



Evidence-Based Medicine Journal Club

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Journal club critique

A disheartening story: Aprotinin in cardiac surgery

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Expanded Abstract

Citation

Mangano DT, Tudor IC, Dietzel C: The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006, 354:353-365 [1].

Background

The majority of patients undergoing surgical treatment for ST-elevation myocardial infarction receive antifibrinolytic therapy to limit blood loss. This approach appears counterintuitive to the accepted medical treatment of the same condition--namely, fibrinolysis to limit thrombosis. Despite this concern, no independent, large-scale safety assessment has been undertaken.

Methods

Design and setting: Prospective observational cohort study in 69 institutions in North and South America, the Middle East, Europe, and Asia.

Subjects: 4374 patients undergoing coronary-artery revascularization. All patients were > 18 years old and completed a pre-surgery interview. Patients were classified as undergoing primary surgery (no previous heart surgery and no other surgery besides a coronary artery bypass graft), or complex surgery (all other surgery).

Intervention: None.

Measurements: The authors prospectively assessed three agents (aprotinin [1295 patients], aminocaproic acid [883], and tranexamic acid [822]) as compared with no agent (1374 patients) with regard to serious cardiovascular, renal, and cerebrovascular outcomes by propensity and multivariable methods.

Results: In propensity-adjusted, multivariable logistic regression (C-index, 0.72), use of aprotinin was associated with a doubling in the risk of renal failure requiring dialysis

among patients undergoing complex coronary-artery surgery (odds ratio, 2.59; 95 percent confidence interval, 1.36 to 4.95) or primary surgery (odds ratio, 2.34; 95 percent confidence interval, 1.27 to 4.31). Similarly, use of aprotinin in the latter group was associated with a 55 percent increase in the risk of myocardial infarction or heart failure ($P < 0.001$) and a 181 percent increase in the risk of stroke or encephalopathy ($P = 0.001$). Neither aminocaproic acid nor tranexamic acid was associated with an increased risk of renal, cardiac, or cerebral events. Adjustment according to propensity score for the use of any one of the three agents as compared with no agent yielded nearly identical findings. All the agents reduced blood loss.

Conclusion

The association between aprotinin and serious end-organ damage indicates that continued use is not prudent. In contrast, the less expensive generic medications aminocaproic acid and tranexamic acid are safe alternatives.

Commentary

The medical and surgical approaches to acute ST-elevation myocardial infarction present an interesting paradox. The medical approach focuses on fibrinolytic therapy. Due to concerns over bleeding, the surgical approach avoids fibrinolytic agents and instead uses agents that mitigate bleeding, so called antifibrinolytic agents, which include aprotinin, aminocaproic acid, and tranexamic acid. These agents were generally considered safe based on a number of secondary analyses of studies that were not primarily intended to assess safety. These relatively small studies were underpowered to detect adverse events and did not involve head-to-head comparisons of the commonly used antifibrinolytic agents. Animal studies suggest that these agents have the potential to cause ischemic damage to multiple organ systems and small, largely single-center studies have suggested increased graft thrombosis and

renal dysfunction [2-6]. Ideally, the safety of these agents would be compared in a large, multi-center, randomized controlled trial. However, because their use is embedded in practice and because regulatory approval of these agents differs by country, conducting such a trial will be difficult if not impossible.

To address the safety of these agents for cardiopulmonary bypass surgery, Mangano and colleagues [1] conducted a large, prospective, observational cohort assessing aprotinin, aminocaproic acid, and tranexamic acid as compared to no agent in 4374 patients undergoing revascularization. Because this was a prospective study, the authors were able to collect a wealth of clinical information, including approximately 7500 data fields per patient. This permitted consideration of variables that might influence both choice of antifibrinolytic agent and clinical outcome. The authors used a propensity score based on 45 treatment-selection covariates and multivariable modeling to control for baseline differences between groups. In doing so, they found that aprotinin, but not aminocaproic acid or tranexamic acid, was associated with serious cardiovascular, renal, and cerebrovascular adverse events. Furthermore, a dose-response relationship was demonstrated, strengthening the inference of causality.

The main weakness of this study is that the authors failed to report details of the surgery itself, such as whether the surgery was on vs. off-pump, time on pump, and number of vessels bypassed. These variables are likely to influence not only choice of antifibrinolytic agent but also outcome, and are, therefore, a source of indication bias that could reflect unfavorably on aprotinin.

Based on the results of this study and those of another observational study suggesting renal toxicity [7], the United States Food and Drug Administration (FDA) held an advisory committee meeting September 21, 2006 to consider the cardiovascular safety of aprotinin. Because of concerns about the methodology of the study by Mangano and colleagues and because it was the only study to suggest cardiovascular adverse events [8], the advisory committee concluded that there was insufficient evidence to support changing the cardiovascular safety labeling of the drug. However, just six days after the committee met, it was revealed that the drug's manufacturer, Bayer, had preliminary results from an observational study of 67,000 cardiac bypass patients that suggested aprotinin was associated with increased risk of death, renal dysfunction, congestive heart failure, and stroke [9]. The FDA subsequently issued a statement indicating it was unaware of this study when the advisory committee met and that it is evaluating the results of this study and the potential implications for the use of aprotinin [10]. In the mean time, the FDA suggests that physicians who use aprotinin should carefully monitor patients for the occurrence of toxicity, particularly to the kidneys, heart, or brain, and promptly report observed adverse events. They go on to recommend that physicians should consider limiting aprotinin use to those situations where the clinical benefit of reduced blood

loss is essential to medical management of the patient and outweighs the potential risks.

Recommendation

The weight of evidence suggests that aprotinin increases the risk for a poor outcome among patients undergoing cardiac operations. Not only is this drug very expensive, it seems to be toxic. Although the risk of excessive bleeding is certainly a cause for concern in certain patients, and treatment with aprotinin can decrease blood loss in selected patients, data are lacking to show that administration of this agent actually improves survival.

Competing interests

The authors declare no competing interests.

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