
CASE REPORTS

Risk of Anaphylaxis From Aprotinin Re-Exposure During LVAD Removal and Heart Transplantation

Carmelo A. Milano, MD,^a Vijay S. Patel, MD,^a Peter K. Smith, MD,^a and Mark Stafford Smith, MD^b

Aprotinin has been shown to reduce transfusion requirements in re-operative cardiac surgery and in implantation of long-term left ventricular assist devices (LVAD). However, it is an antigenic polypeptide and re-exposure is associated with a small incidence of anaphylaxis. This report describes 2 cases of anaphylactic response to aprotinin when the agent was employed for both the LVAD implant and for the subsequent explant and cardiac transplant. Early re-exposure to just the test dose was associated with a significant incidence of anaphylaxis. *J Heart Lung Transplant* 2002;21: 1127–1130.

Aprotinin is a basic, 58-amino-acid polypeptide extracted from bovine lung. It functions as a serine protease inhibitor, reducing kallikrein, plasmin and trypsin activity. Given intravenously, it has been shown to have an anti-fibrinolytic effect as well as an anti-inflammatory and platelet-preserving effect; it reduces bleeding following repeat (redo) cardiac surgery.¹ Furthermore, it has been shown to be useful during left ventricular assist device (LVAD) implantation for reducing post-operative blood loss, transfusion requirements and development of right ventricular failure.^{2,3} However, aprotinin is immunogenic and induces an immunoglobulin G and E (IgG and IgE) response; allergic reaction to a primary exposure is exceedingly rare, but re-exposure has been associated with a small incidence of anaphylaxis.^{1,4–6} When aprotinin has been em-

ployed for LVAD implantation, the question arises whether the agent should be employed during the explantation of the device and subsequent transplantation. Typically, LVADs bridge patients for periods of months to years until a suitable donor heart becomes available. Our practice, and that of others, has been to employ aprotinin for both the implant and again for the transplant and LVAD explant procedure.⁷ Two patients who underwent early device explantation (within 2 months of the implant) and who therefore also underwent early re-exposure to aprotinin, experienced an anaphylactic response within minutes of the test dose administration. Their cases are described in what follows, and raise concerns over the safety of early aprotinin re-exposure.

CASE REPORTS

The first patient was a 46-year-old man with ischemic cardiomyopathy, who was listed for heart transplant. The patient experienced progressive hemodynamic deterioration despite inotropic support and intra-aortic balloon pumping. Therefore, he was taken in urgently for LVAD implantation (Heartmate, Thoratec Corp). He had undergone coronary bypass surgery 5 years earlier, without the use of aprotinin. Redo sternotomy was required, and apro-

From the Departments of ^aSurgery and ^bAnesthesia, Duke University Medical Center, Durham, North Carolina.

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Reprint requests: Dr. Carmelo Milano, Department of Surgery, Duke University Medical Center (3043), Durham, North Carolina. Telephone: 919-684-3243. Fax: 919-684-8563. E-mail: milan002@mc.duke.edu

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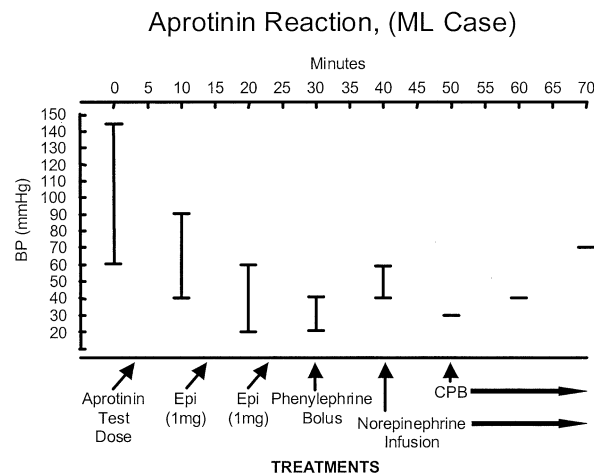


FIGURE 1 Blood pressure and treatments during an anaphylactic reaction to an aprotinin test dose.

tinin was given during the implant procedure. A total of 600 ml of aprotinin was given, including 200 ml in the cardiopulmonary bypass (CPB) prime (10,000 kallikrein inactivator units [KIU]/ml). The entire post-operative chest tube drainage was 2,120 ml. The patient did not require re-exploration for bleeding and was discharged from the ICU on Day 4 post-operatively. Thirty-five days after the LVAD implant, a suitable donor organ became available and he was taken urgently to the operating room for LVAD removal and heart transplant. After the chest was opened, a test dose of aprotinin (1 ml, 10,000 KIU) was administered. The patient was hemodynamically stable prior to the test dose with a blood pressure of 140/60 and an LVAD flow of 5.0 liters/min. Within minutes of test dose administration, he experienced severe hypotension with a systolic blood pressure of <40 mmHg, and an LVAD flow of 1.5 liters/min (see Figure 1). Hemodynamic instability continued despite a variety of treatments including intravenous (IV) fluid boluses, multiple 1-mg epinephrine boluses, IV phenylephrine boluses (2,100 µg), norepinephrine infusion, IV methylprednisolone (1,000 mg) as well as institution of cardiopulmonary bypass (see Figure 1). Even after initiation of CPB, the patient remained hypotensive with a mean blood pressure of 30 mmHg (see Figure 1). Ultimately, the patient stabilized on infusions of dopamine and norepinephrine, and underwent successful removal of the LVAD and cardiac transplantation. During the case, only the aprotinin test dose had been administered, with the remainder of the dose withheld. The patient experienced a slow post-operative recovery but ultimately

returned to normal. The patient remained in the ICU for 3 days, and did not suffer any neurologic or renal dysfunction. He was ultimately discharged from the hospital 15 days after the transplant.

The second patient was a 38-year-old woman with idiopathic cardiomyopathy, who was listed for heart transplantation. Due to progressive congestive heart failure (CHF) with severe bi-ventricular failure, she underwent urgent implantation of a bi-ventricular assist device (biVAD; Thoratec Corp) and was treated with aprotinin. A total of 600 ml of aprotinin was given, including 200 ml in the CPB prime (10,000 KIU/ml). Total post-operative blood loss was 3,010 ml. Her recovery was unremarkable and she was extubated on Day 2 post-operatively and subsequently transferred to the ward. She underwent successful physical rehabilitation and after 54 days of biVAD support, a suitable donor organ became available. She was emergently taken to the operation room for biVAD removal and heart transplantation. After the chest was opened, an aprotinin test dose was administered. Prior to the test dose, the patient was hemodynamically stable with a blood pressure (BP) of 100/60 and an LVAD flow of 4.5 liters/min. Several minutes after the test dose, she became severely hypotensive with reduced LVAD flow. No other drugs had been administered during this period. The hypotension was refractory to a variety of treatments including IV volume boluses, IV phenylephrine (1,200-µg bolus), IV norepinephrine (0.72 mg), IV methylprednisolone (1,000 mg), IV diphenhydramine (100 mg) and ranitidine (50 mg) as well as institution of CPB. The patient remained severely hypotensive with a mean BP <50 mmHg for approximately 2 hours. Ultimately, acceptable BP was achieved with multiple boluses and an infusion of norepinephrine, and the patient underwent successful biVAD removal and heart transplantation. Post-operatively, the patient experienced a significant rise in serum creatinine and oliguria, but ultimately recovered renal function without the need for dialysis. She remained in the ICU for 5 days and was ultimately discharged home 16 days following the transplant.

DISCUSSION

Review of the literature identifies multiple small studies that have reported severe allergic or anaphylactic reactions to aprotinin re-exposure. The reported incidence of this response with re-exposure is very low (see Table I). However, several important observations should be made. First,

TABLE I Incidence of aprotinin anaphylaxis with re-exposure

Author/Reference	Number of Patients	Incidence of Anaphylaxis
Dietrich et al ⁴	248	2.8%
Schulze et al ⁸	86	5.8%
Goldstein et al ⁷	23	4.3%
Scheule et al ⁵	11	9%
Current report	12	17%

most re-exposures occur after a significant interval (years) rather than after <2 months, as was the situation for the cases described in this report. Indeed, Dietrich et al reported an overall incidence of anaphylaxis of 2.8%, but 5 of the 7 events occurred in patients with early re-exposure, at an interval of <6 months (incidence 4.5%).⁴ Similarly, Scheule et al reported 11 patients with documented re-exposure at a mean interval of 77 months. Of these, the only patient who developed a severe anaphylactic reaction was re-exposed at 3 months.⁵ Indeed, we employed the policy of aprotinin administration with both the LVAD implant and subsequent transplant for 12 patients. Two cases of anaphylaxis occurred for a calculated incidence of 17%. This is considerably higher than the rate reported by others; however, the mean interval between exposures for our 12 patients was only 64 days, which is the shortest re-exposure interval among the reports listed in Table I. These episodes of anaphylaxis probably represented IgE-mediated responses, and analyses of human antibody responses to aprotinin revealed the highest levels of aprotinin-specific IgE antibodies between 2 and 6 weeks after exposure, with undetectable levels after 1 year.^{5,6} Therefore, late re-exposures might predictably have a lower rate of anaphylaxis relative to early re-exposures. Although the published rates of anaphylaxis with re-exposure are very low, they may not reflect the risk of early re-exposure when higher IgE titers are present.

Another important point suggested by these cases relates to the use of a test dose to screen for severe allergic response. Manufacturers of aprotinin suggest that a 1-ml test dose (10,000 KIU) precede any re-exposure. For both of the cases presented in this report, a test dose was employed with the remainder of the dose withheld. The hypotensive response to the test dose, however, was profound and not responsive to conventional

therapies (particularly in the second patient, in whom significant post-operative renal insufficiency resulted). There have been 2 other reports of near-fatal anaphylaxis to aprotinin test doses: 1 in a child who ultimately required cardiopulmonary resuscitation, and 1 in an adult.^{9,10} These episodes suggest that screening for anaphylaxis with the recommended test dose is not entirely safe, because the hypotensive response to just the test dose may be severe and difficult to correct.

Surgeons who have advocated the use of aprotinin for both the LVAD implant and for the subsequent transplant procedure emphasize delaying the test dose to a point whereby CPB can be initiated rapidly (i.e., thus employing CPB to treat potential anaphylactic responses).⁷ We advocate this approach but several important points should be made. First, the benefits of aprotinin have been demonstrated predominantly with prophylactic administration prior to initiation of significant dissection, heparinization or CPB.¹ A strategy of delaying its administration until CPB is initiated, during LVAD explantation, may negate some of the potential benefits, because significant dissection is required before cannulation can be achieved in these cases. Furthermore, for the 2 cases presented, CPB was not entirely effective in resolving the hypotension. The physiology of these reactions appears to be marked peripheral vasodilation, which is not directly corrected with CPB. Finally, it is important that the treatment dose not be added to the pump prime prematurely, because if a response to the test dose is identified the circuit would have to be exchanged before the patient could be supported with CPB.

In summary, although primary use of aprotinin for LVAD implantation appears to be safe and beneficial,^{2,3} the cases presented herein question the re-use of aprotinin during early LVAD explant. Benefits in terms of reduced post-operative bleeding should be formally analyzed and weighed against the risks of severe allergic response to the test dose.

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