Currently, there is no specific antidote for argatroban. In order to re-establish normal coagulation, FFP administration is recommended. In our first patient four units were sufficient to correct coagulation. Others have reported FFP not to be effective during argatroban therapy [5]. In that case, however, only 600 mL FFP were given per day and the volume applied thus was possibly insufficient for a bleeding patient. In contrast, a recent case report supports our observation that FFP can effectively compensate for argatroban overdose [7], whereas recombinant activated factor VII was not successful in this respect.

The choice of the anticoagulant on the ICU is still a challenge. For argatroban, we suggest to start routinely with reduced doses compared to the package insert, followed by an adjustment according to aPTT levels. Performed in such a matter, argatroban seems to be a safe drug for anticoagulation in patients with HIT II in the ICU.

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# An unusual fatal reaction to a test dose of aprotinin before elective thoracoabdominal aortic aneurysm repair

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EDITOR:

Aprotinin (Trasylol; Bayer Corporation, Pittsburgh, PA, USA) is a serine proteinase inhibitor which inhibits the contact phase activation of haemostasis, preventing fibrinolysis and reducing thrombin generation [1]. Aprotinin has been shown to reduce blood loss and transfusion requirements in cardiac surgery [2]. As a protein derived from bovine lung, aprotinin possesses antigenic properties in human beings. Aprotinin is well known to produce hypersensitivity reactions of the anaphylactic type. The risk of anaphylaxis with primary exposure to aprotinin is quite rare, but is approximately 2.8% upon re-exposure [2]. Timing of the re-exposure is also important. The majority of re-exposure reactions occurs within the first 3 months [2]. We report an atypical presentation of re-exposure to aprotinin several years after index exposure resulting in rapid, profound biventricular failure with progression to disseminated intravascular coagulation (DIC).

A 65-yr-old male presented for elective repair of a chronic Crawford type III thoracic aortic aneurysm. In 1998, the patient underwent surgical repair of a type A aortic dissection during which aprotinin was used. According to our records, this was the only time when this patient had been exposed to aprotinin. General anaesthesia was induced with fentanyl and midazolam. Neuromuscular blockade was achieved with pancuronium. The trachea was intubated

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with a left-sided double-lumen endotracheal tube. Haemodynamic monitoring included radial artery and pulmonary artery catheters. A transoesophageal echocardiography probe was inserted without difficulty which revealed normal biventricular function with a left ventricular ejection fraction of 60%. Besides the aortic aneurysm, no other abnormal findings were noted on TOE examination. Anaesthesia was maintained with isoflurane in oxygen, as well as fentanyl and midazolam.

Prior to surgical incision, a 1 mL (10 000 KIU) test dose of aprotinin was administered via a right internal jugular central line. Ninety seconds later, the patient developed a supraventricular tachycardia for approximately 10 s and became hypotensive with a mean arterial pressure of 55 mmHg. The tachycardia resolved spontaneously to a normal sinus rhythm at a rate of 80, but the patient remained hypotensive with a mean arterial pressure in the 40's. TOE during the initial event and subsequent hypotension demonstrated severe, biventricular failure with minimal shortening of both ventricles. This initial TOE examination was not consistent with a catastrophic fall in pre-load, which would present as an underfilled hyperdynamic heart. At the onset of hypotension, the patient was given 8 μg of epinephrine. Increasing doses of epinephrine were administered to a total of 80 μg within the first 30 s of the initial hypotension. Despite this treatment, the patient became increasingly hypotensive with mean arterial pressures in the range of 30–40's. Other hallmarks of anaphylaxis such as an increase in peak airway pressure, evidence of bronchospasm or dermatologic manifestations were not observed. Pulmonary artery pressures remained at baseline with a mean of 25. Full resuscitation in accordance with ACLS protocols was initiated for the treatment of the worsening hypotension. The patient developed ventricular fibrillation and was electrically defibrillated. TOE examination revealed no evidence of pulmonary embolus, cardiac tamponade or intracardiac thrombus. The aorta was intact without signs of rupture or dissection. Hypotension continued and severe bradycardia ensued despite continued epinephrine administration. Intravenous heparin (21 000 units) was administered and the patient placed as an emergency on full cardiopulmonary bypass via groin cannulation.

The patient was uneventfully weaned from cardiopulmonary bypass 48 min later. TOE examination at this time demonstrated a return to baseline cardiac function with normal biventricular size and function. After protamine administration, activated clotting time returned to a baseline level. In spite of the heparin reversal, the patient had significant bleeding. The patient was transfused with fresh frozen plasma, platelets, cryoprecipitate, and packed red blood cells. No active surgical bleeding was identified after extensive re-exploration.

In spite of ongoing bleeding from surgical wounds, indwelling catheter sites and voluminous chest tube drainage the patient was transported to the intensive care unit. Laboratory values obtained upon arrival in the intensive care unit were as follows: prothrombin time 17.1 s, INR-1.5, activated partial thromboplastin time 91.7 s, haemoglobin 5.3 g $dL^{-1}$, haematocrit 15%, platelets-160 $\mu L^{-1}$, tryptase level 371 $\mu g\, L^{-1}$ (normal 1.5–13.5). A clinical diagnosis of DIC was made and resuscitative measures including continued blood products as well as recombinant factor VIIa (90 $\mu g\, kg^{-1}$) were administered. In spite of these interventions, the patient continued to exsanguinate and expired.

Due to the temporal relationship of the administration of aprotinin and the sudden unexplained biventricular failure, we conclude that these findings were the direct result of an anaphylactic reaction to a test dose of aprotinin. The expected presentation of anaphylaxis due to a precipitous drop in pre-load did not occur in this patient as confirmed by our TOE findings. Other causes of a catastrophic event such as pulmonary embolism, myocardial infarction or rupture of the aortic aneurysm were ruled out by the TOE examination and a subsequent autopsy.

To our knowledge, this is the first case report of profound biventricular failure due to aprotinin. Furthermore, the described biventricular failure occurred with the administration of only a 1 mL test dose of aprotinin in a patient with a documented previous exposure seven years previously. Hypersensitivity reactions to aprotinin have been extensively reviewed [2]. Out of 53 hypersensitivity reactions where the exposure time was known, only two occurred with re-exposure after 36 months [2]. The anaphylactic reaction in our case was unusual in that no other typical manifestations of anaphylaxis such as bronchospasm or skin manifestations were noted. The serum tryptase level, a marker for mast cell activation indicative of anaphylaxis, was markedly elevated.

Anaphylaxis can produce arrhythmias, infarction and angina [3]. Mast cell degranulation leads to the release of histamine, leukotrienes, prostaglandins and thromboxanes which are known to exert a negative inotropic effect on the heart as well as reduce coronary blood flow [4]. Histamine is also known to be a potent coronary vasoconstrictor particularly in patients with coronary artery disease [5]. *In vitro* studies examining the $H_1$ and $H_2$ receptors of human hearts revealed an initial tachycardia and increased contractility followed by

 

profound myocardial depression [6]. Myocardial depression from anaphylaxis is rare yet has been reported in patients with little to no coronary artery disease [7]. The *post mortem* examination of our patient revealed only mild coronary artery disease.

Ultimately, the profound myocardial depression did not lead to the death of our patient as he was well resuscitated and quickly placed on cardiopulmonary bypass with full restoration of cardiac function in less than an hour. The development of DIC, a later sequela of the anaphylactic reaction, eventually led to the patient's death. The presence of DIC in the setting of anaphylaxis is well known and often fatal with minimal salvaging therapies.

It is well established that aprotinin is not an entirely benign medication as many reports of negative side-effects have been noted. On the basis of our experience and growing evidence, the use of aprotinin should be severely scrutinized by each practitioner before its use, especially in the setting of documented previous exposure, regardless of the interval between exposures. Perhaps most importantly, clinicians should reserve the primary exposure of aprotinin to cases with an extremely high risk of bleeding where aprotinin would most likely decrease transfusion significantly.

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