Evaluating the safety implications of aprotinin use: The Retrospective Evaluation of Aprotinin in Cardio Thoracic Surgery (REACTS)

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Objectives: Aprotinin is a drug used to reduce bleeding in patients undergoing cardiothoracic surgery with cardiopulmonary bypass. A recent cohort evaluation found elevated risks of renal, cardiovascular, and cerebrovascular events when aprotinin was used. We sought to determine the impact of aprotinin on safety variables among patients receiving cardiothoracic surgery with cardiopulmonary bypass from a single US hospital that reserves aprotinin for complex surgeries and Jehovah's Witnesses and does not utilize celite-based activated clotting time determinations.

Methods: We performed a cohort evaluation with multivariate logistic regression, including propensity score adjustment comprising patients from January 1, 2000 and December 31, 2005. We evaluated 3348 patients having cardiothoracic surgery in a single tertiary care medical center. We observed aprotinin use or lack of aprotinin in cardiothoracic surgery. The main outcome measures were odds (expressed as an odds ratio with 95% confidence interval) of developing myocardial infarction, cerebrovascular events, and renal dysfunction after cardiothoracic surgery between groups.

Results: Patients receiving aprotinin were less likely to experience a cerebrovascular event compared with control [0.65 (0.46–0.91)] and did not have an elevated odds of myocardial infarction [1.04 (0.53–2.04)] but were more likely to experience postoperative renal dysfunction [2.03 (1.37–3.01)].

Conclusions: Aprotinin was not associated with negative myocardial or cerebrovascular risks but did increase the risk of renal dysfunction. It is not known whether the renal dysfunction reflects renal damage or a transient reduction in glomerular filtration pressure.

Cardiothoracic surgery (CTS) with cardiopulmonary bypass (CPB) induces platelet dysfunction, thrombin production, and plasmin release.[1,2] Bleeding during or shortly after CTS is a common complication, resulting in transfusion, reexploration, or tamponade.[3,4] Cardiac operations account for 10% of the 11 million units of allogenic blood transfused in the United States annually and carry a real but small risk of blood transfusion infection.[4]

Abbreviations and Acronyms

ACT = activated clotting time
CABG = coronary artery bypass graft
CI = confidence interval
CPB = cardiopulmonary bypass
CTS = cardiothoracic surgery
MI = myocardial infarction
OR = odds ratio
RR = relative risk
TIA = transient ischemic attack

Aprotinin is a serine protease inhibitor derived from bovine lung that attenuates thrombin generation, fibrinolysis, and inflammatory processes.[3,4] In a multicenter, multinational (23 countries), observational study involving 4374 patients having CTS, aprotinin use was associated with an increased risk of renal dysfunction or renal failure among patients receiving primary (odds ratio [OR] 2.34; 95% confidence interval [CI] 1.27-4.31) and complex CTS (OR 2.59, 95% CI 1.36-4.95) as compared with patients receiving no treatment.[5] The use of aprotinin was also associated with a significant increase in the risk of cardiovascular (OR 1.42, 95% CI 1.09-1.86) and cerebrovascular events (OR 2.15, 95% CI 1.14-4.06) among patients having primary CTS but not among patients having complex CTS.

These results are in contrast to those of a meta-analysis of randomized, placebo-controlled coronary artery bypass graft (CABG) trials from 1988 to 2001 where aprotinin (35 trials, 3887 subjects) did not increase the risk of myocardial infarction (MI; relative risk [RR] 0.85, 95% CI 0.63-1.14), renal failure (RR 1.01, 95% CI 0.55-1.83), or stroke (RR 0.53, 95% CI 0.31-0.90) versus controls.[6] Most trials included in the meta-analysis were comprised of patients having complex CTS.

The observational study utilized data from 23 countries, and the meta-analysis was constituted mostly of trials conducted within the United States, which might account for the differences. In the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial, patients from 13 international sites were randomized to receive aprotinin (n = 436) or placebo (n = 434).[7] Among 703 patients with assessable saphenous vein grafts, 15.4% of patients treated with aprotinin and 10.9% of patients treated with placebo had occlusions. However, in the United States, occlusions occurred in 9.4% of patients receiving aprotinin and 9.5% of patients receiving placebo ($P = .72$), and at Danish and Israeli sites, the occlusions occurred in 23.0% of patients receiving aprotinin and 12.4% patients receiving placebo ($P = .01$).[7,8]

Neither the observational trial nor meta-analysis reported average doses of heparin between groups or what type of activated clotting time (ACT) test was being used. Aprotinin induces a drug–lab test interaction with diatomaceous earth-based ACTs (celite-ACT) resulting in abnormally high ACT values. Use of kaolin-based ACTs (kaolin-ACT) or "sonoclot aprotinin insensitive ACTs" do not have the same interaction.[3,9] Studies have found underdosing of heparin when celite-ACTs are used with aprotinin, which may increase the risk of cardiovascular, cerebrovascular, and renal events versus control.[3,10]

Given the dichotomous findings and limitations of the previous studies, we conducted a large cohort evaluation of aprotinin use for CTS from a single US hospital that does not use celite-ACT determinations.

Materials and Methods

Design and Population

This was a cohort evaluation of all patients undergoing CTS at our institution between January 1, 2000 and December 31, 2005. The clinical data were collected prospectively and entered in the clinical database, but the aprotinin data and the analysis of the data occurred retrospectively. To be included in this evaluation, patients had to have undergone CABG surgery (either alone or with valve or other surgery) and utilized a CPB pump. Patients meeting the above criteria and using aprotinin comprised the treatment group, and those patients not utilizing aprotinin comprised the control group. Our institution's aprotinin protocol requires aprotinin to be dosed by either of the two Food and Drug Administration–approved regimens; however, the full-dose regimen is almost exclusively used. The Hartford Hospital Institutional Review Board approved this study with a waiver of informed consent.

Cardiopulmonary Bypass Pump Management

Anticoagulation was initiated with heparin 300 U/kg. The target kaolin-ACT before initiating the CPB pump was greater than 500 seconds for aprotinin-treated patients and greater than 450 seconds for non–aprotinin-treated patients. Kaolin-ACTs (Hemochron, ITC Corporation, Edison, NJ, and I-STAT, Abbott Point of Care, East Windsor, NJ) were taken at baseline, 5 minutes after initial heparinization, after heparin dosage adjustments, and after protamine reversal. During surgery, the threshold for transfusion was a hematocrit level below 18%. Pump flow rates ranged from 1.8 to 2.5 L/min/m^2 at 30°C to 32°C to 2.5 to 3.2 L/min/m^2 at 34°C to 37°C. In some patients, the depth of hypothermia was lowered to 20°C and determined via rectal probe. Cardioplegic solution for myocardial protection was a 4:1 blood to crystalloid mix with added insulin and procaine. There was a high and low potassium cardioplegic solution with both solutions containing lactated Ringer's, dextrose, sodium bicarbonate, and potassium chloride. Cardioplegic solution was given antegrade and/or retrograde and given either warm or cold.

Trial End Points and Definitions

For the purposes of this study, the following definitions were used: All end points were monitored for from the time of surgery until patient discharge. Renal dysfunction was defined as acute or worsening renal failure resulting in 1 or more of the following: (1) an increase in serum creatinine to >2.0 and twice the baseline creatinine level or (2) a new requirement for dialysis. MI was defined

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