

Forty Years of Clinical Aprotinin Use: A Review of 124 Hypersensitivity Reactions

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Since its clinical introduction, the anaphylactic potential of aprotinin has been a major concern. World wide, its use is expanding so there is an increased chance that patients have reexposure from various sources. The risk of anaphylaxis is approximately 2.8% in reexposed patients. From 1963 to 2003, 124 cases of aprotinin-induced anaphylaxis were reported in 61 publications. Eleven

patients died. The reexposure interval was less than 3 months in 72% (38 of 53 patients). This review looks at the profile of patients at risk so preventive measures may be taken. Past and future exposures have to be taken into account before any aprotinin administration.

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Aprotinin was isolated due to its kallikrein and trypsin inhibiting effect in the 1930s [1, 2] and is in clinical use since 1959 [3]. By inhibiting fibrinolysis and preserving platelet function, aprotinin was shown to reduce blood loss and transfusion requirements in cardiac surgery [4, 5], lung [6], and liver [7] transplantations, and surgery for hip replacement [8]. Further disease related indications are hyperfibrinolytic hemostatic disorders and complications of thrombolytic therapies [9]. An early indication was treatment of acute pancreatitis [10], which is no longer valid.

In the 1970s, aprotinin was introduced to cardiac surgery in Europe [11]; however, in the United States, the drug is approved for intravenous application only since 1993 [12]. The most common commercially available preparations are Trasylol (Bayer AG, Leverkusen, Germany) and Antagosan (Aventis Pharma, Frankfurt/M, Germany).

Due to its antifibrinolytic action, aprotinin is added to fibrin sealants in order to achieve hemostasis even when fibrinolytic activity is increased [13]. Ready-to-use fibrin sealant kits have been commercially available in Europe since 1974, and in the United States since 1998. The most common kits are Beriplast (Centeon, Marburg, Germany), Tissucol/Tisseel (Baxter Hyland Immuno Division, Vienna, Austria), and Hemaseel (Hemacure, Montreal, Canada). TachoComb (Nycomed, Roskilde, Denmark), a hemostatic solid equine collagene fleece, also contains a small amount of aprotinin.

Aprotinin is a bovine protein, composed of 58 amino acid residues with a molecular weight of 6,512 Daltons. Since aprotinin can induce hypersensitivity reactions [14, 15], its anaphylactic potential has remained a concern since its clinical introduction. Other side effects like

thrombogenicity and nephrotoxicity are thought to be of limited clinical relevance [16]. The aim of this review, including our own experience, is to define the clinical and serological profile of patients at risk for aprotinin-induced hypersensitivity reactions and to define preventative guidelines.

Material and Methods

Patients

LITERATURE SEARCH. A medline search (1963 to 2003, free text mode, all languages) employing the key words “aprotinin AND (hypersensitivity OR allerg* OR anaphyla*) AND (TG = “human”)” were aimed at publications presenting reports of aprotinin-induced adverse reactions. The search was supplemented by a review of the literature cited in these publications.

The dichotomic characteristics (present-absent) and numeric data available from each publication were collected in a Microsoft-Excel-database (Microsoft Corp, Redmond, WA). These were, in particular, the following: year and type of publication; geographic origin; patients demographic and medical data; clinical features such as application mode (intravenous [IV] or local); history of former aprotinin exposures; and the time interval of these applications. The symptomatology reported served to reclassify the reactions according to the Ring and Messmer severity scale for quantification of intensity of anaphylactoid reactions [17]. Further items of interest were the type and results of prophylactic and diagnostic measures.

REEXAMINATION OF FIVE PATIENTS WITH KNOWN ANAPHYLACTIC REACTION TO APROTININ. Five patients who suffered from anaphylaxis as a result of aprotinin administration, were reexamined, employing serologic tests and histamine release test. Three patients were presented by Dietrich and colleagues [18], a fourth by Schuler and colleagues

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CPB	= cardiopulmonary bypass
ELISA	= enzyme linked immunosorbent assay
ENT	= ear nose throat
FEIA	= fluorescence enzyme immunoassay
HRT	= histamine release test
IV	= intravenous
IgA, IgE, IgG	= immunoglobulin A, E, G
KIU	= kallikrein inhibiting unit
kUA/L	= kilo units of aprotinin-specific IgE per liter
LVAD	= left ventricular assist device
OD	= optical density
RAST	= radio allerge sorbent test
ref.	= reference

[19], and the fifth by Scheule and colleagues [20]. Informed consent for participation in this study was obtained from each patient or their parents, respectively, in conformity with the Helsinki Declaration.

SEROLOGY. Serum samples were analyzed for aprotinin-specific immunoglobulin A (IgA), E (IgE), and G (IgG). Immunoassays (enzyme linked immunosorbent assay, ELISA; fluorescence enzyme immunoassay, FEIA: UniCAP, Pharmacia&Upjohn, Uppsala, Sweden) were performed as described in former publications [20, 21].

HISTAMINE RELEASE TEST. A commercially available whole blood histamine release test (HRT; histamine enzyme immunoassay No. 1153, Coulter-Immunotech, Marseille, France) was employed according to the directions for use.

STATISTICAL ANALYSIS. Values assumed to be distributed binomially are portrayed as means with standard deviation. Sensitivity, specificity, and positive and negative predictive values were calculated by means of a two-by-two frequency table according to Sachs [22]. The 95% confidence intervals were taken from the Documenta Geigy Scientific Tables [23], or approximated according to Sachs [24], when not available from the tables. Counts within the whole group or subgroups were translated into descriptive graphs.

Results

The literature search provided 61 publications presenting 122 patients with 124 aprotinin-induced hypersensitivity reactions [3, 18-20, 25-81]. With the exception of two prospective trials presenting 11 cases [18, 80], all reports were retrospective. Figure 1 summarizes the results according to the categories of interest defined above.

Severity

There were 11 (9%) fatal reactions. Reported symptoms of hypersensitivity (n = 224, more than one symptom per

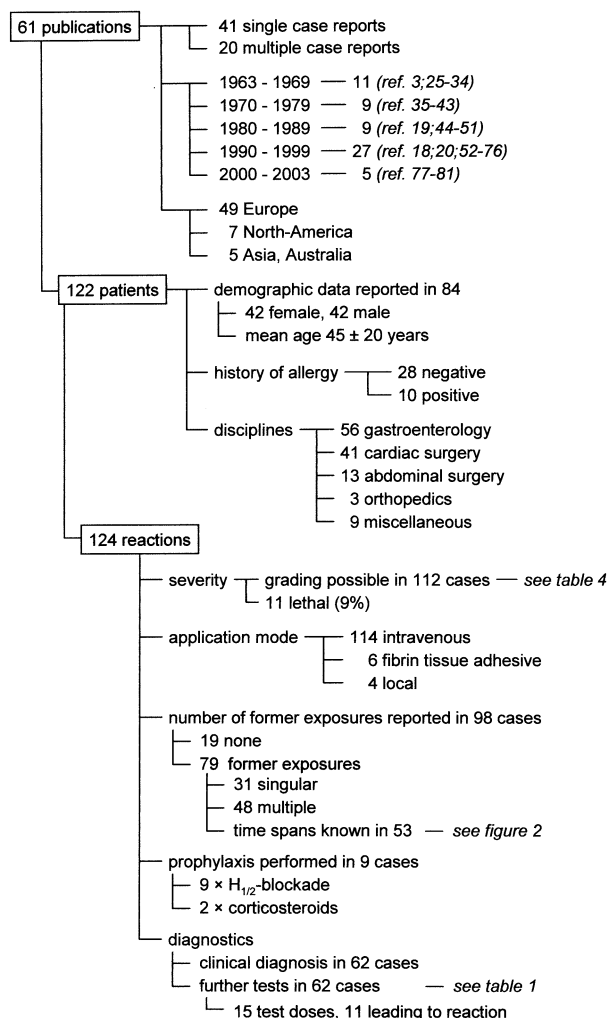


Fig 1. Results – synopsis.

patient) were cardiovascular (36.6%), cutaneous (27.2%), respiratory (17.4%), abdominal (7.6%), vegetative (5.8%), and neurologic (5.4%). In 12 patients, symptoms were not described.

Application Mode

In cardiac surgery, the Hammersmith regimen is generally used with a dosage of 6 million kallikrein inhibiting units (KIU) [4]. In gastroenterology, generally the regimen consisted of intravenous infusions of a few hundred thousand KIU over a few days [25, 48]. Daily aprotinin infusions over less than six days were counted as a single exposure because a measurable immune response cannot be expected within this time frame (8 patients [26;41; 42;45;48]). Occasionally, high aprotinin doses were instilled intraperitoneally in order to reduce the severity of postoperative peritoneal adhesions and the inflammatory response in acute pancreatitis [51, 82].

Former Exposures

Eighty percent of the patients had had previous exposure to aprotinin, 39% of them only once (Fig 1). There are

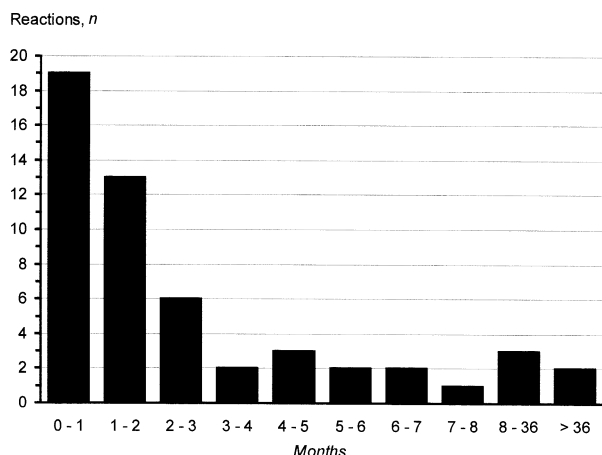


Fig 2. Time spans between repeated aprotinin exposures.

three other publications [18, 57, 67] reporting a total of 501 reexposures revealing an average anaphylactic risk of 2.8% (95% confidence interval: 1.5% to 4.7%).

Time Interval of Reexposure

Aprotinin-induced hypersensitivity reactions at reexposure accumulate during the first 3 months (Fig 2).

Prophylactic Medication

Despite antihistaminic prophylaxis, there were two life-threatening reactions in 9 patients (Fig 1).

Diagnostic Approaches

In 62 patients a total of 136 diagnostic tests were undertaken. Ninety-four tests were done after, 24 before, and

18 during the manifest reaction. They included 98 in vitro and 38 in vivo tests. The most frequently applied in vitro tests were measurements of aprotinin-specific IgE (positive in 27 of 46 [19, 20, 50, 54, 56, 58-60, 63, 65, 70, 72, 74, 76, 78-80]) and aprotinin-specific IgG (positive in 18 of 33 [3, 20, 28, 50, 65, 70, 71, 79, 80]) either before or after the reaction (Table 1). The remainder comprised intrareactive measurements of allergic mediators such as tryptase (positive in 4 of 5 [58, 60, 62, 68, 69, 76]), methylhistamine (positive in 5 of 5 [58-60, 76]), eosinophilia (positive in 2 of 2 [26, 35]), complement activation (positive in 2 of 2 [59, 63]), and postreactive mediator release tests such as the histamine release test (positive in 1 of 2 [59, 62], and the lymphocyte transformation test (positive in 1 of 3 [38, 62, 63]). The most frequently applied in vivo tests were skin tests (positive in 15 of 19 [3, 19, 25-27, 33, 37, 38, 51, 58, 59, 63, 72, 76, 78, 80]), and IV applications of a test dose (positive in 11 of 15 [18, 68, 69, 71, 75-77, 78, 80, 81]).

Assuming that each author performed technically equiquivalent tests, the pooled data from literature and the five reexamined patients result in the sensitivities summarized in Table 1. Table 2 presents additional diagnostic values for IgG, derived from two larger groups examined in earlier publications [21, 80].

Adverse Reactions in Cardiac Surgery

Forty-one cardiac surgery patients with 42 aprotinin-induced adverse reactions were reported. Nine patients were operated upon for congenital heart disease [18, 52, 54, 74, 80], nine for valvular disease [18, 58, 59, 61, 65, 70, 80], four underwent coronary artery bypass grafting (CABG) [18, 66, 75, 78], five were transplanted after implantation of a left ventricular assist device (LVAD) [67-69, 71, 81], and two each underwent aortic surgery

Table 1. Sensitivities of Screening Tests for Aprotinin-Induced Anaphylaxis in Patients With Manifest Allergy^a

Perspective ^b	Tests		Sensitivity	References
	Performed, n	Positive, n	% (95% Conf. Interval)	
In vitro				
Aprotinin-specific serum IgE				
Prospective	5	4	80.0 (28.4–99.5)	[54;70;80]
Retrospective	48	25	52.1 (37.2–66.7)	[19;20;50;54;56;58–60;63;65;70;72;74;76;78–80]
Aprotinin-specific serum IgG				
Prospective ^c	4	4	100 (39.8–100)	[70;80]
Retrospective	36	17	47.2 (30.4–64.5)	[3;20;28;50;65;70;71;79;80]
In vivo				
Skin test				
Prospective	3	0	0 (0–70.8)	[33;80]
Retrospective	17	16	94.1 (71.3–99.9)	[3;19;25–27;37;38;51;58;59;63;72;76;78;80]
Test dose				
Prospective	15	11	73.3 (44.9–92.2)	[18;68;69;71;74–76;78;80;81]

^a This table summarizes the data from the section Diagnostic Approaches (ie, the patients from literature) with those from the five reexamined patients (Table 3). Intrareactive tests and postreactive mediator release tests are not included; ^b Prospective designates a test performed before the manifest reaction, retrospective designates a test performed after the manifest reaction; ^c See also Table 2.

IgE = immunoglobulin E; IgG = immunoglobulin G.

Table 2. Evaluation of Aprotinin-Specific IgG Screening Before Exposure

	Aprotinin Exposures ^a , n			% (95% Confidence Interval)		Predictive Value	
	Total	IgG-Positive	Anaphylaxis	Sensitivity	Specificity	Positive	Negative
Dietrich and colleagues 2001 [80]	121	18	3	100 (29.2-100)	87.3 (80.1-92.1)	16.7 (3.6-41.4)	100 (97.4-100)
Scheule and colleagues 2000 [21]	448	15	1	100 (0-100)	96.9 (95.3-98.5)	6.7 (0.2-32.0)	100 (99.3-100)
Cumulative ^b	569	33	4	100 (39.8-100)	94.9 (92.7-96.4)	12.1 (3.4-28.2)	100 (99.3-100)

^a For reconstruction of the corresponding two-by-two frequency table consider that there was no patient with anaphylaxis in absence of aprotinin-specific IgG; ^b Cumulation limited by different group characteristics: all of Dietrich's patients had at least one documented former exposure, whereas Scheule's group comprised 244 patients with no, 194 with possible, and 10 with documented former aprotinin exposure.

IgG = immunoglobulin G.

[57] or sternal revision [60, 68, 69]. Surgery was not specified in 11 patients [53, 55-57, 64, 77]. Of the 38 cardiac patients with former aprotinin exposure, 24 had been exposed in previous cardiac surgery, seven during operations for congenital heart disease [18, 54, 80], seven during valvular operations [18, 58, 70, 80], six with LVAD implantation [67-69, 71, 81], two during aortic surgery [57], and one each during a combined CABG and valvular procedure [59] and a pericardiectomy [60]. One other patient had been previously exposed in otorhinolaryngology [65]. Thirteen preexposures were not specified. Twenty-eight reactions happened before institution of cardiopulmonary bypass (CPB). In 14 it is not stated whether CPB had been used or not.

Five Reexamined Patients

SEROLOGY. The serologic results are presented in Table 3. A skin test performed 10.5 years after anaphylactic reaction was positive in patient 4.

HISTAMINE RELEASE TEST. Aprotinin was not capable of inducing a significant rise of histamine concentrations in any whole blood sample.

Comment

Primary exposure to aprotinin is quite safe. Millions of doses have been administered over four decades with very few reported hypersensitivity reactions. Reexposure to aprotinin, however, carries a small, but significant risk of adverse reactions. This risk in the subgroup of reexposed patients is about 1.2% to 2.7% [15].

Aprotinin-induced hypersensitivity reactions lead to severe complications. More than half of the classified reactions were life-threatening (grade III-IV, 61 of 110, Table 4), and 9% of all were fatal (11 of 124, Fig 1).

Clinical Profile of Patients at Risk

Most of the recent reactions occurred in cardiac surgery at reexposures within three to six months. The following clinical features indicate an elevated risk for adverse reactions to aprotinin:

Former Exposures

The fact that more than 80% of reactions occurred in patients with former exposures clearly indicates the importance of this point. The history of each patient in

Table 3. Five Reexamined Patients: Clinical Data and Serologic Results

Table 1. FEIA, Reexamination, Patient Control Data and Serologic Results														
Patient			Anaphylaxis				FEIA		ELISA				Reference	
			Application	Severity ^b	Time Interval of		IgE ^c		IgG ^d		IgA ^d			
No.	Sex	Age ^a			Reexposure	Reexamination	kUA/L	RAST-class	OD	Intensity	OD	Intensity		
1	f	5	i.v.	II	29 d	4 yrs	<0.07	0	0.100	(+)	0.067	0	18	
2	m	7	i.v.	II	22 d/4 yrs	2 yrs	<0.07	0	0.078	0	0.102	0	18	
3	f	56	i.v.	II	19 d	8 m	0.36	1	0.014	0	0.046	0	18	
4	m	25	i.v.	III	4 m/2 yrs	10 1/2 yrs	0.29	0	0.028	0	0.152	0	19	
5	m	65	local	III	28 d/14 d	113/62 d	0.45	1	0.150	(+)	0.194	0	20	
						166/115 d	0.31	0	0.113	(+)				
						372/321 d	0.22	0	0.040	0				
Positive control ^e							1.58	2	1.975	+	0.468	(+)		
Cutoff ^f							0.07	0	0.080	0	0.245	0		

^a Years, at the time of reaction; ^b According to Ring and Messmer [17]; ^c kUA/L denominates kilo units of aprotinin-specific IgE per liter; RAST classes: 0 = absent/not detectable (<0.07 kUA/L) or very weak (<0.35), 1 = weak (<0.7), 2 = moderate (<3.5), 3 = high (>3.5); ^d OD denominates optical density, all determinations were performed in duplicate; intensity expressed as arbitrary classes: 0 = absent or not detectable (OD < cut-off), (+) = weakly positive (OD < 3 × cutoff), + = positive (OD > 3 × cutoff); ^e IgE, IgG: patient presented in Scheule and colleagues [70]; IgA: patient negative for IgE and weakly positive for IgG; ^f cutoff: FEIA according to the user's manual, augmented sensitivity ELISA: IgG and IgA: mean plus three standard deviations of twenty (IgG) and ten (IgA) serum samples obtained from healthy volunteers without exposure to aprotinin [21].

ELISA = enzyme linked immunosorbent assay; FEIA = fluorescence enzyme immunoassay; IgA = immunoglobulin, A; IgE = immunoglobulin E; IgG = immunoglobulin G; RAST = radio allegro sorbent test.

Table 4. Severity According to Ring and Messmer [17]

Grade	Symptoms	Patients, n (%)
I	Skin symptoms and/or mild fever reaction	23 (18.5%)
II	Measurable, but not life-threatening cardiovascular reaction (tachycardia, hypotension), gastrointestinal disturbance (nausea), respiratory disturbance	28 (22.6%)
III	Shock, life-threatening spasm of smooth muscles (bronchi, etc)	45 (36.3%)
IV	Cardiac and/or respiratory arrest	16 (12.9%)
Not classifiable		12 (9.7%)

whom aprotinin use is planned, should be thoroughly assessed for previous exposures. Since more than one third of the patients had only a solitary preexposure, aprotinin should be considered a potent allergen.

Disciplines

Since the late 1980s the main use of aprotinin is in cardiac surgery. In Europe, all patients undergoing repeat CABG or repeated surgery for congenital heart disease, valve repair procedures with consecutive valve replacement, or heart transplantation with prior LVAD implantation, have to be considered as preexposed, even when there is no record to be found. Patients from other surgical centers whose local aprotinin policy is unknown should also be considered as preexposed. In orthopedics, patients after consecutive bilateral hip replacements or early revisions have probably received aprotinin. Until the early 1980s aprotinin was mainly used for medical therapy of acute pancreatitis [10], but this is no longer an indication [12].

Application Interval

More than 95% of all reactions upon reexposure occurred within 36 months. Figure 2 clearly shows that there is a time dependency. Therefore, one may speculate that sensitization vanishes gradually over time. Long-term repeated measurements of aprotinin-specific antibodies support this interpretation [83].P>

There might be a certain number of well tolerated repeated exposures (48 patients with multiple exposures before reaction, Fig 1). In these cases sensitization probably required several booster stimuli, a phenomenon which is known from other allergies [84].

Application Mode

Intravenous application seems to have an elevated risk since 92% of all hypersensitivity reactions have been reported from patients who had received aprotinin intravenously at reexposure. Estimates on the general risk of allergy to the intravenously administered drug differ between less than 0.1% [11] and 5.8% [57]. The incidence of allergic reactions to the aprotinin component of fibrin tissue adhesives seems to be about 0.5 per 100,000 applications [79].

Pathophysiologic Considerations

Allergic and anaphylactic reactions are dose independent and require prior immunologic sensitization with formation of specific IgE antibodies [84]. The active region of

the aprotinin molecule represents its immunogenic epitope and is capable of inducing specific antibodies [85]. The incidence of specific serum-IgE is about 14% within the first three months postexposure [83]. This is the same time frame in which the majority of adverse reactions is observed (Fig 2). Seropositivity was transient in the few patients observed so far (Scheule and colleagues [83] and patient 5, Table 3).

It has been assumed that IgG can trigger hypersensitivity reactions by involving the complement system [86]. Cases in which patients had experienced an adverse reaction in the presence of high concentrations of antiaprotinin IgG antibodies support this theory [80].

Pseudoallergic and anaphylactoid reactions are clinically indistinguishable from allergy and anaphylaxis. They are triggered by either a direct drug action on the effector cells or a drug induced mediator release. This pathology must be considered in the 20% of patients without former aprotinin exposure.

Diagnostic Approaches

HISTORY. Former exposures by far represent the major risk factor for aprotinin-induced hypersensitivity reactions and must therefore be carefully searched for in each individual's history, especially previous surgical and medical treatments. In Europe, each patient with a history of cardiac, major orthopedic, or upper abdominal surgery has to be considered to have had previous aprotinin exposure. In a population of patients undergoing cardiac surgery we found 4% to have preformed aprotinin-specific IgG. Most of these patients had a history of cardiac or ear, nose, or throat operations [21]. A remark "aprotinin used" or "not used" in the surgical record or the discharge letter would be beneficial for the hospital team [87].

SEROLOGY. Aprotinin-specific serum-IgG is detectable in about 50% of patients having received only one aprotinin treatment [21, 85, 88]. These IgG antibodies may persist for several years, as in two of the five reexamined patients (Table 3). Before reexposure, any patient with a documented or possible former aprotinin exposure should be screened for aprotinin-specific antibodies. The absence of aprotinin-specific IgG indicates a low risk of a hypersensitivity reaction due to its excellent negative predictive value (Table 2). All other prospective diagnostic tests as shown in Table 1 have large confidence intervals, making their clinical value questionable. When

performed after a clear-cut reaction, antibody screening tests have lower sensitivities than tests performed before (Table 1). This phenomenon can be attributed to an immediate postreactive seroconversion as observed in two patients [54, 70], or by a test performed too late; ie, when transient sensitization has vanished after several months.

At the present time, the former "home-made" screening tests have been replaced by commercially available, certified, and standardized quantitative tests for aprotinin-specific IgE and IgG antibodies (Pharmacia, Uppsala, Sweden; CellTrend, Luckenwalde, Germany). Quantitative testing seems to be advisable, as in the largest reexposure study, in which only patients with a high antibody titer developed an anaphylaxis [80].

OTHER TESTS. Preoperative skin tests are not predictive and therefore should not be used as a clinical indicator. Retrospectively, they work well, possibly due to the antibody triggering effect of the preceding exposure to the allergen. Intravenous test doses, usually 10,000 KIU, appear to be more prognostic (Table 1) but they also have the potential to trigger acute reactions [18, 74, 75, 80, 81]. It is unknown whether the dosage influences the severity of a reaction. A test dose should therefore only be administered once the surgeon is ready for cannulation. Although not without risk, test dose requirements have the important psychological effect of keeping in the anesthesiologist's mind that aprotinin has to be administered with care.

The diagnostic reliability of in vitro mediator release tests cannot currently be assessed due to the heterogeneous methods and their inconsistent results. The complexity of these methods will render it difficult to integrate them into a prospective screening program at present.

PROPHYLACTIC MEDICATION. H₁, H₂ antagonists and corticosteroids are considered an important part of any perioperative regimen to prevent anaphylaxis. In some instances, a prophylactic regimen may not be effective, as in the nine cases in which a reaction occurred despite pretreatment (Fig 1). The outcome in case of anaphylaxis, however, is favorable with a combined prophylactic therapy. These drugs should be added to therapy at the discretion of the physician in charge [89].

WHAT TO DO BEFORE ADMINISTERING APROTININ? The flowchart in Figure 3 demonstrates the steps to take before applying aprotinin. Generally, possible past and future operations with aprotinin exposure should be taken into account according to their probability, bleeding risk, and time lapse in between treatments. In operations without cardiopulmonary bypass, aprotinin reexposures should be avoided within at least six months. One might even suggest 36 months, which, however, seems to be overprotective. At any later date, a negative antibody screening test may ease the decision to reuse aprotinin.

SPECIAL PREVENTATIVE MEASURES IN CARDIAC SURGERY. In cardiac surgery, cardiopulmonary bypass is readily available

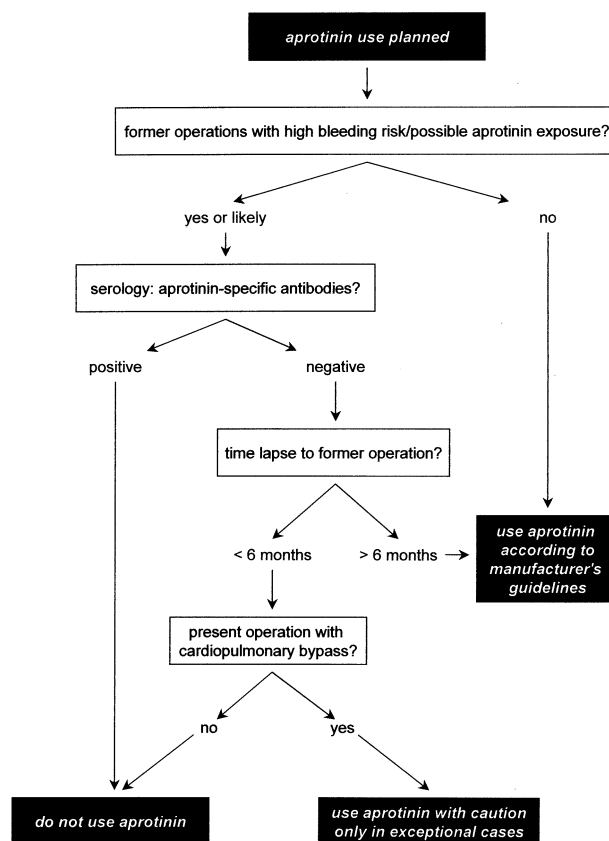


Fig 3. Decision making.

to assist resuscitation in the event of an unexpected anaphylactic reaction. In many severe reactions, aprotinin was administered before the skin incision, and the outcome was seriously affected by delayed onset of extracorporeal circulation. Therefore, aprotinin should only be administered when the cannulation sites for cardiopulmonary bypass are exposed [67]. The loading dose should be added to the priming volume of the extracorporeal circuit only after the test dose is well tolerated.

Aprotinin use should be avoided in all patients undergoing staged palliation of congenital heart disease requiring early reoperation. The same is true for patients receiving LVADs as heart transplantation may soon follow. Valve replacement and CABG procedures are less prone to require repeat surgery within a few months, allowing more liberal use of aprotinin.

LIMITATIONS. The present review is based on details from papers published during the past forty years. A large number of adverse reactions may not have been published and therefore cannot be included in this evaluation. Aprotinin was used for different purposes and in different formulations over time. This diversity is taken into account by a strictly dichotomic and numerical evaluation of the sources (for example: yes/no, time intervals) and by relating subaspects only to the respective subsets of data.

Conclusions

Hypersensitivity reaction to aprotinin is a rare event. The risk in the subgroup of reexposed patients is approximately 2.8%. Patients with repeated intravenous exposure within three to six months seem to be the highest risk group. Most cases reported can be attributed to a transient immunologic sensitization. Taking the patient's history with focus on recent potential aprotinin exposures and screening tests for aprotinin-specific antibodies can identify individuals at risk. Therefore, each patient's actual or possible past and future aprotinin exposures should be taken into consideration before aprotinin is considered. The physician in charge should be prepared for emergency measures when aprotinin is used.

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