

Anaphylactic Reaction After Systemic Application of Aprotinin Triggered by Aprotinin-Containing Fibrin Sealant

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We report a 67-yr-old male after multiple surgical procedures for treatment of arterial occlusive disease who suffered an anaphylactic reaction after administration of aprotinin (Trasylol®) prior to urgent coronary artery bypass surgery. The patient had been treated with aprotinin-containing fibrin sealant in 2004 and in 2007, 2 wk before coronary artery bypass surgery. The postoperative serologic screening revealed positive results for qualitative aprotinin-specific IgG, highly elevated quantitative aprotinin-specific IgG and moderately elevated aprotinin-specific IgE antibodies.

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Aprotinin is a serine-protease-inhibitor derived from bovine lung and indicated for prophylactic use to reduce perioperative blood loss in patients undergoing coronary artery surgery requiring cardiopulmonary bypass circuit (CPB). Side effects, including anaphylactic reactions after re-exposure, especially within a 12-mo period have been reported.

The marketing of aprotinin (Trasylol) has been suspended since November 2007 in Germany and other countries until a comprehensive review of the Canadian BART study (Blood conservation using antifibrinolytics: a randomized trial in a cardiac surgery population study) is performed.^{1,2}

Life-threatening reactions associated with IgG- and IgE-antibodies has been reported after repeated systemic and topical use of aprotinin.³ According to the most recent data available, the incidence of hypersensitivity reactions is 4.1%, 1.9% and 0.4% in <6, 6 to 12, and more than 12 mo re-exposure intervals, respectively.¹ Over the past 10 yr we have had two such

anaphylactic reactions at our institution; the first reported in 1997,⁴ and the second in 2007. Currently, we report on a recent reaction involving a 67-yr-old male patient who had been repeatedly treated with aprotinin-containing fibrin sealant who developed an anaphylactic reaction after systemic aprotinin administration for coronary artery bypass graft (CABG) surgery.

CASE DESCRIPTION

A 67-yr-old male patient (1.75 m; 82 kg) was transferred to our department for surgical therapy of peripheral arterial occlusive disease. The patient had a history of arterial occlusive disease since 1984. Multiple surgical interventions preceded the current hospital admission for surgical therapy, including a femoral endarterectomy and femoral popliteal bypass.

On the first postoperative day (POD), he developed acute ischemia of the left leg, indicating a possible re-occlusion requiring an urgent second endarterectomy. Two milliliters of Tissucol Duo S Immuno (Baxter BioScience) fibrin tissue adhesive with an aprotinin dosage of 3000 kallikrein inhibitor units (KIU)/mL were used in both surgical procedures.

After the procedure, the patient was tracheally extubated and developed an acute cardiac low-output syndrome, and ventricular fibrillation, which required cardiopulmonary resuscitation. After successful resuscitation, the electrocardiogram showed a marked ST depression and the laboratory findings showed a creatine kinase total of 1170 U/L, creatine kinase-MB of 120 U/L and Troponin of 120 mg/mL, indicating an acute myocardial infarction.

After stabilization, the patient underwent coronary angiography which showed severe three-vessel coronary heart disease with a filiformic left main artery stenosis, left anterior descending stenosis, and right coronary artery stenosis. The patient was scheduled for urgent aorto-coronary revascularization using CPB.

⁴Scheule AM, Jurmann MJ, Wendel HP, Häberle L, Eckstein FS, Ziemer G. Anaphylactic shock after aprotinin re-exposure: time course of aprotinin-specific antibodies. *Ann Thorac Surg* 1997; 63:242–4.

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¹<http://www.fda.gov/cder/drug/infopage/aprotinin/default.htm>, accessed on April 1, 2008.

²<http://www.controlled-trials.com/ISRCTN15166455>, accessed on April 1, 2008.

³Beierlein W, Scheule AM, Dietrich W, Ziemer G. Forty years of clinical Aprotinin use: a review of 124 hypersensitivity reactions. *Ann Thorac Surg* 2005; 79:741–8.

Table 1. Protocol of the Anaphylactic Reaction and Surrounding Events

Time	Event
08:17	Induction of anesthesia with fentanyl, midazolam and rocuronium, intubation
08:21	Continuous application of norepinephrine 0,008 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (Arterenol®)
08:20–09:35	Further anesthesia preparation
09:40	Start of surgery
09:43	Sternotomy–patient ready for CPB
09:58	Injection of 2 million KIU aprotinin (Trasylol®) as infusion, pause of infusion after administration of 750.000 KIU due to severe anaphylactic shock stage III (bronchospasm, hypotonia, tachycardia)
Immediately after AR	High dose of norepinephrine (Arterenol) 0.650 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, fractional application of 8 ml (0.8mg) epinephrine (Suprarenin®) 1:10, 250 mg of prednisolon (Solu-Decortin®)
+15 min post AR	Aortic cannulation
+16 min post AR	CPB started
+39 min post AR	Injection of 1. Theophylline (Bronchoparat®) 200 mg 2. H ₁ -inhibitor: dimetidine (Fenistil®) 8 mg 3. H ₂ -inhibitor: cimetidine (Tagamet®) 400 mg into CPB
+48 min post AR	Second application of corticosteroids: 250 mg prednisolon (Solu-Decortin)
+1h 17 min post AR	Additional application of phosphodiesterase-inhibitors to increase chronotropic and inotropic support: milrinone 0,20 $\mu\text{g}/\text{kg}/\text{min}$
+1h 37 min post AR	Weaning from CPB (CPB time: 98 min, cross-clamp time 55 min, reperfusion time 17 min)
+2h 57 min post AR	Closure of thorax: extended hemostasis due to diffuse bleeding
+3h 17 min post AR	End of surgery, Transfer to intensive care unit

AR = adverse reaction; KIU = Kallikrein Inhibitor units; CPB = cardiopulmonary bypass circuit.

Having obtained the patient's informed consent, the patient was scheduled for CABG procedure.

During the CABG procedure, the patient developed a severe anaphylactic reaction from the IV dose of 750.000 KIU of aprotinin despite a negative test dose 5 min prior. After administration of aprotinin at 09:58 the patient's mean arterial blood pressure decreased from 80 mm Hg to <40 mm Hg, he developed tachycardia with heart rates of up to 110 bpm (base rate 65 bpm) and an increase in airway pressure (airway resistance).

The initial blood gas analysis demonstrated a doubling of lactate values from 0.7 mmol/L to 1.4 mmol/L, which steadily increased up to 18 mol/L on the day of operation, an elevated δ Pco₂ to 11.4 mm Hg (increase in dead-space

ventilation) and a rapid decrease of Po₂ to 58.4 mm Hg from 531.0 mm Hg (Fio₂ 1.0).

Table 1 outlines the timetable of the hypersensitivity reaction and provides more details. According to the current classification of anaphylactic and anaphylactoid reactions, this was a type III hypersensitivity reaction (acute life-threatening disease). We treated the anaphylactic shock immediately according to the manufacturer's (Bayer, Leverkusen, Germany) recommendations. The initial treatment after diagnosis included a colloidal solution hydroxyethyl starch 6% (Voluven®), an increased dose of norepinephrine (Arterenol®) of 0.650 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, 0.8 mg of epinephrine (Suprarenin®), 250 mg of prednisolone (Solu-Decortin®), and 10 mL of calcium gluconate-solution 10%.

After further stabilization of the patient's hemodynamics, we initiated CPB as soon as possible. After the start of CPB, we administered 200 mg of theophylline (Bronchoparat®), 8 mg of dimetidine (Fenistil®) and 400 mg of cimetidine (Tagamet®). An additional dose of 250 mg of prednisolone (Solu-Decortin) was administered 48 min after the adverse reaction to attenuate the late phase of his allergic reaction.

Postoperatively, we reviewed the patient's the medical history for any risk factors for his anaphylactic reaction. He had been treated previously with aprotinin-containing fibrin sealant (Tissucol Duo S Immuno, Baxter BioScience) during at least three surgical procedures, two of which were performed during his current hospital admission (2 wk before CABG) and one was performed in 2004. The patient received 2 mL Tissucol Duo S Immuno containing 3000 KIU/mL each time.

Several blood samples (serum) acquired after the adverse reaction to aprotinin were analyzed using the UniCAP/ImmunoCAP Immunoassay (Phadia AB, Uppsala, Sweden)^{2,3} for quantitative measurement of aprotinin-specific IgE, the CellTrend enzyme-linked immunosorbent assay (EIA, CellTrend GmbH, Luckenwalde, Germany) for quantitative measurement of aprotinin-specific IgG and a test for qualitative measurement of aprotinin-specific IgG. The results of the qualitative and quantitative measurements of the 10 samples and a positive control sample are displayed in Table 2.

Qualitative IgG-Measurement

The patient tested far above the positive classification mark in all 10 samples with optical densities (OD, quotient of OD of patient sample and OD of a negative sample).

Quantitative IgG-Measurement (CellTrend EIA)

The quantitative measurement confirmed the qualitative results by showing values higher than upper cut-off of 200 U/mL in 7 of 10 samples and values of 183 (60 min after administration), 173 (180 min after administration), and 153 U/mL (POD 3) in the other three samples.

Quantitative IgE-Measurement (UniCAP)

The samples from the day of surgery (10 min after administration of aprotinin: 1.17 kUA/L, 60 min after administration: 0.86 kUA/L, 120 min after administration: 0.96 kUA/L and 180 min after administration: 1.05 kUA/L) and POD 3 (1.24 kUA/L) showed moderately elevated levels of aprotinin-specific IgE antibodies.

Low levels of aprotinin-specific IgE antibodies were detected in the samples from 14th (0.43 kUA/L), 17th (0.45 kUA/L) to 24th (0.42 kUA/L) POD. The sample forwarded to us by the general practitioner from the 57th POD and the sample made during an ambulatory admission of the patient on the 77th POD showed equivocal levels of aprotinin-specific IgE (<0.35 kUA/L).

DISCUSSION

According to the current classification of anaphylactic and anaphylactoid reactions the patient had a stage III hypersensitivity reaction (acute life-threatening disease).

Table 2. Qualitative Measurements of IgG (quotient between optical density (OD) of Patient Sample and OD of Negative Control, classified pos >3), quantitative measurement of IgG (mgA/L) and IgE (kUA/L = kilo units of aprotinin-specific antibodies per L, classification according to the UniCAP specific IgE alternative scoring method (ASM): 0/1 [0.22–0.31 = equivocal/low], 1 [0.31–0.55 = Low], 2 [0.55–1.4 = Moderate], 3 [1.4–3.9 = High], 4 [3.9–19 = Very High], 5 [19–100 = Very High], 6 [>100 = Very High]^{a,b})

No	Description	Day	Qualitative IgG		Specific IgE (mgA/L)	Specific IgG (kUA/L)	Class
			Quotient	Result			
—	Positive control	—	n.a.	n.a.	n.a.	38.4	4
1	10 min after administration	Day of surgery	40.68	pos	>200	1.17	2
2	Approximately 60 min after administration	Day of surgery	19.76	pos	183	0.86	2
3	Approximately 120 minutes after administration	Day of surgery	21.86	pos	>200	0.96	2
4	Approximately 180 min after administration	Day of surgery	13.7	pos	173	1.05	2
5	Serum sample	3rd POD	23.94	pos	153	1.24	2
6	Serum sample	14th POD	34.81	pos	>200	0.43	1
7	Serum sample	17th POD	38.51	pos	>200	0.45	1
8	Serum sample	24th POD	36.22	pos	>200	0.42	1
9	Sample from GP	57th POD	37.28	pos	>200	<0.35	0
10	Serum sample ambulatory admission	77th POD	35.79	pos	>200	<0.35	0

^a Leimgruber A, Mosimann B, Claeys M, Seppely M, Jaccard Y, Aubert V, Peitrequin R, Nisoli MP, Pécoud A. Clinical evaluation of a new *in vitro* assay for specific IgE, the immuno CAP system. Clin Exp Allergy 1991;21:127–31.

^b ImmunoCAP Specific IgE 0–100 Directions for Use. Phadia AB, Uppsala, Sweden, 2005.

POD = postoperative day.

Although case reports of anaphylactic reactions⁴ caused by IV administration of aprotinin^{5–7} or fibrin sealant^{8,9} are common, publications about a possible sensitization through fibrin tissue adhesives, which subsequently trigger an anaphylactic reaction when IV aprotinin is administered, are rare. The risk of developing an anaphylactic reaction after re-exposure is highest in the first month after exposure and declines considerably after 12 mo. Therefore, re-exposure to systemic aprotinin is contraindicated for the first 12 mo after initial exposure. Although the marketing of systemic aprotinin is currently suspended until a comprehensive review of the Canadian BART study has been performed, the use of aprotinin-containing tissue adhesives should be evaluated.

Our patient had been repeatedly treated with aprotinin-containing fibrin sealant, yet did not develop a hypersensitivity reaction after topic re-exposure to aprotinin-containing fibrin sealant before the CABG surgery. However, after the systemic application of 750,000 KIU of aprotinin he suffered anaphylactic shock. The serological measurements demonstrate an aprotinin-specific IgE rapid decline that was previously reported.^{10–12} However, aprotinin-specific IgG remain at high levels throughout the testing period of 11 wk; an interesting finding, as the literature suggests that IgG decreases over time.^{10–12} This could be explained by the resensitization as a result of administration of several doses of aprotinin within a short period of time, which may have induced additional antibody stimulation.

The use of fibrin sealants is commonly practiced in multiple surgical patient populations. Thus, in cases of repetitive surgery the probability of previous exposure to fibrin sealant and/or other aprotinin-containing solutions such as Trasylol is increased.

To avoid an adverse life-threatening anaphylactic reaction, we suggest that any treatment with aprotinin during the previous 12 mo should be considered a contraindication for the use of aprotinin, as also noted in current Food and Drug Administration guidelines.¹³ Additional immunologic testing to determine aprotinin-specific IgG antibodies may need to be developed pending the fate of aprotinin in clinical use.

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