REVIEW ARTICLE

Strategies for the Prevention of Asthmatic, Anaphylactic and Anaphylactoid Reactions During the Administration of Anesthetics and/or Contrast Media

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Abstract

General anesthetics and contrast media can cause anaphylactic as well as anaphylactoid reactions. These events are of great concern to radiologists and anesthesiologists because of their relatively high prevalence, possible threat to life, and medical-legal consequences. Points discussed in this review are the critical evaluation of risk factors affecting prevention strategies, the need to be aware of pathogenic mechanisms relevant to prevention strategies, the use of alternative products if a culprit agent is known, the recognition of early signs of a reaction, the need to keep records of reactions on a patient's medical chart, the planning of prophylactic therapy, recommended actions after a reaction to an anesthetic or contrast medium, and the suggested establishment of allergy-anesthesiology centers to improve cooperation, and medical-legal issues. As any drug or contrast medium administered during general anesthesia or a diagnostic procedure can induce a potentially life-threatening or fatal event even in the absence of any evident risk factor in the patient's medical history or clinical status, we usually premedicate susceptible individuals at least to attenuate the severity of an unpredictable reaction, although we cannot rely on the efficacy of premedication to completely prevent a severe event. These recommendations, which are based on the literature and on the experience of our working group, aim to provide useful information for physicians and other specialists who operate in the absence of an allergy consultant.

Key words: Allergy. Anaphylaxis. Anesthesia. Bronchial asthma. Histamine. Hypersensitivity. Contrast media. Premedication. Prophylaxis.

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Resumen

Los anestésicos generales y los medios de contraste pueden provocar reacciones anafilácticas y anafilactoides. Estos son incidentes de gran interés para los radiólogos y los anestesiólogos, debido a su relativamente elevada prevalencia, a que pueden ser potencialmente mortales y a que pueden tener consecuencias médico-legales. Las cuestiones que se debaten en esta revisión son la evaluación crítica de los factores de riesgo que influyen en las estrategias de prevención, la necesidad de averiguar los mecanismos patogénicos relevantes para las estrategias de prevención, la utilización de productos alternativos si se conoce el agente implicado, el reconocimiento de los primeros signos de una reacción, la necesidad de conservar registros de reacciones en la historia clínica del paciente, la planificación de tratamientos profilácticos, las acciones recomendadas en caso de una reacción a un anestésico o a un medio de contraste y la propuesta de crear centros de alergia y anestesiología para mejorar la cooperación y los asuntos médico-legales. Debido a que cualquier fármaco o medio de contraste administrado durante la anestesia general o durante un procedimiento diagnóstico puede inducir un acontecimiento fatal o que pueda poner en peligro la vida, incluso si no existe ningún factor de riesgo evidente en los antecedentes del paciente o su estado clínico, normalmente se preanestesia a los individuos susceptibles, al menos para atenuar la gravedad de una reacción imprevista, aunque no se puede confiar en la eficacia de la preanestesia para prevenir completamente un acontecimiento grave. Estas recomendaciones, basadas en la literatura médica y en la experiencia de nuestro grupo de trabajo, pretenden proporcionar una información útil para los médicos y otros especialistas que operan en ausencia de un especialista en alergología.

Palabras clave: Alergia. Anafilaxia. Anestesia. Asma bronquial. Histamina. Hipersensibilidad. Medios de contraste. Preanestesia. Profilaxis.

General Considerations

General anesthetics and contrast media can cause anaphylactic as well as anaphylactoid reactions. They are frequently underdiagnosed and underreported, but it is likely that their incidence is increasing. The pathogenesis of such reactions is complex and not fully understood. However, it is widely recognized that the release of vasoactive mediators from basophils and mast cells may play a central role [1-3].

Exacerbations of obstructive symptoms are also relatively common after the infusion of general anesthetics or contrast media in patients with diagnosed bronchial asthma or chronic obstructive pulmonary disease [1]. Some adverse reactions to iodinated contrast material are considered allergy-like, but systemic reactions, involving cutaneous, cardiovascular, respiratory and digestive systems are largely unpredictable [3]. Reactions to contrast media are more frequent with ionic than nonionic material, but the mortality rates after reactions are almost identical [4]. Iodinated contrast media have a favorable safety profile but the rate of adverse events (especially urticaria and bronchospasm) has been reported to be at least 0.7% [1]. Thus, anaphylactic and anaphylactoid reactions occurring during anesthesia remain a major cause of concern for anesthesiologists. The overall incidence of anaphylactic reactions, considering all agents used in anesthetic approaches (general, local, or regional) has been reported to be 1 in 13 000 anesthetic procedures [5], while the incidence of anaphylaxis after administration of muscle relaxants has been assessed at 1 in 6500 procedures in which such a relaxant was administered [6]. Mortality can be high (3.4%) and anaphylactic deaths can account for as many as 4.3% of all deaths occurring during general anesthesia [7,8].

The most common culprit agents are muscle relaxants, which account for 50% to 75% of all reactions [7,8]. In vitro studies of the effects of increasing concentrations of different anesthetics on the release of preformed and de novo mediators from human basophils and mast cells isolated from lung parenchymal, skin and heart tissue have demonstrated that most general anesthetics are able to induce histamine and tryptase release from human basophils and mast cells [9,10]. Severe bronchospasm may be induced either in the context of a systemic anaphylactic or anaphylactoid reaction or as a single clinical manifestation following the use of a general anesthetic or contrast medium.

Bronchial hyperreactivity is characterized by exaggerated bronchoconstriction in response to a variety of stimuli and a bronchospasm should be elicited in the course of induction and maintenance of anesthesia [11,12]. The prevalence of bronchial hyperreactivity is approximately 10% and this condition is an important risk factor for perioperative bronchospasm, a potentially life-threatening event whose incidence in anesthesia practice varies from relatively low rates of 0.17% or 4.2% [13,14], to higher ones of about 7% [15] or 20% [16]. Obstructive bronchial reactions tend to increase in proportion to the proximity of the latest asthma attack in relation to the date of surgery [11,13,16,17].

Tracheal intubation also constitutes a high risk factor for intraoperative bronchospasm [11,13,16,17] and diagnostic approaches such as bronchoscopy and endobronchial biopsy may aggravate respiratory symptoms in children with difficult asthma [18]. Increased bronchial symptoms in the week following bronchoscopy have also been reported in children [18].

Aspirin-induced asthma is another clinical condition that increases the risk of bronchial obstruction. Although it is not known whether there is a relationship between analgesic intolerance, aspirin-induced asthma, and surgery and/or general anesthesia, there is some evidence that patients with aspirin-induced asthma seem to have a high rate of intra- or postoperative respiratory complications [19,20]. The most critical time for a patient with this type of asthma who is receiving general anesthesia is during instrumentation of the

Risk Factor or Event	Risk-Related agents
Spina bifida	Latex
Penicillin anaphylaxis	Cephalosporin, penicillin
Allergy to eggs/soybean emulsion	Propofol
Gelatin allergy	Plasma volume expanders
Sensitization to exotic fruits	Latex
Urticaria/angioedema	
Previous anaphylaxis related to general anesthesia	All agents
Previous unexplained reactions during general anesthesia	All agents
Multiple drug allergy syndrome	All agents
Penicillin allergy	Cephalosporin
Allergy	All agents
Atopy	All agents
Asthma	All agents
Previous exposure to a general anesthetic	NMBDs
Family history of general anesthesia anaphylaxis	All agents
Allergy to cosmetics	NMBDs

Figure 1. Suggested scale of priority of the main risk factors for anaphylaxis after administration of a general anesthetic. NMBD indicates neuromuscular blocking drugs.

airway. Celiker and colleagues [19] have noted that pain, emotional stress or stimulation during light general anesthesia may precipitate bronchospasm and that although the exact mechanism of aspirin-induced asthma is not fully understood, it is thought to be a disorder of arachidonic acid metabolism [19]. They also point out that an increased production of cysteinyl leukotrienes has been reported to be characteristic [19].

Given this background immediate reactions of an asthmatic, anaphylactic, or anaphylactoid nature in the context of general anesthesia or administration of contrast media are of great concern to radiologists and anesthesiologists because of the relatively high frequency, possible threat to life, and legal consequences. In this article we aim to review the available literature and the clinical experience of the A Cardarelli Hospital Radiocontrast Media and Anesthetic-Induced Anaphylaxis Prevention (CHRAIAP) working group, in order to discuss possible strategies for reducing

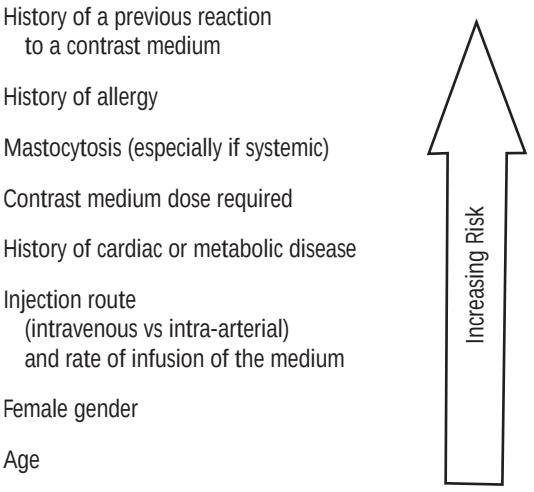

Figure 2. Suggested scale of priority for the main risk factors for anaphylaxis upon administration of a contrast medium.

the risk of such reactions after the administration of general anesthetics and contrast media. In addition to the interest of these recommendations for anesthesiologists, allergists and radiologists, they should be useful to physicians managing high-risk patients in the absence of an allergy consultant.

Critical Evaluation of Risk Factors Affecting Prevention Strategies

The prevention of anaphylaxis after administration of general anesthetics would require the identification of patients at risk, but this approach is not easy to implement considering the large number of drugs, diagnostic reagents, devices containing latex, antiseptics and blood products that are all routinely used in anesthesia. The low accuracy of diagnostic tests also plays a part. Classically, systemic reactions to contrast media are described as unpredictable at the individual level; however, at the population level, certain risk factors have been suggested [21,22]. Figures 1 and 2 show the main potential risk factors as well as our group's approach to defining levels of priority.

Mild respiratory allergy (allergic rhinitis and mild bronchial asthma) is not usually considered a consistent risk factor unless the disease is exacerbated. Skin disorders such as mastocytosis and chronic urticaria–angioedema should be considered risk factors for release of preformed vasoactive mediators (eg, histamine and tryptase), whether immunoglobulin-E–mediated or not.

Severe anaphylactoid reactions to isosulfan blue dye requiring resuscitation are reported to occur in 1.1% to 2% of women with breast cancer undergoing sentinel lymphadenectomy [23-25]. This is a typical example of systemic reactions which can be observed during the associated administration of a general anesthetic and a contrast medium.

Whether it is absolutely necessary to avoid the use of β-blockers and angiotensin-converting enzyme inhibitors is still debated [26].

Taking into account these risk factors may be useful for reducing the incidence of anaphylactic or anaphylactoid reactions, although such factors must be considered as valid for populations rather than individuals.

Awareness of Pathogenic Mechanisms Relevant to Prevention Strategies

Sufficient knowledge of pathogenic mechanisms involved in systemic reactions to general anesthetics and contrast media is essential to optimize prevention strategies. It is widely recognized that anaphylactic (immunoglobulin-E–mediated) events usually occur after repeated administration of sensitizing agents (especially general anesthetics and, in some cases, contrast media). These events are somewhat predictable in high-risk patients or in subjects who have had anaphylactic reactions previously. Direct mediator release during anaphylactoid reactions may sometimes occur upon the first administration of a general anesthetic or contrast medium, on the other hand. This is the reason why anaphylactoid events are largely unpredictable.

Knowledge of pathogenic mechanisms is also useful in case of the less common reactions to local anesthetics such as lidocaine, prilocaine, and mepivacaine [27]. Type I anaphylactic events are exceptional, whereas type IV delayed reactions are more frequently described [28-30]. However, in most cases, other nonallergic mechanisms (eg, toxic or psychogenic ones) are involved.

Although anaphylactic reactions are usually immediate, in some cases delayed events may occur an hour after the administration of a general anesthetic or contrast medium (incidence ranging from 0.2% to 17.5%) [31-33].

Use of an Alternative Contrast Medium or Anesthetic If a Culprit Agent Is Known

If patient interviews, medical history taking, or previous diagnostic tests are able to identify a culprit agent or agents, an alternative product must be used. If the reaction is attributed to a neuromuscular blocking drug, there is risk from other such agents and consequently it is proper to use a regional blocking agent or volatile anesthetics if such techniques are suitable.

After assessment of the risk–benefit ratio, alternative procedures such as magnetic resonance imaging or ultrasound imaging can sometimes be carried out in patients considered at high risk or who have previously experienced a high-osmolar contrast-medium–induced reaction. Such patients who require re-exposure to a contrast medium can be administered a low-osmolarity contrast medium, as such agents are associated with a lower incidence of side effects [34,35]. In these cases up to a 10-fold reduction in the incidence of severe repeat reactions has been reported [36]. However, due to frequent cross-reactivity between different contrast media, a change of agent is no guarantee against a repeat reaction.

Other agents such as antibiotics, nonsteroidal anti-inflammatory drugs, and latex, which can be responsible for systemic reactions, should be replaced with alternatives.

Recognition of Early Clinical Manifestations

Early recognition of signs and maintaining a high level of suspicion of the possibility of a generalized reaction during the use of general anesthetic or contrast media is essential to prevent further reaction or a fatal outcome. As mentioned, it is important to consider various categories of patients to be at risk; examples are those with metabolic disorders, those suffering from pruritus or other skin symptoms likely to be induced by the nonspecific release of histamine and other mediators. It is not only atopic individuals who are at risk.

During general anesthesia, anaphylactic and anaphylactoid reactions cannot be distinguished clinically, according to Mertes and coworkers [37]. However, in that study, in which a classification of symptom severity was applied, it was found that clinical manifestations seemed to be more severe in patients with documented anaphylaxis than in individuals presenting with an anaphylactoid reaction. Cutaneous manifestations were more frequent in anaphylactoid reactions, but they were not confined to that setting; cardiovascular and broncho-obstructive events, on the other hand, were more frequent during anaphylaxis. In the case of cardiovascular and respiratory complications, clinical symptoms may also occur as isolated events, which can easily be misdiagnosed, according to those authors, if we consider all diseases presenting identical clinical manifestations [37]. The lack of an adequate diagnosis could lead to a potentially fatal re-exposure to the same agent [38].

The common findings that clinical manifestations of intraoperative reactions differ from those of anaphylactic reactions outside of anesthesia might be explained by the

Table 1. Differential Diagnosis of Anaphylaxis During General Anesthesia.

Arrhythmia
Bronchial asthma
Cardiogenic shock
Jarisch–Herxheimer reaction
Hereditary angioedema
Hemorrhage
Mastocytosis
Overdosage of a vasoactive drug
Pericardial tamponade
Postextubation stridor
Pulmonary embolus
Pulmonary edema
Sepsis
Tension pneumothorax
Vasovagal reaction
Venous air embolism

Table 2. First-line Emergency Drugs and Instruments to Have Available in the Examination Room Where Contrast Media Are Used and in All Minor-Surgery Rooms

Oxygen
Adrenaline 1:1000
Antihistamine (type 1), injectable
Corticosteroids for intravenous infusion
Atropine
Short-acting β_2 agonists, for inhalation
Fluids for intravenous infusion (normal saline or Ringer's solution)
Anticonvulsive drugs (eg, diazepam)
Sphygmomanometer
One-way mouth "breather" barrier

fact that patients are draped during anesthesia and cannot complain of cutaneous symptoms such as pruritus or a sense of flushing [39]. Moreover, concomitantly administered drugs may alter the expression and degree of clinical manifestations. The difficulty in recognizing anaphylactic symptoms in anesthetized subjects may also be explained by the need to exclude various other clinical conditions (Table 1) [26].

As regards reactions to contrast media, pruritus and mild urticaria are the commonest immediate manifestations, presenting in up to 70% of affected patients [40]. More severe reactions involve the respiratory and cardiovascular systems, and the majority of fatal events related to these media are immediate anaphylactic reactions [34,41]. Delayed skin reactions are usually mild to moderate, although severe reactions such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and cutaneous vasculitis have been reported [32].

Short-term Prevention of Anaphylactic or Anaphylactoid Events

Given this background, it is useful to have available a trolley with resuscitation drugs in examination rooms where contrast media will be used and in all rooms where local anesthetics are used for minor surgery, such as dentists' offices or dermatology clinics [35] (Table 2). Another important suggestion is to observe patients for 20 to 30 minutes after injection of a contrast medium or after a surgical intervention in order to assure early recognition of the onset of delayed reactions [33].

Record Reactions on a Patient's Medical Chart

Each reaction occurring during general anesthesia or the administration of a contrast medium should be entered into a patient's medical record by the anesthesiologist or radiologist in order to prevent future reactions. Bilò et al [42] described a case of intraoperative gelatin-induced anaphylaxis whose diagnosis was delayed because the use of gelatin during surgical procedures was twice omitted from the patient's medical records.

It is also important to underline the need to ensure that the results of allergy investigations and subsequent anesthesia be available to the patient and the anesthesiologist [6,22].

Finally, patients should be encouraged to wear a warning bracelet with certain essential information, such as the occurrence of anaphylaxis induced by a specific drug, the name of a safe alternative product if known or an indication to look for a letter in a specific place. The accompanying letter should contain all details on the patient's condition.

Planning Prophylactic Treatment

It is important to emphasize that a prophylactic treatment that is useful in all clinical conditions does not exist, because different pathogenic mechanisms might require different therapeutic approaches. Since, from a general point of view, the use of any drug may be responsible for many adverse and potentially harmful events, this is also valid for the agents administered for prevention of reactions induced by general anesthetics and contrast media. Consequently the decision to use a prophylactic treatment or not, the choice of drug, the modality of administration, the dosage, etc, should be made after an appropriate evaluation of the risk–benefit ratio.

The Rationale for the Prophylactic Use of Antihistamines

The pathophysiologic effects of histamine in anaphylaxis have been shown to be mediated through type 1 and 2 (H_1 and H_2) receptors, individually and in combination [43-45]. An important study of the role of histamine release during the induction of anesthesia and the start of surgery by Lorenz et al [46] found that histamine release is very common, occurring in about 13% to 16% of episodes of mediator release after each drug administration in the induction sequence. Moreover, histamine-related cardiorespiratory disturbances were shown to occur with remarkably low plasma histamine levels. The authors also demonstrated a reduced incidence of histamine release within each concentration band of histamine (and consequently histamine related symptoms) in patients treated with anti-H_1-H_2 agents. As a consequence of these findings, Lorenz et al suggested the use of these agents in all patients undergoing surgical procedures. The suggestion of generalized use of antihistamines during general anesthesia has not been accepted by other authors [47,48]. The main clinical effects of H_1 and H_2 receptor stimulus in humans are summarized in Table 3.

The effect of histamine on the coronary arteries blocked by H_1 antagonists and the effects on atria and ventricles blocked only by H_2 antagonists suggest the utility of a combination of these drugs in the prevention of cardiovascular events during anaphylactic or anaphylactoid reactions [43]. Some cardiovascular side effects (such as arrhythmias) of anti-H_1 drugs may be explained by the particular cardiotropic properties of some of these agents [49,50]. The first generations of antihistamines often induced sedation and in some cases, generalized convulsions in susceptible individuals [51,52].

In case of scheduled procedures in which contrast media or a general anesthetic will be used, we suggest the use of newer anti-H_1 drugs for their relevant pharmacologic characteristics

Table 3. Main Effects of Activating Histamine Types 1 and 2 (H_1 and H_2) Receptors

H_1 Receptor Activation Effects	H_2 Receptor Activation Effects
Increased activation	Increased activation
Pruritus and pain	Gastric acid and secretion
Vascular permeability	Vascular permeability
Hypotension	Hypotension
Flushing	Flushing
Headache	Headache
Tachycardia	Tachycardia
Bronchial obstruction and stimulation of cough receptors	Bronchial obstruction
Prostaglandin generation	Mucus production in the airways
Release of histamine, leukotrienes and other mediators	Ventricular inotropic action
Recruitment of eosinophils and other cells	Atrial chronotropic action
Decreased activation	Decreased activation
Atrioventricular node conduction time	Neutrophil, basophil, chemotaxis and enzyme release
	Cytotoxicity and proliferation of lymphocytes

(high efficacy, low dosage, once-a-day administration, or mild side effects such as drowsiness). Unfortunately, these antihistamines are not available for intramuscular or intravenous administration and consequently cannot be used if rapid treatment is required in an emergency.

The associated use of anti-H_1 and anti-H_2 antagonists is able to minimize bronchospastic reactions following the inhalation of histamine [53] and prevent hemodynamic irregularity induced by nonspecific histamine release after the administration of plasma expanders, morphine, protamine, chymopapain, and contrast media [54,55].

Most authors have found that the combined use of anti-H_1 and anti-H_2 agents may give better protection against anaphylactic or anaphylactoid reactions than the administration of these drugs separately [43,44,56-60]. The associated use of anti-H_1 and H_2 blockers as prophylactic agents has also been demonstrated to be valid in children [61]. On the other hand, Moneret-Vautrin et al [62] demonstrated that the association of both types of antihistamine did not improve the inhibition of allergic skin reactivity in patients suffering from anaphylaxis to muscle relaxants.

The experience of administering a regimen including an anti-H_1 agent plus an anti-H_2 agent plus corticosteroid therapy is very scarce [63].

CHRAIAP Recommendations on Pharmacological Pretreatment of Patients at Risk

Nonemergency conditions. In all scheduled cases, the standard pre-medication suggested by our working group includes the combined intake of anti-H_1 plus H_2 agents and corticosteroids for at least 2 days (the last tablets administered 1 hour before the beginning of general anesthesia or contrast medium infusion). We use this standard therapy in all patients with ascertained risk factors screened for a low or medium degree of risk in the scales in Figures 1 and 2. This therapy is also used in our hospital as a precautionary treatment to avoid medical-legal complications when a patient's medical history is unclear and consequently adequate assessment of risk is not possible.

When preliminary evaluations suggest a high degree of risk, we usually use higher dosages of anti-H_1 agents and corticosteroids and/or we prolong the time of drug administration (eg, over 3 or 4 days). In some cases we use an additional dose of corticosteroids (eg, methylprednisolone 20-40 mg) an hour before administration of a general anesthetic or contrast medium.

In other situations we cannot use the usual therapy due to the possibility of significant side effects in certain susceptible individuals (eg, avoidance of corticosteroids in patients with uncontrolled hypertension and/or diabetes). In such cases, an appropriate evaluation of the cost–benefit ratio is essential, especially in individuals at significant risk for generalized reactions. In situations, in which the risk of systemic reaction balanced or exceeded the risk of inducing side effects with the use of prophylactic drugs, we usually administer the full therapy but encourage strict clinical surveillance (eg, frequent monitoring of blood pressure, blood glucose levels, etc).

Patients with atopic or nonatopic asthma have usually undergone preliminary assessment of lung function (spirometry). According to the severity of bronchial obstruction, patients are pretreated with inhaled corticosteroids and long-term β_2-agonists in addition to the usual premedication.

Emergency conditions. When clinical conditions are critical, a general anesthetic or contrast medium may be required quickly. In such cases we apply rapid parenteral premedication with H_1 and H_2 receptor blockers plus corticosteroids just before surgery or the imaging procedure.

Why Prophylactic Medication Is Sometimes Ineffective

Generalized reactions to general anesthetics and contrast media are known to be largely unpredictable, and in some cases clinical events are too severe to be controlled by a standard premedication. In most cases, it is likely that preventive therapy

might be insufficiently effective to completely prevent the onset of reactions because the physician has not adequately considered the role and the importance of risk factors or has underprescribed the medication.

In patients with a history of severe reaction, especially to contrast media, current premedication procedures appear to reduce the severity of symptoms but may not prevent the occurrence of repeat reactions [23,34,64]. Similarly, pretreatment with antihistamines and corticosteroids does not appear to protect against life-threatening intraoperative reactions to latex [39,65,66]. In the case of latex hypersensitivity the only effective measure is primary prevention through the creation of a latex-free environment.

However, it is important to consider that a reduction in the severity of symptoms is still a relevant goal in high-risk individuals. In fact, it is likely that in the absence of a prophylactic medication, reactions induced by general anesthesia or contrast media could be life-threatening and, in some cases, fatal events.

Suggested Pretreatment for Delayed Reactions to Contrast Media

As mentioned, anaphylactic reactions are classically immediate, but delayed events may occur, especially after the administration of contrast media [31-33]. In a case reported by Romano et al [31] the usual pretreatment regimen with prednisone (50 mg/d) and cetirizine (20 mg/d) was started 3 days before the radiologic examination but did not prevent the onset of cutaneous symptoms about 24 hours after repeat exposure to a contrast medium (iopamidol). Given the need to perform a new angiography 2 months later, the authors suggested a novel pretreatment protocol including 6-methyl-prednisolone (40 mg/d) plus oral cyclosporine (100 mg/12 h) starting 1 week before re-administration of the contrast medium and continuing for 2 weeks afterwards. This regimen was effective in preventing a delayed hypersensitivity reaction. This and other studies have demonstrated the lack of efficacy of anti-H_1 plus anti-H_2 regimens in preventing allergic reactions not induced by an immediate-type of mediator release.

Concluding Remarks on the Use of Prophylactic Medication

Although the body of evidence on prophylactic medication before general anesthesia or administration of a contrast medium seems to favor treating susceptible individuals, certain issues are still debated [68]. Table 4 shows arguments for and against the use of prophylactic medication. Each physician should choose to premedicate or not on the basis of a careful evaluation of the risk factors in the individual patient.

In some cases, prophylactic medication may be used as a precaution in patients exhibiting in clinical situations that is difficult to interpret. Prophylaxis is not advised for unselected patients with no known risk factors.

Recommendations

Suggestions made in other sections of this review have been summarized in Table 5.

Allergy-Anesthesia Centers for Optimizing Cooperation

From a pharmacologic point of view anesthesiology constitutes a unique setting because a patient is exposed to a large variety of drugs and substances over a relatively short period of time. Any drug administered during surgical interventions can induce potentially life-threatening anaphylactic or anaphylactoid reactions, and these are probably underdiagnosed. Constantly evolving practices, the relative complexity of allergy research, and the largely unpredictable characteristics of events suggest that specialized centers for allergy in relation to anesthesia should be created, at least in high specialty hospitals [37]. Only a specialized team of expert anesthesiologists and allergists are able to evaluate and treat patients at high risk of generalized reactions. Moreover, only well trained specialists are able to produce position papers or guidelines useful to physicians managing high-risk individuals in hospitals lacking an allergy department.

Table 4. Arguments in Favor of and Against Premedication

In favor of premedication
A serious anaphylactic reaction, even if not life-threatening, may contribute to major morbidity, a prolonged hospital stay, and high costs.
Although controversial, pre-medication is widely used in clinical practice.
Pharmacological and clinical data on the efficacy of anti-H_1 plus anti-H_2 agents and corticosteroids as single drugs indirectly suggest the utility of this classical association.
Medical-legal and opportunity considerations
Against premedication
The large number of unselected patients who need to receive the therapy to prevent a potentially life threatening event
The cost
The potential risk of side effects in some patients
Delay in performing radiological or surgical procedures
Encourages overconfidence on the part of physicians who inject contrast media or general or local anesthetics
Possible neglect of appropriate measures to assess patients and to treat anaphylaxis

Table 5. Recommended Actions After a Reaction to a General Anesthetic or a Contrast Medium

If an incident is attributed to a neuromuscular blocking agent used during general anesthesia, a regional block or volatile agents should be used if such techniques are suitable.
If the reaction is attributed to other agents, such as antibiotics, nonsteroidal anti-inflammatory drugs, or latex, use alternative products.
After a high-osmolar contrast-medium–induced reaction, appropriate alternative procedures, such as magnetic resonance imaging or ultrasound imaging, or a low-osmolar contrast medium should be substituted.
Establish the cause of the event. The lack of an adequate diagnosis could lead to a potentially fatal re-exposure to the same agent in the future.
Record each reaction during the administration of a general anesthetic or contrast medium on patient's medical record so as to prevent future reactions.
In patients with prior severe reactions, especially to a contrast medium, premedication procedures appear to reduce the severity of symptoms, although they may not prevent the occurrence of repeated reactions.

Table 6. Admissions, Operations and Procedures Requiring Contrast Media from 2002 through 2006 at the A Cardarelli High Specialty Hospital.

	2006	2005	2004	2003	2002	Total
Admissions	110 574	106 293	103 686	99 197	101 014	520 664
Surgical procedures	21 925	21 922	20 738	20 880	20 139	105 604
Procedures with contrast media	21 260	16 900	15 989	12 505	8701	75 355
Fatal or near-fatal events	0	0	0	0	0	0

In nonemergency interventions, it is the anesthetist's responsibility to ensure that any suspected anaphylactic reaction is adequately investigated using pre- and postoperative diagnostic procedures [69]. It has been reported that up to 30% to 40% of individuals suffering from anaphylactoid reactions during anesthesia did not benefit from further allergic evaluation. Consequently, these individuals are likely to experience new reactions after re-exposure to the same pharmacologic agents.

In our high-specialty hospital, informal cooperation between allergists, anesthesiologists, and radiologists started about 15 years ago. Five years ago these specialists formed the CHRAIAP working group, which to our knowledge is the first such group in Italy to produce internal guidelines for managing patients at risk of developing systemic reactions related to diagnostic or therapeutic procedures. It is important to emphasize that as a likely consequence of the strict cooperation between the members of this working group, no fatal or near-fatal reactions have been recorded since 2002, in spite of the high number of diagnostic and therapeutic procedures performed annually (Table 6).

Medical-Legal Issues

The previously described characteristics of anaphylactic and anaphylactoid reactions during the use of general anesthesia or contrast media are a frequent cause for litigation especially in cases of life-threatening or fatal events. Given the lack of a gold standard diagnostic procedure to recognize individuals at higher risk of reactions, a rigorous but formally unobjectionable interview is required to screen all individuals who are candidates for surgery or an imaging procedure involving a contrast medium.

When there has been an anaphylactic reaction to general anesthesia, it is difficult to justify lack of performance of skin prick tests to alternative anesthetics when the patient is not in an emergency situation [22].

Patients should be well-informed about the risk related to diagnostic and therapeutic procedures as well as about the risks of precautionary measures adopted after the evaluation of the risk–benefit ratio, and written informed consent should be obtained. Patient information is an important prerequisite in the effort to reduce perioperative complications and to avoid medical-legal consequences in case of severe reactions despite usual preventive measures [20,70].

The CHRAIAP working group suggests particular attention to the management of all potentially at-risk individuals, particularly those with a history of severe reactions. We also suggest the adoption of reasonable prophylactic measures when an effective assessment of the risk is not possible. However, anesthesiologists and radiologists in our working group avoid using drugs or contrast media, if possible, if there is suggestion of risk in the patient's medical history, however small the risk might be.

Concluding Remarks

Although our knowledge of systemic reactions during the administration of general anesthetics or contrast media has

increased substantially over the past 30 years, they remain a major cause for concern and a source of continuing debate among anesthesiologists, radiologists and allergists given the medical-legal consequences involved. Any drug or contrast medium can induce a life-threatening and sometimes fatal anaphylactic or anaphylactoid event even in the absence of any evident risk factor in the patient's medical history.

Unfortunately, fatal or near-fatal events may be induced by diagnostic or surgical procedures usually considered as routine and carried out in patients suffering from less severe disorders. This is the reason why we usually prefer to premedicate all susceptible individuals in order to at least attenuate the severity of an unpredictable reaction, although we cannot rely on the efficacy of premedication to completely prevent a severe event.

Both preclinical and clinical studies are required to better understand the pathophysiology of reactions induced by general anesthetics or contrast media and thus to offer protection for patients. Our positive experience suggests that creating similar working groups, at least in high specialty hospitals, would be helpful. In the meantime, these guidelines based on the literature and on the experience of our working group have aimed to provide useful information to physicians and other specialists who operate in the absence of an allergy consultant.

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