

Anaphylactic and Anaphylactoid Reactions

Clinical Presentation

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INTRODUCTION

The frequency of anaphylactoid reactions (AR) to iv anesthetics is calculated, according to the gravity of the symptoms, as being from 1/5000 to 1/7000 anesthetized patients (1,2). At present, anaphylactoid accidents contribute to the anesthetic morbidity and mortality rate, since at least 6% are fatal and some cause a postanoxic vegetative coma (3). Such an evolution should remain an exception if adequate treatment is given immediately. Ninety percent of allergic reactions caused by anesthetic products and their adjuvants, brought on during general or local anesthesia, are of type I, immediate, appearing in the first 10 min after the iv injection of the substance (4–6).

Watkins has suggested the term anaphylactoid shock (AS), without pretending to judge what the nature of the mechanism might be. Indeed, besides anaphylaxis, nonspecific histamine release and nonimmunological activation of the complement are other possibilities (7,8). Identical reactions, occurring 30 min to 2 h after injection, point *ipso facto* toward an allergy to latex (9).

Table 1
Relative Frequency of Clinical Signs
During Peranaesthetic Anaphylactoid Shocks

	Laxenaire et al. (2) <i>n</i> = 154, %	Facon et al. (14) <i>n</i> = 96, %
Collapsus	92	77
Tachycardia	94	—
Bradycardia	6	—
Cardiac arrest	14	2
Cutaneomucous signs	79	52
Bronchospasm	39	24

Delayed reactions in the days following the general anesthesia take the form of a rash, a high temperature, arthralgia, asthenia, general physical discomfort, and may even be eczematous or urticarial. These forms are very rare, and their mechanisms are little known since they are only exceptionally studied. The responsibility of preservatives and solvents may be in question here (10–12).

CLINICAL REACTIONS

Cutaneomucous, cardiovascular, and bronchial signs, either isolated or associated, are the dominant features (2,4,8,13). Their frequency is variable (Table 1) (2–14).

Cutaneomucous Signs

Cutaneomucous signs are often the first warning signals. They can be preceded by prodromes if the subject has not yet fallen asleep: itching, burning, pins and needles, tingling, and so on. Then a lobster-red erythematous eruption appears in the areas richest in mast cells: the neck, the upper breast, and the face. Sometimes it is a maculopapulous erythema, or a local or general urticaria. This eruption may remain local or become general in a few minutes.

A cutaneomucous edema is less frequent. It occurs after the erythema and may only affect the patient upon awakening. It infiltrates the subcutaneous tissue and mucosae. It most often affects the eyelids and the lips, but may affect the tongue, the respiratory tract, the hands, and even become generalized.

Accompanying signs are often noted: runny eyes, rhinorrhea, and conjunctival hyperemia. The cutaneous symptoms are the result of the effects of histamine, leukotriens, and prostaglandins. They may be nonexistent during severe collapsus. There is no more cutaneous vascularization, so the systemic histamine is not transported there. The allergenic substances, furthermore, do not reach the cutaneous mast cells in the dermis, which consequently do not degranulate. When blood pressure rises again and the skin is normally irrigated, the erythema appears.

Respiratory Signs

Respiratory signs are present in one-third of cases, in the form of a dry cough, a tachypnea, a hypersecretion, or bronchospasm. The latter can occur before intubation, making insufflation of the lungs by means of a mask impossible, or after intubation when the patient is on a respirator. Then insufflation pressure rises, and the patient becomes maladjusted to the apparatus.

A pulmonary edema causing a syndrome of severe respiratory distress can also occur (15). Onset is generally late. Bronchoconstriction can be explained by the action of histamine on the H1 bronchial receptors. However, it is also linked to a vagal reflex induced by the stimulation of epithelial irritant receptors. It can be reduced by atropinization (16).

The other mediators play an important part—especially the leukotriens, which increase the effects of histamine on the smooth bronchial muscle, the PAF, and the anaphylatoxin C5a. Furthermore, the PAF and the anaphylatoxins C3a and C5a induce a hyperaggregability of blood platelets and leucocytes in the pulmonary capillaries. This can cause a pulmonary edema.

Cardiovascular Disorders

A severe collapsus is the dominant factor: blood pressure drops considerably or is unrecordable. Tachycardia is the rule (120–150 beats/min⁻¹). The pulse is hard to take and may sometimes only be perceptible in the main artery stems. Its total disappearance is not rare. Exceptionally, bradycardia may occur especially if the patient is treated with β -blockers (17,18).

Rhythm and conduction disorders are frequent and occur very early, since they can be noted in the 30 s following the onset of the shock (19): varied ectopic rhythms, lengthening of the PR space, auriculoventricular blocks of varying degrees, and even ventricular fibrillation (20,21). These rhythmic disorders occur more frequently in patients with preexistent cardiac diseases (21). Among these, the mitral valve prolapse (MVP) affects 2–4% of men and 17% of women (22,23). About 30% of these subjects present disorders of ventricular excitability, which are markedly more frequent than in a normal population (24). A study carried out in an anesthetic milieu on MVP sufferers showed no spontaneous arrhythmia (25). However, in the case of AS, MVP could make the cardiac dysfunction more serious (26). Transitory repolarization disorders go unnoticed in the absence of continuous electrocardiogram recordings. Because of these rhythmic disorders, some shocks immediately result in cardio-circulatory inefficiency.

Cardiac arrest is thus not exceptional. It is most often of anoxic origin, following a severe, irreducible bronchospasm or a prolonged shock: At first the shock is vasoplegic, but becomes cardiogenic subsequently. Anoxic cardiac arrest unquestionably worsens the prognosis of anaphylactic shock. It is responsible for 5% of deaths and irreversible cerebral lesions. Sometimes the cardiac arrest occurs first, a few dozen seconds after the injection of the drug. No bronchial or cutaneous sign accompanies it. It reveals cardiac anaphylaxis, which results from the wealth of the cardiac muscle in H1 and H2 receptors and mast cells (19). If the patient is highly sensitized, the cardiac muscle is endowed with sensitized mast cells and becomes the target organ for the antigen–antibody reaction, which occurs locally a few seconds after the arrival of the antigen in the heart. Histamine and the other mediators are massively released locally, and immediately cause serious rhythmic disorders and cardiac inefficiency (19,20).

The accidental onset of anaphylactoid shock in patients under close medical supervision in intensive care or during surgery has allowed the hemodynamic evolution of this shock to be described. It takes place in two phases: a hyperkinetic phase followed by a hypokinetic one if adequate treatment is not given (Table 2) (27–29).

The hyperkinetic phase lasts 2–3 min and combines a drop in systemic vascular resistance with low blood pressure. The media-

Table 2
Hemodynamic Formulae of Anaphylactic Shock
Observed at Different Stages (after Nicolas et al. [29])

	Onset of shock	After a few min without treatment	Prolonged shock
Systemic vascular resistance	↘	↘	↗
Cardiac output	↗	↘	↘
Systolic volume	↗	↘	↘
Cardiac rate	± ↗	↗	↗
Central venous pressure (CVP)	stable	↘	↘
Pulmonary capillary wall pressure (PCWP)	stable	↘	↘

tors, and particularly histamine, induce capillary vasodilation. It also combines tachycardia and an increase in the volume of systolic ejection linked to the chronotropic and inotropic effects of histamine on the cardiac muscle H1 and H2 receptors, and to the endogenous catecholamines that are released. However, central venous pressure and pulmonary capillary pressure remain stable despite peripheral blood stasis. The result is a rapid rise in cardiac output.

The hypokinetic phase is characterized by persisting vasodilation, low blood pressure, and tachycardia. CVP and PCWP diminish. Indeed, the capillary stasis resulting from the vasodilation causes a rise in the hydrostatic pressure in the capillary, thus favoring fluid movement outside the vessels and the constitution of an interstitial edema. Hypovolemia is induced, resulting in a drop in cardiac flow. In patients with known cardiac disease, CVP and PCWP are often elevated (21).

Neurological Signs

Neurological signs show both the gravity of the anoxia and a certain degree of cerebral edema. This double aggression sometimes has brutal consequences: convulsions, sphincteral incontinence, and bilateral pyramidal syndrome. Late awakening is often observed, not being caused by the amount of anesthetic injected. Prolonged anoxic coma with serious after effects or even death is exceptional.

When the neurological signs are less intense, they selectively affect various functions, such as the psyche (disorientation, agitation, fear of dying) or the sense organs, causing dizziness, hearing disorders, troubled vision, or a metallic taste in the mouth. Speech can also be affected (logorrhea, dysarthria), as can awareness (obnubilation). These signs are obviously not detected if the subject is asleep.

Digestive Signs

Digestive signs reflect the contraction of the smooth muscles, the edema, and intestinal hypersecretion. Hypersialorrhea, nausea, vomiting, diarrhea (which may be profuse), and abdominal pains are observed. Subjective signs go unnoticed when the accident occurs upon injection of the general anesthetic. Diarrhea sometimes appears only upon awakening.

Miscellaneous Signs

Other signs have been mentioned: profound asthenia occurring immediately after the acute phase, and secondary thermal disorders ranging from violent trembling with cutaneous horripilation and a tendency to hypothermia (between 35–36°C) to rare cases of hyperpyrexia (between 38–39°C).

According to the mechanism of the accident (Table 3), the dominant symptoms are different: When it is an authentic case of anaphylaxis, cardiovascular signs dominate, whereas cutaneomucous signs dominate in cases of nonspecific histamine release.

EVOLUTION—COMPLICATIONS

If adequate treatment is given immediately, the evolution is most often favorable in <30 min (21). The erythema, bronchospasm, and low blood pressure are the first signs to regress. Tachycardia can persist for a few hours, as can facial edema. The latter often appears only belatedly. Delayed awakening is not rare and witnesses to transitory cerebral anoxia.

In some cases, the low blood pressure is only partially corrected. An adequate blood volume replacement must then be continued and adrenalin doses increased. This situation can be found in patients

Table 3
Clinical Signs According to Mechanism^a

	Anaphylaxis <i>n</i> = 151,%	Nonspecific histamine release <i>n</i> = 57,%	
Low blood pressure	62	35.1	*
Cardiac arrest	9.0	3.5	*
Generalized erythema	60.3	75.4	*
Bronchospasm	37.1	42.0	NS

^a Personal results: cases observed between 1985 and 1988.

**p* < 0.01 ns: not significant.

treated with β -blockers or even in common cases of AS, since it has been calculated that a loss of up to 35% of blood volume may occur within 10 min (21).

The anaphylactic shock can progress in waves and present several relapses in the following 24 h (30,31). Fifty-two percent of patients have only one episode, whereas in 20% the shock evolves in waves that are spaced out from 1 to 8 h. In 28%, clinical signs, such as low blood pressure, bronchospasm, and laryngospasm, persisted for 5–32 h despite appropriate and efficient treatment and in spite of corticotherapy (32). The risk of relapse means that the patients must be carefully followed for 24 h, even if their symptoms seem to have disappeared.

Complications owing to prolonged shock and so to anoxia are quoted: cardiogenic shock, kidney failure, respiratory distress syndrome, hepatic insufficiency, intravascular disseminated coagulation (33,34), digestive hemorrhagic forms (2,35), sudden intracranial hypertension (36), and vegetative coma. In 6% of cases, the evolution was fatal either because there were aggravating factors that complicated resuscitation or because adequate treatment was administered too late (21,37).

SPECIAL CLINICAL FORMS

In patients treated with β -blockers, anaphylactoid shock is particularly serious, whether the cause be an allergy to hymenoptera, iodine contrast products, or anesthetic substances (31,32,37,38). The

risk with selective β -blockers (β -1) (atenolol, acebutolol, betaxolol, metoprolol, and so forth) seems identical to that with nonselective β -blockers (39). Stopping the treatment 24 or even 48 h before anesthesia does not seem to offer sufficient safety (37).

In pregnant women, AS seems to us to be often especially serious. The reasons for this are not well known (40,41).

The placenta is very rich in histaminase, an enzyme that catalyzes histamine: the maternal plasmatic content rises after 5–6 wk of pregnancy and quickly reaches 400–1000 $\times$ the normal figure. Thus, *a priori*, the fetus seems to be well protected from the maternal amines released during anaphylaxis. Furthermore, the placenta serves as a filter for IgE. These antibodies do not cross the placental barrier (42,43), so the fetus is partially protected: in case of IgE-dependent anaphylaxis, it will suffer the consequences of the maternal hemodynamic and hypoxic disorders. If the fetus is extracted rapidly, no suffering will take place. IgG-dependent shocks are quite a different matter, as can be seen with dextrans because these IgG antibodies cross the placental barrier. Even if the shock is moderate for the mother, there may be a fatal outcome for the fetus.

CONCLUSIONS

The increasing incidence of anaphylactoid reactions occurring during anesthesia enables good descriptions of clinical reactions. The rapid onset of treatment generally provides a complete recovery, and it may be expected that the incidence of fatal cases will become negligible with the institution of adequate fluid therapy and adrenalin infusion.

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