

Drug Allergy in Mastocytosis

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KEYWORDS

- Mastocytosis • Mast cell diseases • Clonal mast cell disorders • Drug allergy
- Drug hypersensitivity • Anaphylaxis

KEY POINTS

- Mastocytosis in adults is associated with a history of anaphylaxis in 22% to 49%.
- Drugs are known to elicit anaphylaxis in patients with mastocytosis, but data on patients with drug hypersensitivity and mast cell diseases are scarce.
- In unselected patients with drug hypersensitivity, only a few patients with unrecognized mast cell disease have been described.
- In patients with drug anaphylaxis, basal serum tryptase determination and careful skin inspection are recommended to exclude mast cell disease.
- The risk of systemic reactions during general anesthesia can be reduced by an assessment of a patient's personal risks (previous reaction to a drug or during surgery) and by avoiding specific trigger factors (patient's temperature changes, infusion of cold solution, tissue trauma, friction and other mechanical factors).

INTRODUCTION

Patients with mastocytosis have an increased risk of anaphylaxis with a prevalence reported between 22% and 49% in adults and between 6% and 9% in children.^{1,2} Fatal anaphylaxis has been described after Hymenoptera sting; anesthesia; the intake of drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), codeine, and peri-operative drugs; foods and unknown causes.^{2–4}

Immunologic drug hypersensitivity reactions may commonly be divided into immediate (<1 h) and nonimmediate (>1 h) reactions depending on the time of onset of symptoms.⁴ Immediate reactions, possibly IgE-mediated, appear within 1 to 6 hours after drug intake and usually include urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea), and anaphylaxis.⁵ However, the frequency of underlying mast cell diseases (MCD) in patients with drug hypersensitivity is still unknown.

Conflict of Interest: None.

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Drug Anaphylaxis in Patients with Mastocytosis

Drugs are among the listed trigger factors for anaphylaxis in patients with mastocytosis. There are no data on drug-induced urticaria alone. Nevertheless, published data are based on case reports and a few small case series that do not lead to clear indications.

NSAIDs, β -lactam antibiotics, radiocontrast media (RCM), aminoglycosides, streptomycin, phenylephrine, codeine, and local and general anesthesia have been listed as trigger factors in patient histories.^{1,2} However, there are no formal confirmations by positive skin test or provocation test described in the literature.

MCD in Patients with Drug Hypersensitivity

In patients with anaphylaxis, a few recently published case reports have indicated an association between severe systemic reactions during general anesthesia and persistent high tryptase values, but bone marrow biopsy was performed only in some cases.^{6–8} In addition to reactions to general anesthesia or antibiotics, anaphylaxis to iodinated contrast media has been described in a patient who was subsequently diagnosed with systemic mastocytosis (SM).⁹ Another paper reports a case of an acetylsalicylic acid-dependent anaphylaxis to carrot in a young patient with SM, and oral allergy syndrome to raw carrots was confirmed by oral provocation test.

Only selected studies have tried to investigate undetected MCD. In contrast to studies in patients with Hymenoptera venom allergy, where 88% of patients with anaphylaxis and raised tryptase values had a clonal MCD (SM or monoclonal mast cell activation syndrome), the association between severe systemic reactions to drug and MCD is far lower.¹⁰ An Italian study determined the frequency of MCD in patients with food- or drug-induced anaphylaxis: out of 86 patients with drug hypersensitivity only 7 patients (8.1%) had increased serum tryptase levels greater than 11.4 ng/mL.¹¹ However, only one out of five bone marrow-tested patients was finally diagnosed with SM. No case of monoclonal mast cell activation syndrome was documented. Moreover, the study authors observed that the severity of reactions was significantly greater in patients with drug hypersensitivity.

These data were confirmed in another publication where the clinical, biologic, and molecular characteristics of 83 patients with anaphylaxis and other symptoms attributable to MCD without skin involvement were analyzed. In patients with clonal MCD the most common trigger for anaphylactic episodes was Hymenoptera sting, whereas drugs were mostly involved as a trigger in nonclonal MCD.¹²

In other studies on drug hypersensitivity, which included serum tryptase measurements after reactions, bone marrow biopsy to diagnose MCD was not performed.^{13–16}

MCDs AND GENERAL ANESTHESIA

The literature on perioperative drug safety in patients with mastocytosis is very limited, and is taken from a few case reports and some small case series that often give conflicting information on single drugs and drug groups tolerated or not by these patients. Large cohort studies looking at the prevalence of reactions during general anesthesia in patients with SM have not been published. Thus, it is not possible to provide general recommendations regarding drugs or groups of drugs that are either well tolerated or not tolerated. A recent review of the available literature on surgical procedures in patients with mastocytosis tries to provide indications on how to manage perioperative courses and avoid known trigger factors.¹⁷

Given the improvement of anesthetic procedures in the last few decades, those drugs reported as potential trigger factors in early case reports are no longer considered to be

valid in most countries. Particular attention to physical potential trigger factors should be observed: sudden temperature changes in patients and the operating room, infusion of cold solutions, wide tissue trauma, frictions, and other mechanical factors should all be avoided. Because mast cell degranulation can be triggered by anxiety, premedication with sedatives, such as benzodiazepines, should be considered in selected patients.

Risk Factors

The current literature does not make it possible to quantify the risk of systemic reaction during general anesthesia in patients with mastocytosis. Anaphylaxis in children with pediatric-onset mastocytosis is rare and limited to patients with extensive skin disease (>40% of body surface) and higher serum tryptase levels.² In a retrospective study of patients with pediatric mastocytosis that includes 24 general anesthetics and five cases of sedation and local anesthesia in 22 patients, adverse reactions were limited to flushing in 9% and gastrointestinal reactions with nausea, vomiting, and/or diarrhea in 18% of patients.¹⁸ Patients did not follow any prophylactic treatment with H₁ and H₂ blockers or steroids, but they continued their chronic antimediation therapy; no special anesthetic recommendations were reported. Moreover, a review of pediatric cases of anesthesia in children with mastocytosis has suggested that the risk for most pediatric patients is probably overstated by mastocytosis Web sites.¹⁹

Risk for adults seems higher and occurs mainly in systemic forms of mastocytosis, such as indolent SM, regardless of skin involvement.² The risk is probably lower in patients that never have experienced anaphylaxis and/or have tolerated previous general anesthesia. Instead, patients who have reported anaphylaxis, especially those that have experienced systemic reactions after drug administration or during anesthesia, should be considered at higher risk and an allergy evaluation should be strongly considered for these patients before elective procedures.

Value of Premedication

Currently, there is no evidence of the efficacy of premedication with antihistamine (anti-H₁ and anti-H₂) and corticosteroids to prevent systemic reactions in patients with mastocytosis. However, there is no evidence to the contrary either: some groups of specialists suggest premedication only in selected cases, whereas other groups recommend pretreatment in all patients in addition to their chronic antimediation therapy.²⁰

A reasonable, but unproved approach is to consider premedication with an intravenous antihistamine (eg, chlorphenamine, 10 mg, diphenhydramine, 25 mg) 1 hour before anesthesia ± corticosteroids (eg, prednisone, 40–60 mg, 13, 7, and 1 hour before anesthesia) at the discretion of the anesthetist. This is extrapolated from the regimen used in patients with contrast media allergies. The value of adding an H₂ blocker (eg, ranitidine 1 hour before anesthesia) remains unknown.³ To prevent anxiety-triggered mast cell degranulation, premedication with sedatives, such as benzodiazepines, should be considered.

Tryptase

Tryptase is a serine protease predominantly retained in the granules of mast cells and released after their activation and degranulation. An increase from baseline level during allergic symptoms is suggestive of IgE-mediated mast cell activation and correlates with the clinical severity of the reaction.²¹

Serum tryptase peaks at 30 to 90 minutes after the onset of symptoms and decreases in a few hours. Total serum tryptase level greater than 11.4 µg/L is consistent

with systemic anaphylaxis.²² Thus, it is important to measure tryptase value in all patients immediately after a reaction to confirm mast cell activation, and also to compare the acute value with the basal tryptase value, which should be measured several days after full recovery of the patient.

Anesthesia in Childhood Mastocytosis

Anaphylaxis in children with pediatric-onset mastocytosis is rare and probably overstated. Even with these patients, however, the anesthetist should be aware of the clinical conditions of the patient and should have a thorough understanding of mastocytosis and its manifestations.^{18,19}

So far, there is no evidence of a higher risk of reactions in patients with pediatric-onset mastocytosis. Although a range of equally effective drugs is available, those with minimal histamine release should be selected (eg, fentanyl and vecuronium instead of morphine and atracurium or mivacurium). Medications and equipment to treat perioperative anaphylaxis should be readily available.

Anesthesia in Adult Patients with Mastocytosis

The risk of anaphylaxis seems to be higher in adults with mastocytosis than in children, but it is not currently possible to clarify whether the severity of the reaction during anesthesia is a consequence of a higher mast cell load and if the frequency of reactions is higher compared with the general population. Randomized, controlled trials regarding the safety of anesthetic drugs in patients with mastocytosis are not available; thus, the indications for their use can be based only on case reports and case series, or on the use of those drugs considered safer in the general population (Table 1).

In general, histamine-releasing drugs (ie, certain opioids and neuromuscular blocking agents) should be avoided if possible or administered slowly. Induction agents are generally considered to be well tolerated (thiopental is associated with the highest number of reports). Inhalant anesthetics of the fluran family have not been associated with anaphylaxis.^{17,23}

Muscle relaxants with the highest unspecific histamine release are atracurium and mivacurium. Rocuronium and succinylcholin have been described as being associated with the highest number of allergic reactions.²³ Vecuronium, pancuronium, and cisatracurium have not been reported to cause a high number of reactions perioperatively.

Opioids, such as morphine and codeine, should be avoided if possible because they have been associated with mast cell activation in patients with mastocytosis. Fentanyl and related agents remifentanyl, sufentanyl, and alfentanyl do not seem related to a high risk of reactions.²³

Local Anesthesia

There are not enough data to support an increased risk for mastocytosis in patients with local anesthesia. A recent retrospective study on mastocytosis in pregnancy reported good tolerance to epidural amide-type local anesthesia, and reported mild symptoms of mast cell mediators release (generalized erythema and flushing) in 5 (11%) out of 45 patients only.²⁰ Moreover, labor induction was carried out in nine vaginal deliveries using oxytocine (N = 8) and dinoprostone (N = 1) without any symptom. At the discretion of the anesthetist, prophylactic antiallergic therapy was given in 38% of cases, using different combinations of antihistamines and corticosteroids.

Table 1
Perioperative drugs associated with a lower or higher risk of reactions during surgical procedures in mastocytosis

Perioperative Drugs	Low Risk	Avoid ^a
Intravenous analgesics		
Opioids	Fentanyl Sulfentanyl Remifentanyl Alfentanyl	Morphine Codeine
Analgesic	Paracetamol (acetaminophen)	
General anesthetics		
Hypnotics	Propofol Etomidate Ketamine	Thiopental
Benzodiazepine	Midazolam	
Halogenated gases and nitrous oxide	Desflurane Isoflurane Sevoflurane Nitrous oxide	
Neuromuscular blocking agents		
Depolarizing neuromuscular blocking agents		Succinylcholine
Nondepolarizing steroidal neuromuscular blocking agents	Pancuronium Vecuronium	Rocuronium
Nondepolarizing benzylisoquinolin neuromuscular blocking agents	Cis-atracurium	Atracurium Mivacurium
Anticholinergic	Atropine	
Plasma substitutes	Cristalloids Albumin	Gelatin
Local anesthetics	Amide-type	

^a If other agents can be used that are equally effective.

General recommendations for anesthesia

1. Children have a low risk of anaphylaxis during anesthesia, except for those with extensive skin disease and especially active disease-forming blisters. The latter group of children should be anesthetized with caution (the same as with adults).
2. Patients with previous reactions during anesthesia or toward other drugs should be considered for allergy assessment before surgery to identify responsible allergens.
3. The anesthetist must be informed about the form of mastocytosis, basal serum tryptase levels as a marker of the total mast cell load, and previous anaphylactic episodes.
4. Any regular maintenance medication taken to maintain mast cell stability and limit the effects of mast cell mediators should be continued during the operation.
5. Emergency medications and equipment to treat anaphylaxis should be immediately available and the anesthetist should monitor the patient closely during surgical procedures.
6. Where possible, prudence recommends administration of incremental dose infusion rather than single boluses of needed drugs (opioids, muscle relaxants) known to activate mast cells.

7. Potential physical trigger factors and stress should be avoided and premedication with sedatives, such as benzodiazepines, should be considered.
8. When possible, anesthesiology records from previous surgeries tolerated in the recent past should be obtained.
9. If the patient has no history of general anesthesia, most experts recommend administration of safer drugs as mentioned previously along with premedication with an H₁ antihistamine.

MCD AND USE OF RCM

Anaphylaxis triggered by RCM in patients with mastocytosis is mainly reported in some case reports, along with a few cases in large studies on patients with mastocytosis, mainly adults as a consequence, perhaps, of greater RCM exposure.^{1,2,5,9}

In a Spanish study on patients with anaphylaxis and other mast cell–mediator release symptoms, drug reactions were triggers of severe systemic reactions in 19% of patients but none were RCM.¹² Very limited data have been published about subjects with systemic reactions to RCM in the general population who subsequently underwent specific evaluation for mastocytosis. In an Italian study on patients with food and drug anaphylaxis only 8.1% of patients with drug hypersensitivity had high tryptase values (>11.4 µg/L), one of whom was allergic to RCM in absence of MCD.¹¹ In a large European multicenter study performed in patients with adverse reactions to RCM, no patients were diagnosed with SM.²⁴

Because of the limited data available, it is not possible to assess the risk of anaphylactic reactions in patients with mastocytosis or mast cell activation syndrome who have been exposed to RCM, compared with the general population. No specific recommendations have been proposed to prevent anaphylaxis in patients with mastocytosis and previous drug anaphylaxis.^{3,25} Although many groups suggest giving premedication to prevent or reduce severity of possible reactions, the use of premedication has to be established.

Therefore, because RCM may induce in the general population severe reactions, sometimes fatal, and even with nonionic RCM, it seems reasonable to take a cautious approach in patients with mastocytosis by performing premedication in selected cases and alerting medical staff about the management of possible severe reactions.

OTHER DRUGS

Antibiotics

There are a few reports on anaphylaxis triggered by antibiotics, especially β-lactams (amoxicillin, ampicillin, penicillin V), but also with aminoglycosides.^{1,2,26} A case of anaphylaxis has been recently described that occurred during penicillin skin testing, which was nevertheless negative, in a suspected β-lactam–allergic woman with high levels of basal tryptase.²⁷

NSAIDs

There are some reports of adverse reactions to NSAIDs in patients with mastocytosis, mostly to aspirin and pyrazolones but also to different NSAIDs (diclofenac, ibuprofen, naproxen).^{1,2} Moreover, the case of anaphylaxis elicited by ingestion of carrots together with acetylsalicylic acid, 500 mg, in a young man with mastocytosis, but not when taken separately, underlines that even in patients suffering from MCD sometimes cofactors (eg, aspirin or alcohol) are needed to provoke anaphylaxis.^{2,28}

In general, only a small proportion of patients with mastocytosis seem to develop idiosyncratic reactions to NSAIDs, even if they may develop into very severe

reactions.²⁹ Because most adult patients have a history of exposure to acetylsalicylic acid or other NSAIDs in their lifetime, the tolerance of these medications can be easily obtained through patient history. In a patient who has been taking NSAIDs without any allergic or other adverse reactions, there would not be any need to discontinue it specifically from a mastocytosis standpoint. In contrast, in patients with a history of NSAID reactions, the consequences could be very severe and even fatal. Therefore, all NSAIDs (including parenteral forms, such as ketorolac) should be strictly avoided in these patients. These patients should also consider wearing a medic alert bracelet.

Opioids

Opioids are known as histamine-releasing drugs. In vitro studies have demonstrated that morphine and buprenorphine have a concentration-dependent capacity to induce histamine and tryptase release from mast cells.³⁰ Other authors observed mast cell activation with codeine and meperidine.³¹ Moreover, some clinical reports confirm these data by describing adverse reactions after intake of codeine and morphine.^{2,32} Anecdotal experience suggests that fentanyl and derivatives are generally well tolerated.

General Considerations

Considering the overly limited data on tolerance or on the hazards of antibiotic and analgesic drugs for patients with MCD, it is not possible to give general recommendations that apply to all patients. As a general consideration, medications previously and continuously tolerated by the patient are allowed. Moreover, if the tolerance of an analgesic, NSAID, or antibiotic drug is unknown, a graded provocation test can be performed. Finally, it is important to refer all patients with adverse reactions to drugs to an allergy specialist, especially patients with mastocytosis, for appropriate counseling and testing (eg, skin testing, provocation test) at a specialized center under close supervision.

SUMMARY

Drug-induced anaphylaxis might occur in patients with mastocytosis; however, the association between mastocytosis and drug anaphylaxis does not seem to be as strong as it is with Hymenoptera sting anaphylaxis. In patients with mastocytosis, anaphylactic reactions triggered by different drugs, such as anesthetics, RCM, antibiotics, NSAIDs, codeine, and narcotics, have been reported. Therefore, in case of anaphylaxis, MCD should be considered in the differential diagnosis; the level of serum tryptase during acute reaction and at baseline and an accurate skin examination might provide useful clues for a differential diagnosis. Patients with mastocytosis with previous drug anaphylaxis may have a greater risk of new reactions to drugs and they should be considered for allergy evaluation.

Regarding general anesthesia, based on data available in patients with mastocytosis, it can be concluded that the risk for children with pediatric-onset mastocytosis seems limited and prophylactic antiallergic premedication may not be obligatory. It is, however, important to continue chronic antimediator therapies in children and adults. Severe reactions have been reported in some adults with mastocytosis. Anesthetic agents to be administered to adult patients need to be carefully selected. The anesthetist should be informed of the diagnosis of mastocytosis and prepared for an emergency treatment of anaphylaxis and should try to avoid possible trigger factors. There is no evidence of the efficacy of premedication before anesthesia or RCM administration to prevent or reduce severity of reactions; however, there is no

evidence to the contrary and in practice it should be considered, depending on the risk of the individual patient.

Finally, given the current limited information available regarding safety of antibiotics and NSAIDs, it is not possible to state clear indications, but it is reasonable to suggest that patients take medications previously and continuously tolerated or, otherwise, to perform drug provocation tests under medical supervision.

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