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Antifibrinolytic usage in cardiac surgery: An update

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Over the past 2 years aprotinin has gone from being highly recommended for bleeding prophylaxis in cardiac surgical patients to being banned from clinical usage internationally. How did this transpire and what can be learned?

BACKGROUND

As of 2007, based on the most recent Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists (STS/SCA) guidelines, usage of antifibrinolytic therapy including the lysine analogues tranexamic acid (TA) or ε-aminocaproic acid (EACA) and especially aprotinin was recommended to reduce the number of patients who required blood transfusions and to reduce total blood loss after cardiac procedures[1]. Subsequently a large international survey raised very serious safety concerns regarding aprotinin and risk of renal failure and death leading to a «black box warning» and an alert from Food and Drug Administration (FDA)[2]. Based on further developments aprotinin was ultimately removed from the marketplace[3]. This monograph will review the mechanisms of action of antifibrinolytic drugs used in cardiac surgery along with an outline of some of the most relevant developments ultimately leading to the withdrawal of aprotinin from the marketplace.

ANTIFIBRINOLYTICS

Tranexamic acid (TA) and ε-aminocaproic acid (EACA) are small molecular weight 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 t-PA) thus displacing it from the fibrin surface and inhibiting the proteolytic action of the serine-histidine enzyme site of plasminogen/plasmin[3]. On a molar basis tranexamic acid is at least 7 times more potent than ε-aminocaproic acid. The plasma half-life of TA and EACA are both approximately 80 to 120 min. Both TA and EACA have demonstrated efficacy to decrease blood loss and transfusion requirements during cardiac operations[4-6].

Concerning issues of safety, of interest is the observation that high cerebrospinal fluid concentrations of TA such as may be consequent to very large dosages of TA as employed during cardiac surgery[7], or if TA is applied directly to brain tissue[8], can produce cerebral excitotoxicity as a consequence of a direct, dose-dependent decrease in GABA receptor activity[9], and may be sufficient to cause clinical seizures in susceptible cardiac surgical patients[10]. Other surveys have made similar observations, reporting a four-fold increase in seizure activity in cardiac surgical patients receiving TA versus those in whom aprotinin had been administered[11]. This may represent a significant but unrecognized hazard of TA therapy if it is used in higher dosages.

While available, aprotinin represented the only clinically available member of a unique pharmacopeic class of agent, a non-specific serine protease inactivator. Both *in vivo* and *in vitro* aprotinin was functioning to inactivate a variety of serine-based enzymes in dose-related fashion; enzymatic activators and amplifiers that are particularly involved in a variety of inflammatory and hemostatic cascades and, as such, aprotinin was felt to significantly decrease the inflammatory responses to cardiac surgery and cardiopulmonary bypass (CPB)[12]. Aprotinin had also been shown to decrease microvascular bleeding through a variety of mechanisms including plasmin inactivation and enhanced platelet functionality and had been repeatedly demonstrated to decrease re-exploration rates in cardiac surgical patients leading to its previously strong recommendation[1].

EFFICACY OF ANTIFIBRINOLYTICS

In a metaanalysis of all randomized clinical trials published in English-language peer-reviewed journals between 1980

and 1993, the efficacy of TA, EACA, DDAVP and aprotinin was assessed by Fremes et al[6]. These authors concluded that the literature supported the prophylactic use of TA or EACA, and more strongly supported 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 determined that only in aprotinin-treated patients was there a reduction in the proportion of patients receiving transfusions. Laupacis and Ferguson conducted a more recent meta-analysis assessing 60 studies and concluded that aprotinin and tranexamic acid, but not desmopressin, decrease the exposure of patients to allogeneic blood transfusion perioperatively in relationship to cardiac surgery[13]. Levy and colleagues conducted a meta-analysis of 72 trials (8,409 patients) demonstrating that treatment with aprotinin decreased mortality almost two-fold compared with placebo. Treatment with aprotinin and with lysine analogues decreased the frequency of surgical re-exploration. These two treatments also significantly decreased the proportion of patients receiving any allogeneic blood transfusion. By contrast, the use of desmopressin resulted in a small decrease in perioperative blood loss, but was not associated with a beneficial effect on other clinical outcomes. Aprotinin and lysine analogues did not increase the risk of perioperative myocardial infarction; however, desmopressin was associated with a 2.4-fold increase in the risk of this complication[14]. In a further review of randomized, placebo-controlled studies of aprotinin, an association had also been made between aprotinin administration and decreased risk of perioperative stroke, further emphasizing its potential utility and safety[15].

BART STUDY

The most recent study of antifibrinolytic agents in cardiac surgery was the Canadian-based BART study (Blood conservation using Antifibrinolytics: a Randomized Trial in high-risk cardiac surgery patients)[16]. The BART trial represented the largest prospective, randomized, blinded head-to-head comparison of 3 major antifibrinolytic agents in current clinical usage.

The BART study assessed clinically-relevant dosages of 3 antifibrinolytics: aprotinin, EACA or TA, in which cardiac surgical patients at high risk of death, massive hemorrhage and life threatening complications defined as surgical interventions with an average mortality at least twice the norm for isolated primary coronary artery bypass graft (CABG) surgery and a risk of re-operation exceeding 5 percent were enrolled. These comprised adult patients undergoing cardiac surgical procedures requiring use of CPB for reoperative cardiac surgery, isolated mitral valve replacement, combined valve/CABG operations, multiple valve replacement/repair and surgery of the ascending aorta or arch were enrolled. In the aprotinin group patients received a 2 million kallikrein inactivator units load (KIU) and a maintenance infusion of 500,000 KIU per hour with an additional 2 million KIU added to the CPB circuit; patients randomized to EACA received 10 gm loading dose and a maintenance infusion of 2 gm/h with no additional EACA to CPB circuit; while patients allocated to TA received a loading dose of 30 mg/kg and a maintenance infusion of 16 mg/kg/h with an additional 2 mg/kg added to the CPB circuit.

Overall in the BART trial 2,331 high risk cardiac surgical patients were randomly allocated to one of three groups within which 781 patients received aprotinin, 770 received tranexamic acid, and 780 were administered aminocaproic acid, and for which the primary outcome was defined as blood loss from chest drains exceeding 1.5 liters over any 8 hour period, red cell transfusions of 10 red blood cell units or more, death due to hemorrhage or re-operation for hemorrhage or tamponade in the first 24 hours, while secondary outcomes included all cause 30 day mortality[16].

The rate of massive bleeding using aprotinin was 9.5 percent (n = 780) as compared to 12.1 percent (n = 770) using tranexamic acid (relative risk 0.79; 95 percent confidence intervals 0.58 to 1.04) and 11.8 percent (n = 780) using aminocaproic acid (relative risk 0.80; 95 percent confidence intervals 0.60 to 1.07). Of relevance to the previously reported association between aprotinin and dialysis-dependent renal failure[16], the use of aprotinin was not shown to significantly increase the risk of renal failure or the need for postoperative renal replacement therapy despite an increase in the proportion of patients who had a doubling of serum creatinine levels. In addition, re-exploration for bleeding and important blood losses through chest tubes, one of the main indications for surgery, were improved by the use of aprotinin. The two other components of the primary outcome were not improved. Finally, aprotinin did not appear to prevent massive bleeding or save the life of patients who had massive bleeding. Of particular note, 30-day all cause mortality rate was 6.0 percent in patients receiving aprotinin compared to 3.9 percent the tranexamic acid group (relative risk 1.55; 95 percent confidence intervals 0.99 to 2.42) and 4.0 percent for aminocaproic acid (relative risk 1.52; 95 percent confidence intervals 0.98 to 2.36). The relative risk of death comparing aprotinin to the two lysine analogues combined was 1.53 (95 percent confidence interval, 1.06 to 2.22).

REGULATORY DEVELOPMENTS

Based on concerns raised by two previous observational studies of antifibrinolytic therapy in cardiac surgery regarding a prothrombotic potential associated with aprotinin rel-

ative to lysine analogues and demonstrating an apparent risk of renal failure and death associated with aprotinin administration[17,18], a «black box warning» and an alert from Food and Drug Administration (FDA) had already been issued[2]. At time of their publication the safety concerns raised by these studies appeared to conflict with the safety analyses of several large meta-analyses of prospective randomized trials of antifibrinolytic therapies[12,13,19,20]. A subsequent written commentary underscored the confounds associated with observational studies versus prospective randomized trials[21]. However, more recent retrospective database analyses further increased concerns regarding increased mortality associated with aprotinin usage in patients undergoing CABG[22,23].

In one of these, a risk-adjusted model in which a total of 1,343 patients (13.2%) received aprotinin, 6,776 patients (66.8%) received aminocaproic acid, and 2,029 patients (20.0%) received no antifibrinolytic therapy, survival was worse among patients who received aprotinin having a higher mortality rate and larger increases in serum creatinine levels than those who received aminocaproic acid or no antifibrinolytic agent[22]. A similar database analysis using electronic administrative records compared outcomes of hospitalized patients with operating-room charges for the use of aprotinin (33,517 patients) or aminocaproic acid (44,682 patients) on the day CABG[23]. Patients who received aprotinin alone on the day of CABG surgery had a higher mortality than patients who received aminocaproic acid alone. Apparently neither the characteristics of the patients nor the surgeons explained the difference, which persisted through several approaches to control confounding[23].

These studies were all either observational or case control reviews and were thus still potentially susceptible to «confounding by indication» in which patients who had greater or more extensive co-morbidities and/or who underwent more extensive surgeries received aprotinin thus introducing very significant confounders in assessment of risk and causality of adverse outcomes[21]. Accordingly, it was to the BART study that clinicians and regulators turned in order to assess whether aprotinin was truly associated with increased risk of death and renal failure.

EARLY TERMINATION OF THE BART TRIAL

When in November 2007, after approximately 2,400 of the planned 2,900 patients had been treated the BART Data Safety Monitoring Board recommended early termination of the BART trial following completion of the most recent data safety review due to a persistent trend for increased mortality in aprotinin-treated patients, the responses were significant. After the notification of the FDA and other international regulatory agencies of these safety concerns by the BART executive, on 11/5/2007 the FDA announced that Bayer, the manufacturer of Traysolol (aprotinin), would suspend the marketing of aprotinin until a comprehensive review of the Canadian study (BART) showing an increased risk of death could be performed[3]. To date, this has not been rescinded.

Currently, one of the most recent publications assessing risk of aprotinin was a meta-analysis which identified 49 trials involving 182 deaths among 7,439 participants[24]. The summary relative risk (RR) for death with aprotinin *versus* placebo was 0.93 (95% confidence interval [CI] 0.69-1.25). In the 19 trials that included tranexamic acid, there were 24 deaths among 1,802 participants. The summary RR was 0.55 (95% CI 0.24-1.25). From the risk estimates derived for individual drugs, an indirect summary RR of death with use of aprotinin *versus* tranexamic acid of 1.69 (95% CI 0.70-4.10) was calculated. To calculate direct estimates of death for aprotinin versus TA, 13 trials with 107 deaths among 3,537 participants were identified. The summary RR was 1.43 (95% CI 0.98-2.08). Among the 1,840 participants, the calculated estimates of death for aprotinin compared directly to EACA was 1.49 (95% CI 0.98-2.28). No evidence of an increased risk of myocardial infarction with use of aprotinin compared with the lysine analogues was found in either direct or indirect analyses. Compared with placebo or no treatment, all 3 drugs were effective in reducing the need for red blood cell transfusion. The RR of transfusion with use of aprotinin was 0.66 (95% CI 0.61-0.72). The RR of transfusion was 0.70 (95% CI 0.61-0.80) for TA, and it was 0.75 (95% CI 0.58-0.96) for use of EACA. This analysis also confirmed that aprotinin was also effective in reducing the need for re-operation because of bleeding (RR 0.48, 95% CI 0.34-0.67). The overall conclusion was that the risk of death tended to be consistently higher with use of aprotinin than with use of lysine analogues without clear advantages to offset these harms. The authors recommended that either tranexamic acid or epsilon aminocaproic acid should be recommended to prevent bleeding after cardiac surgery.

SUMMARY

In attempting to reconcile the multiple randomized and blinded prospective studies showing efficacy of aprotinin without evidence of increased risk of complications with the results of the more recent BART trial, the importance of the large size and the «head-to-head» nature of the BART trial cannot be underemphasized. Transfusion of allogeneic blood products in response to increased blood loss is independently associated with adverse outcomes and increased mortality[25,26]. By decreasing bleeding and allogeneic transfusions, any increased risk of aprotinin was more than offset by its efficacy in decreasing hemorrhage

and related complications leading to unchanged or improved outcomes as demonstrated in multiple placebo-controlled trials. It was only through the large, multi-institutional and multidisciplinary BART investigations involving head-to-head blinded comparisons of several antifibrinolytics that these relative differences in mortality were detected. What is unfortunate is that it required well over a decade after obtaining the regulatory indication of aprotinin for cardiac surgery before such important head-to head comparisons were conducted.

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