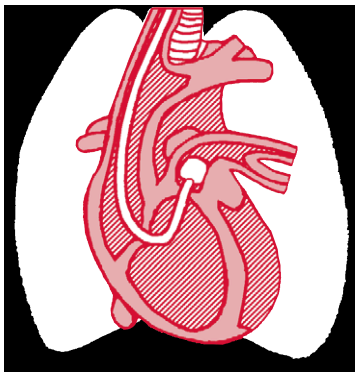




CASE CONFERENCE

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Aprotinin-Induced Cardiovascular Collapse After a Negative Test Dose in a Patient Scheduled for Repeat Mitral Valve Surgery

Phillip L. Beaulieu, MD,* Sweeta D. Gandhi, MD,* Zafar Iqbal, MD,*

Elizabeth G. Butler, MD,† G. Hossein Almassi, MD,†

Paul S. Pagel, MD, PhD,* and Jerrold H. Levy, MD‡

APROTININ REDUCES PERIOPERATIVE blood loss and transfusion requirements during cardiac surgery,^{1,2} but this antifibrinolytic serine protease inhibitor also has the potential to cause anaphylaxis during repeat exposure.³ The incidence of anaphylactic reactions to aprotinin reexposure has been reported to range between 1.2% and 2.8% in pediatric and adult cardiothoracic surgical patients, respectively.³⁻⁵ Notably, the incidence of aprotinin-induced hypersensitivity was higher (4.5%) in patients with a reexposure interval less than 6 months,³ and the majority (72%) of reported cases occurred within 3 months of the initial exposure.⁶ Several guidelines (published at the manufacturer's web site, www.trasylol.com) about the use of aprotinin in patients previously exposed to the drug have been proposed based on anecdotal observations.^{3,6} However, precise identification of patients who may be at greatest risk of developing anaphylaxis or those in whom aprotinin should be strictly avoided has proven to be very difficult, in part because aprotinin anaphylaxis during reexposure is a relatively unusual event. For example, neither preoperative skin testing⁵ nor detection of antiaprotinin antibodies^{7,8} was able to positively predict aprotinin anaphylaxis during reexposure. A small quantity of aprotinin ($1-2 \times 10^4$ KIU) is commonly administered as an in vivo antigenic challenge before the loading dose is initiated, based on previous recommendations,^{3,8} and a positive response to this test dose (eg, transient hypotension, tachycardia, bronchospasm, and cutaneous erythema) may alert the anesthesiologist and surgeon to the potential for anaphylaxis.³ In this report, the authors describe a patient with a history of recent aprotinin exposure who suffered hemodynamic collapse requiring cardiopulmonary resuscitation shortly after an aprotinin infusion was initiated despite a negative response to a test dose. The report emphasizes that a negative aprotinin test dose does not reliably exclude the possibility of an anaphylactic reaction to the drug during reexposure.

CASE REPORT*

A 66-year-old man with no known drug allergies presented to the authors' medical center for evaluation of recurrent dyspnea. A mitral valve annuloplasty and a Maze cryoablation had been performed 8 weeks before this admission for the treatment

of severe mitral regurgitation and chronic atrial fibrillation. The patient received aprotinin during the initial operation (total dose including cardiopulmonary bypass prime = 7.1×10^6 KIU). Tricuspid and mitral valve replacements had been planned in addition to the Maze procedure and exclusion of the left atrial appendage in the original case, and the decision to use aprotinin was based on an anticipated prolonged cardiopulmonary bypass time. On direct inspection of the native mitral valve during surgery, the etiology of the mitral regurgitation was confirmed to be related to marked dilation of the left atrium and mitral annulus and not to a structural abnormality of the valve itself. As a result, an annuloplasty was performed by using a 28-mm Carpentier Edwards Physio ring (Edwards Lifesciences, Irvine, CA). Intraoperative transesophageal echocardiography (TEE) also revealed that the tricuspid regurgitation described during the cardiac catheterization was not as severe as originally characterized. Inspection of the tricuspid valve also revealed no specific structural abnormalities, and the decision was made not to proceed with the planned tricuspid valve replacement. A dual-chamber pacemaker was implanted on the third postoperative day for the treatment of complete heart block. The patient was subsequently discharged from the hospital and was making an uneventful recovery until signs and symptoms of congestive heart failure abruptly recurred. The patient was initially medically managed with oral metoprolol, furosemide, spiro lactone, lisinopril, and sublingual nitroglycerin. He was also treated with coumadin because of the history of an enlarged left atrium and atrial fibrillation. A TEE examination was performed that revealed posterior dehiscence of the mitral valve annuloplasty ring and severe mitral regurgitation. The patient was brought to

*From the Departments of *Anesthesiology and †Cardiothoracic Surgery, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, WI; and ‡Department of Anesthesiology, Emory University Medical Center, Atlanta, GA.*

Jerrold H. Levy is a consultant for Bayer and Dyax.

Address reprint requests to Paul S. Pagel, MD, PhD, Clement J. Zablocki Veterans Affairs Medical Center, Anesthesia Service, 5000 W National Avenue, Milwaukee, WI 53295. E-mail: pspagel@mcw.edu

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*P.L. Beaulieu, S.D. Gandhi, Z. Iqbal, E.G. Butler, G.H. Almassi, and P.S. Pagel

the operating room for definitive repair. Lisinopril and coumadin were withheld for 2 and 5 days before surgery, respectively.

The patient was premedicated with intravenous midazolam (2 mg) and fentanyl (100 μ g). Under local anesthesia, a right radial artery catheter was inserted, and a right internal jugular pulmonary artery catheter was inserted for the measurement of continuous pulmonary arterial pressures. Peripheral intravenous access was limited, and an 8.5F central venous catheter was inserted into the right subclavian vein for rapid fluid administration. The induction of anesthesia was performed by using intravenous etomidate (0.3 mg/kg), fentanyl (5 μ g/kg), and pancuronium (0.1 mg/kg). After tracheal intubation, anesthesia was maintained with isoflurane (end-tidal concentrations of 0.5 to 1.0 minimum alveolar concentration), fentanyl (1-3 μ g/kg/h), propofol (25 μ g/kg/min), and pancuronium (intermittent bolus doses of 0.01 mg/kg guided by neuromuscular monitoring). The dual-chamber pacemaker had been previously programmed in a DDD mode at a rate of 60 beats/min with atrial and ventricular capture. The patient remained hemodynamically stable throughout anesthetic induction and endotracheal intubation. An intraoperative TEE examination confirmed the presence of the mitral valve annuloplasty ring dehiscence and severe mitral regurgitation. Biatrial chamber enlargement was appreciated, and the left ventricle (LV) was also modestly dilated. No regional wall motion abnormalities were present, and the LV ejection fraction was estimated to be 55%.

As the patient was prepared for surgery, an intravenous bolus of aprotinin (2×10^4 KIU) was administered via the central venous catheter. Hemodynamics remained unchanged during and for 10 minutes after the administration of the aprotinin test dose. No evidence of airway reactivity was observed. Therefore, an intravenous aprotinin loading dose (2×10^6 KIU) was begun according to the method of Royston et al,¹ but profound hypotension (systolic arterial pressure between 30 and 40 mmHg) occurred within 3 minutes after the infusion had been initiated (total amount of aprotinin infused after the test dose = 2×10^5 KIU). An anaphylactic reaction to aprotinin was suspected, the drug infusion was immediately stopped, and cardiopulmonary resuscitation including chest compressions was begun. A modest increase in peak airway pressure (35 cmH₂O) was also appreciated. However, ventilation was not substantially compromised, and pharmacologic interventions were not required for management. A right anterior needle thoracostomy was performed, and a tension pneumothorax was excluded as a potential cause for circulatory collapse. Cardiopulmonary bypass equipment and the perfusionist were immediately available in the event that conventional resuscitation efforts were unsuccessful. The patient received multiple intravenous boluses of phenylephrine and epinephrine (total doses of 3 and 5 mg, respectively) with resultant systolic arterial pressures between 50 and 60 mmHg. The patient was also treated with intravenous dexamethasone (10 mg), diphenhydramine (50 mg), and ranitidine (150 mg). Intravenous infusions of epinephrine (0.15-0.25 μ g/kg/min) and norepinephrine (0.15-0.25 μ g/kg/min) were also begun with a gradual improvement in arterial pressure. A TEE examination showed that the LV was markedly underloaded despite aggressive volume resuscitation with crystalloids and colloids (total volume of fluids administered = 5.5 L). The heart rate remained between

60 and 80 beats/min during early attempts at resuscitation despite administration of inotropic drugs because of the presence of the DDD pacer and underlying complete heart block. An electrophysiology consultation was urgently obtained, and the pacemaker reprogrammed to a rate of 90 beats/min to improve cardiac output. Finally, an intra-aortic balloon pump (IABP) was inserted through the left femoral artery to enhance coronary perfusion. As a result of these maneuvers, the patient was hemodynamically stabilized with a mean arterial pressure exceeding 70 mmHg. The anticipated surgery was postponed, and the patient was transferred to the surgical intensive care unit for additional treatment. Over the next several hours, the epinephrine and norepinephrine infusions were gradually weaned, the patient was extubated with adequate arterial blood gases, and the IABP was discontinued. The patient suffered no neurologic or renal sequelae, was discharged from the intensive care unit on the second day after the episode, and was rescheduled for mitral valve surgery at a later date.

DISCUSSION

Anaphylaxis during an aprotinin infusion after a negative test dose in patients reexposed to the drug has been infrequently described. The routine use of an aprotinin test dose (1×10^4 KIU) was initially advocated by Dietrich et al³ who analyzed 248 reexposures to aprotinin during cardiac surgery. The authors identified 7 patients with hypersensitivity reactions within this study, 4 of whom had received test doses of the antifibrinolytic drug. Two of these 4 patients had no response to the test dose but developed anaphylaxis during the administration of the aprotinin loading dose. In a subsequent investigation by the same group, 3 of 121 patients developed anaphylactic reactions to aprotinin reexposure.⁸ All 3 patients with aprotinin-induced anaphylaxis had been pretreated with histamine subtype 1 and 2 receptor (H₁ and H₂, respectively) antagonists and corticosteroids. Two of the 3 patients did not react to an aprotinin test dose, but both of these patients developed anaphylaxis within 5 minutes after the loading dose had been initiated. Williams et al⁹ described a patient undergoing repeat aortic and mitral valve replacement for the treatment of endocarditis. The patient did not respond to a 2×10^4 KIU aprotinin test dose but subsequently developed bronchospasm, tachycardia, and refractory hypotension requiring treatment with intravenous vasopressin during administration of the loading dose. The present patient also tolerated the test dose of aprotinin without complication, but cardiovascular collapse occurred shortly after beginning the loading infusion of the drug. This presentation is very similar to those that have been previously reported.^{3,8,9}

In a recent review of 124 published hypersensitivity reactions, Beierlein et al⁶ reported that 11 of 15 patients with a history of previous aprotinin exposure had a positive response to the drug when a test dose was used. These data suggested that an aprotinin test dose may have some prognostic value in predicting the development of anaphylaxis, but, unfortunately, the sensitivity of the test (73.3%) cannot allow the exclusion of such an event with any substantial degree of confidence. It certainly remains plausible that the relative sensitivity with which a positive test dose predicts anaphylaxis during aprotinin reexposure may be higher than described⁶ because the link between a positive test dose and discontinuation of planned use

of aprotinin would probably not be reported. Nevertheless, as shown by the current and previous cases,^{3,8,9} a negative test dose during aprotinin reexposure does not appear to be a reliable predictor of anaphylaxis during infusion of the drug. More ominously, an aprotinin test dose may also directly precipitate a severe anaphylactic reaction in the patient reexposed to the drug.^{3,8,10,11} Taken as a whole, these reports question the utility of an intravenous aprotinin test dose in the setting of repeated drug exposure. Quantitative detection of high titers of antiaprotinin immunoglobulin G antibodies may be more prognostic of the development of hypersensitivity reactions during aprotinin reexposure than other *in vitro* or *in vivo* tests,^{6,8} but this contention was based on observations from a very small number of patients and will require additional study to confirm.

The present patient received aprotinin during the original mitral valve surgery that had been performed 8 weeks before his return to the operating room. Thus, an increased risk of an anaphylactic reaction to aprotinin reexposure was present. The avoidance of aprotinin has been recommended within 6 months of previous exposure unless clear benefits of antifibrinolytic therapy are present.^{3,6} The authors considered the risk of aprotinin reexposure but believed that the use of aprotinin in the present patient was justified because of his presenting clinical condition, the anticipated difficulty of the planned surgical procedure, and the likelihood that large quantities of autologous blood products would be required to obtain adequate hemostasis in the absence of antifibrinolytic therapy. Drug prophylaxis, including H₁ and H₂ antagonists and corticosteroids, has been recommended in patients at risk for anaphylaxis resulting from aprotinin reexposure.³ However, at least 9 cases of anaphylaxis have been reported despite perioperative administration of antihistamines and corticosteroids,⁶ suggesting that drug prophylaxis is not consistently beneficial in this setting. Thus, the authors chose not to use H₁ and H₂ antagonists and corticosteroids preoperatively but did administer these drugs as part of the resuscitation efforts after the anaphylactic reaction occurred.

The availability of cardiopulmonary bypass before administration of aprotinin has been advocated by several authors,^{3,6,10} but mortality in association with anaphylaxis-induced hypotension has been reported despite high-flow cardiopulmonary bypass.^{10,12,13} The authors were prepared to immediately institute femoral-femoral cardiopulmonary bypass in the present patient had drug therapy and other maneuvers been unsuccessful. It is important to emphasize that aprotinin should be withheld from cardiopulmonary bypass prime until after uneventful administration of the loading dose of the drug has been completed in patients at highest risk for anaphylaxis. It may also be more prudent to withhold administration of the loading dose until sternotomy has been performed so that cardiopulmonary bypass may be rapidly initiated in the event of an anaphylactic reaction. As in the current case, the use of intra-aortic counterpulsation during the resuscitation of a patient with aprotinin-induced anaphylaxis can also be considered. The authors believed that the enhanced coronary perfusion provided by the IABP was vital for the preservation of LV contractile function because this patient with congestive heart failure was receiving large doses of inotropic drugs and was at risk for the development of acute myocardial ischemia. In fact, substantial increases in cardiac index (from 1.6 to 2.2 L/min/m²) were

observed after intra-aortic balloon counterpulsation had been initiated concomitant with volume resuscitation. Lastly, the presence of a DDD pacemaker and underlying complete heart block also initially hampered the resuscitation because compensatory tachycardia in response to hypotension and vasoactive drugs did not occur. In fact, a maximum heart rate of 85 beats/min was observed after intravenous boluses of epinephrine. Reprogramming the pacemaker to a higher maximum rate in the DDD mode also facilitated the resuscitation efforts in this case by restoring atrioventricular synchrony at a more appropriate heart rate.

COMMENTARY†

Anaphylaxis is always a potential consideration in cardiac surgical patients who receive multiple foreign substances in their perioperative care. The agents most often associated with anaphylaxis in this setting include anesthetic drugs (neuromuscular blocking agents), antibiotics, blood products, and different polypeptides (aprotinin, latex, and protamine).¹⁴ As a result, test doses are often administered before giving the full therapeutic dose. However, test doses are used empirically in clinical practice and may represent misnomers because they most likely represent an initial dose for antigenic exposure and are not based on any scientific supporting data. The test dose, in fact, actually alerts the clinician that an anaphylactic reaction can occur and reminds them to consider this when giving an antigen in question.

When a test dose is administered, clinicians are often monitoring patients for acute cardiopulmonary dysfunction that is the hallmark of anaphylaxis.¹⁴ In this author's view, cardiac anesthesiologists are also the most qualified physicians to treat the symptom complex of bronchospasm and upper airway edema in the respiratory system, vasodilation and increased capillary permeability in the cardiovascular system, and acute cardiovascular collapse, something they do everyday in managing patients with biventricular dysfunction for cardiac surgery. Their skills, including the ability to perform transesophageal echocardiography, provide them with the ability to rapidly diagnose and appropriately treat the acute hypotension that can occur in anaphylaxis. This is best shown in a previous report from this journal in which Ford et al¹⁵ reported a retrospective descriptive study on 23 cardiac surgical patients referred to their Anesthetic Allergy Clinic in Australia for reactions assumed to be anaphylaxis. Most reactions occurred before the beginning of cardiopulmonary bypass, and they noted the response to epinephrine was immediate and effective in 88% of cases. After cardiopulmonary bypass, the causes of reactions were protamine and blood products. There was no mortality in their series of patients.¹⁵

Acute cardiovascular collapse occurred in the case described here by Beaulieu et al some time after the test dose and within minutes after the loading dose. There are important points to consider in this case. First, the anaphylaxis diagnosis is presumptive because there were no immunologic testing, tryptase levels, or other supporting information. Presumptively, the temporal sequence suggests it was anaphylaxis and the clinical

†J.H. Levy

findings suggested the diagnosis. Also, a total of 10 minutes has been suggested to wait after the test dose before administering the loading dose. This time is not specified in the case. Furthermore, despite the 10-minute window suggested this will only account for approximately 90% of the reactions.^{16,17} Most importantly, as stated by the authors, "a negative test dose during aprotinin reexposure does not appear to be a reliable predictor of anaphylaxis during infusion of the drug. More ominously, an aprotinin test dose may also directly precipitate a severe anaphylactic reaction in the patient reexposed to the drug." This was first reported by Dietrich et al³ who evaluated 248 reexposures to aprotinin and noted reactions in 7 patients; 4 of the reacting patients had received test doses, and 2 of those patients showed no response to the test dose but developed an anaphylactic reaction during the loading dose. They later reported 3 of 121 patients with anaphylaxis after aprotinin reexposure, and 2 of the 3 patients did not react to the test dose, but both developed anaphylaxis within 5 minutes after the loading dose.⁸ The 3 patients had also been pretreated for anaphylaxis with antihistamines and corticosteroids, therapy that may have modified the onset of the reactions. This perspective was also stated in the previous aprotinin (Trasylol; Bayer, West Haven, CT) US package insert (December 2003), "Even after an uneventful test dose, an anaphylactic reaction can occur." The newly updated aprotinin US package insert (December 2006) has further strengthened and heightened awareness of possible anaphylactic or anaphylactoid reactions by warning, "Fatal reactions have occurred with an initial (test) dose as well as with any of the components of the dose regimen (<http://www.univgraph.com/bayer/inserts/trasylol.pdf>). Fatal reactions have also occurred in situations where the initial (test) dose was tolerated."

Of importance is the fact that the patient had a previous aprotinin exposure 8 weeks earlier; thus, his risk for anaphylaxis to aprotinin was high, around 5% based on previous reports.^{3,6,8} The previous package insert had a boxed warning stating this regarding reexposure, whereas the newly updated package insert has further strengthened and heightened awareness of this issue by warning, "The risk for anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure and a history of any prior aprotinin exposure must be sought prior to aprotinin administration. The risk for a fatal reaction appears to be greater upon reexposure within 12 months of the most recent prior aprotinin exposure." Further, administration of aprotinin to patients with a known or suspected previous aprotinin exposure during the last 12 months is now contraindicated.

The test dose and loading dose should only be performed when the conditions for rapid cannulation are present as stated in the

previous and updated package inserts. The updated package insert also warns, "aprotinin should be administered only in operative settings where cardiopulmonary bypass can be rapidly initiated." The authors were appropriately prepared to immediately institute femoral-femoral cardiopulmonary bypass in their patient if resuscitation was unsuccessful. Furthermore, their application of intra-aortic balloon pump counterpulsation as part of the resuscitation of the patient further adds to the insightful management by using mechanical support. The only important perspective to add is the consideration of vasopressin for vasodilatory shock in this patient.¹⁸ In a human vascular model, the authors showed the ability of vasopressin to reverse mediator-induced vasoplegia, a finding of anaphylactic shock.¹⁹ Increasing reports are also suggesting use of vasopressin in anaphylactic shock.^{20,21}

An important question to consider is why does a patient not react to a test dose? Unfortunately, everything in medicine is reflected by percentages and odds ratios that never capture 100% of the patients whenever deciding on therapeutic approaches. For example, after antigen exposure in anaphylaxis, 90% of the reactions occur within the first 10 minutes.¹⁴ Unfortunately, there may be outliers with most reactions subsequently occurring within 20 minutes.¹⁴ Finally, as reported, reactions can occur up to 2 hours later, reactions that may reflect immunoglobulin (Ig) G and not IgE antibody formation, with potential for delayed responses; responses also may be influenced by previous antihistamine and/or corticosteroid pretreatment.¹⁴ Risk/benefit considerations need to be considered whenever reexposing patients to agents known to produce hypersensitivity reactions.

As this author stated previously in an editorial in this journal, anaphylaxis continues to be a vexing problem for anesthesiologists.²² Education regarding prevention, recognition, evaluation, and reporting is important. Rapid epinephrine or other vasopressor administration for acute cardiovascular dysfunction is important for anaphylaxis. The authors have continued research efforts to develop new ways to reverse the pathologic vasculopathy associated with mediator release including histamine, thromboxane, and others. Currently, antibody tests are being developed to assess patients at high risk for reexposure anaphylaxis, especially evaluating IgG antibodies to aprotinin. Aprotinin is also included in many tissue glues so occult exposure may occur.²³ The test dose, now referred to as the "initial (test) dose" in the updated package insert (and as questioned here by Beaulieu and colleagues), reminds clinicians that after reexposure patients are at an increased risk for anaphylactic reactions and that risk/benefit ratios need to be considered when exposing them a second time.

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