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Management of Protamine Allergy With Bivalirudin During Coronary Artery Revascularization

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A patient with impaired left ventricular function was scheduled for coronary artery bypass grafting. The patient's history revealed a life-threatening allergy to fish proteins. Therefore, because of the threat of cross-reactivity to protamine, a standard anticoagulation protocol with heparin/protamine was disapproved. Instead, complete coronary artery revascularization was successfully performed off-pump using bivalirudin as the anticoagulant.

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Bivalirudin is a short-acting direct thrombin inhibitor that is routinely used in the United States during acute percutaneous coronary artery interventions. However, besides this indication, according to the most recent American College of Chest Physician guidelines, bivalirudin has the highest degree of recommendation as an alternative anticoagulation approach in patients undergoing cardiac operations who have been diagnosed with heparin-induced thrombocytopenia syndrome with active antibodies [1]. In the current case, bivalirudin was used not within the context of heparin-induced throm-

bocytopenia or heparin allergy but in a patient with a life-threatening fish protein allergy and at high risk for a severe anaphylactic reaction to protamine sulfate.

A 52-year-old man with double-vessel coronary artery disease and impaired left ventricular ejection fraction (0.30) was admitted to our hospital for coronary artery bypass grafting (CABG). In view of the patient's age, in accordance with the departmental standards, he was scheduled for off-pump CABG with complete arterial revascularization. However, his medical history revealed severe anaphylaxis to fish proteins. The first time that the patient ingested fish, he had to be resuscitated due to massive anaphylactic shock. The second time, during a stay in Asia, the patient ate vegetable soup that contained water in which fish had previously been boiled, and again urgent hospitalization was required for severe anaphylactic shock.

Protamine sulfate is a polycationic peptide belonging to a group of low molecular weight peptides derived from fish sperm. Protamine sulfate is mainly used as an antidote for heparin or is complexed to insulin to delay absorption and prolong the pharmacologic effect [2]. Within the context of cardiac operations, massive, even lethal, anaphylactic immunoglobulin G- and E-mediated reactions to protamine have been described, including anaphylactic shock and catastrophic pulmonary artery vasoconstriction [3]. Risk factors for these adverse reactions include drug sensitization due to long-term insulin therapy or fish allergy [1].

Our patient had experienced massive anaphylactic reactions to fish protein. Therefore, he was considered to be at high risk for a severe anaphylactic reaction to protamine. The team discussed several strategies, including:

1. an intracutaneous injection of a small dose of protamine after protective administration of high dosages of corticosteroids to evaluate the anaphylactic sensitivity to protamine during this condition;
2. the performance of off-pump CABG with low dosages of heparin (target activated clotting time values of 200 to 300 seconds) and use of a completely heparin-coated cardiopulmonary bypass (CPB) circuit in case a transition to CPB became necessary, without protamine administration; and
3. the use of bivalirudin for off-pump CABG or anticoagulation for CPB, if transition was necessary.

Viewing the documented experience with bivalirudin in off-pump and on-pump CABG, we decided to use this agent as the anticoagulant [4, 5].

Bivalirudin is a short peptide that inhibits thrombin directly by bivalent bondage. Within a short period of 25 minutes, thrombin cleaves the bivalirudin molecule and thrombin achieves back its procoagulant action. Approximately 80% of bivalirudin is eliminated by this proteolytic mechanism and about 20% is eliminated through the renal system. The safety and efficacy of bivalirudin use during cardiac operations has been documented in two randomized multicenter trials comparing bivalirudin anticoagulation with heparin/protamine anticoagulation in off-pump CABG and cardiac operations using CPB [4, 5].

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However, when used in this indication, attention has to be paid to its unique pharmacology. In areas of stagnant blood such as reservoirs, chest holes, or clamped vessels, bivalirudin concentrations decrease due to the progressing proteolysis and increasing concentrations of effective thrombin may lead to thrombus formation. Therefore, when bivalirudin is used in cardiovascular operations, areas of stagnant blood should be avoided by such things as using shunting lines and by intermittent flushing [6].

After sternotomy and both internal thoracic arteries had been prepared, bivalirudin was given according to the standard off-pump CABG protocol with a bolus of 0.75 mg/kg, followed by a continuous infusion of 1.75 mg/kg/h during the grafting procedure. The right internal thoracic artery was dissected free from the chest wall and anastomosed as a free T-graft to the left thoracic artery. Next, the left thoracic artery was anastomosed to the left main coronary artery and the right thoracic T-graft was anastomosed to the right coronary artery. Because of the theoretic danger of clot formation in stagnant blood when bivalirudin is used as the anticoagulant, all grafts were clamped and flushed at intervals of 20 minutes to avoid clot formation in the vessels and coronary embolization.

The bivalirudin infusion was stopped when the distal coronary anastomosis was finished, and the diffuse bleeding stopped 30 minutes thereafter so that the chest could be closed. The operation was uneventful, and the patient was transferred to the intensive care unit with moderate inotropic support. Postoperative blood loss was 400 mL. The patient was weaned from mechanical ventilation 6 hours after arrival at the intensive care unit and was discharged from the hospital 5 days after the operation.

Comment

The risk is very high that a massive anaphylactic reaction will develop in patients with an allergy to fish proteins after the administration of protamine. Our patient's anaphylactic reactions to even minor amounts of ingested fish were dramatic. Therefore, administration of even small amounts of subcutaneous protamine was considered a risk, and in effect would not have completely ruled out a dramatic anaphylactic reaction after intravenous administration of protamine even under the protection of high-dose corticosteroids. Experience regarding potential bleeding complications when heparin is used for on-pump CABG with low-dose anticoagulation with tip-to-tip heparin-bonded CPB circuits without protamine reversal is meager. The bleeding risk was considered to be high in view of the large wound areas after preparation of both internal thoracic arteries.

In contrast, the safety and efficacy of bivalirudin for anticoagulation during cardiac operations has been prospectively studied [3, 4]. In addition, bivalirudin anticoagulation during off-pump CABG was associated with improved early graft patency compared with heparin/protamine reversal in one larger single center investigation, and one center reported excellent safety and efficacy data in more than 200 patients when bivalirudin was used as standard anticoagulant in off-pump CABG [6–8].

Taking into account this compact body of evidence, the decision was made to use bivalirudin for anticoagulation in our patient. The current case demonstrates the value of an alternative anticoagulation strategy during cardiac operations besides heparin/protamine reversal. Therefore, bivalirudin should be a first-line alternative anticoagulant approach in the case of acute heparin-induced thrombocytopenia and anaphylaxis to heparins and also when adverse reactions to protamine are expected.

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Complex Surgical Valve Repair After Failed Percutaneous Mitral Intervention Using the MitraClip Device

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Catheter-based techniques of percutaneous valve intervention are recently being performed in an increasing number of patients. We finally report a case of successful, but complex surgical mitral valve repair 32 days after failed percutaneous intervention with severely aggravated mitral pathology caused by the catheter-based

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