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Fatal anaphylactoid response to protamine after percutaneous transluminal coronary angioplasty

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A generalized skin erythema and severe hypotension developed following administration of protamine for the reversal of heparin anticoagulation after an unsuccessful attempt at percutaneous transluminal angioplasty in a patient who had never been exposed to protamines before. Evidence of classical pathway complement activation was present indicating that this reaction could have been triggered by a non-immunological mechanism. The patient could not adequately be resuscitated because of the presence of severe coronary artery disease.

Introduction

The widespread use of protamine for the reversal of heparin anticoagulation has attracted great attention because of its potentially harmful side effects. However, most of the adverse reactions are reported in patients undergoing heparin neutralization after cardiopulmonary bypass or in patients previously exposed to protamines. Here we report a case of fatal protamine reaction in a patient with no history of prior protamine exposure who underwent an unsuccessful attempt of percutaneous transluminal coronary angioplasty.

Case report

A 64-year-old man was admitted for unstable angina. He had never had surgery before, had no known allergies and had none of the previously reported risk factors attributed to protamine allergy, such as the use of protamine-containing NPH insulins, a prior vasectomy or a history of fish allergy[1,2]. The electrocardiogram showed normal sinus rhythm and flattening of the ST segment in V_{5-6}. The stress test performed the evening before catheterization was clinically and electrically positive at 100 W with an ST segment depression of more than 1·5 mm in II, III and aVF and ST segment elevation in V_{1-4} lasting for more than 10 min.

The coronary angiography showed a proximal total occlusion of the left anterior descending coronary artery, its distal bed being collateralized by the dominant right coronary artery. The right coronary artery showed several significant stenoses. A localized hypokinesia of the anterior wall was present, with normal global ventricular function. At the end of the diagnostic study, it was decided to attempt recanalization of the occluded left anterior descending coronary artery, by percutaneous transluminal coronary angioplasty. For anticoagulation 20 000 units of heparin (Liquemine^{R}, Hoffmann-LaRoche, Basel, Switzerland) and 250 mg of aspirin were administered intravenously. The occluded left anterior descending coronary artery could not be passed and elective bypass surgery was recommended to the patient. He had been asymptomatic during the entire intervention.

Before removal of the catheter placed in the femoral artery, i.e. about 45 min after anticoagulation, heparin was reversed with 200 mg protamine hydrochlorid (Protamine 1000, Hoffmann-La Roche, Basel, Switzerland) as an intravenous bolus. Approximately 2 min later, the patient developed a generalized skin erythema, became restless and complained about general itching, but without evidence of bronchospasm. The arterial blood pressure (120/80 mmHg) and heart rate (84–94 beat min^{-1}) remained unchanged. Diphenhydramine (50 mg), a histamine-receptor-blocking agent, and prednisone (100 mg) were given intravenously. However, 10 min later, systolic blood pressure dropped (< 70 mmHg). A crystalloid solution was rapidly administered together with 1·0 mg of adrenaline subcutaneously, without any effect on blood pressure. Therefore a second dose of 1·0 mg of adrenaline was infused slowly into a peripheral vein. Systolic blood pressure transiently increased (> 90 mmHg) but the patient complained about typical chest pain. An ST elevation of more than 1·5 mm was observed in the infero-lateral leads, and the systolic blood pressure dropped progressively (< 50 mmHg). Cardiopulmonary resuscitation was started, the patient was intubated and ventilated with 100% oxygen. Peak airway pressure was above 35 cmH_2O, indicating the occurrence of bronchospasm and/or acute pulmonary oedema. Several episodes of ventricular fibrillation occurred necessitating defibrillation. However, although adequate blood pressure could be maintained initially by cardiac massage and intravenous administration of inotropes, irreversible electro-mechanical dissociation developed, and the patient could not be resuscitated.

To corroborate the diagnosis of protamine-induced adverse reaction, different components of the complement system were determined in plasma, left from the blood sample routinely taken before percutaneous

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Table 1 Total haemolytic complement (CH_{50}) and the complement components C3 and C4 before and after adverse protamine reaction

	Before	After	Normal values
CH_{50}(%)	132	50	75–125
C3 (g l^{-1})	1·59	0·88	0·63–1·35
C4 (g l^{-1})	0·56	0·26	0·10–0·40

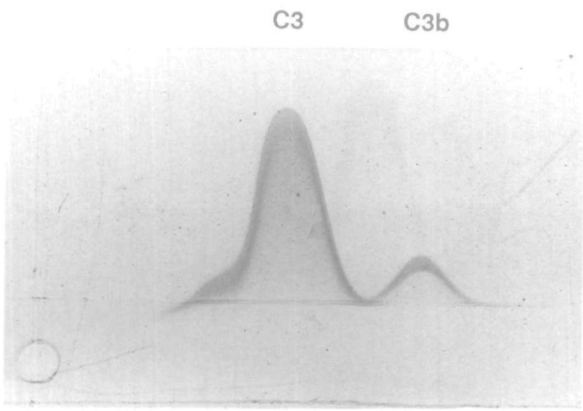

Figure 1 Two-dimensioned immunoelectrophoresis showing activation of C3. Without activation, no C3b is visible.

transluminal angioplasty, and from a blood sample taken during cardiopulmonary resuscitation.

The results of complement fragments are given in Table 1 and Fig. 1. Histamine could be measured only in the first blood sample and was, with 23·7 nmol l^{-1}, well above the normal value of less than 10 nmol l^{-1}.

At autopsy, there was a haemopericardium containing 400 ml of fresh blood associated with a perforation of the right ventricle measuring 0·3 cm in diameter (most probably due to the temporary pacemaker during resuscitation). The hypertrophic heart (535 g) showed extensive arteriosclerosis with an occlusion of the left anterior descending coronary artery, 1·8 cm after its origin and a stenosis, occluded by a fresh thrombus, in the right coronary artery, 5 cm distally of its ostium. A recent antero-septal and postero-lateral infarct was present. The aortic valve showed signs of inactive endocarditis with multiple perforations of the leaflets. Both lungs showed congestion and oedema. The thoraco-abdominal aorta and its branches showed severe arteriosclerosis.

Discussion

The patient probably died from acute occlusion of the right coronary artery supplying blood to the inferior and, via collaterals, to the anterior myocardial wall. This occlusion was triggered by the adverse reaction to protamine.

It appears that protamine can induce more than one type of adverse response in humans. Complement activation through the classical pathway, timely related to protamine administration, can occur after cardiac catheterization in patients with previous exposure to protamine[2]. The depletion of haemolytic complement activity, C4 and C3 and the presence of circulating C3b suggests that the classical complement pathway was activated in our patient despite no history of prior exposure to protamine. This indicates that complement was most probably not activated by an immune complex[3] but rather by an interaction between the polycation protamine and the polyanion heparin[4,5]. C-reactive protein which is increased during myocardial ischaemia, enhances this reaction[6]. Split products of complement activation such as C3a and C5a or complement-induced release of histamine has been proposed as being one of the causes of protamine-induced hypotension[7,8]. However, we cannot exclude that a non-specific, non-immunological protamine-induced release of cellular mediators, e.g. histamine, caused the severe hypotension. As in another case reported[8], our patient had an increased plasma histamine level prior to protamine exposure, which suggests that elevated circulating histamine concentrations could favour adverse reactions to protamine.

Some patients may poorly tolerate protamine-induced haemodynamic changes. Slow administration through a free-running intravenous catheter[9] may reduce rapid release of vasoactive substances and allow spontaneous compensatory mechanisms to become operative. If protamine is suspected to have caused adverse side effects it calls for immediate therapeutic intervention. This includes cessation of protamine administration and restoration of blood pressure with intravenous fluids, and cardio-circulatory support drugs. Maintenance of pulmonary gaseous exchange with supplemental oxygen and, if necessary, with assisted ventilation is mandatory. As in our patient, this aggressive therapy may interfere with an adequate myocardial oxygen supply-demand ratio[10], leading to ventricular arrythmia, fibrillation and eventually electro-mechanical dissociation.

Cardiac catheterization can be safely performed without the use of protamine. We therefore advocate that it should be administered only if it can significantly contribute to reduce bleeding in a heparinized patient. The occlusion of the right coronary artery by a fresh thrombus in our patient may have been favoured by the reversal of heparin activity, combined with low blood flow due to systemic hypotension.

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