Clinical Reports

Thrombocytopenia accompanying a reaction to protamine sulfate

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Catastrophic pulmonary vasoconstriction, an idiosyncratic reaction to protamine, occurred following cardiopulmonary bypass in a patient with mitral regurgitation. One minute following intravenous injection of 10 mg of protamine, systemic blood pressure decreased precipitously, accompanied by elevated pulmonary arterial pressure, decreased left atrial pressure, and a dilated and poorly contracting right ventricle. These changes spontaneously reversed over five minutes. Rechallenge with protamine was uneventful. Platelet count decreased from 76,000/mm³ to 12,000/mm³. Transient thrombocytopenia occurs predictably in dogs given protamine rapidly. Suggested mechanisms of idiosyncratic pulmonary vasoconstriction in patients should consider the role of the associated thrombocytopenia.

Key words

ALLERGY: protamine, anaphylactoid reactions, mediators, complement; BLOOD, COAGULATION: protamine; COMPLICATIONS: hypotension; LUNG: vasoconstriction.

Protamine sulfate has been implicated as the cause of severe pulmonary vasoconstriction in certain patients.¹ This event appears to be idiosyncratic in man, considering the unchanged pulmonary arterial pressures documented in several prospective studies.²⁻⁴ Protamine administration is a benign event with most patients. In contrast, pulmonary vasoconstriction from protamine is a reproducible phenomenon in dogs⁵⁻⁷ and pigs;⁸ studies reveal transient leukopenia and thrombocytopenia⁵ and pulmonary petechiae.⁷ This report describes haematologic and immunologic changes accompanying an instance of protamine-induced pulmonary vasoconstriction in a patient.

Case report

A 69-year-old man with severe mitral regurgitation received fentanyl anaesthesia for mitral valve replacement. The patient gave a history of allergy to myelogram dye but not to fish. He had not undergone vasectomy and had not previously received protamine or any form of insulin. Cardiac catheterization revealed a right ventricular pressure of 12/1.3 kPa (90/10 mmHg), pulmonary artery pressure of 12/5.3 kPa (90/40 mmHg), and pulmonary capillary wedge pressure of 4.0 kPa (30 mmHg), with a v-wave to 6.0 kPa (45 mmHg). Cardiopulmonary bypass employed a Sci-Med® membrane oxygenator, and lasted 98 minutes. An intravenous infusion of epinephrine at a rate of 2 µg·min⁻¹ was used to aid termination of cardiopulmonary bypass. The Figure displays tracings of left radial artery pressure, pulmonary artery pressure, and central venous pressure, beginning 16 minutes after weaning from bypass. Five minutes before protamine administration 20 ml of venous blood was with-

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FIGURE Compressed waveforms of radial artery pressure, pulmonary (PULM) arterial pressure, and central venous pressure (CVP) beginning 16 minutes after the end of cardiopulmonary bypass (CPB). Each arrow indicates bolus intravenous administration of 10 mg of protamine sulfate. Ordinate values are in mmHg.

drawn. Systemic blood pressure was 15.3/7.3 kPa (115/55 mmHg); pulmonary artery pressure was 7.1/2.0 kPa (53/15 mmHg). A test dose of protamine, 10 mg bolus via central venous catheter, was injected at the time indicated by the first large arrow in the Figure. Surgical manipulation at this time was minimal. The aortic cannula had already been removed and the sternal retractor was undisturbed. Within one minute, pulmonary hypertension (11.6/3.6 kPa or 87/27 mmHg) and systemic hypotension (10/5.3 kPa or 75/40 mmHg) ensued, accompanied by ST segment depression on the electrocardiogram. Left atrial pressure, measured by water manometer on the surgical field, dropped precipitously from 10 cm to 2 cm, and the right ventricle appeared dilated and poorly contracting. Flushing and bronchospasm were absent. Systemic and pulmonary pressures returned to pre-protamine levels within five minutes without intervention.

Four minutes after protamine injection additional venous blood was withdrawn. Another intravenous bolus of protamine, 10 mg, indicated by the second large arrow in the figure, was given via central venous catheter without untoward sequelae. The remaining protamine dose, 140 mg, was injected intravenously over five minutes. The overall fluid requirement for this patient was not increased compared with similar cases. The venous blood specimens were analyzed for white blood cell count, platelet count, and serum concentrations of C_3 , C_4 , and IgE. These analyses were repeated on specimens drawn 18 hours postoperatively, and on the sixth postoperative day.

Laboratory test results appear in the Table. White blood cell count was slightly elevated, but demonstrated no change during the drug reaction. Serum levels of complement proteins C_3 and C_4 were mildly depressed after cardiopulmonary bypass; these values were also stable, as were serum IgE levels. Platelet count, however, decreased dramatically to $12,000/\text{mm}^3$ following administration of protamine. Two hours later, platelet count was $209,000/\text{mm}^3$; two units of washed, autologous, packed red cells obtained from the pump circuit had been administered in the interim.

Discussion

This case demonstrates several features of pulmonary vasoconstriction previously shown in dogs. First, severe thrombocytopenia occurs.⁵ Second, the haemodynamic alterations reverse within minutes even when untreated.⁵ Third, rechallenge with protamine is benign.⁶ The absence of transient leukopenia⁵ is a discrepancy possibly explained by a species difference.

The evidence for increased pulmonary vascular resistance (PVR) is indirect, since cardiac output was not measured during the incident. However, the indirect evidence is quite compelling. If PVR had been unchanged then cardiac output would have had to increase 2.2-fold to generate the pulmonary artery and left atrial pressures measured. This increase in cardiac output would require a 4.5-fold reduction in systemic vascular resistance – a most unlikely event. Indeed, observation of the beating heart was enough to demonstrate a severe reduction in cardiac output.

There are confounding factors which may have influenced the data reported. Epinephrine was

TABLE Laboratory test results

Study	Normal range	Before protamine	Time after first protamine dose		
			4 min	18 hours	6 days
White blood cell count	4,000–10,000/mm ³	11,900	11,000	12,500	8,000
Platelet count	150–450 × 10 ³ /mm ³	76,000	12,000	110,000	292,000
C ₃	91–198 mg/dl	83	106	106	177
C ₄	26–83 mg/dl	15	21	20	33
IgE	0–103 IU/ml	34	36	48	98

Abbreviations: C₃, serum concentration of the third component of complement protein; C₄, serum concentration of the fourth component of complement protein; IgE, serum concentration of class E immunoglobulins.

infused throughout the period reported. The vasoactive and platelet aggregating effects⁹ of epinephrine have been well established. However, the epinephrine infusion is unlikely to have participated in the response demonstrated for two reasons. First, the infusion was stable and remained unaltered during the period reported. Second, the dose of epinephrine administered was reasonably low.

The mechanism by which protamine induces pulmonary vasoconstriction is unknown. One possibility is that platelet aggregates plug pulmonary capillaries and thus increase pulmonary vascular resistance and pressure. Protamine causes platelet aggregation *in vitro*.¹⁰ However, when added to a heparinized sample of blood, it reverses the increased sensitivity of platelets to aggregation by ADP or epinephrine as well as directly decreasing platelet sensitivity.⁹ Bjoraker *et al.* demonstrated trapping of platelet aggregates in the pulmonary systems of patients in response to protamine infusion; this was associated with decreases in systemic blood pressure and platelet count.¹¹

Another explanation for the pulmonary changes is a protamine-induced release of a vasoactive substance or substances which results in constriction of smooth muscle in the pulmonary vasculature. The lack of adverse response to immediate rechallenge is suggestive of depletion of some vasoactive substance. Thrombocytopenia occurs possibly as an independent, concurrent effect of the vasoactive mediator. This coincidence is not unreasonable; for example, thromboxane A₂ is known to cause both platelet aggregation and vasoconstriction, although this fact alone cannot implicate it as the mediator. Lowenstein *et al.* suggest a complement mediated reaction.¹ Best *et al.*¹² demonstrated

complement consumption in a protamine reaction of the anaphylactoid type. In Best's patient, flushing was prominent and jugular venous pressure was low. Complement levels of C₃ and C₄ were stable in this patient. However, this does not exclude a complement mediated phenomenon since the assay for C₃ measured both the protein and its split products.

Jaques measured histamine levels in dogs following administration of protamine;⁵ no change in histamine levels was found although the assay at that time was crude and insensitive. In an attempt to implicate serotonin as the mediator, Radegran *et al.* administered methysergide prior to protamine in dogs.¹³ The cardiovascular effects were not blocked. The mediator involved in protamine reactions remains unknown. Further investigations will hopefully reveal which, if any, substances are involved.

Both Jaques⁵ and Radegran⁶ reported the benign nature of rechallenge with protamine following adverse response. Although the latter report⁶ demonstrates that additional heparin "recharges" the system, neither investigation demonstrated that the adverse response from protamine was dependent upon a complete or partial heparin effect. In this report, rechallenge was uneventful following an initial dose of 10 mg of protamine, hardly enough to reverse the complete anti-coagulation that had been established for cardiopulmonary bypass. These data are also consistent with the elaboration of a vasoactive substance as the mediator of protamine-induced vascular changes.

It is intriguing to note that this patient, like four of the five patients reported by Lowenstein *et al.*, suffered from mitral valvular disease. It is conceivable that the associated changes in pulmonary

haemodynamics in these patients engender some alteration of the vascular endothelium, normally a site of prostacyclin synthesis, which influences the response to protamine. Of course, this case report provides no evidence to support this conjecture.

In summary, this report documents a dramatic change in platelet count in a patient with mitral regurgitation during an adverse response to protamine. Rechallenge with protamine was haemodynamically uneventful. Any hypothesis of the mechanism of idiosyncratic pulmonary vasoconstriction in patients should include both an explanation and a role for the associated thrombocytopenia.

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Résumé

On a remarqué une vasoconstriction pulmonaire majeure, réaction inattendue à la protamine, chez un patient porteur de régurgitation mitrale à la suite de chirurgie extra-corporelle. Une minute après l'injection intraveineuse de 10 mgs de protamine, la pression artérielle systémique s'est effondrée rapidement, alors que la pression artérielle pulmonaire s'est élevée et que la pression auriculaire gauche s'est abaissée. La ventricule droit, se contractant faiblement, s'est dilaté. Tout est redevenu normal sans intervention en dedans de cinq minutes. Une nouvelle injection de protamine ne produisit aucun effet. La numération des plaquettes a diminué de 76,000/mm³ à 12,000/mm³.

On a observé déjà une brève thrombocytopenie chez des chiens à qui on avait rapidement injecté de la protamine. Peut-être y a-t-il là un filon à explorer pour expliquer ce phénomène. Cependant, toute hypothèse cherchant à expliquer une vasoconstriction pulmonaire cryptogénétique devra fournir une cause à cette thrombocytopenie et aussi lui attribuer un rôle.