

Allergic Emergencies Seen in Surgical Suites

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Introduction

The use of anesthetic agents, drugs, chemicals, and other substances during anesthesia can lead to a certain number of anaphylactic or anaphylactoid reactions. The incidence of such reactions to agents used during general anesthesia is about 1/3500 cases. Generalized allergic reactions to agents usually occur within minutes after the induction of anesthesia. There are multiple risk factors. Two different mechanisms are involved, IgE-mediated immediate hypersensitivity (we refer to reactions caused by this mechanism as anaphylactic) and, in the case of all presently available muscle relaxants (MR), nonspecific histamine release (we refer to reactions caused by this mechanism as anaphylactoid). The same clinical manifestations occur in both types of reactions. The main agents used for induction of anesthesia are neuromuscular blocking agents (MR), hypnotics, morphinomimetics, neuroleptics, and benzodiazepines. Other drugs that may be used include plasma substitutes, such as fluid gelatins or dextrans, ethylene oxide, and protamine. In addition, contact with latex medical devices, such as surgical gloves, face masks, and so forth, can also induce an anaphylactic reaction.

Epidemiology

Studies from Australia, France, and the United Kingdom indicate that all mechanisms included, the incidence of adverse perioperative reactions is about 1/3500 procedures. An epidemiological study in France reported 1585 cases of perioperative anaphylactic or anaphylactoid

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shock occurring over a period of 2 yr (1990–1991) (1). An allergic mechanism was been demonstrated in 52% of these cases. The agents involved were: muscle relaxants (70.3%), latex (12.6%), and at a lower rate, other drugs and substances used during anesthesia. A more recent survey, covering the period from 1994 to 1996, showed a decrease in the role of MR (61.6%) and an increase in the role of latex (16.6%) as causal factors of perioperative anaphylactic shock (2).

The Main Substances Involved in Anaphylactic Shock

Muscle Relaxants (MR)

The MR used most frequently at present are shown in Fig. 1. Suxamethonium ranks first as a cause of severe allergic reactions, followed by vecuronium. *D. tubocurarine*, mivacurium and atracurium are more potent histamine releasers in vivo than vecuronium or rocuronium (3). In asthmatic patients, cardiovascular effects occur more frequently with atracurium (37%) than with vecuronium (13%, $p < 0.05$) (4). Nevertheless, severe adverse reactions are mainly owing to the presence of specific IgE antibodies to the quaternary or tertiary ammonium ions present on the MR molecules. MR do not require preliminary binding to a carrier molecule to be antigenic. Experimental data, including a positive skin test, a positive Prausnitz-Kustner reaction, specific in vitro histamine release, and RAST test results, demonstrate the presence of IgE antibodies (5–7). The existence of these IgE antibodies explains the frequently observed crossreactivity that occurs between different MR agents (7). Nevertheless, such crossreactivity is not found in all of the patients who have had an MR-induced perioperative allergic reaction. This is because crossreactivity depends on the configuration of the antibody binding site, which may correspond to the quaternary ammonium epitope only or it may include a larger adjacent part of the MR (8). Because MR contain two ammonium ions, they can directly crosslink IgE on the surface of mast cells and basophils and thereby initiate mediator release. MR with a rigid backbone between their two ammonium ions (e.g., pancuronium and vecuronium) appear to be less likely to initiate anaphylaxis than a flexible MR molecule, such as suxamethonium (9).

The diagnosis of the IgE-mediated reactions to MR is based on the clinical history and, most importantly, the presence of a positive intradermal or prick skin test done with the relevant MR at the appropriate concentration (9,10). Intradermal skin tests done with higher concentrations of MR than those listed in Table 1 may give false-positive results since at a high concentration, MR induce nonspecific histamine release from mast cells (11). The skin test of allergically

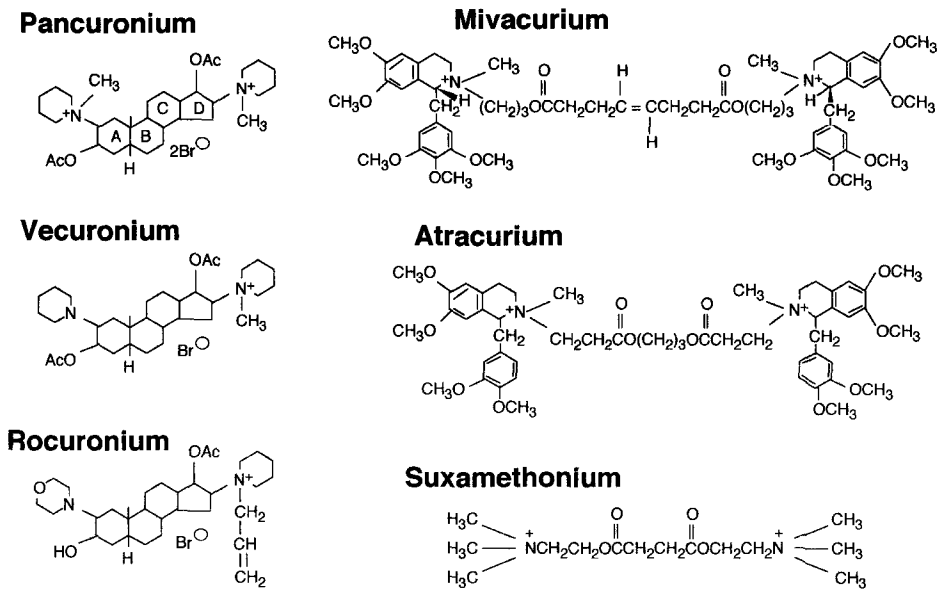


Fig. 1. Formulas of the main muscle relaxants used in general anesthesia.

Table 1
Concentration of Muscle Relaxing Agents Used in Skin Testing

Agent	Maximal concentration for specific skin test (µg/mL)
Suxamethonium	100
Pancuronium	200
Alcuronium	50
Vecuronium	400
Atracurium	10
Rocuronium	100
Mivacurium	2

sensitized patients can remain positive for at least several years. Specific IgE antibodies may be also detected by a RAST-type technique. Several such assays have been proposed, for example, with a sepharose-quaternary ammonium complex as the solid phase, the results of which correlate highly with skin tests (12), or the use of *p*-aminophenylphosphoryl-choline immobilized on agarose beads (13).

An important question is: How do people become sensitized to these agents? It seems that they may become sensitized through environmental contact with quaternary or tertiary ammonium ions that are present in drugs, foods, cosmetics, disinfectants, and certain industrial

materials. An autoimmune disease with IgE autoantibodies against cell-membrane phosphorylcholine is another interesting hypothetical possibility. As risk factors for sensitization to these agents, female sex ranks first, since 80% of sensitized patients are women. By contrast, atopy by itself is not considered a risk factor for MR sensitization (14).

The possibility of preventing allergic reactions to MR by preoperative testing has been investigated, but the answer is not yet clear. In a recently published paper, we reported that systematic preoperative screening by skin testing for MR allergy, when done by anesthetists, led to 67% false-positive reactions compared to the same tests performed in an allergy department (15). Furthermore, we recently evaluated the prevalence of MR sensitivity in a general population and found that 9.3% of this population had either a positive skin prick test to one or more MR or specific IgE to quaternary ammonium ions in a serological assay (16). Since the rate of apparent MR sensitivity is much higher than the anticipated rate of perioperative allergic reactions to these agents, we do not recommend systematic preoperative screening for MR allergy for adults in the general population. However, in patients with a clinical history of a previous reaction to an MR, it is possible to recommend the use of those MR that do not give a positive skin test (17).

Alternatively, the preoperative iv infusion of MR-related monovalent haptens, which can inhibit an IgE-mediated reaction by competing with divalent MR for cell-bound IgE, has been recommended as a means of preventing systemic reactions owing to IgE-mediated mediator release (18).

Hypnotics

Thiopental, a commonly used hypnotic, was the first hypnotic reported to be associated with perioperative allergic reactions. The incidence of these reactions is estimated to be about 1/30,000 operations. True allergic reactions to this agent have been identified by positive specific skin tests and by serological detection of specific IgE by RAST (19). The antigenic determinants on thiopental are the pentyl and ethyl groups at position 5 of the pyrimidine ring nucleus. However, technical difficulties, including nonspecific binding, the poor solubility of thiopental at physiologic pH, and a low sensitivity, make the use of RAST in clinical practice inefficient. At high pH, thiopentone binding to the immunoabsorbent material can generate substituted ammonium ions that are normally internalized within the thiopentone molecule. Specific IgE against quaternary ammonium ions in subjects sensitive to MR can bind these substituted ammonium ions and simulate sensitivity to thiopentone (19). Other hypnotics, for

example, etomidate, an imidazole derivative, or ketamine, a phencyclidine derivative, have been reported to cause perioperative allergic reactions rarely (20).

The previously reported high incidence of reactions to propanidid and althesin was owing to the presence of the solvent cremophor EL. As a consequence, the use of these agents was prohibited in many countries (20). Propofol induces true IgE-mediated allergy in a few patients, but the previously high incidence of adverse reactions decreased greatly when other solvents were substituted for cremophor EL (21).

Opioids

Although opioids are among the drugs most commonly prescribed in hospitals, anaphylactic reactions to these drugs are rare. The incidence of intraoperative shock to these drugs was the same in 1989 and 1993. Skin testing gives a few false-positive immediate reactions. If a narcotic is absolutely necessary, it is possible to test the patient with a less histamine release-inducing molecule, such as fentanyl, by intradermal injections of gradually increasing doses of this drug. IgE antibodies to morphine and meperidine have been detected (22). Allergenic determinants identified on morphine encompass the *N*-methyl group and the cyclohexenyl ring with a hydroxyl at C-6. Crossreactivity among morphine, codeine, and other narcotics has been alleged.

Neuroleptics and Benzodiazepines

Sedative neuroleptics in the family of butyrophenons, such as for instance droperidol, are often used in anesthesia. Adverse reactions to these substances are exceedingly rare. Adverse reactions previously reported with some benzodiazepines were owing to the presence of cremophor EL as the solvent.

Protamine

Recent advances in medicine, such as cardiac catheterization, phoresis, dialysis, and cardiopulmonary bypass technology, have increased the need for heparin anticoagulation. To antagonize heparin's effect and prevent hemorrhagic complications after these procedures, protamine has likewise been used more frequently. With its increased use have come increasing reports of adverse reactions to protamine, consisting of rash, urticaria, elevation of pulmonary artery pressure, systemic hypotension, and at times death. These adverse reactions are thought to be caused by several different mechanisms, including specific IgE and IgG antibodies, complement activation,

nonspecific histamine release, and prostaglandin activation (23). In cases with a true reagenic mechanism, the skin test can be positive, but a negative skin test does not rule out this type of allergy. Furthermore, high concentrations of protamine ($>10 \mu\text{g/mL}$) have been reported to give nonspecific positive intradermal tests. Patients who use protamine-containing insulin or who have received iv protamine are at a significantly greater risk, and those with detectable IgE and/or IgG antibodies to protamine are also at increased risk. As an alternative to protamine, hexadimethrine, a heparin antagonist unrelated to protamine, can be used; its use is however sometimes associated with renal toxicity. Another possibility is autoreversal to lower-dose heparinization (with a higher hemorrhagic risk). Diabetic patients who are allergic to protamine should use "protamine-free" insulin.

Antibiotics

Antibiotics are commonly administered during surgical interventions requiring anesthesia. Perioperative adverse reactions to penicillin and vancomycin and to topically administered bacitracin have been reported. More recently, adverse reactions to rifamycin SV, a semisynthetic antibiotic derived from natural rifamycin, which is applied topically at the end of surgery to prevent local infections, have been reported. The diagnostic approach in these cases will depend on the type of antibiotic thought to have caused the reaction. Positive immediate skin test reactions and specific *in vitro* histamine release have been demonstrated with some antibiotics (24). Recently, we have demonstrated that, in addition to being able to detect immediate hypersensitivity to rifamycin by skin testing, we could also detect IgE antirifamycin antibody serologically after coupling poly-L-lysine-conjugated-3-formylrifamycin SV to an activated cellulose solid phase (25). We also showed that crossreactivity among rifamycin SV, rifampicin, and rifabutin exists.

Agents Other than Drugs

Latex

In spite of discrepancies between the results in the literature about the prevalence of latex sensitization (that is, the presence of detectable IgE in the serum) in the general population, it seems reasonable to accept a mean value near 3% (26). However, sensitization to latex evaluated by either skin testing or an *in vitro* technique does not mean that the person will have a clinical allergic reaction on contact with latex. Nevertheless, true latex allergy is now the second most

common cause of anaphylactic reactions during surgery (2). Clinical history plus skin prick tests and/or a RAST or AlaStat serological assay is used to diagnosis latex allergy (27). Some population groups, especially health care workers and workers from industries where latex goods are manufactured, are at a high risk of becoming sensitized to latex. The prevalence of latex sensitization has been estimated to be between 5 and 11% in occupationally exposed workers (28). Children with spina bifida, who from birth have multiple surgical interventions, are also known to be at increased risk for latex allergy. The prevalence rates of latex sensitization in this group of patients has been reported to be between 34 and 64%. Recently, investigating children with spina bifida, children with multiple surgeries for another disease, and a control group of children with <1 general anesthetic experience, we reported that the frequency of latex sensitization was the same in multiply operated spina bifida patients (59%) and in a group of children who had had multiple surgeries for other reason than spina bifida (55%), whereas it was nonexistent (0%) in the control group (29). These results suggest that it is the number of surgical procedures rather than the presence of spina bifida *per se* that is related to sensitization to latex. All these risk factors are potentiated by the atopic status of the individual, and atopy also increases the risk of latex sensitization in the general population. Food sensitization is also frequently associated with latex allergy (27).

Preoperative screening for latex sensitization should be considered in patients who are members of a high-risk group or who have a clinical history of possible latex allergy. However, systematic preoperative screening in the general population has a very low positive predictive value and we advise against it (30). Medical and operative procedures in patients who are known to be allergic to latex should be undertaken in a latex-free or latex-controlled environment (no use of latex gloves, no direct contact with other latex devices). When possible, the procedure should be scheduled as the first case of the day to reduce exposure to latex (23). From a more general point of view, we recommend that only low-allergen latex gloves (or synthetic, non-latex gloves) be purchased and used. In addition, to reduce latex aeroallergen levels and exposure, only power-free latex gloves should be used (31). These measures will reduce the occurrence of reactions among sensitized personnel and should reduce the rate of sensitization to latex (32).

Ethylene Oxide

Ethylene oxide (C₂H₄O), a gas widely used for sterilization of medical material, is involved in severe, but nonfatal allergic reactions

in 4.2% out of 1,000,000 dialysis units sold (20). Association of latex and ethylene oxide sensitivity has been described in children with spina bifida. IgE antibodies to ethylene oxide can be detected by the RAST technique. Other sterilization procedures (e.g., steam, X-irradiation) can be used if necessary (23).

Other Agents

The incidence of anaphylactoid reactions owing to dextran was evaluated to be between 0.008 and 0.069%. Skin tests with an immediate reaction to dextran are rarely positive. The presence of specific antidextran IgG antibody is correlated with a level-dependent increase in the risk of dextran allergy. The prevention of such reactions consists of giving an iv injection of 20 mL of a low-mol-wt dextran within 5 min before perfusion of normal dextran, allowing an interval of 2 min to ensure adequate diffusion.

Fluid gelatins are produced by hydrolysis of collagen and chemical modification. The frequency of anaphylactoid reactions to these substances has been evaluated to be between 0.003 and 0.14%. The mechanism of adverse reactions to fluid gelatins is either nonspecific histamine release or a true allergic mechanism with the presence of specific IgE antibodies (20).

In addition to these reactions, adverse reactions with blood transfusion, plasma protein fractions, albumin, and its stabilizer, sodium caprylate, have also been reported (23).

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