

An immediate, allergic skin reaction to aprotinin after reexposure to fibrin sealant

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BACKGROUND: The safety of fibrin tissue adhesives has been a concern since they entered wide clinical application. Most commercially available kits contain the proteolytic inhibitor, aprotinin, to stabilize the fibrin clot. A bovine protein, this substance has an allergenic potency.

CASE REPORT: This case report presents a patient who had a generalized allergic skin reaction, probably triggered by aprotinin upon reexposure to fibrin sealant injected subgaleally to achieve closure of a liquor fistula after neurosurgical treatment. The serologic investigation revealed aprotinin-specific IgE and IgG. From 1990 through 1998, reports of five allergic reactions following 1 million exposures to fibrin sealant were made to the manufacturer. The clinical relevance of allergic reactions to aprotinin contained in fibrin sealants and measures to avoid them are discussed.

CONCLUSION: These hypersensitivity reactions are extremely rare (incidence, 0.5/100,000 for all reactions and 0.3/100,000 for serious reactions), but they must be kept in mind as possible adverse events after repeated applications of fibrin sealants within a few weeks.

Fibrin tissue adhesives are used to restore tissue integrity in many neurosurgical, other surgical, and nonsurgical procedures.^{1,2} While commercially available preparations of biologic sealants have entered wide clinical application in Europe since the late 1970s, such ready-made kits based on fractions of pooled human plasma were approved by the United States FDA for the first time in 1998.

Fibrin tissue adhesives imitate the terminal stretch of the coagulation cascade and form a clot immediately after mixture of the thrombin and fibrinogen components. European formulations usually contain small doses of the proteinase inhibitor, aprotinin, to inhibit early fibrinolysis *in vivo*.³ A foreign protein isolated from cattle lungs, this substance bears the risk of immunization of the recipient.⁴ Although the use of fibrin tissue adhesives is increasing, only a very few cases of adverse reactions to the aprotinin component have been reported.⁵⁻⁸

CASE REPORT

A 48-year-old woman with two cerebral metastases of breast cancer, one located in the left frontotemporobasal region and the other in the left insular region, underwent surgery for extirpation of both tumors. Postoperatively, a liquor fistula with subgaleal liquor accumulation developed at the operation site and was treated by lumbar drainage and pressure dressing. After removal of the drainage system, the subgaleal liquor mass required repeated punctures. Twenty-nine days after the operation, 4 mL of fibrin sealant (Tissucol, Immuno GmbH, Heidelberg, Germany), containing 6000 kallikrein-inhibiting units of aprotinin, was injected into the cavity after 12 mL of liquor had been removed by puncture. Twenty-one days after the first application, another 4 mL of fibrin sealant was injected following liquor drainage.

About 30 minutes after the second application, the patient complained about pruritus and presented with generalized allergic exanthema. There was no circulatory impairment. The skin reaction was treated with 250 mg of prednisolone hydrogen succinate and 4 mg of dimethindene maleate, both given intravenously. After 2

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hours of uneventful observation, she was discharged from the outpatient clinic and sent home. The exanthema disappeared on the same day. Before the reaction, she had received no medication other than the fibrin sealant, and no history of allergic disease had been reported.

Her history comprised radical mastectomy with subsequent radiation and chemotherapy at the age of 41 years, extirpation and radiation of a brain metastasis in the left frontobasal region 4.5 years thereafter, and gamma-knife radiation of a local recurrence of the brain metastasis an additional 20 months later. After another 10 months, the two recurrent brain metastases once more required surgical intervention. Neither fibrin sealant nor other products containing aprotinin were administered during these interventions.

MATERIALS AND METHODS

A serum sample obtained 34 days after the reaction was examined for aprotinin-specific IgE, IgG, and IgA by means of an automated fluorescence EIA (FEIA, UniCAP, Pharmacia & Upjohn, Uppsala, Sweden) and a standard ELISA, respectively. ELISAs were performed as described previously,⁹ using as a positive reference the serum of a patient presented in Scheule et al.¹⁰ and as negative controls the sera of healthy volunteers without contact with aprotinin (dilution in 0.9% sodium chloride solution, 1-in-100 for IgG and 1-in-500 for IgA). A γ -chain-specific alkaline phosphatase-conjugated goat anti-human IgG (Sigma, St. Louis, MO) and an α -chain-specific peroxidase-conjugated goat anti-human IgA (Jackson Immuno Research Laboratories, West Grove, PA) were used in dilutions of 1-in-10,000 and 1-in-3,000, respectively. Evaluation of IgG and IgA was performed in a semiquantitative fashion, as established standards are currently lacking.

RESULTS

The results of testing for antibodies are detailed in Table 1.

Diagnosis in our patient and assessment of causality

The characteristic symptoms of generalized allergic skin reaction appeared about 30 minutes after reexposure to aprotinin. No other potential allergens were administered at this time. In the absence of aprotinin-specific IgA, formation of cross-reacting antibodies against nutritional bovine proteins seems to be rather unlikely. Immunization of the recipient due to exposure to other bovine products, such as cosmetics, cannot be ruled out but seems also to be improbable. As no serum samples were saved before the onset of the reaction, preexisting immunization can only be speculated on. Therefore, the presence of aprotinin-specific antibodies 34 days after reexposure provides strong evidence of immunization on the occasion of the first contact with aprotinin 21 days before the adverse skin reaction.

There was a reasonable temporal relationship between the second administration of fibrin sealant and the onset of the allergic skin reaction. Alternative causes—in particular, concomitant allergenic medication—were excluded. There was no exposure to aprotinin in the past 7.25 years, which included a mastectomy, until the first fibrin sealant injection for treatment of liquorrhea. Exposure to aprotinin before mastectomy is unknown, although unlikely, as the medical history does not include antecedent operations. Strong evidence of the biologic plausibility of this reaction emanates from previous reports on allergic or anaphylactic reactions following reexposure to aprotinin⁵⁻⁸ and from the demonstration of aprotinin-specific antibodies at the time of serum sampling 5 weeks after the event. Furthermore, the 3-week span between the first and second application is enough to allow the formation of antibodies, which indicates previous immunization to aprotinin, most probably by the first fibrin sealant application. However, definite confirmation by positive reexposure is lacking. According to the World Health Organization criteria for the assessment of causality of adverse drug reactions,^{21,22} the causal relationship has to be classified as “probable.”

DISCUSSION

Fibrin tissue adhesives

Fibrin tissue adhesives have been in clinical use since the late 1970s.¹³ In 1994, European producers sold most fibrin sealant for use in general and cardiothoracic surgery, neurosurgery, and gastroenterology. Neurosurgical applications comprise closure of cerebrospinal fluid leaks, sealing of vascular anastomosis sites, reinforcing of aneurysmal clippings and peripheral nerve anastomoses, and hemostasis after resection of brain tumors. Experiences with fibrin sealant as a matrix for local delivery of chemotherapy were promising.^{1,2}

Currently, the protein components of the most frequently sold fibrin tissue adhesives are of human origin, with the exception of aprotinin. Until the early 1990s, most formulations of fibrin tissue adhesives were prepared with bovine thrombin, and some still are. The risk of allergic reactions to this bovine component has remained unknown: there are only a few reports.¹⁴

Aprotinin

This polyvalent proteinase inhibitor has been in clinical use since the early 1960s. Initially, high IV doses were administered to treat acute pancreatitis.¹⁵ Currently, aprotinin is mainly used intravenously in cardiac surgery for its beneficial effect on the perioperative blood loss and (probably) on the systemic inflammatory response to cardiopulmonary bypass.¹⁶ However, in Europe, more patients come into contact with aprotinin as a component of commercially available fibrin tissue adhesives; this may occur in North America in the future.

TABLE 1. Spectrum of aprotinin-specific antibodies

	Fluorescence EIA:		ELISA			
	IgE*		Total IgG†		IgA†	
	kU _A /L	Classification	OD	Intensity	OD	Intensity
Patient	1.84	2	2.262	+	0.094	—
Positive control‡	1.58	2	1.975	+	0.468	(+)
Cutoff§	0.35	0	0.033	—	0.245	—

* Kilo units of aprotinin-specific IgE per L; classification according to the conventional RAST kU_A/L = k classes: 0 = absent or not detectable (<0.35 kU_A/L), 1 = weak (<0.7), 2 = moderate (<3.5), 3 = high (<17.5), 4 = very high (>17.5).^{11,12}

† All determinations performed in duplicate; intensity expressed as arbitrary classes: — = absent or not detectable (OD < cutoff), (+) = weakly positive (OD < 3 × cutoff), + = positive (OD > 3 × cutoff).

‡ IgE, IgG: patient presented in Scheule et al¹⁰; IgA: patient negative for IgE and weakly positive for IgG.

§ Cutoff: fluorescence EIA according to other investigators.^{11,12} ELISA: IgG and IgA: mean plus 3 SD of 20 (IgG) and 10 (IgA) sera obtained from healthy volunteers without contact with aprotinin.

Aprotinin and immunogenicity

A foreign protein, composed of 58 amino acid residues with a molecular weight of 6512 Da, aprotinin can induce an immune response.⁴ The active region of the aprotinin molecule represents the main immunogenic epitope.¹⁷ Hypersensitivity reactions occur in about 2 percent of patients upon IV reexposure.¹⁸ Small doses of aprotinin as administered to the patient in this case report are immunogenic in up to 39 percent of pediatric patients after a single exposure during cardiac surgery.⁹

Reviewing 44 published case reports, we found that 30 anaphylactic reactions (68%) occurred within 3 months of previous exposure, a time lapse that is congruent with the clinical events in our patient. Twenty-eight (93%) of these reactions occurred upon IV administration of aprotinin, but only two (7%) happened upon the application of fibrin sealant, which indicates that the incidence of manifest reactions is much lower for local applications of small doses of aprotinin.

Immediate hypersensitivity reactions are caused by histamine release from mast cells due to binding of two surface-bound IgE antibodies.¹⁹ By involvement of the complement system, antibodies of the IgG class can trigger reactions that are clinically undistinguishable from anaphylaxis.²⁰ The clinical presentation ranges from local edema, cutaneous, and gastrointestinal symptoms to respiratory and circulatory arrest.

Incidence and clinical implications

Since the beginning of computerized registration of adverse drug reactions in 1990, five reports from Germany (including this case) of allergic and anaphylactic reactions at least possibly related to the administration of Tissucol have been made to the manufacturer. Of these, three reactions were serious, but none was associated with death. In relationship to about 1 million Tissucol exposures (average dose, 1.3 mL/administration) between January 1990 and June 1998, the

incidence is 0.5 per 100,000 applications for all allergic and anaphylactic reactions and 0.3 per 100,000 applications for serious reactions. Even in a worst-case scenario, assuming that 90 percent of the reactions had not been reported, the projected incidences were as low as 5 and 3 incidents, respectively, per 100,000 applications. This illustrates that hypersensitivity reactions upon Tissucol administration are extremely rare.

This case report indicates that patients with specific antibodies may have an increased risk for allergic or anaphylactic reactions if reexposed to aprotinin within a few weeks. Because the predictive value of skin tests is doubtful,¹⁸

screening for aprotinin-specific antibodies may provide a more conclusive alternative. This test should not be applied uncritically to every patient intended to receive aprotinin, but it could be useful in identifying individuals with an increased risk for allergic or anaphylactic reactions among those patients who had a definite or possible contact with aprotinin during the past few months. Thus, a meticulous documentation of any use of drugs containing aprotinin may contribute to the prevention of adverse drug reactions.

Immediately after hypersensitivity reactions, aprotinin-specific antibody tests may become negative for at least a few days.¹⁰ If clinical suspicion of a reaction arises, testing should be performed on a serum sample obtained before the reaction, if available, or on serum collected after an interval of several weeks. In patients with aprotinin-specific antibodies or with a documented history of recent IV or local aprotinin exposure, the risk of an allergic or anaphylactic reaction upon reexposure should be carefully balanced with the expected benefit. The risk of such a reaction is extremely low, but it has to be kept in mind, especially in cases of repeated applications within a few weeks.

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