congenital or valvular disease. During this first period, preoperative coagulation defects associated with congenital heart disease and the type of equipment used to perform CPB may have increased the contribution of fibrinolysis to bleeding disorders after cardiac surgery. Since then, myocardial revascularization procedures have taken over as the most frequent of cardiac surgical procedures in adults, and a renewed interest in the use of EACA has emerged. The prophylactic use of TA to decrease blood loss after CPB was first reported in 1988.

The routine administration of EACA to all patients undergoing CPB lasting more than 60 min was suggested by Marin in 1964.[23] He noted an increased fibrinolysis and abnormal bleeding in patients undergoing long perfusions but did not specify when EACA should be administered. Subsequently, several investigators administered EACA either before CPB to treat preoperative fibrinolysis[24,25] or to prevent postoperative bleeding,[26,27] or after CPB to control haemorrhage[28] or to prevent blood loss.[29] The results of these open and/or uncontrolled studies were varied. A double-blind, placebo-controlled, randomized experiment by McClure in children undergoing repair of congenital heart disease demonstrated that EACA reduced blood loss in the period after cessation of CPB to the end of the operation, but not in the following 24 hr.[30] The authors suggested that the beneficial effect of EACA was secondary to a reduction in the fibrinolysis that occurs after the chest is open and during bypass. Increased fibrinolysis during this period has been demonstrated by several other investigators.[16,23,31–35]

The usefulness of EACA to treat excessive bleeding after aortocoronary bypass was reported by Lambert in 1979.[36] Using the prothrombin time, partial thromboplastin time, fibrinogen level, and tri-F titer tests, hyperfibrinolytic bleeding was the most frequently identifiable coagulation disorder and was diagnosed in 20% of the patients. All these patients were treated successfully with EACA alone, or with EACA supplemented with cryoprecipitate or fresh-frozen plasma. In a double-blind, placebo-controlled, randomized administration of EACA after weaning from CPB, Vander Salm demonstrated a small but significant decrease of postoperative bleeding after elective coronary artery bypass graft operation.[17] Interestingly, platelet counts one hour after operation were higher in the EACA-treated group, possibly suggesting an effect of EACA on platelets.

Prophylactic administration of EACA (i.e., beginning before skin incision) decreased chest tube blood loss 24 hr postoperatively, and the need for blood transfusions, in a controlled study by DelRossi *et al.* of 350 patients undergoing various elective operations with CPB.[18] There was no evidence of a hyperthrombotic state or other side effects in the EACA-treated group. Similarly, prophylactic TA de-creased bleeding after cardiac operations, without coagulation-related complications, in a controlled study of 38 patients by Horrow *et al.*[16] However, the latter could not demonstrate a reduction in the transfusion of red blood cells, but patients in the placebo group received more fresh frozen plasma. Preliminary results of a retrospective study comparing EACA with TA indicated that these two agents similarly reduced postoperative blood losses and the need for packed red cells.[37]

Prophylactic EACA and TA may exert their beneficial

effect by inhibiting fibrinolysis, especially in the period from sternotomy to the end of CPB, but it is also possible that they help to preserve platelet function during and after CPB by reducing the effect of plasmin on GPIb platelet receptors.[38]

Aprotinin: general considerations

Chemical structure and activity

Discovered in 1930, aprotinin is a naturally occurring inhibitor of proteolytic enzymes which is isolated from bovine lung. Aprotinin is a polypeptide with a molecular weight of 6512 daltons, known to inhibit human trypsin, plasmin, tissue and plasma kallikrein by forming reversible enzyme-inhibitor complexes. Each complex has a specific dissociation constant which influences the concentration of aprotinin necessary to produce enzymatic inhibition (the enzymatic activity of aprotinin is generally expressed in KIU, kallikrein inactivator units).[13] For example, the trypsin-aprotinin complex has the lowest dissociation constant and therefore the concentration of aprotinin necessary to inhibit trypsin is low.[13,39] Effective inhibition of plasmin and plasma kallikrein occurs when aprotinin plasma concentrations reach values of 125 KIU · ml^{-1} and 250–500 KIU · ml^{-1} respectively.[39,40]

Pharmacokinetic behaviour and side effects

Following a bolus dose of aprotinin, a two-phase elimination was demonstrated by Kaller using radioactive aprotinin, with an initial half-life of 0.7 hr and a terminal half-life of seven hours. The initial half-life represents the distribution of aprotinin in the extracellular compartment whereas the terminal half-life corresponds to the accumulation of aprotinin in tissues like the kidneys and cartilage.[41]

The epithelial cells of the renal proximal tubule have a great avidity for aprotinin, which accumulates in these cells and then is eliminated as small peptides or amino acids.[13] Experimental studies using high doses of aprotinin in dogs have reported reversible obstruction of renal proximal tubules secondary to the accumulation of the drug.[42] Results from animal studies regarding the renal toxicity of aprotinin are inconclusive, but any adverse effect appears to be related to the dose of the drug and temperature of the kidney.[43] Although the use of high doses of aprotinin and hypothermia during CPB could theoretically lead to renal toxicity, extensive clinical experience has not shown untoward renal effects in this setting.[43–46] The only evaluation of renal function in patients receiving high-dose aprotinin also reported no untoward effect on serum electrolytes, osmolarity and creatinine, and creatinine clearance.[47]

The only major side effect caused by aprotinin is a hypersensitivity reaction, which is more likely to occur after previous exposure to the drug, and has an overall incidence of approximately 0.1%.[13,42] Previous exposure to aprotinin was the only exclusion criterion in a study by Bidstrup *et al.*, presumably on this basis.[46] However, repeated use of aprotinin in a small series of 15 patients by Freeman was not associated with allergic phenomena.[48]

The use of antifibrinolytic agents raises the fear of thrombotic events but, contrary to synthetic antifibrinolytic agents, aprotinin can also reduce activation of clotting by inhibiting kallikrein. To our knowledge, the only report of unusual thrombus formation was by Böhrer in 1990 who associated the early formation of thrombi on the pulmonary artery catheter (within 45 to 55 min after insertion) in three cardiac surgical patients with the use of 4.5 million KIU of aprotinin.[49] As pointed out in an accompanying editorial, it must be noted that the authors were not using heparin-coated catheters and that further studies are necessary to assess the risk of thrombus formation in this context.[50] Also, results of trials designed to investigate the influence of high-dose aprotinin on the rate of graft closure in operations for myocardial revascularization should become available in a near future.

Noncardiac uses and dosage

Aprotinin was first used in clinical practice in 1953 for its inhibition of trypsin in the treatment of acute pancreatitis, and later for its inhibition of plasmin in haemorrhage associated with abruptio placentae, prostatectomy and neurosurgery for ruptured intracranial aneurysm.[13] To control haemorrhage, the recommended dosage is an *iv* bolus of 200,000 KIU, followed by a continuous infusion of 100,000 KIU · hr^{-1} until haemostasis is achieved (product monograph). A few of the other investigated indications for aprotinin are the prevention of respiratory insufficiency in traumatic shock,[51] the reduction of the size of myocardial infarction,[13] and the preservation of myocardial viability after prolonged cardioplegia.[52]

Aprotinin in cardiac surgery

Usual dosage

Aprotinin has been used since 1964 in cardiac surgery with some clinical success, at doses not exceeding 400,000 units. The administration of 10,000–20,000 KIU aprotinin to patients presenting increased fibrinolytic activity associated with abnormal bleeding after CPB resulted in rapid remission of bleeding in five patients studied by Tice *et al.* in 1964.[53] In 1968, Mammen reported a considerable reduction of the activation of the fibrinolytic system (as assessed by euglobulin lysis times, thrombin times, thromboelastography, and fibrinogen split products) during CPB in patients receiving aprotinin (100,000 units in pump

TABLE Influence of aprotinin on blood losses, percentage of patients transfused, and volume of blood transfused

Author (reference)	*n*	*Postoperative blood loss ml or G of haemoglobin*	*% of pts transfused*	*ml transfused*
Royston (45)	22*	A 286 ± 48 ml	36	¶
		C 1509 ± 388 ml	100	¶
van Oeveren (44)	22	A 357 ml	¶	¶
		C 674 ml	¶	¶
Alajmo (57)	34	A 486 ± 47 ml	¶	213 ± 85 ml
		C 830 ± 117 ml	¶	409 ± 140 ml
Bidstrup (46)	80†	A 309 ± 133 ml	20	¶
		C 573 ± 166 ml	95	¶
Dietrich (58)	152‡	A 761 ± 51 ml	58	1015 ± 113 ml
	317§	C 1070 ± 43 ml	82	1783 ± 100 ml
Fraedrich (59)	80†	A 652 ± 382 ml	42.1	242 ± 359 ml
		C 1204 ± 705 ml	68.4	937 ± 843 mi
Wildevuur (60)	28†	a 14 ± 3 G	¶	¶
		C 64 ± 6 G	¶	¶
Dietrich (56)	40†	A 738 ± 411 ml	37	163 ± 308 ml
		C 1431 ± 760 ml	75	838 ± 963 ml
van Oeveren (11)	60†	A 17 ± 9 G	38	¶
		C 37 ± 12 G	68	¶
	22‡	a 19 ± 9 G	38	¶
Blauhut (47)	26‡	A 300 ml (approx.)	15	¶
		C 600 ml (approx.)	62	¶
Harder (61)	80†	A 559 ± 109 ml	31.5	¶
		C 911 ± 170 ml	57.2	¶
Havel (62)	22	A 610 ± 310 ml	¶	¶
		C 1000 ± 440 ml	¶	¶
Murkin (63)	38*	A ¶	5	¶
	38§	C ¶	21	¶

*Reoperation; †double-blind study; ‡nonrandomized study; §historic controls; ¶data not available from the publication; A: high dose aprotinin; C: control group; a: 2 million KIU in CPB prime only; blood losses were significantly reduced by A or a when compared with C.

prime, infusion of 100,000 units per hour of extracorporeal circulation, and 100,000 units at the end of CPB).[54] In 1971, Ambrus *et al.* treated patients with a 4-hour infusion of aprotinin (total dose: 400,000 units) which was started prior to sternotomy.[55] These patients suffered less blood loss than controls.

Since 1987 numerous studies have evaluated the efficacy of higher doses of aprotinin for prophylactic reduction of bleeding associated with heart surgery. These European studies generally used a total dose of approximately five million KIU of preservative-free aprotinin: two million KIU at induction of anaesthesia, an infusion of 500,000 KIU · hr^{-1} after the initial bolus until the end of surgery, and an additional bolus of two million KIU in the priming solution of the pump. The use of high doses was rendered possible by the introduction of the preservative-free formulation of aprotinin (500,000 units per vial, without 0.9% benzyl alcohol), which is not yet available in North America.

The rationale underlying these higher doses is to obtain concentrations of aprotinin capable of inhibiting plasmin and, eventually, plasma kallikrein, depending on what is considered to be the predominant mechanism of action of aprotinin in reducing bleeding following CPB. The concentration of aprotinin obtained while using this dosage regimen ranges from 185 to 335 KIU · ml^{-1} at the start of CPB and from 80 to 190 KIU · ml^{-1} at the end of CPB.[11,44,46,56]

Thus, while plasma concentrations capable of totally inhibiting plasmin are achieved using this regimen, higher doses are necessary to produce predictably complete inhibitory concentrations of kallikrein.[39]

Efficacy studies

The majority of studies evaluating the efficacy of aprotinin in heart surgery were open, randomized studies of patients undergoing primary heart surgery. The Table summarizes the results of these studies in terms of mean blood loss and transfusions.[11,44–47,56–63] Reductions in blood loss, in the number of patients receiving any blood product, or in the quantity of blood products transfused was reported by all investigators. Unfortunately, the number of donors to whom the recipient is exposed (an indication of the relative risk of transfusion-related complications) is often difficult to determine from the published results.

Acetylsalicylic acid intake by patients increases the

risk of perioperative bleeding.[64] Royston *et al.* studied the efficacy of aprotinin in 17 patients taking acetylsalicylic acid at the time of surgery. Despite the well known irreversible inhibition of platelet aggregation by acetylsalicylic acid, the authors noted a dramatic fall in postoperative blood losses (290 ± 126 ml vs 2070 ± 890 ml in the control group).[65] The mechanism by which aprotinin reduces blood loss in this context is unknown.

Aprotinin was also administered to ten patients with endocarditis who underwent valve surgery, a condition where considerable blood loss is expected.[46] Five patients had clinical and laboratory evidence of disseminated intravascular coagulation. Blood losses were greatly reduced, compared with a retrospective control group. While the use of aprotinin in the presence of secondary fibrinolysis may be questioned, the authors reported no complication associated with its administration to the five patients presenting with disseminated intravascular coagulation.

Although the use of aprotinin in emergency cardiac surgery for patients who have received exogenous plasminogen activators has not been reported, laboratory data indicate the efficacy of aprotinin in inhibiting streptokinase-plasmin complexes.[66] The possible rebound effect of streptokinase-plasmin complexes still present in the circulation after cessation of aprotinin remains a concern.

While it has been suggested that aprotinin administered at the end of CPB has no beneficial effect, successful control of life-threatening bleeding in six patients several hours after CPB was recently reported by Angelini *et al.* using a high-dose regimen.[67] The authors speculated that this was a group of patients in whom the postoperative bleeding was due to hyperfibrinolysis (undocumented by laboratory data), and that, otherwise, aprotinin might have little value when given after CPB in patients with no such haemostatic defect.

Mechanism of action

Only since 1988 has an elaborate haematological testing been performed in an attempt to understand the mechanism of action of aprotinin in heart surgery. Two main hypotheses emerge from the literature to explain aprotinin's role in haemostasis: the first based on its antiplasmin and the second on its antikallikrein property. Both hypotheses postulate that an acquired platelet defect is responsible for the increased bleeding after CPB.

The antiplasmin hypothesis is based on the demonstration that aprotinin preserves GPIb platelet receptors and could therefore preserve the adhesive capacity of platelets in the postoperative period. The synthetic surface of the CPB circuit activates the contact phase of coagulation, resulting in an increase of factor XIIa and kallikrein which in turn transforms plasminogen in plasmin. Plasminogen activation by extrinsic (tissue type) plasminogen activator has also been demonstrated[35,68] and is considered by some to be the principal mechanism of plasminogen activation during CPB.[69] Plasmin lowers the number of platelet receptors GPIb, reducing platelet adhesion after CPB.[2] This acquired platelet defect could thus be prevented by aprotinin's antiplasmin action. Five minutes after the initiation of CPB, a mean decrease of 50% in the number of GPIb platelet receptors in control vs aprotinin-treated patients was demonstrated by Wildevuur *et al.*[60] and van Oeveren *et al.*[11] In the latter study, antiplasmin activity was further demonstrated by the absence of increase in fibrin degradation products in patients receiving aprotinin, contrary to the control group.

It has been demonstrated by Dietrich *et al.* that the antikallikrein effects of aprotinin inhibit the contact phase of coagulation, leading to diminished generation of thrombin.[56] Thrombin is a powerful platelet aggregator, and platelet aggregation during CPB is thought to lead to postoperative platelet dysfunction. Thus, the protective effect of aprotinin on platelets would be secondary to its inhibition of coagulation rather than to a direct protective effect.

Despite general agreement that aprotinin acts by preventing platelet dysfunction, it is puzzling to note that the favourable effect of aprotinin on the bleeding time has not been demonstrated consistently. A smaller increase in the bleeding time after CPB was reported by Bidstrup *et al.*[46] and by Dietrich *et al.*[56] in the aprotinin-treated patients compared with controls, whereas post-CPB bleeding time was not reduced by high-dose aprotinin in the study by van Oeveren *et al.*[11] However, bleeding time is affected by more than just the number and function of platelets.[70] While this may help explain the apparent discrepancy between the alleged effect of aprotinin on platelets and on the bleeding time, Marx *et al.* did not demonstrate a protective defect of aprotinin on platelets in a recent laboratory investigation of coagulation parameters during CPB and suggest that the previously demonstrated haemostatic effects of aprotinin derive primarily from its antifibrinolytic action.[71]

Appropriate dose of aprotinin

Since 1987, the dosage regimen of aprotinin usually consists of a total of approximately five million KIU aprotinin administered at the time of operation, despite reports by earlier studies that 300,000 to 400,000 KIU produced good results.[54,55] The justification for the high-dose regimen is to obtain a concentration of aprotinin sufficient to produce an antiplasmin (125 KIU · ml^{-1}) or an antikallikrein (250–500 KIU · ml^{-1}) effect.[39] These concentrations were originally calculated from a model of enzymatic kinetics[72] and subsequently confirmed experimentally *in vitro* and *in vivo* in a piglet animal model.[40]

However, in the clinical situation, lower concentrations could be effective. Indeed as stated by Philipp,[72] 125 KIU · ml^{-1} of aprotinin are necessary to completely inhibit plasmin when 100% of plasminogen is transformed to plasmin, but a lower concentration of aprotinin would be sufficient when activation of plasminogen is incomplete. Furthermore, "most of the liberated proteinases are rapidly inhibited and eliminated by the natural inhibitors, which are present in molar excess over the proenzymes/enzymes."[39]

This concept is further substantiated by the apparent effectiveness of aprotinin to control haemorrhage in non-cardiac surgery at concentrations less than those mentioned above. For example, the recommended dose of aprotinin for the treatment of a hyperfibrinolytic state is 200,000 KIU as a bolus followed by an infusion of 100,000 KIU · hr^{-1} (product monograph). A continuous infusion of 250,000 KIU · hr^{-1} of aprotinin for 24 hr has previously been shown to produce an aprotinin plasma concentration of only 50 KIU · ml^{-1}.[13,73] Thus, the dosage recommended by the manufacturer to treat an hyperfibrinolytic state can be expected to produce a concentration of aprotinin less than 50 KIU · ml^{-1}, which is far below the theoretical anti-plasmin level of 125 KIU · ml^{-1}.

The effectiveness of lower doses of aprotinin (approximately two million KIU) administered as an infusion after induction of anaesthesia,[74] as a bolus before CPB,[75] or added to the prime solution of the CPB machine,[11,60] has also been reported in cardiac surgical patients. Both a single dose of two million KIU in the prime of the CPB circuit and a high dose of six million KIU resulted in a 60% reduction of postoperative blood losses compared with the placebo group. Both aprotinin-treated groups had similar reductions of transfusion requirements.[11] Very high doses of aprotinin (6.9 ± 0.8 million KIU), in order to achieve aprotinin plasma concentrations of at least 200 KIU · ml^{-1} at the end of CPB, were not more effective than the standard high dose (5.9 ± 0.4 million KIU) or the low dose (two million KIU) for the reduction of postoperative blood loss.* The favourable haemostatic effect obtained by reducing the dose of aprotinin does not justify, at present, the use of high or very high doses.

Nonetheless, studies are still necessary to determine the optimal dose of aprotinin and the best timing of administration in relation to CPB, with respect to clinically important endpoints such as transfusion requirements, as opposed to postoperative chest drainage which may contain a variable proportion of red cells and inflammatory exudate. In effect, aprotinin seems to reduce loss of red cells proportionately more than the total drainage of chest fluid.[45]

Aprotinin and the activated coagulation time

Aprotinin's capacity to inhibit kallikrein and thus the contact phase of coagulation has led to the investigation of its effect on the whole blood activated clotting time (ACT), a test based on the acceleration of the contact phase of coagulation. The ACT is prolonged in patients receiving heparin and aprotinin compared with patients receiving the same dose of heparin, without aprotinin.[11,56,58,76,77] The effect of aprotinin on the ACT prior to heparin administration remains controversial. Either no change[76] or an increase in the ACT[56,58] has been reported.

Despite this prolongation of the ACT by aprotinin, no special recommendations to any modification of the dosage of heparin and/or protamine have been made except by de Smet *et al.*[77] who reported that aprotinin synergistically enhanced the anticoagulation by heparin and suggested that reduced doses of heparin could be advantageous for routine use during CPB to reduce the adverse effects of heparin-protamine complexes. While prolongation of the ACT in this study may have been the result of platelet inhibition or of inhibition of the intrinsic clotting system, it is also possible that it may have been secondary to the interaction of aprotinin with diatomaceous earth (Celite®), the activator used in the Hemochron (Int. Technidyne Inc., N.J.) automated timing system. Using kaolin rather than Celite-activated test tubes did not result in a significant prolongation of the ACT in association with aprotinin concentrations of up to 180 KIU · ml^{-1}.* At the present time it would seem prudent to maintain the same heparin dosage for extracorporeal circulation even in patients receiving high doses of aprotinin.

Efficient use of antifibrinolytics

Efficiency has now become a major factor in the approval of any therapeutic modality by hospital administrators. Based on the demonstration of reductions of blood loss and improved haemostasis in patients undergoing CPB, at least two groups have recommended the routine use of aprotinin for open heart surgery.[11,78] While such treatment appears to be efficacious and may eventually prove

**Dietrich W, Spannagl M, Jochum M, Richter JA.* Effect of different aprotinin dosages on hemostasis in open heart surgery. Presented at the 13th annual meeting of the Society of Cardiovascular Anesthesiologists held in San Antonio, May 5–8, 1991.

**Wang JS, Hung WT, Karp R, Lin CY.* Increase in ACT of heparinized blood in patients on aprotinin is caused by the Celite activator. Presented at the 13th annual meeting of the Society of Cardiovascular Anesthesiologists held in San Antonio, May 5–8, 1991.

to be effective, it carries a substantial cost. Surgical skill, the use of various anaesthetic techniques, differing CPB circuits, awareness of the risks associated with blood products and the setting of stricter criteria for transfusion are but a few of the variables which may differ from one institution to another. Thus, it is important to identify precisely those patient populations most at risk of bleeding, and to analyze thoroughly the cost of a new therapeutic modality versus its expected benefit, before implementing new strategies with a view to reducing the need for transfusion of blood products in cardiac surgical patients.

Patients most at risk of being transfused

It is generally accepted that not all groups of cardiac surgical patients are equally exposed to blood products but few data are available to substantiate this impression. A recent study of 1480 cases at the Montreal Heart Institute attempted to stratify cardiac surgical procedures according to use of blood products.[79]

This retrospective report on the transfusion of blood products in adult cardiac surgery using CPB indicated that primary and repeat combined procedures (a combination of myocardial revascularization and valvular surgery), and repeat valve surgery were associated with the greatest exposure to foreign blood products, patients being exposed to 10, 13 and 10 units of any blood product respectively. Reoperations for myocardial revascularization were associated with an intermediate consumption of blood products (exposure to eight units of homologous blood products). Finally, primary myocardial revascularization or valve surgery were associated with the smallest demand for blood products, patients being transfused an average of five and six units of any blood product respectively.

Unfortunately, it is not always possible to determine, from the published data, the number of units to which cardiac surgical patients are exposed. This variable is important as it determines, in part, the risk of acquiring transfusion-related diseases.

Cost vs benefit analysis

This is a very complex issue that takes into account not only direct costs (cost of the drug and of blood products), but also ensuing effects of the treatment such as: length of stay in the operating room, in the intensive care unit and in the hospital; need for surgical reexploration; treatment of transfusion or drug-related complications; etc. Furthermore, financing of the medical system will greatly modify the issue in different institutions. For example, in Canada, blood products are provided free of charge to hospitals by the Canadian Red Cross and efforts to reduce consumption will not be rewarded by increased budgets locally. Increasing efficiency will increase the number of patients treated per year but also related costs, and will result paradoxically in a deficit since allocation of budgets to Canadian Hospitals is predetermined annually.

The issue of cost is especially relevant with aprotinin, which is an expensive drug. At the present time, the cost of a high-dose aprotinin treatment is appraximately $1,500 (an ampule of 100,000 KIU costs $26 Can at our institution). Routine use of the drug would entail an expense of more than $2,000,000 per year, if the drug remains similarly priced despite the upcoming introduction of the 50 ml vials on the Canadian market. On the other hand, drugs like EACA and TA are inexpensive and could be used extensively, with little impact on the hospital's budget. The prophylactic administration of synthetic antifibrinolytics requires up to 20 g EACA or 2 g TA which cost $89 and $33 per patient respectively.

Based on economic concerns, it appears illogical to administer an expensive drug like aprotinin to low-risk primary procedures, when less expensive alternatives (such as blood transfusions in this country) have already demonstrated their efficiency. Also, in first-time procedures, the beneficial effect of the drug on consumption of blood products is likely to be minimal when surgical blood loss is already minimal[79,80] and/or when transfusion practice does not follow established guidelines. Indeed, excessive and inappropriate transfusions in a number of American hospitals have been shown to result from noncompliance to national consensus recommendations.[81] Application of these recommendations at the institutional level should result in significant decreases of perioperative blood component use at a minimal cost.

Reduced operating times, less need for work after regular hours, and shorter stays in the intensive care unit may still justify the short-term cost of a drug like aprotinin. However, appropriate data must become available to substantiate a beneficial effect of the drug on these variables. Similarly, data demonstrating the beneficial effect of aprotinin on transfusion-related complications must also become available to justify the cost of the drug in the long term. While the initial low cost of synthetic antifibrinolytics is attractive, data on the cost of potential side effects must ensure that these do not outweigh the initial economic benefits.

Conclusion

The predominant haemostatic defect induced by CPB is difficult to define with certainty. The apparent opposition between platelet dysfunction and fibrinolysis as the mechanisms put forward to explain these defects may well be resolved when a better understanding of the changes induced by CPB are elucidated. Accordingly, the mechanism by which natural or synthetic antifibrinolytics exert their effects has been difficult to define. Nonetheless, these substances appear to be effective in the treatment or the

prevention of excessive bleeding associated with cardiac surgery.

Pharmacological intervention is but one of the many useful strategies presently available to reduce bleeding after CPB. However, the administration of these drugs should not attempt to replace attentive and meticulous surgical and anaesthetic care. In particular, the importance of an appropriate transfusion practice cannot be overemphasized.

While principles regarding the efficient use of these drugs have been put forward, the comprehensive data on which authoritative conclusions may be reached are not yet available. Pending availability of this data, the present use of antifibrinolytics at the Montreal Heart Institute is the following:

1 patients undergoing elective primary myocardial revascularization or valve surgery do not receive prophylactic antifibrinolytics;
2 patients undergoing a primary combined procedure or any reoperation receive prophylactic EACA as an intravenous loading dose of 10 g, followed by an infusion of $1\ g \cdot h^{-1}$ during surgery and the first three to four hours in the ICU;
3 EACA, in doses of up to 15 g administered in a two-hour period, may be used to treat excessive chest tube drainage in the ICU;
4 EACA is used, rather than TA, because of familiarity with the drug and availability at the hospital pharmacy;
5 the efficacy of low-dose aprotinin (up to one million $KIU \cdot 24\ hr^{-1}$) is presently being investigated (a) prophylactically in patients at high risk of receiving homologous blood transfusions and (b) in the treatment of excessive chest tube drainage in the ICU.

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