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REVIEW ARTICLE

Anesthetic considerations in pediatric mastocytosis: a review

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Abstract Mastocytosis is an orphan disease rarely encountered by practicing anesthesiologists. Children with mastocytosis often present for procedures or surgery requiring anesthesia. Because many of the medications commonly used in pediatric anesthesia have been reported to initiate mast cell activation, parents are often very anxious about their child's perioperative experience. Laboratory investigations of serum histamine assays associated with different anesthetic drugs have not been shown to predict mast cell degranulation in these patients. However, the pediatric literature suggests that children with disease limited to the skin rarely suffer serious side effects from anesthesia, and there are no reported fatalities. Preoperative prophylaxis is usually based on expert opinion and case reports. Detailed tables summarizing reports of anesthetic medications used for children with mastocytosis undergoing anesthesia, reported side effects, and suggested prophylaxis regimens are included in this review.

Keywords Mastocytosis/complications · Mastocytosis/therapy · Anesthesia · Child · Urticaria pigmentosa/therapy

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Introduction

Mastocytosis is characterized by an increase in mast cell activity in the body [1]. First described in the late nineteenth century, mastocytosis is an orphan disease with an estimated overall prevalence of less than 0.4 % of the population [2–6]. Seen more commonly in the pediatric population, most children with mastocytosis have a good prognosis despite the fact that sufferers have been shown to respond unpredictably to a variety of stimuli. As a result, perioperative management of these patients may be a challenge; both anesthesia and surgery involve unavoidable "triggers" of mast cell degranulation. The objective of this review is to provide a basic update on recent advances in our understanding of the pathophysiology of mastocytosis, available published guidelines for perioperative management, a summary report on anesthetic drugs administered in the pediatric population, and suggestions for dealing with practical issues that may arise when counseling families who present for anesthesia.

Background

The true significance of the mast cell's innate function is in the early stages of investigation. It is now thought that the mast cell may be of substantial importance in the body's immune defense and its inflammatory response to environmental antigens. Knockout mice for stem cell factor (SCF, or "mast cell growth factor") or its receptor lack mast cells and are susceptible to overwhelming bacterial infection [7]. Mast cells may interact with other immunologically relevant cell lines, for example polymorphonucleocytes and T-lymphocytes, by chemotactic or phagocytic processes, respectively, augmenting the body's natural immune defenses [7]. Mast

cells also have complement receptors which, in the face of existing inflammation, can facilitate mast cell activation [8].

Mast cells are induced to release biologically active contents via two known pathways—an IgE–antigen complex interacting with a high-affinity mast cell surface IgE receptor (FceR1), and via a non-receptor G-protein (pertussis toxin-sensitive GTP-binding protein) believed to exist within the mast cell surface [9, 10]. Cationic peptide "secretagogues", for example substance P and bradykinin, are associated with mast cell secretion via the latter mechanism [11]. Degranulation is not a predictable outcome of mast cell activation, because mast cells may secrete peptides (e.g., MIP-1 beta, which leads to T cell homing) with little or no degranulation [7].

Mastocytosis is a complex disease which may masquerade as other conditions, for example: anaphylaxis, leukemia, basophil activation, or even cardiac conditions leading to profound hypotension [10]. A recent consensus statement describes three categories of mast cell activation (MCA): primary syndrome (e.g., mastocytosis, including monoclonal disease), secondary MCA syndrome (e.g., reactive allergic reactions, often found in mastocytosis patients), and idiopathic MCA syndrome (i.e., no trigger or clone lineage found) [10]. A patient is diagnosed with an MCA syndrome if the clinical presentation is consistent with mast cell mediator release, if the patient's serum tryptase increases by 20 % + 2 ng/ml within 15–60 min of an anaphylactoid incident, and if the patient responds to standard anti-mast cell mediator therapy [10]. Under a currently recognized WHO-classification scheme, mastocytosis is also subdivided into two general groups, a cutaneous form and a systemic form [12]. Cutaneous mastocytosis subtypes include urticaria pigmentosa (the overwhelming majority of children with mastocytosis), solitary cutaneous mastocytoma (10–35 % of children with skin disease), and diffuse cutaneous mastocytosis (seen almost exclusively in children) [1, 12–14]. The more severe or systemic forms of mastocytosis, involving the bone marrow or other extracutaneous sites, are typically seen in the adult population but in only approximately 10 % of children with cutaneous disease [5].

Clinical course

Most mastocytosis cases present in children under the age of 2 years where it is usually confined to the skin and runs a benign, albeit bothersome, course, with resolution in most cases at approximately 9–10 years of age [1, 6, 13, 15]. Over one-half of children with mastocytosis are symptomatic, and the most common symptoms include flushing and pruritis, mostly related to mastocyte release of histamine, prostaglandin-D2 (PG-2), and leukotriene-C4 [1, 4, 16–19]. Bronchospasm, a typical sequela of IgE-mediated reactions, it not a common mediator-related incident in mastocytosis [17, 20, 21]. Children often report gastrointestinal symptoms, for example abdominal pain and diarrhea, and neurologic manifestations including mental status changes, syncope, and seizures under stress conditions [5, 22, 23]. There may also be a relationship between pediatric mastocytosis and some cases of attention deficit or autism disorder [24]. Cardiovascular shock and hemorrhage are rarely seen in the pediatric mastocytosis population in the absence of extensive skin involvement [1].

There seems to be no correlation between the severity of skin involvement in children with mastocytosis and the likelihood of systemic disease [1]. Fewer than one-half of adolescent cases progress into adulthood, where the course may become systemic in up to 30 % of affected children, usually as an indolent form [13, 15, 17, 19]. It is unclear which disease subtype seen in adolescence will progress into the adult form of the disease [25]. All adult cases are assumed to be systemic until clinical evaluation proves otherwise [26].

Pathogenesis

Mast cells start in the bone marrow as pleuripotent stem cells and eventually migrate to the peripheral connective tissues (i.e., vessels and peripheral nerves) where they are activated and mature into the adult form [27, 28]. SCF found in the marrow and mast cells themselves binds to a surface tyrosine kinase receptor on the progenitor cells to regulate growth and differentiation. Matured mast cells are likewise found in most solid tissues, including the lung, heart, and central nervous system [20, 29]. Mast cell forms are not found in plasma, because differentiation is not complete until the cells reach peripheral tissues [30].

Mast cell markers include surface tyrosine kinase receptors, for example CD34, CD13, CD117 ("C-KIT", seen in those with and without mastocytosis), and CD25 (a marker for abnormal mast cells) [18, 28, 30]. Under the predominant theory of the adult form of the disease, an "activating" point mutation at the C-KIT locus (Asp816Val, or codon 816) codes for an abnormal cell membrane receptor protein for SCF, producing clonal mast cell lines that lack normal growth and differentiation [31–33]. However, C-KIT mutations have not been found in all patients with mastocytosis, particularly children [1, 32]. The C-KIT mutation is found in up to 90 % of adults with the systemic form of the disease but fewer than 30 % of those whose disease is limited to the skin [12]. Other C-KIT progenitor mutations found in children with the cutaneous form of the disease include Asp816Phe, D816F, R815K, E839K, G839L, V533D, and V559A [1, 14]. There

are also "familial" KIT mutations, A533D, K509I, del419, but their clinical relevance is unknown [12, 15]. Although there seems to be a correlation between the C –KIT mutation and the more severe forms of the disease, patients' genotypes have not been shown to consistently correlate with a particular phenotype [26, 31, 34].

Current thinking is that pediatric and adult forms of mastocytosis may be separate entities, a theory supported by the observed genotypic differences between the two forms and the tendency for the childhood form to be self-limiting [1, 14, 25, 31]. Whether mastocytosis is a disease of clonal proliferation, neoplasia, activation ("gain of function"), non-death, a reactive process, or altered function of mast cell growth factor—or a combination of these processes—is unclear [20, 25, 30, 32, 33, 35]. Gastric mucosal samples from 27 patients with systemic mastocytosis contained fewer mast cells than controls, suggesting a humoral basis for symptoms rather than receptor protein mutation-associated hyperplasia [36]. This hypothesis is supported by the notable heterogeneity of the disease and the general opinion that the disease is not heritable. In a recent multicenter study of skin samples from 50 children with urticaria pigmentosa (80 %), mastocytoma (11 %), and diffuse cutaneous mastocytosis (9 %), fewer than one-half of the mutations found involved codon 816, but all were activating for C-KIT [25]. These findings suggest that pediatric mastocytosis is at times a disease of clonal proliferation, as the adult form is largely considered to be, and a reactive process, as previously hypothesized.

Diagnosis

Under an international consensus of the Year-2005 Working Conference on Mastocytosis, preliminary diagnosis now begins with determination of whether the patient has "mastocytosis in the skin" (MIS) [12]. This diagnostic scheme simplifies the approach to pediatric patients, who are likely to have skin involvement only, and provides rational treatment choices in this very heterogenous disease. In suspected cases, a thorough physical examination and determination of serum tryptase level, complete blood count, and hepatic enzyme levels are recommended [1].

Mastocyte skin density may be increased in mastocytosis patients by a factor of 10 [1]. Although not consistently present, a typical mastocytosis lesion is a maculopapular rash, with the appearance of wheal-and-flare on rubbing (Darier's sign) [1]. Under the Year-2005 Working Conference guidelines, suspect lesions are biopsied for mast cell density and tryptase immunohistochemistry. Biopsies of specimens typically contain discrete groups of mastocytes as stained by dyes specific for metachromatic granules (e.g., Giemsa or toluidine blue) which are spindle-shaped, in contrast with the ovoid shape of normal mastocytes [37]. Polymerase chain reaction (PCR) KIT-mutation analysis at codon 816 may be undertaken in both children and adults, but is not required for a MIS diagnosis [12].

Because bone marrow involvement is rare in children, bone marrow biopsy is pursued in all suspected adult cases but reserved for only those pediatric patients with systemic signs or symptoms, serum tryptase levels >20 ng/mL, organomegaly, or for those with MIS extending into puberty [12, 13]. In children, serum tryptase levels are monitored, with examination for other signs and symptoms of systemic disease (cytopenia, leukocytosis, abnormal differential count, hepatomegaly, lymphadenopathy) until puberty [12]. Tryptase is a protease specific for and present in all mast cells, and serum levels may correlate with mast cell burden, especially after activation [1, 4, 13, 35, 38, 39]. In a significant number of both children and adults with mastocytosis confined to the skin, however, the serum tryptase level may be normal (1–15 ng/mL) [13, 40]. It is unclear if children whose tryptase levels remain normal should be monitored past adolescence. In one review of 180 children monitored throughout childhood, 2/26 (7.5 %) of children with mastocytomas and 12/61 (19.4 %) of children with UP had persistent lesions [17].

Preoperative preparation

So far, no known investigation has been found to consistently predict mast cell degranulation in these patients [4, 26]. Furthermore, there are no evidence-based guidelines for preoperative prophylaxis of patients (adult or pediatric) with mastocytosis [26]. Pretreatment regimens have been based on accumulated case reports and, in the past, antihistamine prophylaxis was standard practice following reports of cardiovascular collapse in adult patients undergoing anesthesia [41, 42]. Although it is believed that children with systemic disease are more likely to have elevated serum tryptase levels, the literature contains insufficient information to substantiate treating these children differently in the perioperative period from those with disease limited to the skin [27]. Various preprocedure prophylaxis regimens, not yet validated, are found in the recent literature (Table 1).

Cardiovascular collapse has been reported in the adult mastocytosis population spontaneously and also under conditions of stress, including anesthesia and surgery [41–44]. To date, only two cases of non-fatal cardiovascular collapse in a child undergoing anesthesia and surgery have been reported. In the first reported case, an infant with bullous mastocytosis became hypotensive requiring cardiopulmonary resuscitation upon repeat exposure to

Table 1 Suggested prophylaxis regimens found in the medical literature

Author/year	Prophylaxis indication	Children vs adults	Preop sedation	Anti-histamines	Steroids	Baseline tryptase level	Skin testing	Med alert bracelet
Castells/2011 [1]	Anesthesia, procedures	Children				✔		✔
Ahmad/2009 [27]	Anesthesia	Children	✔			✔		
Carter/2008 [4]	Anesthesia	Children				✔		
Heide/2008 [26]	Anesthesia, narcotics, radiographic contrast	Children	✔	✔	✔		✔	✔
Valent/2007 [12]	Anticipated trigger exposure	Children, adults		✔				
Escribano/2002 [86]	Anesthesia, radiographic contrast	Adults		✔		✔		✔
Worobec/2002 [54]	Anticipated trigger exposure	Adults		✔				

sufentanil (this was reportedly the infant's second exposure to sevoflurane) [45]. Although protease levels were not measured, the etiology of collapse was believed to be hemorrhage secondary to mastocytosis-related heparin release. In the second report, a teenage female developed an anaphylactoid reaction during general anesthesia after administration of midazolam, fentanyl, lidocaine, propofol, and cefazolin [46]. After subsequent workup the patient was diagnosed with systemic mastocytosis on the basis of elevated tryptase levels, 17–18 ng/mL. However, the diagnosis in the latter case has been questioned because the WHO criteria for the systemic form of mastocytosis was not present [47]. In a multicenter, retrospective review of 22 children with mastocytosis undergoing a total of 29 procedures under anesthesia, there were no significant perioperative complications; patients received only pre-existing medications, including antihistamines, and the anesthesia technique was not controlled [4]. Similar findings were noted in a 2009 case series of 6 children and an accompanying literature review in which there were also no serious anesthesia-related complications in either the author's own experience or the available literature [27].

The reported incidence of anaphylaxis during anesthesia is approximately 1 case per 5,000–20,000 patients per year; this estimate may be increasing secondary to improved accounting measures [48–50]. Patients with mastocytosis experience both immune (IgE-related) and non-immune anaphylaxis, and the overall incidence of anaphylaxis in patients with mastocytosis has been reported to be higher than in the general population [1, 16, 35, 51]. Unlike patients who do not have mastocytosis, however, the serum tryptase level in mastocytosis patients experiencing anaphylaxis does not fall within the normal range at several hours but can remain persistently elevated [18]. In some cases this laboratory finding may lead to the initial diagnosis of mastocytosis. Anaphylaxis in children without mastocytosis is most commonly associated with food allergies; the anaphylaxis initiator in children with mastocytosis, however, is often less clear [51]. In a recent retrospective study of 46 nonsurgical pediatric mastocytosis patients, anaphylaxis occurred in 3 patients with extensive skin involvement (e.g., $\sim$50 % body surface area) but in no children with only limited skin involvement [51].

The treatment of mastocytosis is symptom-based and the use of medications to prevent attacks is largely based on their hypothetical utility in anecdotal reports of mastocytosis. H_1-receptors facilitate preformed histamine release and are also involved in changes in capillary permeability [52]. In addition, H_1-receptors interact with H_2-receptors during vasodilation, prompting a recommendation that H_1 and H_2-receptor antagonists be given together as prophylaxis [3, 15, 26, 52–54]. Glucocorticoids, as anti-inflammatories and mast cell stabilizers, are recommended in specific circumstances, for example anesthesia and surgery, or the rare case of recurrent cardiovascular collapse [12, 15, 27, 30]. Use of cromolyn sodium, another mast cell stabilizer, remains controversial and is typically reserved for treatment of gastrointestinal symptoms but not as preoperative prophylaxis [3, 12, 26]. Leukotriene antagonists are now used more frequently for minor symptom relief but not as standard prophylaxis [12, 30, 37]. Aspirin has proved to be an effective prophylactic in selected cases, presumably secondary to its antiprostaglandin actions, but its association with serious anaphylactoid reactions for some patients has discouraged routine administration to the mastocytosis population [4, 26].

A pre-procedure baseline serum tryptase level is recommended by most authors, and at least one recommends coagulation studies in blood-loss cases [1]. Pre-procedure skin testing and antigen-specific IgE assays for

perioperative medications are not recommended for mastocytosis patients on a routine basis. These tests have not been demonstrated to have a positive predictive value as perioperative screening tools and may escalate care if improperly conducted [4, 21, 52, 53, 55, 56]. Furthermore, skin testing utilizes the parent compound and not the drug's byproducts or metabolites that may be the actual cause of mast cell degranulation [1, 3, 4, 39].

Intraoperative management

Common perioperative incidents and specific anesthetic drugs have been categorized as initiators of mastocyte degranulation on the basis of case reports and the drugs' association with histamine release in general. In reality, few drugs may be responsible for mast cell degranulation under anesthesia [27]. Many of the anesthesia drugs on the list of initiators (e.g., gallamine and decamethonium) are outmoded and no longer used [17]. Non-medicinal initiators include mechanical friction and pressure, psychological stress (histamine can stimulate neurons), physical exertion, thermal stress (both hot and cold), and a variety of foods. Mast cell degranulation in patients with mastocytosis is unpredictable, and does not occur consistently in any given patient [4, 27, 57]. It is also unclear when drugs that elicit histamine release in normal patients or under study conditions will produce the same response in mastocytosis patients undergoing anesthesia [1]. With the exception of sufentanil, it has not yet been claimed that commonly used anesthesia drugs are associated with serious perioperative outcomes for children with known preexisting disease [45] (Table 2).

Theoretically, narcotic-related and muscle relaxant-related histamine release can be minimized by use of newer generation drugs of high potency (requiring less drug) and slow administration [1, 4, 53, 58–60]. An inverse relationship has been noted between narcotic potency and the tendency to induce histamine release. Studies of codeine, meperidine, and morphine indicate significantly more histamine release in vivo than with the newer semisynthetic opioids, fentanyl, sufentanil, and remifentanil [58, 59, 61, 62]. A similar propensity for clinically significant histamine release has been observed for the older-generation muscle relaxants (e.g., mivacurium, tubocurarine, and atracurium) compared with newer products, for example vecuronium and cisatracurium, when administered in standard clinical doses [48, 63–67]. Furthermore, a drug's basic (versus acidic) character may affect mast cell activation, because positively-charged cations, for example narcotics and muscle relaxants, are believed to be involved in mast cell activation via non-receptor-mediated G-protein activation [9, 11, 65, 66]. There are insufficient data in the literature to conclude that a particular drug's tendency to stimulate histamine release under experimental conditions is a predictor of mast cell degranulation in children with mastocytosis [1].

Codeine is the prototypic mastocyte initiator and may be used as a control in allergy skin testing, although the practice is on the decline [27, 50, 68–70]. Rocuronium, the most commonly used muscle relaxant in anesthesia today, is associated with a significant incidence of anaphylaxis during anesthesia but has not yet been categorized as an initiator in mastocytosis [50]. In a manufacturer-sponsored, prospective, randomized clinical trial, rocuronium up to 1.2 mg/kg IV was administered to 45 adult patients under N_2O/O_2-sufentanil anesthesia and plasma histamine levels were not found to be significantly increased [71]. Rocuronium has, however, been associated with increased intradermal histamine levels by use of a microdialysis technique [65]. Vecuronium up to 0.4 mg/kg administered intravenously has been associated with histamine release under halothane anesthesia but without clinically significant effect on hemodynamics [72, 73]. Fentanyl has been associated with anaphylaxis in adult mastocytosis patients but has been used without significant adverse outcomes in pediatric patients undergoing anesthesia [4, 27, 41]. Sufentanil was first implicated as an initiator in 2001 after repeat exposure of an infant with bullous mastocytosis (see above) [45]. Propofol, a routinely-used intravenous induction agent which is increasingly recognized as a cause of anaphylaxis and has been shown to cause histamine release in vivo, is regarded as a safe alternative in the mastocytosis patient population [21, 48, 74, 75]. Intravenous midazolam 0.2 mg/kg has been shown to induce histamine release in a susceptible adult patient population but has also been used safely in children with mastocytosis [15, 27, 76, 77]. The volatile anesthetics, which have been used extensively with both pediatric and adult mastocytosis patients, have not been causatively associated with clinically evident mast cell degranulation in the medical literature; theoretically, either a β-agonist effect or inhibition of calcium influx into mast cells is believed to prevent mast cell degranulation [27, 52, 78]. There is a paucity of literature on local anesthetic-mediated histamine release, but lidocaine (and other amide local analgesics) rarely leads to an allergic response and has been shown in vitro to down-regulate the immune response, possibly via T cell suppression and increased intracellular mast cell calcium concentrations [79–81]. Paracetamol (*N*-acetyl-*p*-aminophenol) has also been shown, in vitro, to reduce histamine release in a mast cell leukemia cell line [82]. In a recent unpublished report, ketorolac was associated with a fatality in an adult mastocytosis patient but there are no such reports involving the pediatric mastocytosis population [1, 4]. Other anesthesia drugs used for children with

Table 2 Selected anesthetic medications administered in 57 reported cases of childhood mastocytosis

Medication[a]	Cases reported (*N*)	Adverse incidents reported (*N*)	Pretreatment[b] (*N*)	Experimental histamine release	References
Acetaminophen	6	Vomiting (2)	Yes (1 patient with vomiting)	See "Paracetamol"	[4]
Alfentanil	2	No	Yes	Yes	[6, 45, 62]
Bupivacaine	4	Vomiting (1)	No	Not available	[4, 27, 83]
Cisatracurium	4	No	Yes (4)	Yes No[b]	[4, 27, 64, 65, 67]
Codeine	17	Bullae (1) Urticaria (1) Laryngospasm (1)	Not specified	Yes	[27, 68, 69, 85]
Fentanyl	22	Vomiting (2) Flushing (1)	No	Yes No	[4, 23, 27, 48, 58, 60, 66, 75, 88]
Halothane	4	No	Yes (1)	Not available	[6, 83, 84]
Isoflurane	12	No	Yes (3)	Not available	[4, 27]
Ketamine	5	Vomiting (1)	Yes (patient with vomiting)	Yes	[4, 48]
Lidocaine	17	Vomiting (2) Flushing (2)	Yes (1 patient with vomiting)	Inhibits mast cell histamine release in vitro	[4, 80, 83]
Meperidine	2	No	Not specified	Yes	[60, 62, 84]
Midazolam	21	Vomiting (2)	Yes (1 patient with vomiting)	Yes	[4, 23, 27, 48, 76, 77, 88, 92]
Morphine	2	0	Not specified	Yes	[48, 53, 60, 83]
Ondansetron	7	Flushing (2)	Yes (both patients with flushing)	Not available	[4, 27]
Paracetamol	8	0	Yes (4)	Attenuates mast cell histamine release in vitro	[27, 83, 84]
Propofol	17	Vomiting (3)	Yes (2 patients with vomiting)	Yes	[4, 6, 23, 27, 48, 74, 88]
Remifentanil	1	0	Yes	No	[27, 58, 62]
Rocuronium	1	Vomiting (1)	No	Yes	[4, 65]
Sevoflurane	21	Vomiting (1) Flushing (2)	Yes (1 patient with vomiting)	Inhibits histamine-induced endothelial cells calcium influx	[4, 27, 45, 75, 78, 88]
Succinylcholine	16	Not specified	Not specified	Yes	[65, 85]
Sufentanil	2	Cardiac arrest (1)	Not specified	Yes	[45, 59]
Thiopental	2	Circulatory arrest (1)	Not specified	Yes No	[4, 45, 48, 63]
Vecuronium	3	0	Not specified	Yes No	[1, 4, 7, 48, 63, 65, 67, 70, 75]

[a] Administered concomitantly with other drugs in anesthetic

[b] Pretreatment includes antihistamines and/or corticosteroids

[c] "No" indicates no detected histamine levels or an insignificant change in levels

mastocytosis without significant problems (both with and without prophylaxis) include remifentanil, cisatracurium, thiopental, ketamine, acetaminophen, isoflurane, sevoflurane, and nitrous oxide, and local and regional anesthesia [4, 13, 27, 83, 84]. It is important to note many drugs categorized as initiators have been administered concomitantly with other anesthetic drugs in a complex and stimulating perioperative environment.

Intraoperative crisis management

Following the first reports of cardiac arrest in mastocytosis patients undergoing anesthesia and surgery in the 1990s, most experts advocate that cardiovascular decompensation should be a foreseeable concern in all cases, including pediatric anesthesia cases in which current evidence suggests major side effects are unlikely [21, 27, 41, 42, 85].

Epinephrine should be on hand for all mastocytosis patients in the perioperative period; in addition to giving cardiovascular support, epinephrine may hinder mast cell degranulation via β_2-adrenergic receptor stimulation [41]. Avoidance of β-adrenergic antagonists has been recommended on the theory that β-blockade counteracts epinephrine resuscitation effects [18, 86]. The need for aggressive treatment of other intraoperative signs of mediator release, for example flushing, is less clear. For children with mastocytosis, isolated flushing tends to be benign and self-limited [17, 87]. Perioperative hemorrhage theoretically associated with heparin and possibly tryptase release from mast cells has been treated with protamine and plasma coagulation factors, respectively, but such therapy has not been prospectively studied [42, 88–90]. Recommended perioperative antidotes for the variety of mast cell mediators may vary among authors (Table 3).

In the event of anaphylaxis-like incident, particularly if mastocytosis is suspected as the cause, the serum tryptase level can be monitored to aid diagnosis. During the early phase of immune-mediated anaphylaxis, both serum histamine and tryptase levels increase. The serum half-life of histamine is less than 30 min and levels fall abruptly within 1 h of anaphylaxis [18, 49, 66]. In both IgE-like and nonimmune anaphylaxis-like incidents, tryptase, with a longer serum half life of approximately 90 min, peaks as histamine levels are declining and will not typically fall to normal levels for 4–6 h after the incident [91]. After a

Table 3 Selected mast cell mediators with proposed antidotes

Mediator	Sign or symptom	Antidote	References
Histamine	Hypotension	Epinephrine	[12, 15, 26, 30, 43]
		Glucocorticoids	[12, 15, 26, 54, 86]
		Acetylsalicylic acid[b]	[12]
		H_1-antagonists	[26]
	Shock	Epinephrine	[12, 26, 30, 43]
		Glucocorticoids	[12, 26, 54]
		H_1-antagonists	[26]
	Tachycardia	Avoid beta-blockade[a]	[86]
	Pruritis	H_1-antagonists	[15, 54]
		Antileukotrienes	[30]
		Disodium cromolyn	[86]
	Urticaria	H_1-antagonists	[15, 54]
		Antileukotrienes	[30]
	Gastric hypersecretion	H_2-antagonists	[12, 20, 54, 86]
		Proton pump inhibitors	[12, 86]
	Abdominal pain	Disodium cromolyn	[12, 15, 20, 54, 86]
		H_2-antagonists	[30, 86]
		Glucocorticoids	[12]
Prostaglandin-D2	Flushing	Acetylsalicylic acid[b]	[4, 43]
		NSAIDs[b]	[4, 43, 86]
	Syncope	Acetylsalicylic acid[b]	[20, 43]
		NSAIDs[b]	[4, 20, 43]
Heparin	Hemorrhage, surgical	Protamine[c]	[3, 12, 90]
		Fibrinogen, coagulation factors[c]	[12]
	Hemorrhage, gastric	H_2-antagonists	[12, 15]
		Proton pump inhibitors	[12, 54]
Thromboxane	Bronchoconstriction, vasoconstriction	Antileukotrienes	[30]
Leukotrienes	Vasoconstriction/vasodilation, increased capillary permeability	Antileukotrienes	[15, 30]
Tryptase	Fibrinolysis	Fresh frozen plasma[c]	[89]
		Antifibrinolytics[c]	[89]

[a] Mast cell stabilizer hypothesized to counter effects of epinephrine

[b] Aspirin and/or NSAIDs should be administered under controlled conditions only

[c] Clinical efficacy unclear

mastocytosis-related anaphylaxis-like incident, serum tryptase levels may return to normal but again increase as mast cell burden increases [39]. Paradoxically, children with mastocytosis, particularly those with mild disease, may have normal serum tryptase levels [35, 40]. The source of elevated serum tryptase can be identified by determining if there is a predominance of the pre-β-form of tryptase (seen in anaphylaxis) or the pre-α-form (originating primarily in mast cells) [35, 39]. Histamine levels alone are not helpful in diagnosis of a mastocytosis-related incident, because histamine's half life may be shorter than the time needed to suspect this diagnosis, and basophils and several other conditions may be associated with histamine release [18]. If reliable tryptase testing (by fluoroimmune enzyme assay) is unavailable or if results are inconclusive, 24-hour urine histamine and PGD_2 (which is not released by basophils) levels may be considered, although diagnostic values for MCA have not yet been validated [10]. If a particular agent is suspected, IgE-specific assays are recommended at the time of the incident or shortly thereafter [49].

Postoperative management

There is no evidence in the pediatric literature to support continued administration of steroids, antihistamines, or leukotriene antagonists in the postoperative period. However, it may be prudent to continue all treatments prescribed before anesthesia and surgery [26]. For children with mildly symptomatic MIS, the decision to maintain treatment postoperatively may best be made with the family after thorough discussion of the risks and benefits, including newly prescribed medications incidental to the procedure, and the ease of access to healthcare.

Children with mastocytosis have been successfully managed as outpatients, but some authors recommend these patients be hospitalized overnight after anesthesia [13, 75, 92, 93]. Although there is no published consensus on the matter, children with mastocytosis overwhelmingly tend to have a benign perioperative course, thus the need for extended postanesthesia observation may be less of a concern for children with MIS than for adults.

Follow-up counseling

Because mastocytosis in the adult population can be unpredictable, with fatal outcomes, some authors advocate medical alert bracelets for all patients with the disease [26, 92]. These bracelets are increasingly advised for children with food allergies. Whether or not the benefit of a medical alert bracelet outweighs the stigma of a chronic disease is a consideration [2]. At a minimum, all health care providers and school personnel overseeing children with mastocytosis must be educated about known initiators, recognition of symptoms, and use of an epinephrine autoinjector in the event of an anaphylactoid incident. Children with limited cutaneous disease should be followed at least annually to monitor disease progress [1, 26].

Mastocytosis has been reported to run in families but the pattern of inheritance is unclear. There are reports of both single and multiple generations with the disease, and discordant monozygotic and dizygotic twin sets [43, 94–96]. It is speculated that mastocytosis may be vertically transmitted in a heterozygous fashion, involving de novo mutation at the gamete and/or post-zygotic level [94]. Although not generally regarded as heritable, autosomal recessive and dominant transmission with incomplete penetrance have also not been ruled out [14, 40, 93].

Support websites for lay persons available on the Internet include Mastokids (http://www.mastokids.org), The Mastocytosis Society (http://www.tmsforacure.org), and The UK Mastocytosis Support Group (http://www.ukmasto.co.uk). Although these sites may be a valuable source of support for families and sufferers alike, content may be inflammatory as a result of dissemination of information that is outdated, not supported by current data, or relevant only to the adult form of the disease. As a consequence, parents may assign numerous allergies to their children, or even avoid surgery altogether [27, 92]. The anesthesiologist may be presented with a "protocol" significantly narrowing the anesthetic options, or there may be a demand for skin testing. It is incumbent upon the anesthesiologist to educate parents with updated information while offering reassurance that current evidence suggests that children with cutaneous mastocytosis undergoing anesthesia and surgery generally fare very well.

Conclusion

Mastocytosis is a rare disease found in all age groups, with the more benign forms occurring predominately in children. Our understanding of the mast cell's biological function is in early stages of investigation. Genotype and phenotype differences noted between children and adults strongly suggest two different disease states, although limited data and the absence of large, prospective trials makes this claim uncertain. Retrospective record reviews indicate that children with mastocytosis limited to the skin who undergo anesthesia are likely to experience only minor reactions, not necessarily related to the mastocytosis disease state. With the exception of a single case report involving sufentanil, commonly used anesthesia medications have been administered to children known to have mastocytosis in the perioperative period with good

outcomes; there is a trend to administration of newer-generation drugs reputed not to release histamine under clinical conditions. Parents, primary care providers, and anesthesiologists can be reassured that despite prudent preparation for cardiovascular decompensation, as in any properly conducted anesthesia, current literature suggests that children with mastocytosis are likely to have a relatively uneventful perioperative course.

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