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Review

Management around invasive procedures in mastocytosis
An update

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ABSTRACT

Objective: Mastocytosis is a chronic hematologic disorder that is characterized by the accumulation of aberrant mast cells and typically involves the skin and/or bone marrow. Patients with mastocytosis are at increased risk of anaphylaxis. Based on theoretical assumptions, medical procedures requiring general anesthesia or radiocontrast media are deemed hazardous for patients with mastocytosis. The objective of this article is to provide a comprehensive overview of the actual risk of iatrogenic anaphylaxis and provide recommendations for daily practice.
Data Sources: Various scientific search engines were used (eg, PubMed and Medline).
Study Selections: Because of the paucity of high-level studies on this topic, all available evidence was considered, including case reports.
Results: Reliable data on the incidence of iatrogenic anaphylaxis in mastocytosis are lacking. However, although the incidence as reported in (retrospective) cohort studies is higher than in the general population, it is still lower than commonly anticipated, with an incidence of 5.4% in 1 study. Adequate premedication and avoidance of certain physical stimuli can further decrease this risk by 10-fold. The role of drugs as elicitors of anaphylaxis is perhaps overestimated, and physical stimuli are at least as important in inducing release of mast cell mediators.
Conclusion: This article provides practical recommendations for the management of invasive procedures in patients with mastocytosis based on current knowledge of this topic.

Introduction

Mastocytosis is a chronic myeloproliferative disorder of mast cells (MCs). It is a rare disease, with an estimated prevalence of 10 to 13 in 100,000.[1,2] To establish the diagnosis of systemic mastocytosis (SM), an accumulation of neoplastic MCs must be detected in the bone marrow, as opposed to cutaneous mastocytosis, which is confined to the skin. However, recent experience has shown that adult-onset mastocytosis in the skin is associated with SM in most cases if adequate workup is performed.[3] The World Health Organization has defined diagnostic criteria for SM and various subtypes, ranging from indolent SM to more advanced subtypes.[4] When MCs are activated, they release large amounts of granule-stored mediators. Hence, anaphylaxis is a threat for all patients with SM because of their high MC load, with a lifetime prevalence of up to 50% for adult patients.[5] The best-known trigger for anaphylaxis in patients with SM is Hymenoptera venom, but many cases of anaphylaxis in SM are idiopathic or the result of a combination of stimuli.[6,7] Conventional allergy tests such as measurement of specific immunoglobulin E (IgE) and skin tests for suspected allergens often produce negative reactions. There are

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Table 1
Summary of Published Data on Iatrogenic Anaphylaxis in Adult Patients With Mastocytosis

	Anaphylaxis from general anesthesia	Mild reaction to general anesthesia	Anaphylaxis from radiocontrast media	Mild reaction to radiocontrast media	Anaphylaxis related to delivery	Other cause of iatrogenic MC mediator-related symptoms (n)
González de Olano et al,[7] 2007	1/163	0/163	0/163	1/163	N/A	NSAID (4), β-lactam (2), streptomycin (1), phenylephrine (1), codeine (1)
Matito et al,[15] 2007	2/66	1/66	N/A	N/A	N/A	Epidural (3/76)[a], sedation (1/67), local anesthesia (4/515)
Brockow et al,[6] 2008	0/74	N/A	2/74	N/A	N/A	Local anesthesia (1), NSAID (1), codeine (1), amoxicillin (1)
Gülen et al,[16] 2013	0/84	0/84	0/84	0/84	N/A	NSAID (2)
Hermans et al,[17] 2016	0/136	0/136	1/136	0/136	N/A	NSAID (2)
Case reports[10–14,18]	3	N/A	1	N/A	1	Percutaneous coronary intervention (1)
Choo et al,[19] 2000	—	—	—	—	0/11	N/A
Matito et al,[20] 2011	—	—	—	—	0/45[b]	N/A
Ciach et al,[21] 2016	—	—	—	—	0/23	N/A
Total[c]	3/523	1/449	3/457	1/383	0/79	26/602

Abbreviations: MC, mast cell; N/A, not available; NSAID, nonsteroidal anti-inflammatory drug.
[a]One patient developed anaphylaxis and 2 patients had a mild reaction (flushing, erythema, or hives).
[b]Five of 45 patients had mild MC mediator symptoms (pruritus, generalized exanthema, or flushing).
[c]Excluding case reports.

various non–IgE-mediated mechanisms that can cause MC degranulation, including physical stimuli (temperature change, exercise, strong odors, pressure, and friction) and emotional stress. Another often feared elicitor is medication, with anesthetic agents, opiates, and radiocontrast media as the main culprit drugs.[8] In past decades, several case reports have mentioned severe, sometimes fatal, iatrogenic anaphylaxis in mastocytosis, reinforcing the currently common notion that this is a serious risk for patients with SM.[9–13]

Based on these data and hypotheses, undergoing an invasive procedure often causes anxiety for patients with SM and the involved professionals. The anxiety is often aggravated by a lack of experience with this rare disease and the diversity of protocols among different hospitals regarding the perioperative management of patients with SM. However, anesthetic techniques have changed and several potentially hazardous drugs are have become obsolete. Furthermore, modern anesthesiologists pay more attention to the general perioperative environment such as temperature and stress.[8,14] Therefore, the actual risk of perioperative anaphylaxis might be overestimated and current protocols probably could be adjusted. In this review, we focus on the actual risk of anaphylaxis from invasive procedures in patients with mastocytosis and provide recommendations for prophylactic measures.

Incidence of Iatrogenic Anaphylaxis in Mastocytosis

Several population studies on mastocytosis illustrate the rarity of iatrogenic anaphylaxis. These data are presented in Table 1.[6,7,10–21]

Anesthesia and Surgery

The most complete study on this topic reviewed the medical records of 459 adult patients with mastocytosis who underwent 676 anesthetic procedures, of which 66 involved general anesthesia.[15] According to Matito et al,[15] 8 of 676 procedures (1.2%) were complicated by a mild reaction and 3 (0.4%) were complicated by anaphylaxis. However, most were low-risk procedures, namely local anesthesia (76%), epidural anesthesia (11%), or sedation (10%). The risk of MC mediator-related symptoms was considerably higher with general anesthesia, where 4 of 66 procedures were complicated by a reaction (6%). Anaphylaxis occurred in 2 of 4 patients who had not received premedication. Information on the exact procedures is not provided. These rates are higher than the incidence of hypersensitivity reactions from anesthesia in the general population, which is estimated at 1:1,250 to 1:18,600 procedures, depending on the country of investigation.[22] When looking at the entire cohort of Matito et al,[15] patients who developed any type of reaction less frequently received premedication than asymptomatic patients (45% vs 87%, respectively). The incidence of anaphylaxis was significantly higher in patients who did not receive any premedication (5.4% vs 0.4%, respectively). Other risk factors for anaphylaxis were major surgery and a history of anaphylaxis in general, regardless of the trigger of anaphylaxis.[15]

Other, smaller, cohort studies have reported even lower rates of perioperative anaphylaxis in patients with SM; of a combined total of 457 adult patients, only 1 had a history of perioperative anaphylaxis. A reaction to local anesthesia was not reported in any of these studies.[6,7,16,17] Table 1 presents the published data from cases. Of course, these numbers can be biased because most relied on the patient-reported medical history.

Radiocontrast Media

To date, there have been no studies specifically designed to identify the risk of anaphylaxis from radiocontrast media in patients with SM. In the general population, the incidence of mild immediate reactions is 0.5% to 3%, and the incidence of severe immediate reactions is 0.01% to 0.04% of all intravenous administrations.[23,24] Indirect evidence has shown similarly small numbers of adverse reactions in patients with SM; in 4 cohort studies encompassing 457 adult patients, radiocontrast-related hypersensitivity reactions were reported in 3 patients, of whom only 1 developed anaphylaxis.[6,7,16,17] Data on premedication are incomplete for these patients. Furthermore, a review on fatal anaphylaxis from radiocontrast media described 34 cases without known mastocytosis. Autopsy of 8 of these fatalities failed to diagnose SM after adequate investigation.[25]

Pregnancy and Delivery

Data from 2 cohort studies on pregnancy and delivery in patients with SM are reassuring, although the number of patients is small. In the first cohort, labor was uneventful in all 23 women. However, details on the administration of premedication were not provided.[21] The second study described the course of 45 pregnancies.[20] Five women developed MC mediator-related symptoms during delivery, consisting of pruritus, erythema, or flushing. No one developed anaphylaxis. Premedication was administered before 17 deliveries (38%). One case report described a woman with indolent SM in whom delivery was complicated by anaphylactic shock despite pretreatment with dexamethasone and diphenhydramine. This

Table 2
High-risk Procedures That Form Indications for Premedication (Any of the Following Criteria)

Characteristics of procedure
General anesthesia
Major surgery
Gastrointestinal or cardiac surgery[a]
Patient characteristics
Previous MC mediator-related symptoms during procedure
History of anaphylaxis (regardless of trigger)
Atopic background
Use of β-blockers[b], ACE inhibitors[c], NSAIDs[c]
Severe mastocyte infiltration of the skin

Abbreviations: ACE, angiotensin-converting enzyme; MC, mast cell; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a]Risk factor on theoretical grounds; no clinical evidence.
[b]Beta-blockers can attenuate the effect of epinephrine in anaphylaxis but are a not risk factor.
[c]ACE inhibitors and NSAIDs can augment an anaphylactic reaction as cofactors.

patient previously experienced 1 episode of idiopathic anaphylaxis during another pregnancy.[18] For comparison, the risk of anaphylaxis during delivery is 2.7:100,000 deliveries in the general population. However, these reactions are caused in most cases by IgE-mediated drug allergies.[26]

Theoretical Background

Known Triggers of MC Activation

As stated earlier, many substances other than IgE can trigger release of MC mediators. Interestingly, MCs in the skin and airways of patients with mastocytosis are not more reactive than those of patients with asthma or healthy controls.[27] Specific drugs that are known to induce histamine release are codeine, morphine, benzylisoquinolines (eg, mivacurium, atracurium), and some antibiotics (eg, vancomycin, polymyxin B).[28] The potential of codeine and morphine to induce MC degranulation was proved extensively in vitro and in vivo.[29] Most other opiates do not have this effect when tested in vitro, showing a certain class effect.[30,31] For muscle relaxants, there also appears to be considerable variation in their ability to induce release of MC mediators, with succinylcholine and cis-atracurium appearing as the safest drugs in this context.[32,33] Radiocontrast media could trigger MC degranulation by multiple mechanisms, for instance, the direct effect of their high osmolality on the cell membrane or nonspecific binding of contrast molecules to membrane receptors and components of the complement system.[25] However, in vitro tests did not show degranulation after stimulation of human MCs with radiocontrast media.[34] Unfortunately, most of these assumptions are based on in vitro research, which is notoriously complicated for MCs because they are continually interacting with adjacent cells in vivo.[35]

Next to medication, several physical stimuli might induce MC mediator release during invasive medical procedures or act as costimulatory factors.[6] Among these are friction, pressure, temperature changes, and emotional stress. The reaction to physical stimuli can vary among patients but severe anaphylaxis from physical stimuli alone is rare. Mostly they serve as cofactors in combination with other stimuli.[6] Moreover, MCs have a great phenotypic variation depending on the tissue they reside in. The composition of released mediators can vary accordingly and the range can vary depending on the kind of stimulus. For instance, procedures involving the gastrointestinal tract might be more prone to MC degranulation because these organs contain many MCs.[36]

Risk Factors for Anaphylaxis

Previous cohort studies have shown that anaphylaxis is more common in patients with mastocytosis who have a history of idiopathic anaphylaxis, particularly those with indolent SM without skin involvement.[6,17,37,38] Furthermore, higher total serum IgE levels and older age are associated with an increased risk of anaphylaxis.[8,37] Of note, many studies on risk factors for anaphylaxis focused on Hymenoptera venom–related anaphylaxis and it is not clear whether these data can be extrapolated to iatrogenic anaphylaxis in patients with mastocytosis. Moreover, most studies included patients without mastocytosis, which is an essentially different population. For instance, increased serum tryptase levels are associated with a higher risk of anaphylaxis in patients without mastocytosis,[39–41] whereas a bell-shaped curve is described in mastocytosis.[42] In the latter, patients with a serum tryptase level of approximately 12 to 40 μg/L had the highest risk of Hymenoptera venom–related anaphylaxis, and this risk decreased with a further increase of serum tryptase levels.[42] A recent Swedish study found similar results regarding serum tryptase levels and the risk of anaphylaxis in mastocytosis.[37] Thus, a higher MC load might be "protective" against anaphylaxis, possibly through a favorable antigen-to-MC ratio, although this is purely speculative.

Rationale for Premedication

Because the available data on the risk of iatrogenic anaphylaxis are conflicting, the value of premedication remains unclear. Although the overall risk of severe anaphylaxis appears to be low, a distinction must be made between low- and high-risk procedures (Table 2). For the latter, it seems reasonable to administer premedication. However, it is less evident which drugs should be used as prophylaxis. The most important mediators in acute anaphylaxis are histamine, leukotrienes, prostaglandins, proteoglycans, tumor necrosis factor-α, and platelet activating factor.[43] Therefore, premedication should consist of drugs that block these mediators. Histamine receptor antagonists provide relief from only cutaneous symptoms such as erythema and pruritus and do not protect against anaphylaxis.[44] There is additional evidence showing the synergistic effect of H_2-receptor antagonist on the pharmacokinetics of H_1-receptor antagonists, arguing for combining these 2.[45] Leukotriene antagonists appear less effective in attenuating MC mediator-related symptoms, although randomized trials in patients with mastocytosis are lacking.[46] Furthermore, benzodiazepines are valuable to remove the trigger of emotional stress and thus could lower the risk of perioperative anaphylaxis in patients with SM.[15]

Despite the paucity of randomized clinical studies on this topic, corticosteroids are widely used in protocols for the prophylaxis of acute anaphylaxis. There are several well-designed in vitro studies that prove that corticosteroids have an acute effect on MC degranulation and activation, probably through membrane-bound glucocorticoid receptors.[29,47–49] Studies that have used skin tests with allergens as a model for MC reactivity have reported contradictory results, possibly reflecting the difference in duration of corticosteroid use, because only corticosteroid use of short duration suppressed skin test reactivity.[50,51] One randomized clinical trial performed in the 1990s compared prophylaxis with 32 mg of methylprednisolone at 12 and 2 hours before the administration of radiocontrast media with placebo. Methylprednisolone lowered the risk of hypersensitivity reactions from 4.9% to 1.7%.[52] Although the total number of reactions was small and the 2 studies did not include patients with mastocytosis, these data suggest some benefit from the inclusion of corticosteroids in a premedication regime. Hence, the administration of corticosteroids shortly before a procedure might attenuate MC degranulation and makes more sense than administering corticosteroids only when a patient has developed anaphylaxis and extensive degranulation has already occurred.

Previously Published Protocols for Perioperative Prophylaxis

In brief, there are few published practical guidelines on prophylaxis for invasive procedures in patients with mastocytosis. A European

Table 3
Safety of Perioperative Drugs for Patients With Mastocytosis[8,36,53,55,59]

	IV hypnotics	Inhaled hypnotics	Local anesthetics[a]	Neuromuscular blocking agents
Recommended	Etomidate Propofol Ketamine	Desflurane Isoflurane Nitrous oxide Sevoflurane	Amide type (eg, lidocaine)	Succinylcholine Cis-atracurium Pancuronium Vecuronium
Unclear	Thiopental		Ester type (eg, procaine)	Rocuronium
Discouraged				Rapacuronium Atracurium Mivacurium
	Analgesics	Antiseptics	Plasma substitutes	Miscellaneous agents
Recommended	Fentanyl Sufentanil Remifentanil Alfentanil Acetaminophen	Chlor-hexedine Povidone iodide	Albumin Gelatin	Atropine Ondansetron Oxytocin
Unclear	Morphine[b] NSAIDs[c]		HES	Protamine
Discouraged	Codeine Nefonam			Aprotinin (fibrin glue)

Abbreviations: HES, hydroxyethyl starch; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a]Severe systemic reactions to local anesthetics are very rare and often related to immunoglobulin E.
[b]Titrate slowly; rapid infusion can aggravate mast cell mediator release.
[c]Avoid if not used previously.

Academy of Allergy and Clinical Immunology position paper on drug hypersensitivity in MC disease stated that the evidence on the risk of iatrogenic anaphylaxis is low, as is the evidence for premedication. Based mainly on expert opinion, the investigators recommended the administration of H_1 antagonists, benzodiazepines, and corticosteroids before invasive procedures. Also, the importance of cofactors such as temperature changes and pressure was stressed.[8] Other published reviews made similar statements but often did not go further than generalities, without providing tangible advice regarding which medication and dosages to use as premedication. Lists of drugs that should be avoided in mastocytosis are based on theoretical assumptions and some case reports.[36,53,54] To create a protocol based as much as possible on evidence, well-established guidelines for prevention of radiocontrast in general were taken into account when writing these recommendations.[55–57]

Practical Recommendations

Based on the aforementioned considerations and published expert reviews and protocols on this topic,[8,36,44,53,56–58] we have composed structured recommendations for lowering the risk of anaphylaxis from medical procedures in patients with all forms of mastocytosis.

General Considerations

A risk analysis should be performed to determine whether premedication is indicated. Risk factors that could necessitate premedication are presented in Table 2, but this list is not complete and individual considerations are necessary for each patient. We recommend that a plan of action be established before the procedure by a multidisciplinary team consisting of a specialist in mastocytosis, an anesthesiologist, and the physician performing the procedure. It is preferable to involve the patient in this stage to lessen the patient's concerns. A detailed survey on previous anaphylaxis and known drug allergies is of paramount importance in the prevention of iatrogenic anaphylaxis. A comprehensive workup for specific drug allergies should be considered only if a patient previously experienced drug-related anaphylaxis, because patients with mastocytosis also can develop "ordinary" IgE-mediated allergies. When drug sensitization testing is not possible, drugs that previously caused adverse reactions should be avoided. There is no current role for preoperative drug sensitization testing in the absence of previous allergic reactions.[54] Nonsteroidal anti-inflammatory drugs should be avoided if the patient has not used them previously. Conversely, if nonsteroidal anti-inflammatory drugs have been used previously without any problems, then they can be continued. As outlined earlier, several physical stimuli can induce MC degranulation, and all members of the treatment team need to be aware of this. Ambulatory surgery also is possible in patients with mastocytosis, because premedication can be given orally in most cases.

Prophylactic Treatment Before High-Risk Procedures

We have outlined our protocol for the management of high-risk procedures in patients with mastocytosis. Specific medications and dosages can vary among countries. Also, physicians can choose to partly follow the protocol, for example, to administer only a histamine receptor antagonist prior to low-risk procedures.

Preoperative

- Administer benzodiazepine to decrease anxiety 1 to 2 hours before the procedure
- Corticosteroids
  - 12 and 2 hours before procedure: 0.5 mg/kg of prednisolone or equivalent for oral administration (maximum dose 60 mg); or
  - For an emergency procedure: 200 mg of hydrocortisone intravenously
- Histamine receptor antagonists
  - 2 hours before procedure: 10 mg of levocetirizine or equivalent fast-working H_1-receptor antagonist orally and 300 mg of ranitidine or equivalent H_2-receptor antagonist orally; or
  - 15 minutes before procedure: 2 mg of clemastine or equivalent H_1-receptor antagonist intravenously and 300 mg of ranitidine or equivalent H_2-receptor antagonist intravenously

Perioperative

- Close monitoring and anesthesiologist present in the room
- Limit changes in room temperature (increase or decrease)
- Avoid pressure or friction of the skin as much as possible, especially in patients with extensive cutaneous mastocytosis
- Avoid drugs as noted in Table 3[8,36,53,55,59]
- Keep epinephrine ready to use (adjust to patient's weight)

Postoperative

- Avoid drugs as noted in Table 3
- General considerations for avoidance of physical stimuli still need to be adhered to

Local Anesthesia

Local anesthesia is generally safe in patients with mastocytosis. Rare cases of anaphylactoid reactions associated with local anesthetic procedures were probably the result of physical stimuli or IgE-mediated allergies. Moreover, vasovagal collapse is sometimes mistaken for anaphylaxis. Premedication is not advised in procedures in which only local anesthesia or epidural anesthesia is used.

Radiologic Contrast Media

Iodized radiocontrast media have a higher risk of anaphylaxis than gadolinium, although there are some (rare) cases of severe anaphylaxis after gadolinium administration in the general population.[55] There is no rationale for the avoidance of contrast media. Premedication is indicated only when a patient has previously experienced anaphylaxis from radiocontrast media or in patients who are estimated to have a high risk of radiocontrast-induced anaphylaxis (Table 2).

Cardiologic Interventions

Mastocytosis can first present with cardiac symptoms such as unexplained syncope or Kounis syndrome (coronary spasms). Because MCs are constitutively present in the heart, a cardiologic intervention could pose a risk for anaphylaxis. To date, merely 1 case report was published of anaphylactic shock during percutaneous coronary intervention in a patient who had a history of unexplained syncope.[59] Of course, the administration of radiocontrast media can trigger anaphylaxis. Therefore, we suggest using the same considerations for prophylaxis before percutaneous cardiologic interventions as for radiocontrast media. However, it must be noted that this suggestion is based mostly on theoretical assumptions because randomized studies are lacking.

Delivery

Based on the available data, premedication before an uncomplicated delivery is not strictly necessary. However, it can be considered for patients who previously experienced anaphylaxis unrelated to delivery, especially for those with previous idiopathic or iatrogenic anaphylaxis. Premedication also is indicated for deliveries for which general anesthesia is required. No teratogenicity has been described for H_1 antagonists, although sedative H_1 antagonists can induce sedation in the newborn child when used directly before delivery. Cetirizine is the preferred H_1 antagonist in pregnant women. Ranitidine also can be used safely during pregnancy and labor.[60]

Children

Prophylaxis of anaphylaxis in children with mastocytosis is beyond the scope of this review. Although the incidence of anaphylaxis is much lower in pediatric than in adult mastocytosis, iatrogenic anaphylaxis has been reported in children and the same recommendations for premedication probably apply, with lower doses if necessary.

Acute Treatment of Anaphylaxis

For anaphylaxis, the patient should be treated according to current guidelines for anaphylaxis.[44] The first step is to remove the trigger. Next, timely administration of epinephrine is the single-most important lifesaver in this context. Of note, the dosage of epinephrine for anaphylaxis is lower than in the setting of cardiac arrest (0.5 mg for body weight >60 kg), and it should be given intramuscularly in the mid-outer thigh. Intramuscular epinephrine can be repeated after 5 to 10 minutes if the first dose is not effective. If intramuscular epinephrine appears ineffective after 2 to 3 doses, then continuous intravenous administration can be considered.[44] After stabilizing the patient, histamine receptor antagonists are effective mainly for relief of cutaneous symptoms.[45] Although the evidence is weak, corticosteroids might attenuate protracted anaphylaxis and can be administered once all first-line treatment steps are completed.[19,44]

Conclusion

The risk of iatrogenic anaphylaxis in patients with mastocytosis is generally lower than most physicians anticipate. However, the risk is increased compared with the general population, and anaphylaxis might be more severe in patients with mastocytosis. Adequate perioperative management lowered the incidence of anaphylaxis from 5.4% to 0.4% in 1 study, securing the indicated treatment. A structural, patient-tailored risk assessment and the subsequent therapeutic plan are pivotal in this context. The role of drugs as elicitors of anaphylaxis is probably overestimated, and physical stimuli are at least as important in inducing release of MC mediators.

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