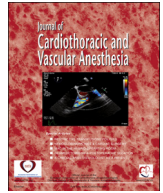




Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvonline.com

Editorial

Protamine, is something fishy about it? The spectre of anaphylaxis continues

As perioperative clinicians, we administer different pharmacologic and biologic agents or manage patients during procedures in which they are given multiple foreign substances. Because almost any drug or environmental agent has the potential to cause a life-threatening allergic reaction, clinicians always must be aware of these idiosyncratic and unpredictable responses, including anaphylaxis.^{1,2} Protamine, the subject of this editorial, is one of the potential agents that can cause anaphylaxis during cardiac surgery.

Of all the different pharmacologic strategies patients are subjected to in cardiovascular medicine, probably the most quirky practice is our management of anticoagulation with heparin and acute reversal with protamine after separation from cardiopulmonary bypass (CPB).³ Heparin, a mast cell product, is isolated from pig intestine and includes a complex mix of acidic glycosaminoglycans that function primarily by binding to circulating antithrombin to inhibit thrombin, factor Xa, and other coagulation proteins.⁴ For cardiac surgery and CPB, we administer high doses of this biological product, then, to reverse its effects we administer protamine, a highly basic arginine-rich polypeptide isolated from salmon sperm that binds as a nonspecific acid-base, polyanionic-polycationic interaction. This longstanding practice seems like an extension of medieval medicine. However, it continues to be the standard of care for cardiac surgery despite the development of multiple different novel non-vitamin K anticoagulants including direct thrombin inhibitors and multiple attempts to develop protamine replacement molecules for many years with limited success due to efficacy, ease of acute reversal, and costs.⁵⁻⁷ Despite the widespread use of this practice, 2 major adverse events can occur that are related to immunologic reactions to heparin or protamine. For heparin, although anaphylaxis can occur, the more common immunologic response is heparin-induced thrombocytopenia due to an IgG antibody directed against a neo-epitope of platelet factor 4 and platelets.^{8,9} For protamine, anaphylaxis occurs due to either IgE or IgG antibodies.¹⁰

In this edition of the *Journal of Cardiothoracic and Vascular Anesthesia*, the authors reported 3 cases of

anaphylaxis to protamine and asked the important question of whether redosing is safe. They also note how to manage anticoagulation and potential reversal following additional re-heparinization and an urgent return to CPB.¹¹ In their 3 cases of assumed protamine anaphylaxis characterized by circulatory and respiratory collapse, they redosed protamine in 2 patients and avoided re-exposure with “tincture of time” in 1 case. They conclude that redosing of protamine after repeated anticoagulation for cardiopulmonary can be managed safely in patients with “proven protamine anaphylaxis,” and speculate on safety of this practice. However, $n = 2$ cases where re-exposure to protamine was tolerated is not realistically a safe practice; rather just what the authors did without any hemodynamic compromise. As they noted in their discussion, based on our previous description, there may be a post-anaphylaxis refractory period, possibly caused by consumption and/or depletion of inflammatory mediators. There is also the potential that these reactions were IgG mediated, and the antibodies were acutely consumed; thus, potentially preventing an immediate subsequent response. Although tryptase levels were increased in all the patients, there also may have been concomitant IgG responses. It is known that patients who have high IgE levels to protamine also likely have high IgG, as reported previously by Weiss et al.¹² Protamine also can degranulate mast cells directly,¹³ and perhaps there was an idiosyncratic response in some of the patients in which the reaction was potentially nonimmunologic. Mast cell activation also releases tryptase, as we previously have demonstrated.¹⁴ Protamine also has been shown to activate complement nonspecifically by binding to heparin and should be administered slowly to prevent mast cell degranulation.¹⁵ Thus, other potential explanations may explain why protamine could be rechallenged without life-threatening cardiopulmonary collapse.

As previously mentioned, protamine can produce multiple adverse reactions following intravenous administration, including nonimmunologic mast cell degranulation, complement activation, or IgG- and IgE-mediated responses that account for the systemic responses. Because of the different mechanisms for protamine reactions reported, the literature is

confusing regarding different etiologies regarding its adverse hemodynamic effects and description of reactions. As the authors note, patients at greatest risk for protamine reactions have been sensitized previously from protamine-containing insulins. We reported an incidence of 0.6% (1 of 160) to 2% (1 of 50) in NPH insulin-dependent diabetics undergoing cardiac surgery, a rate $10\times$ to $30\times$ greater than other patients from a total of 4,796 patients evaluated.^{16,17} However, the incidence in our general patient population was also 1 in 1,500, identical to what the authors report in their patients as well.^{16,17}

Protamine is known to cause acute pulmonary hypertension leading to acute right ventricular failure, also called catastrophic pulmonary vasoconstriction, as previously described, and is mediated by complement activation.^{15,18} However, multiple mechanisms can cause complement activation, including heparin-protamine interactions or by antiprotamine-IgG antibody interaction and C5a-mediated thromboxane release.¹⁵ Protamine also has the potential to inhibit carboxypeptidase N, a critical proteolytic enzyme that cleaves anaphylatoxins produced by complement activation and bradykinin, converting them to inactive metabolites.¹⁹ If heparin-protamine-mediated complement activation was the primary mechanism for hypotension in the authors' patients, then re-exposure is not an immunologic process and likely can be performed. In previous reports in patients receiving protamine-containing insulins, the antiprotamine IgE antibodies were risk factors for acute protamine reactions, as was the presence of antiprotamine IgG.¹²

The idiosyncratic and unpredictable nature of anaphylaxis and its spectrum of reactions are an ongoing issue for clinicians, especially managing patients in a perioperative setting in which a spectrum of foreign substances are administered.^{2,20} Clinicians need to always be ready to treat the acute cardiopulmonary collapse that occurs following anaphylaxis, and what better clinicians to do this than cardiac anesthesiology and critical care intensivists. Every day we manage acute biventricular dysfunction and acute respiratory failure and have all the tools in our pharmacologic armamentarium to treat these patients when the unpredictable adverse hemodynamic effect occurs. However, we still want to caution clinicians that re-exposure to a foreign substance that was implicated previously in adverse reaction needs to be considered carefully, and the risk versus the benefits of re-exposure considered for a potential foreign substance that may produce anaphylaxis. Finally, despite all of our sophisticated pharmacologic and technologic advances, we still employ routine administration of heparin, an extract of pig intestine for anticoagulation, and reverse this with protamine, an extract of salmon sperm. Frankly, despite this routine, there still seems to be something quite fishy about this practice, and it is note-worthy that we still do not have alternative therapies for anticoagulation and acute reversal for extracorporeal circulation.

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