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ORIGINAL ARTICLE

Institutional response to FDA warning on aprotinin and impact on outcomes

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ABSTRACT

Introduction - New evidence of potential risks of aprotinin in 2006 generated public concern about a previously approved drug that was routinely used. In response, we assembled a team of experts within the institution to form guidelines for the appropriate use of aprotinin in cardiac surgery. We report the basis for the guidelines, their implementation, follow-up and resulting patterns of change in aprotinin use.
Methods - We proposed a three-tier system for aprotinin use, according to risk of bleeding and transfusion, and evidence of benefit of aprotinin. Specific recommendations were made with regard to discussion with the patient and documentation regarding aprotinin use and options for patients who refuse the drug. Guidelines were disseminated and accessible on all anesthesia workstations. Aprotinin use was compared before and after institution of guidelines in equivalent categories.
Results - Aprotinin was used in 58.5% (469/802) of cases from March 2005 to January 2006. Following institution of guidelines from March 2006 to January 2007, aprotinin was used in 19.7% (151/767) cases representing a 67.8% reduction in usage. In the subset of groups with large reductions in aprotinin use (pre- 82%, n = 239; post-guidelines 17%, n = 241) there was a significant decrease in acute kidney injury (%ΔCr 43.8 vs. 31.7%, p = 0.05).
Conclusion - In response to new data and regulatory guidelines, we formulated guidelines based on expert review of data. We reduced aprotinin use, but more importantly, introduced an evidence-based approach to the use of aprotinin, consistent with regulatory guidelines. This model of guideline implementation can be useful in similar scenarios.

Keywords: *Aprotinin, Bleeding, Cardiac surgery, Anesthesia, Guidelines.*

INTRODUCTION

Clinical guidelines are useful tools for making clinical management more efficient, and for assisting physicians in making decisions based on scientific data and expert opinion (1, 2). However, whether these guidelines result in actual improvement in clinical care and outcomes is unclear. Wide variability in improvements after guideline implementation limits generalizability. A unique situation arises when a drug in common clinical use is associated with higher risk of morbidity and mortality and a more efficient alternative does not exist. Aprotinin, an unquestionably efficient antifibribolytic agent, commonly used in cardiac surgery was reported to be associated with higher risk of short and long-term mortality. While its efficacy as a hemostatic agent was never doubted, its negative safety profile prompted new questions about its continued use.
In early 2006, two studies on the risk of

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aprotinin in cardiac surgery (3, 4) prompted the US Food and Drug Administration (FDA) to issue an advisory on its use.[1] These publications generated significant concern within the scientific community and among the lay public about the risks associated with a previously approved drug that was routinely used in cardiac surgery. In response to these concerns, and other evidence suggesting its efficacy in specific situations (5), we assembled a team of experts within the institution to create guidelines for the appropriate use of aprotinin in cardiothoracic surgery. We report the basis for creating these guidelines, as well as the implementation and follow up process, patterns of change in use of aprotinin in our institution, and resulting change in outcomes, specifically acute kidney injury (AKI) and postoperative bleeding.

METHODS

Based on available evidence from randomized trials and observational studies on aprotinin and other antifibrinolytics in a variety of surgical settings, we proposed a three-tiered system for using aprotinin (*Table 1*). Category A included those surgeries in which patients are at high risk of bleeding/transfusion, and available evidence indicated that the use of aprotinin is beneficial in modifying that risk. Category B included those surgeries associated with a higher than normal risk of bleeding/transfusion, and that aprotinin use may be beneficial in reducing that risk. The guidelines stated that the decision to use aprotinin in these patients should be made on a case-by-case basis taking into account the potential benefits and risks of aprotinin administration. Category C included those cases where the risk of bleeding/transfusion was not higher than normal and that available evidence did not definitively support the use of aprotinin. In addition, two special patient categories were identified: those that refuse transfusion of blood products, and those with re-exposure to aprotinin. For the first special category, aprotinin use was considered beneficial in a setting where treatment of bleeding was not an option, e.g. Jehovah's Witness. Re-exposure to aprotinin was not recommended if prior exposure to the drug occurred within the last six months.

Specific recommendations were made with regard to discussion and documentation with the patient regarding the use of aprotinin and options for patients who refuse the drug. Emergent cases in which discussion was not feasible required two team physicians to agree to the use of aprotinin with documentation of reasons for its use.

Guidelines were circulated among all anesthesia, surgery and pharmacy staff, and were posted on a special website accessible on all automated anesthesia workstations to enhance knowledge of the guidelines and education on FDA concerns regarding the drug.

The process was also approved by the institutional risk management and pharmacy committees. Data was gathered with Duke University Medical Center Institutional Review Board approval on all cases where aprotinin was used. Patients in whom aprotinin was used were categorized as noted in the guidelines.

Aprotinin use was quantified in each risk category. Sub-groups were made within each risk category according to reduction in aprotinin use. Comparisons were then made between these subgroups with regard to outcomes pre- and post-guideline implementation. In all cases that aprotinin was not used, aminocaproic acid was the default antifibrinolytic agent used.

[1]http://www.fda.gov/cder/drug/advisory/aprotinin.htm. Accessed May 7, 2007.

Table 1 - *Guidelines for the use of aprotinin in cardiac surgery in our centre.*

Category	Description
A	Surgeries in which patients are at high risk of bleeding/transfusion, and available evidence indicates that the use of aprotinin is beneficial in reducing that risk, and that its potential benefit exceeds its potential risks. The use of aprotinin is encouraged for the following indications:
A1	Reoperative cardiac surgery involving repeat sternotomy. This will include all patients scheduled to undergo elective or emergent re-sternotomy for any cardiac operation involving cardiopulmonary bypass (CPB).
A2	All elective or emergent surgical procedures involving replacement of the thoracic aorta with the use of partial or total CPB, with or without aortic valve surgery. Examples include aortic dissection repair, total or hemi-aortic arch replacement; aortic root replacement (Bentall procedure); open thoracic or thoracoabdominal aortic aneurysm surgery with partial CPB support.
A3	Ventricular assist device placement involving primary or repeat sternotomy.
A4	Bilateral orthotopic lung transplantation with CPB.
A5	Pediatric Cardiac surgery: Neonatal open cardiac surgical repairs with CPB including but not limited to: Norwood procedures, Aortic arch reconstruction, Arterial switch procedure, truncus arteriosus repair.
B	Those surgeries where there is a higher than normal risk of bleeding/transfusion, and that available evidence indicates that aprotinin use may be beneficial in reducing that risk. However, the indication for aprotinin will be based on individual cases, accompanying co-morbidities, or a combination of factors that increase the likelihood of perioperative bleeding. The primary surgeon will evaluate the risk-benefit ratio of aprotinin versus another antifibrinolytic, such as aminocaproic acid (amicar), and discuss its use with the patient prior to suggesting its use.
B1	Combined procedures such as coronary artery bypass graft (CABG) surgery with valve surgery with primary sternotomy. Examples are primary CABG and mitral valve repair/replacement.
B2	Multiple valve procedures (involving three valves) or double valve surgery combined with other procedure such as CABG surgery with primary sternotomy on CPB.
B3	Hepatic dysfunction, indicated by abnormal liver function laboratory tests.
B4	Active endocarditis.
B5	Any indication in Category A if the preoperative serum creatinine is greater than 1.4 mg/dL.
B6	Any cardiac surgical procedure involving CPB in patients with end stage renal disease (ESRD), where the likelihood/risk of bleeding is higher than normal.
B7	Any emergent or elective cardiac surgical procedures with recent exposure (within last five days) to anti-platelet agents, excluding aspirin. The use of aspirin alone is not an indication for aprotinin use. This group of patients includes those likely receiving ADP inhibitors clopidogrel (Plavix®), ticlopidine (Ticlid®); or glycoprotein IIb/IIIa inhibitors abciximab (Reopro®), eptifibatide (Integrilin®), tirofiban (Aggrastat®).
B8	Pediatric Cardiac Surgery: Stage II and III single ventricle palliation if performed after six months of initial Aprotinin exposure. Redo sternotomy procedures requiring CPB. Any complex aortic replacement procedure with CPB. Cases involving CPB in which blood conservation is mandatory i.e. Jehovah Witness.
C	Cases where the risk of bleeding/transfusion is not higher than normal and that available evidence does not definitively support the use of aprotinin. Its use is discouraged in the following categories:
C1	All cardiothoracic surgical procedures not involving CPB.
C2	Port access surgical procedures.
C3	Isolated, primary CABG surgery involving the use of CPB.

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C4	Isolated single or double valve surgery with primary sternotomy involving the use of CPB.
C5	Heart transplantation with primary sternotomy.
C6	Pediatric Cardiac Surgery: Aprotinin should be avoided in uncomplicated procedures in children over three months of age that are at low risk of having significant postoperative bleeding. Examples include atrio-ventricular septal defect (AVSD) repair, tetralogy of Fallot (TOF) repair, atrial septal defect (ASD) repair, and non-CPB repairs.
	Special Categories
D1	Patients that refuse transfusion of blood or blood products.
D2	Although these patients may be scheduled to undergo procedures where the risk of bleeding is not higher than normal (e.g., category C surgical procedures), there is no available treatment for bleeding, i.e., transfusion of blood or blood products is not an option. In these cases, all necessary steps are taken to ensure maximum attention to hemostasis and reduction of perioperative bleeding. The use of aprotinin to reduce the risk of bleeding will be discussed with the patient by the surgical team, including the Center for Blood Conservation, including the risks and benefits of the use of aprotinin and other available alternatives.
D3	Patients with re-exposure to aprotinin.
	Patients who have been exposed to aprotinin for a surgical procedure more than two weeks or less than six months prior to the current procedure. An example includes patients scheduled for heart transplantation with aprotinin exposure for LVAD implantation during the above period. Re-exposure to aprotinin within two weeks is not considered to confer higher risk of anaphylaxis, although aprotinin will be administered only if the attending surgeon believes that the benefit of repeat administration of aprotinin exceeds the risk, and only after satisfactory exposure of the surgical field to allow immediate institution of CPB if necessary.
D3	Aprotinin dosage adjustment for special cases
	Patients weighing less than 50 kgs will receive aprotinin (if indicated) at half the regular dose.
E	Discussion and consent for using aprotinin
E1	If aprotinin will be used for the surgery, the attending surgeon will discuss with the patient that the potential benefit of aprotinin exceeds the potential risk and briefly document that 'Aprotinin use was discussed' with the patient in the preoperative note. This may be a part of the note dictated in the surgical outpatient clinic or in the progress notes page of the inpatient chart by the attending surgeon.
E2	Patients will have the option of refusing exposure to aprotinin in category A or B cases. This will be documented in the chart and alternative antifibrinolytic therapies discussed and used.
E3	In emergent situations, when discussion with the patient or family regarding aprotinin use is not feasible (for example, the intubated patient from an outside hospital), the surgical team comprising the attending surgeon and anesthesiologist should jointly agree to use aprotinin and document on the patient's medical record that the benefits of aprotinin use outweigh its risks to the patient. The note should reflect the emergent nature of the surgery and the fact that discussion with the patient or family members was not feasible.

AKI was defined using peak postoperative rise in serum creatinine relative to the preoperative baseline (%ΔCr). Mean %ΔCr was compared before and after guideline implementation with a simple t-test. A similar secondary analysis of subgroups with smaller reductions in aprotinin use (< 50% patients) was also performed.

RESULTS

Aprotinin was used in 58.5% of all cardiac surgery cases (469 of a total 802 patients) before institution of guidelines from March 2005 to January 2006. Following guidelines institution, aprotinin was used in 19.7% of cases (151 out of 767 patients) from

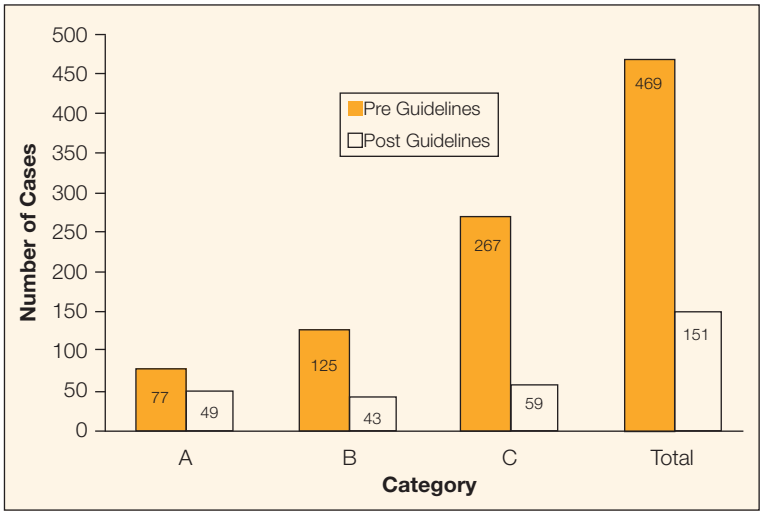

Figure 1 - *Impact of guidelines on aprotinin use.*

March 2006 to January 2007, representing a 67.8 % reduction in usage. The greatest reduction in use was noted for category C indications (78 %) followed by categories B (66 %) and A (36 %) (*Figure 1*). Although its use was discouraged for category C indications, aprotinin was used in some cases after consideration of risks and benefits by the operating team. The guidelines were reviewed after one year following new evidence (6) and the revised FDA warning on re-exposure anaphylaxis risk.[2] An electronic method of documentation was introduced to track compliance with guidelines and identify patients with previous exposure to aprotinin within the last 12 months per the revised FDA warning.

In the subset of groups with large reductions in aprotinin use (pre-guideline usage = 82 %, n = 239; post-guidelines usage = 17 %, n = 241) there was a significant decrease in postoperative AKI (% ΔCr 43.8 % vs. 31.7 %, p = 0.05; *figure 2*). In the secondary analysis of sub-groups with smaller reductions in aprotinin use (pre-guidelines usage = 49 %, n = 562; post-guidelines usage = 23 %, n = 525) there was a non-significant reduction in AKI (% ΔCr 34.2 vs. 32.8 %, p = 0.76). Chest tube drainage showed a statistically insignificant increase in the lower risk categories.

DISCUSSION

Our report highlights two issues: the response to a warning from a regulatory body, and the clinical effect of this response. We responded to new FDA warning regarding aprotinin with generating internal guidelines, implementing and disseminating information, and measuring outcomes as a result of this change in practice. This led to a significant overall reduction in usage of aprotinin with change in measured short-term outcomes. With regard to these outcomes, specifically, AKI, in this retrospective study, there was a significant decline in post-cardiac surgery AKI associated with reduced aprotinin use (vs, aminocaproic acid). Notably, this effect appeared unrelated to bleeding risk group (*Figure 2*) and was accompanied by greater chest tube drainage but not red cell transfusion. While the implementation of guidelines resulted

[2]http://www.fda.gov/medwatch/safety/2006/dec06.htm#Trasylol. Accessed on May 7, 2007.

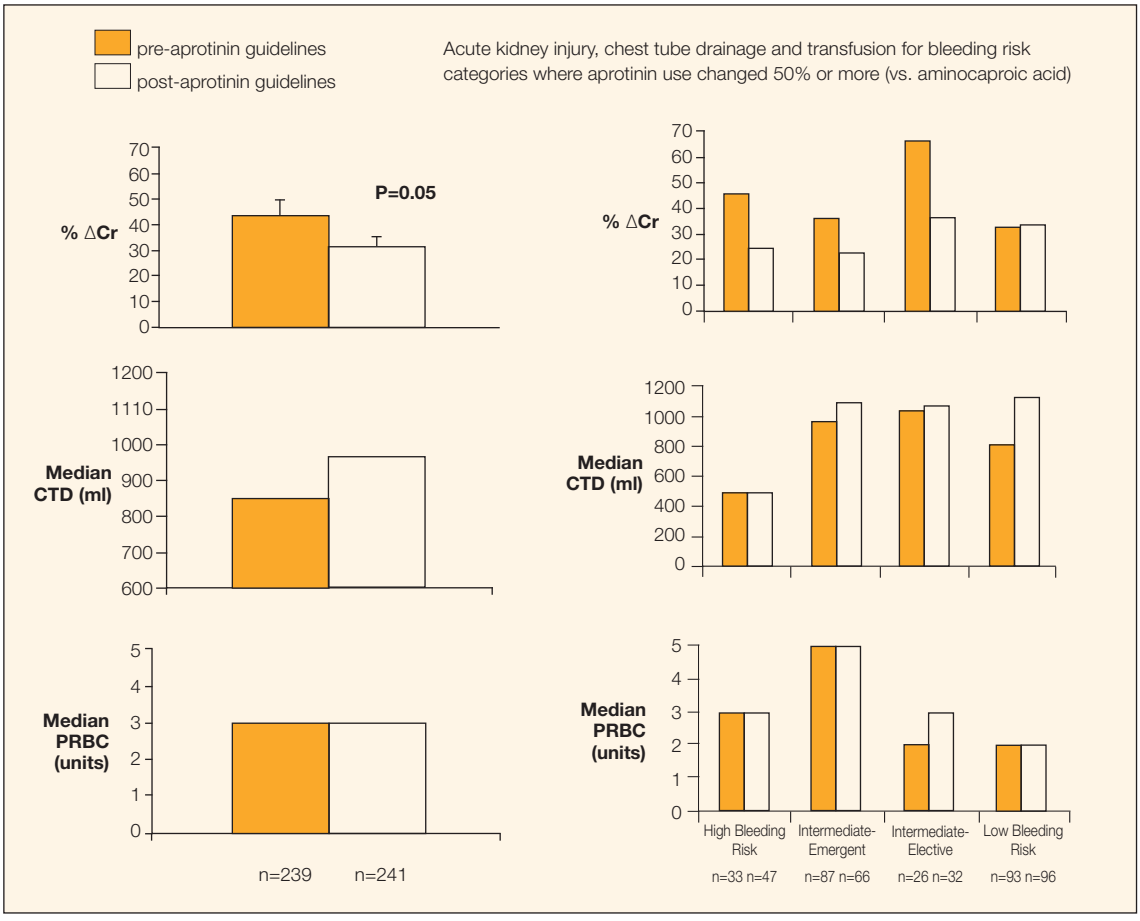

Figure 2 - *Bleeding risk grouped into high, intermediate and low (corresponding to categories A, B and C, respectively). The intermediate risk sub-group was further sub-divided according to emergent or elective surgery. Abbreviations: %ΔCr = peak percent change in postoperative creatinine compared to baseline; CTD = chest tube drainage; PRBCs = packed red blood cells.*

in a change in outcomes, the overall effects of reduction in aprotinin use on long-term outcomes is still unclear. For instance, despite an increase in incidence of postoperative AKI in the higher bleeding risk groups, the impact on mortality or long-term renal outcomes remains unknown. In the higher risk sub-groups, the increase in AKI with no increase in chest tube drainage suggests that aprotinin use is associated with higher renal risk without the lower bleeding/transfusion benefit compared to aminocaproic acid. However, conclusions to be drawn from such a small dataset are limited, but do not support a rationale that aprotinin nephrotoxicity is offset by its hemostatic advantage over aminocaproic acid in high risk patients.

Wide variability in improvements in outcomes following implementation of clinical guidelines has been attributed to several reasons. Chief among them has been variability in implementation of guidelines themselves due to problems with dissemination of information, and/or lack of availability of resources to implement guide-

lines. Most often, efficient generation of guidelines with acceptance by all invested parties, comprehensive coverage of all clinical scenarios and dissemination of information have resulted in improvements in outcomes. In our report, we highlight most of these factors that led to successful response with measurable outcomes. Whether these improved longer-term outcomes is under continued investigation.

In summary, we report our institution's response to new data and FDA guidelines regarding potential risks of aprotinin, and the resulting change in outcomes as a result of this response. Our institution responded with the swift creation of guidelines based on expert review of current data, consensus among anesthesiologists, surgeons, pharmacists and administrators, and implementation of measurable tools to track compliance with guidelines. Aprotinin use was reduced after implementation of these guidelines, but more importantly, an evidence-based approach to the use of aprotinin was introduced, consistent with regulatory warnings and public concern. This resulted in a change in some short-term adverse outcomes. While aprotinin use is no longer recommended under any clinical situation, we feel that this model of guideline implementation can be useful in similar scenarios with other drugs.

No conflict of interest acknowledged by the authors

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