



Management of Patients During Acute Reaction Induced by Drugs

Patrizia Bonadonna, MD^{1,*}

Mauro Pagani, MD²

Alessandra Arcolaci, MD¹

Address

^{*1}Allergy Unit, Azienda Ospedaliera Universitaria Integrata of Verona, Piazzale Scuro 1, Verona, Italy

Email: patrizia.bonadonna@aovr.veneto.it

²Medicine Ward Borgo Mantovano Hospital, Medical Department, ASST of Mantova, Mantua, Italy

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Abstract

Purpose of review Anaphylaxis is the most severe form of an allergic reaction and is characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems; medications are able to provoke immediate acute reactions whose severity varies from mild (i.e., urticaria) to severe reactions (anaphylaxis). The management and prevention of anaphylactic reactions represent a crucial challenge for allergists that must perfectly know the symptoms and the best treatments of this severe disease.

Recent findings Acute treatment of anaphylaxis is based on the immediate administration of adrenaline, which represents the drug of choice and should be given immediately to any patient with suspected anaphylaxis. In case of drug-induced anaphylaxis, the allergological work up includes skin tests, in vitro tests, and drug challenges. Desensitization safely permits the administration of the needed medication and provides a temporary tolerance to the drugs that patients have presented immediate reactions to, including anaphylaxis and delayed reactions non-SCARS (severe cutaneous adverse drug reactions).

Summary First of all, this review focuses on the best treatment of anaphylaxis provoked by drugs and underlines the allergological work up of the patients. In the second part, special conditions, such as anaphylaxis during chemotherapy or radio contrast media (RCM) administration or in patients with mastocytosis, are analyzed.

Introduction

Medications are able to provoke immediate acute reactions whose severity varies from mild reactions to anaphylaxis. Anaphylaxis is the most severe form of an allergic reaction and is characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems; it is usually, but not always, associated with skin and mucosal changes [1]. While the prevalence of anaphylaxis is estimated to be as high as 2% and appears to be increasing, the fatality rate is extremely low (i.e., < 0.0001% prevalence in the general population, or < 0.5% case fatality rate in those hospitalized or presenting to the emergency department with anaphylaxis) and appears to be decreasing [2, 3]. Nonetheless, it is mandatory to recognize people at risk of

anaphylaxis and decide on correct measures to take, with the aim of reducing the risk of death from anaphylaxis even further. Although any drug has the potential to cause anaphylaxis, a recent study has demonstrated that, among the 25% of cases where a culprit drug was identified, antibiotics accounted for 40% of the fatal episodes—most often penicillins, followed by cephalosporins, sulfa-containing drugs, and macrolides. Radiocontrast agents accounted for 27% of fatalities with antineoplastic drugs attributed to 12.5%. The remainder of culprit drugs were identified as serum, opiates, antihypertensives, nonsteroidal anti-inflammatory drugs (NSAIDs), and anesthetic agents [4].

Pathogenetic mechanisms

Drug-induced anaphylaxis can occur via both IgE-mediated and non-IgE-mediated pathways. Regarding IgE-mediated anaphylaxis, most drugs act as haptens or prohaptens in order to be immunogenic, because of their overly small dimensions. As regards non IgE-mediated anaphylaxis, many mechanisms may provoke very severe, drug-induced reactions, including direct IgE-independent mast cell activation, complement activation, and kallikrein activation [5••].

In addition, drug-induced anaphylaxis can also be provoked by contaminants, as observed in 2007 in USA and Germany, where 80 people died due to anaphylactic reactions to heparin contaminated with oversulfated chondroitin [6], or evidenced in 8 children treated with contaminated vincristine [7].

In addition to the “classic” immediate drug reactions, with the development of biological therapies, clinicians have begun to observe acute reactions during the infusion of these treatments. These reactions are predictable, common, and usually mild reactions that typically occur during the first administration of biological. The pathogenesis is not well understood but the release of proinflammatory cytokines seems to have a very important role in the majority of reactions [8•].

Clinical characteristics

The clinical manifestations of anaphylaxis depend on the organ systems involved. Table 1 describes the most common sign and symptoms observed during anaphylactic reactions. Symptoms and signs of anaphylaxis usually occur within 2 h of exposure to the allergen, usually faster than 30 min with parenteral medication [9, 10]. In a large case series of fatal anaphylaxis, the median time from symptoms to arrest has been reported as 30, 15, and 5 min for food, insect venom, and parenteral medication, respectively [11]. The most

Table 1. Clinical characteristics of anaphylaxis

System involved	Symptoms and/or signs
Cutaneous	Urticaria; angioedema; erythema (flushing); pruritus; eczema
Respiratory	Nasal congestion; sneezing; hoarseness; cough; laryngeal edema; dyspnea; cough bronchospasm; wheezing; chest tightness
Cardiovascular	Hypotension, syncope, tachycardia
Gastrointestinal	Nausea; vomiting; abdominal pain; diarrhea
Neurologic	Lightheadedness; dizziness; confusion
Oro-pharyngeal	Tingling; angioedema; vocal cord dysfunction
Others	Chills; fever; pain

common clinical manifestations are cutaneous symptoms, followed by respiratory and cardiovascular involvement [12]. Anaphylaxis, however, can develop in the absence of cutaneous manifestations; respiratory or cardiovascular symptoms or signs are the potentially life-threatening features [13]. In addition, it is possible to observe nausea and vomiting [11]. Widely accepted criteria to help clinicians identify likely anaphylaxis [14, 15] emphasize the rapid onset of its multiple symptoms and signs. Table 2 shows the clinical criteria for a correct diagnosis of anaphylaxis.

After adequate treatment, symptoms usually disappear without problems, even if, between 0.4 and 15% of reactions follow a biphasic course characterized by an asymptomatic period of several hours (1–36 h; mean of 10 h in one case series) followed by recurrent symptoms [16, 17•]. A delay in giving adrenaline (epinephrine), insufficient adrenaline, or failure to administer a glucocorticosteroid may increase the risk of biphasic reactions [13, 18].

Table 2. Clinical criteria for the diagnosis of anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criterion is fulfilled following exposure to an allergen

- 1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least 1 of the following:
 - a. Respiratory compromise (e.g., dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
- 2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)
 - a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
 - d. Persistent GI symptoms (e.g., painful abdominal cramps, vomiting)
- 3) Reduced BP after exposure to a known allergen for that patient (minutes to several hours)
 - a. Infants and children: low systolic BP (age specific) or > 30% decrease in systolic BP
 - b. Adults: systolic BP < 90 mmHg or > 30% decrease from that person's baseline

PEF, peak expiratory flow; BP, blood pressure; GI, gastrointestinal

Anaphylaxis is a clinical diagnosis that builds on the criteria shown in Table 2. Retrospectively, the diagnosis may be supported if serum tryptase is elevated within a few hours after the reaction when compared with the patient's baseline levels. The differential diagnosis of anaphylaxis includes medical diseases, which affect the organ systems most frequently involved in anaphylaxis, such as status asthmaticus, vasovagal syncope, pulmonary embolism, anxiety and panic disorder, and hypoglycemia [13].

Regarding acute reactions during infusions of biologicals, typical symptoms include fevers, rigors, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, or changes in blood pressure and heart rate [19].

Management

Acute treatment of anaphylaxis begins with a rapid evaluation of vital signs, followed by immediate administration of adrenaline, which represents the drug of choice for anaphylaxis and should be given immediately to any patient with suspected anaphylaxis. Adrenaline exerts effects on (i) α -1 receptors causing peripheral vasoconstriction, thereby reversing hypotension and mucosal edema; (ii) β -1 receptors by increasing both the rate and force of cardiac contractions, thereby reversing hypotension; and (iii) β -2 receptors reversing bronchoconstriction and reducing the release of inflammatory mediators [20]. Treatment should be provided even if the diagnosis is uncertain since there is no contraindication to the use of adrenaline [13]. The recommended dose of adrenaline for anaphylaxis is 0.01 mg/kg (maximum 0.5 mg) administered intramuscularly every 5–15 min as necessary [21, 22]. Intramuscular administration into the anterolateral thigh is recommended as it allows for more rapid absorption and higher plasma adrenaline levels compared with subcutaneous or intramuscular administration in the upper arm [23, 24]. In patients who do not respond to intramuscular adrenaline, intravenous administration of the drug can be performed by adding 1 mg of adrenaline to 1 L of 0.9% normal saline and providing 2 mg/min (2 mL/min) to be titrated up to 10 mg/min (10 mL/min) if necessary [21]. The administration of adrenaline was associated in rare occasions to myocardial infarction, but this could be part of the natural history of anaphylaxis, because there are abundant mast cells in the human heart and the mediator of anaphylaxis could be provoked coronary artery spasms [25–28]. However, as already mentioned above, there are no absolute contraindications to treatment with adrenaline in a patient experiencing anaphylaxis; benefits outweigh the risks in the elderly and patients with pre-existing cardiovascular disease [13].

In some cases, as in patients that are treated with beta blockers, glucagon should also be considered; doses of 1–5 mg of the drug can be administered intravenously over 5 min. Glucagon acts by direct activation of adenylyl cyclase bypassing the beta adrenergic receptors [29]. All patients receiving emergency adrenaline must be transported to a hospital very quickly. Ideally, patients should be placed in a recumbent (supine) position, unless respiratory compromise contraindicates it, to prevent or to counteract potential circulatory collapse. Pregnant patients should be placed on their left side [9, 30••]. Once supine, patients should not be allowed to sit up until clearly fully stabilized, owing to the risk of “empty ventricle syndrome” which can precipitate a profound loss of blood pressure and death [31].

Patients with asthma, particularly those with poorly controlled asthma, are at increased risk of a fatal reaction. In these patients, anaphylaxis may be mistaken for an asthma exacerbation and inappropriately treated solely with asthma inhalers. Therefore, if there are ongoing asthma symptoms in an individual with known anaphylaxis, adrenaline should be given [32].

Supportive therapy such as inhaled beta2-agonists (for patients experiencing bronchospasm) and antihistamines (for control of cutaneous symptoms) can also be helpful, but should never replace epinephrine as the first-line therapy. Oxygen therapy should also be considered in any patient with symptoms of anaphylaxis, particularly for those with prolonged reactions. Intravenous crystalloid solutions should also be provided since massive fluid shifts can occur rapidly in anaphylaxis due to increased vascular permeability [30••].

Corticosteroids have a slow onset of action and, therefore, these agents have not been shown to be effective for the acute treatment of anaphylaxis. Theoretically, however, they may prevent biphasic or protracted reactions and, hence, are often given on an empirical basis. In this regard, a recent non-randomized study suggested a number needed to treat (NNT) of 173–176 to prevent a biphasic reaction [33]. If anaphylaxis fails to respond to intramuscular epinephrine and intravenous fluids, an intravenous infusion of epinephrine may be required; however, these infusions should be given by a physician who is trained and experienced in its use and has continuous blood pressure and cardiac monitoring equipment immediately available. Following acute treatment, patients should be observed for a period of time due to the risk of a biphasic response or possible recurrence of the reaction as adrenaline wears off. The observation period should be individualized and based on the severity of the initial reaction along with access to care. Experts have recommended observing patients for 4–6 h following an anaphylactic reaction, with prolonged observation times for patients with severe or refractory symptoms [32].

Long-term management

Only a few patients (less than 10%) after drug-induced anaphylaxis undergo a subsequent allergological evaluation [34]. Nevertheless, an allergological work-up is mandatory for patients with severe reactions caused by drugs. Indeed, it has been demonstrated that a referral to an allergist or immunologist can improve outcomes by further refining the diagnosis and establishing the cause of the event, with clear results in the prevention and management of future events [35].

Diagnosis

The allergological work up is essentially based on the clinical history that must be focused on the characteristics of symptoms, on their time of onset after the exposure to the drug, and on the presence of co-factors, for example, exercise, food, or alcohol [36]. Skin tests could be an important diagnostic tool in some cases of drug-related anaphylaxis, for example, for penicillins or platinum compounds [37]. In vitro testing (CAP-RAST, basophil activation testing) is available for numerous drugs, but their diagnostic accuracy has not been established [5••].

Drug challenge

Drug provocation tests (DPT) are primarily indicated to exclude hypersensitivity in non-suggestive history of drug hypersensitivity; to provide safe pharmacologically and/or structurally non-related drugs in proven hypersensitivity; to exclude cross-reactivity of related drugs in proven hypersensitivity; and, to establish a firm diagnosis in suggestive history of drug hypersensitivity with negative, non-conclusive, or non-available allergologic tests. In case of anaphylaxis, DPT may be required if diagnostic doubt remains [13].

Desensitization

Desensitization (DS) is a therapeutic approach delivered through DS protocols to patients in need of first-line drug therapy. It safely permits the administration of the needed medication and provides a temporary tolerance to the drugs that patients have presented immediate reactions to, including anaphylaxis and delayed reactions non-SCARS (severe cutaneous adverse drug reactions). The principles of IgE DS are based on in vitro and in vivo mast cell models [38, 39]. The administration of suboptimal progressive doses of antigen induces the inhibition of signal transduction and calcium flux through the activation of inhibitory pathways, which control the release of granule mediators [40], preventing cell activation and anaphylaxis. Choosing a safe starting dose, typically 1/1000 to 1/100 of the target dose, doubling the incremental steps and allowing for a sufficient time between steps such as a minimum of 15 min, are critical features to safe and successful DS [41].

Anaphylaxis in special conditions

Anaphylaxis during chemotherapy

Antineoplastic agents are the third cause of fatal drug-induced anaphylaxis in the USA [4]; the most implicated agents are platinum compounds and taxanes.

The pathogenesis of severe hypersensitivity reactions provoked by the platinum compounds cisplatin, carboplatin, and oxaliplatin probably involves IgE-mediated mechanisms [42, 43]. In this regard, several authors have observed positive skin tests performed with the different platinum salts in patients with hypersensitivity reactions [44, 45••].

In vitro tests are still under development and are not available in clinical practice. However, some authors detected specific platin IgE (sIgE) in patients with hypersensitivity reactions [46, 47]. The role of specific IgE was also investigated by Cajado et al. in 24 allergic patients (12 carboplatin and 12 oxaliplatin) and 17 controls. The authors observed a better sensitivity of oxaliplatin sIgE compared with carboplatin (75 vs 58.3%), but oxaliplatin sIgE was also detected in 3/12 controls (25%) lowering the specificity [48].

As regards taxanes, the pathomechanism of hypersensitivity reactions is not well defined and until a few years ago, it was thought to be non-IgE-mediated with direct mast cell or complement activation provoked by moiety itself or solvents. However, in the last few years, positive skin tests in patients with suspected hypersensitivity reactions to paclitaxel and docetaxel were reported by different authors [47, 49••, 50] which led to the speculation that at least in some cases, allergic reactions are IgE-mediated.

Anaphylaxis induced by chemotherapy differs in its presentation because, in addition to the classical symptoms, atypical symptoms have emerged, such as chills and fever during reactions to oxaliplatin and pain during taxanes-induced anaphylaxis [51••].

In case of severe reactions, if the chemotherapeutic drug cannot be stopped or replaced, the subsequent administration could be performed with a DS protocol.

Personalized DS protocols are generated to enable the delivery of a specific drug and target dose, based on in vitro protocols that have suboptimal incremental doses delivered at 10–15-min time intervals. The starting dose of the drug is 1/1000 or 1/100 of the dose target, as suboptimal doses trigger minimal mediator release. Continued incremental escalation of the drug, doubling the dose and the rate at each step at fixed time intervals, generates a temporary hyporesponsive status until the target dose is delivered [52].

An example of DS protocol is shown in Table 3.

Anaphylaxis provoked by radiocontrast media

Adverse reactions to iodinated contrast media (ICM) are not uncommon and can be provoked by toxicity or hypersensitivity pathomechanisms. In the past, high-osmolality ICM were associated with a high incidence of immediate reactions [52, 53] but, nowadays, after the introduction of non-ionic low-osmolality ICM in the 1970s, the prevalence of allergic reactions to ICM is

Table 3. Example of DS protocol for paclitaxel infusion

Full Dose	500.0 mg				Total mg to be injected in each bottle
Solution 1	300 cc of		0.017 mg/ml		5.000
Solution 2	250 cc of		0.200 mg/ml		50.000
Solution 3	250 cc of		1.984 mg/ml		496.096
Step	Solution	Rate (cc/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.0083	0.0083
2	1	5	15	0.0208	0.0292
3	1	10	15	0.0417	0.0708
4	1	20	15	0.0833	0.1542
5	2	5	15	0.2500	0.4042
6	2	10	15	0.5000	0.9042
7	2	20	15	1.0000	1.9042
8	2	40	15	2.0000	3.9042
9	3	10	15	4.9610	8.8651
10	3	20	15	9.9219	18.7870
11	3	40	15	19.8438	38.6309
12	3	75	186	461.3691	500.0000
	Total time =	351	minutes		

estimated to be 1:170,000, that is, 0.05–0.1% of patients undergoing radiologic studies with ICM [54, 55]. These percentages are generally higher for ionic ICM (0.16–12.66%) than for non-ionic ICM (0.03–3%) [55, 56].

Immediate reactions to ICM were not originally considered to be allergic, but rather anaphylactoid-like, owing to the capacity of former contrast media to induce nonspecific histamine release [57] through various mechanisms involved in immediate non-allergic reactions like: (i) the direct membrane effect, possibly related to the osmolality of the ICM solution [58]; (ii) activation of the complement system [59]; and (iii) direct formation of bradykinin [60]. But, several studies support the finding of specific IgE-mediated immunological mechanisms in immediate reactions, and positive skin test results with ICM have been reported in patients who experienced severe immediate reactions [61–63] and nowadays, according to the ENDA/EAACI position paper, at least 50% of hypersensitivity reactions to contrast media are caused by an immunological mechanism [62].

Although severe anaphylactic reactions can occur, symptoms of immediate hypersensitivity reactions are usually mild with the skin being the organ most commonly involved [64] with erythema and urticaria with or without angioedema, which appear in more than 70% of patients [65]. Severe symptoms include dyspnea, nausea, vomiting, and hypotension. In the most severe cases, anaphylactic shock and acute coronary syndrome (Kounis syndrome) can occur [66].

Brockow et al., in their ENDA/EAACI position paper on skin testing in patients with hypersensitivity reactions to ICM [62], suggested that skin testing may be a useful tool to diagnose ICM allergy, with a specificity as high as 96–100%, and may play an important role in the selection of a safe compound in previous reactors. Currently, according to different studies, the negative predictive value of skin testing for ICM appears to be between 94.2 and 97% [67••, 68, 69] and none of the reactions in patients who had negative skin test results were severe, which may reassure physicians who are hesitate to perform further evaluations in patients with negative skin test results. Furthermore, serial measurements of serum tryptase can help to identify the type of reaction [70, 71]: a twofold increase at the onset of the reaction above baseline levels is suggestive of anaphylaxis [72]. In vitro methods, basophil activation test and lymphocyte transformation test, are not currently used in routine diagnosis and still need to be validated and further research is required.

In case of a negative skin test result for the culprit ICM, a DPT should be performed (not in the case of a previous severe reaction), while, if skin testing gives a positive result for the culprit ICM, a DPT should be performed with an alternative ICM that gave a negative skin test result in order to identify a safe alternative [73].

The percentage of patients with positive skin tests varies according to the time between reaction and testing with an optimum in patients tested within 2–6 months [62]. This is in accordance with the results reported by the French CIRTACI group [74]. At later time points, the frequency of positive tests decreased significantly, especially for patients in the immediate group. This could be due to loss of sensitization over time as reported for other drug allergies [64] or a decreased reliability of the patients' history.

The value of premedication is rather controversial and may induce a false sense of security, especially when it is administered systematically without a prior allergy study [73]. It has only been shown to reduce the occurrence of mild

immediate reactions and has not been demonstrated to be useful for immediate moderate to severe and non-immediate reactions [75–77]; therefore, the use of premedication is being questioned.

While performing the ICM infusion, first-line drugs for treatment of anaphylaxis must always be available, as should the equipment and trained personnel be required for its management, including for potential cardiac arrest. If symptoms appear, the infusion should be interrupted immediately and an appropriate treatment administered (see paragraph above).

There is no evidence that seafood or inorganic iodine levels present in seafood or in topically applied iodine-containing solutions are related to anaphylactoid events from ICM [78].

In regard to other radiologic contrast media, immediate hypersensitivity reactions to gadolinium derivatives are the most frequently described, with an incidence of 0.07% in adults and 0.04% in children [79, 80]. The symptoms described with gadolinium chelates are very similar to those of immediate reactions to ICM and are mostly mild [80, 81], with the most common clinical manifestation being urticaria (50–90% of cases). Anaphylactic reactions are rare, with an incidence of 0.004 to 0.01% [80, 82].

Regarding barium contrast media, the most common adverse reactions are mild and non-allergic and include diarrhea, constipation, nausea, and vomiting, while the prevalence of allergic reactions is less than 2 per million [83, 84].

Contrast media are increasingly used worldwide, with millions of explorations being performed every day. Therefore, although these reactions are rare, they occur regularly and are often severe and even life-threatening [63].

Anaphylaxis and mastocytosis

Mastocytosis (MC) is a proliferative disorder of hematopoietic mast cell progenitors, leading to an expansion and accumulation of excessive numbers of mast cells in one or more organs, such as the skin, bone marrow, gastrointestinal tract, liver, and spleen [85].

Cutaneous mastocytosis (CM) is usually most frequent in childhood, while systemic mastocytosis (SM) mainly affects adults and involves one or more extra-cutaneous organs (bone marrow, gastrointestinal tract, lymph nodes, and spleen), with or without skin involvement. The majority of cases of SM show a somatic “auto-activating” point mutation at codon 816 of kit-receptor gene [86].

Mastocytosis has a wide variety of clinical manifestations, other than typical skin lesions, which are always due to the inappropriate release of mediators by mast cells (MCs) (e.g. pruritus, urticaria, angioedema, flushing, nausea, vomiting, abdominal pain, diarrhea, anaphylaxis and osteopenia/osteoporosis). In rare cases of aggressive disease, the clinical features are related to end-organ dysfunction due to MC tissue infiltration (e.g., hypersplenism, pathologic bone fractures, ascites, malabsorption, and cytopenias) [87].

The incidence and severity of anaphylaxis are greater in patients with mastocytosis compared with the general population. The triggers that can induce a massive degranulation of MC and cause anaphylaxis in adult subjects with mastocytosis are numerous, but hymenoptera stings seem to be the most

frequent (19–53% of cases of anaphylaxis), followed by foods (3–16% of cases) and drugs (5–9%) [88–90]. On the other hand, recurrent episodes of anaphylaxis may suggest underlying systemic mastocytosis. Although it is not uncommon that patients with idiopathic anaphylaxis have received diagnoses of mastocytosis, the association between mastocytosis and drug- or food-induced anaphylaxis does not appear to be as strong as the association with insect venom-induced anaphylaxis [91]. The increased mast cell numbers in mastocytosis, as well as the increased releasability of mast cell in mast cell activation syndromes [92], may lead to a higher frequency and severity of immediate hypersensitivity reactions and increase the risk of anaphylaxis to drugs [89]. The most commonly implicated agents are opioids, NSAIDs, muscle relaxants, and perioperative drugs [5••].

Anesthetic procedures can induce mast cell mediator release associated with mechanical irritation of tissues, stress, or drugs, such as neuromuscular blockers, opioids, hypnotics, and analgesic [93–97], and are considered to generate a greater risk in patients with mastocytosis, which has been seen in reports of severe reactions (e.g., systemic hypotension, anaphylaxis, and coagulopathy) resulting in patient death [98–103]. According to a Spanish study, they reported that the incidence of perioperative anaphylaxis in adult patients with mastocytosis is 0.4% [104], thus, greater than in the general population which is 0.01% [105]. Some studies have reported that the neuromuscular blockers most frequently involved in anaphylaxis during anesthesia are succinylcholine (60.6%) and atracurium (19.6%) [106], with a relatively high rate of IgE-mediated anaphylaxis elicited by succinylcholine and rocuronium, compared with other muscle relaxant agents [107]. Volatile anesthetic agents are not generally considered histamine-releasing drugs [108]. It is generally believed that most opioids are able to induce histamine release directly, a property thought to be responsible for many reactions that occur more frequently than IgE-mediated reactions to these drugs [109]. When needed, drugs, such as opioids and muscle relaxants, can be used, especially when there is no history of previous adverse reaction [110••]. If available, drugs with lower mast cell-releasing properties in vitro can be selected by the anesthetist, although clinical evidence for this approach is lacking [11]. It is not routinely recommended to perform skin tests to anesthetic drugs in patients with mastocytosis before an anesthetic procedure [93, 94, 104], whereas, mastocytosis patients with reactions during anesthesia should be referred for allergy testing to rule out reactions to specific drugs, and drugs, which are suspected to have caused previous reactions and/or tested positive on subsequent allergy testing, should be avoided [111]. There is no evidence based in the literature to support the value of premedication with antihistamines and corticosteroids prior to anesthesia in mastocytosis patients. However, there is no evidence to the contrary and, in practice, most specialists in referred centers recommend anti-mediator pre-treatment [112].

In regard to RCM, although anaphylaxis has been described in few case reports in patients with mastocytosis [89], in the current literature, there is no evidence of a greater risk of anaphylactic reactions to RCM in patients with mastocytosis, compared with the general population [88, 113]. The value of prophylactic administration of premedication in all adults with mastocytosis without previous reactions to RCMs, as is done in many centers, remains unproved and has to be further established by more data [110••].

In regard to NSAIDs, according to a work group report of the Mast Cell Disorder Committee [110●●], patients who tolerate aspirin and other NSAIDs before a diagnosis of mastocytosis generally continue to tolerate these medications and no avoidance is necessary, while graded challenges of an NSAID in any patient with mastocytosis, who has no history of their use, can be used to establish safety. In the same way, in regard to antibiotics, medications previously and continuously tolerated by patients are allowed, whereas, in patients with a history of an antibiotic reaction, the culprit drugs and those belonging to the same antibiotic family should be avoided until ruled out by allergy testing.

Mastocytosis is not a contraindication for vaccine or monoclonal antibodies therapy [110●●].

Skin testing is safe for patients with a history of anaphylaxis and mastocytosis and after a drug hypersensitivity reaction, allergy testing is recommended [111].

Conclusions

In conclusion, data on the frequency of drug hypersensitivity in mastocytosis and vice-versa are currently scarce, and evidence for an association appears to be limited [111]. Nevertheless, clonal mast cell disorders should be ruled out in cases of severe anaphylaxis: basal serum tryptase determination, physical examination for cutaneous mastocytosis lesions, and clinical characteristics of anaphylactic reaction might be useful for differential diagnosis [111].

Compliance with Ethical Standards

Conflict of Interest

Patrizia Bonadonna declares that he has no conflict of interest. Mauro Pagani declares that he has no conflict of interest. Alessandra Arcolaci declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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