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Pediatric Mastocytosis: Routine Anesthetic Management for a Complex Disease

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Abstract

BACKGROUND—Pediatric mastocytosis consists of a spectrum of clinical variants characterized by increased numbers of resident mast cells in various organ systems. Mast cells are instrumental in mediating anaphylaxis and patients with mastocytosis are at risk to develop provoked and unprovoked episodes of anaphylaxis.

METHODS—The authors examined peri-anesthetic records of patients with pediatric mastocytosis who were anesthetized for diagnostic and surgical procedures from 1993 to 2006. In addition, the authors conducted a literature review of the experience of the use anesthetics in pediatric mastocytosis.

RESULTS—Twenty-two patients with pediatric mastocytosis, with a median age of 3.2 years (range 6 months to 20 years) at the time of the procedure, were anesthetized for 29 diagnostic and surgical procedures. All variants of the disease are represented in this series. Most patients had a history of flushing, pruritus, GERD and abdominal pain; one patient had history of spontaneous anaphylaxis. Routine anesthetic techniques were used and despite the complexity of the disease, the peri-operative courses were uncomplicated and without serious adverse events.

CONCLUSIONS—We review the main features of pediatric mastocytosis, its anesthetic and perioperative implications, and describe a practical approach to the anesthetic management of pediatric patients with the disease. While many drugs used routinely in anesthesia reportedly cause mast cell degranulation, deviations from routine anesthesia techniques are not necessarily warranted. However, an understanding of the anesthetic implications of the disease and meticulous preparation to treat possible adverse events are advised.

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Implication statement

Pediatric mastocytosis is characterized by a spectrum of clinical variants which have in common, an increase in mast cells in various organ systems; and that can be associated with unprovoked anaphylaxis. Given the complex nature of the disease, understanding the pathophysiology is important for the management of patients with pediatric mastocytosis. This article suggests that commonly administered anesthetics may be used for patients with pediatric mastocytosis.

Conflict of interest: None

INTRODUCTION

Mastocytosis represents a spectrum of disease variants characterized by a pathologic increase of mast cells in cutaneous and extracutaneous sites including the gastrointestinal tract, liver, spleen, lymphoid tissues, and bone marrow. The prevalence of the disease is approximately one in 25-30,000 and its clinical manifestations vary with age of onset (pediatric vs. adult), disease variant (systemic vs. cutaneous), severity (indolent vs. aggressive) and associated hematologic disorders. The symptoms of mastocytosis are related to an increased mast cell burden in specific organ systems, spontaneous or induced (immunological and non-immunological) release of mediators from mast cells, and the associated hematologic consequences. Patients with all variants of disease may exhibit symptoms of gastro-esophageal reflux disease (GERD), flushing, pruritus, urticaria, and hypotension. More importantly, all patients with mastocytosis are at risk for unprovoked anaphylaxis that can occur during anesthesia.[1, 2]

Patients with pediatric mastocytosis often need diagnostic and therapeutic procedures that require sedation or anesthesia. Because mast cells are implicated in the pathophysiology of anaphylaxis and patients with mastocytosis have an increased mast cell burden, drugs used in anesthesia which degranulate mast cells raise justified concerns about potential adverse reactions. These concerns are re-enforced by existing literature implicating opioids, muscle relaxants, analgesics, and volatile anesthetics as drugs that may directly or indirectly activate mast cells.[3, 4] However, while heightened awareness of potential consequences of mast-cell mediator release is warranted, the fear of anaphylaxis should not prevent the use of opioids or muscle relaxant deemed beneficial during the peri-operative period.

The dearth of information available on anesthetic management of children and adolescents with mastocytosis creates a challenge. The prevailing information consists mainly of single case reports,[5-8] and one series from 1987 with data from patients with two of the four sub-variants of pediatric-onset cutaneous mastocytosis who received drugs currently seldom used in pediatric anesthesia.[9] In three of the single case reports, all patients had uncomplicated anesthetics after pre-medication with H1 antihistamines.[5-7]. In the fourth case study, the patient had cardiac arrest.[8] The remaining study consists of a retrospective analysis of 15 children with cutaneous mastocytosis, urticaria pigmentosa (N=12) and solitary mastocytoma (N=3), who received general anesthesia for 29 procedures.[9] Two patients were pre-medicated with H1 antihistamines and most anesthetics were uncomplicated, although two children had cutaneous eruptions after administration of codeine. In this report, we contribute to this experience by reviewing the anesthetic management of 22 patients encompassing multiple variants of pediatric mastocytosis.

MATERIALS AND METHODS

Patients with pediatric mastocytosis who required anesthesia for invasive procedures were included in this study. Patients were evaluated at the NIH from 1993 to 2006 as participants in an IRB-approved research protocol designed to study the pathogenesis, natural history, and the management of pediatric mastocytosis. Consent was obtained from parents or guardians for participation in the study and for review of operative records. In addition, assent was obtained from children older than six years. Although all participants were enrolled in a research protocol at the NIH Clinical Center, some procedures were performed at other institutions. Of the 22 patients, 17 children had 23 procedures performed at the NIH and five had six procedures performed outside the NIH. The anesthetic technique used for the procedures was chosen at the discretion of each anesthesiologist. In some cases, an intensivist administered sedation. A multidisciplinary team was involved in the care of these patients and

included an allergist at NIH. Unless there was a clear history of adverse reactions to a given drug, no anesthetics or analgesics were specifically avoided.

The authors collected data on patient demographics, primary diagnosis, disease variant following the WHO classification of mastocytosis (Table 1),[10] physical findings, genetic analysis,[11] diagnostic and therapeutic procedures, anesthetic techniques, drugs used peri-operatively, length of anesthetics, and peri-anesthetic events. We evaluated anesthetic and procedural complications and noted hemodynamic lability, temperature changes, airway complications, changes in oxygen saturation, and cutaneous eruptions up to 48 hours after the procedures.

RESULTS

Patient Demographics

Twenty-two patients with pediatric mastocytosis were anesthetized for 29 diagnostic and surgical procedures (median age at time of first anesthetic = 3.2 years [range 6mos - 20 yrs], Table 2). Among the cohort of patients (15 males and 7 females), 14 had cutaneous mastocytosis (CM) without systemic involvement: six had urticaria pigmentosa (UP), two had maculopapular CM (MPCM), five had diffuse cutaneous mastocytosis (DCM), and one had a mastocytoma (MAST). Eight patients had indolent systemic mastocytosis (ISM), of which all had UP (Table 2). The onset of disease ranged from birth to 12 months.

Upon questioning, parents would often report “allergies” to opioids and other histamine releasing drugs in their children. However, further questioning revealed that in most cases, these reports reflected parents’ concerns about the administration of those drugs to their children given their diagnosis of mastocytosis rather than an actual history of adverse reaction to those drugs.

One patient (5 %) was on chronic corticosteroid therapy, nine (41%) on H1 and H2 antihistamines, and five (23%) on other drugs including inhaled beta-agonists, inhaled corticosteroids, stimulant therapy for attention deficit disorder, and proton-pump inhibitors. All drugs were administered on routine schedules throughout patients’ hospitalizations.

Pre-operative symptoms consisted of those associated with cutaneous and systemic mastocytosis including cutaneous, gastrointestinal and neurologic manifestations. The most common cutaneous manifestations were flushing (N=19) and pruritus (N=17). Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain, were seen in ten patients. GERD was reported in five patients whose symptoms were controlled on H2 antihistamines or proton pump inhibitors. Other symptoms included headache in five, syncope in three and anaphylaxis in one patient (Table 3). This latter patient with systemic disease had episodes of unprovoked anaphylaxis documented by hypotension, loss of consciousness, and significant increases in serum tryptase (a marker of mast cell burden) over its baseline value. Among the 22 patients, median serum tryptase was 24.5 ng/ml (range: 2 ng/ml to 440 ng/ml; normal value <20 ng/ml, Mayo Clinic Diagnostic Laboratories, (Table 2).

PROCEDURES AND ANESTHETIC MANAGEMENT

The anesthetic management of 29 procedures (23 performed at the NIH and six at other institutions) is shown in Table 4. Preoperative allergy skin testing to drugs used during the anesthetics was not performed. Routine prophylactic H1 and H2 blockers and steroids were not administered prior to anesthetics; however, if patients were on chronic therapy (N=13), their medications were continued as scheduled. Fifteen patients (68%) were pre-medicated with midazolam (0.1 to 0.5 mg/kg) and one (5%) with fentanyl (1.0 mcg/kg).

General anesthesia was administered for 24 procedures and sedation and local anesthesia for five (Table 4). General anesthesia was induced with volatile anesthetics in 11 procedures, propofol in eight, sodium thiopental in two, and ketamine in three procedures. After induction of general anesthesia, the trachea was intubated in 7 patients (5 with and 2 without muscle relaxant), a laryngeal mask airway was inserted in one, and mask ventilation was continued in five patients. For the other 11 general anesthetics, the patients were allowed to spontaneously ventilate and oxygen was delivered by nasal canula. Over all 29 procedures, the average duration of anesthetics was 67 minutes (range 20-360 minutes).

All peri-operative courses were uncomplicated and no patient exhibited hemodynamic instability, signs of hypermetabolism, or significant changes in temperature. One patient with DCM (patient 13) developed induration on his left heel after a 6-hour procedure, despite careful attention to appropriate positioning and padding of pressure points. The area was treated with heat and foot elevation and the injury resolved completely within 18 hours. Two patients developed flushing without hemodynamic lability during or after the procedures. Four patients experienced nausea and vomiting shortly after the procedure, which was treated with ondansetron. Hypotension or bronchospasm associated with mast cell mediator release were not observed during any anesthetic. Intravenous opioids (fentanyl, morphine, or meperidine) were used during and after the procedures followed by oral acetaminophen or ibuprofen as needed for pain (Table 4).

DISCUSSION

We report a series of 29 anesthetics in 22 patients with pediatric mastocytosis where commonly used anesthetic regimens were used. Preoperative drug skin testing was not performed, prophylactic antihistamines or corticosteroids were not administered, and scheduled maintenance medications were continued. We adopt an approach that advocate the administration of incremental, rather than single boluses of needed drugs (opioids, muscle relaxants) known to activate mast cells in those patients without a previous history of adverse events. In addition, we recommend a thorough understanding of mastocytosis and its manifestations and meticulous preparation to treat, albeit rare, possible adverse events during anesthetics.

Review of the literature from 1968 to August 2006 using MeSH headings mastocytosis, anesthesia and analgesia, and anaphylaxis reveals reports of serious adverse reactions in adults with mastocytosis. [1-3, 12-15] In contrast to adults,[2] we found no reports of anesthesia-related deaths,[5-9] and few reports of serious anesthesia-related complications in children with mastocytosis.[8,9] Our experience in pediatric mastocytosis supplement the scarce literature by describing anesthetics in children including those with systemic disease, a variant not included in earlier reports.

Several drugs used in this series (NSAIDS, opioids, sedative hypnotics, and volatile anesthetics) are reported to cause mast cell mediator release. However, previous studies of drug-induced mast cell activation were conducted *in vitro* or in animals and may not reflect the human response.[16] In limited human studies, d-tubocurarine, tubocurarine, pancurionum and gallamine triethiodide are associated with histamine release; however, these agents are seldom used in current anesthesia practice and alternatives were used in our patients.[17-19] Meperidine and morphine cause increases in histamine levels in humans more frequently than fentanyl and sulfentanil.[20] We used fentanyl, morphine and meperidine and observed no evidence of hemodynamic lability. With regard to NSAIDs, as sensitivity occurs within the general population and it is expected some mastocytosis patients would have adverse reactions to NSAIDs. In fact, a lethal idiosyncratic reaction to ketorolac was observed in one adult with mastocytosis at this institution (unpublished data). Therefore, we administer NSAIDs with

caution in mastocytosis patients and only in the absence of a clinical history of sensitivity. We perform graded administration of an NSAID on any patient who has no history of their use to establish safety.

One patient with DCM (# 14) developed an area of induration on the heel after a six hour procedure. The basis of such an event can be appreciated when one considers that patients with DCM (Fig 1) have marked skin infiltration with mast cells, as compared to the UP seen in cutaneous disease (Fig 2). In mastocytosis patients, mechanical pressure can sometimes lead to blister formation.[21] Therefore, special attention to position and to protection of pressure points has to be given to patients with pediatric mastocytosis during anesthesia.

Serum tryptase (constitutively expressed in patients with mastocytosis) levels are a reflection of mast cell burden. In patients with mastocytosis, further elevations of serum tryptase levels from baseline strongly suggest the diagnosis of anaphylaxis and mast cell degranulation. We thus routinely obtain baseline serum tryptase level to serve as a reference point that can be valuable in the diagnosis of possible anesthesia-associated adverse events.[22]

In our series, routine skin testing to anesthetic drugs, muscle relaxants or opioids was not performed prior to anesthetics. Skin tests, in general, are not reliable predictors of adverse reactions to drugs because only the intact drug, not their metabolite (which in some are responsible for the allergic reaction) are examined. Some drugs directly degranulate mast cells in the skin (codeine),[23] but may be used in most individuals without a problem. Therefore, we advocate conducting a detailed review of prior clinical reactions to any agent and such agents be avoided.

Our experience with the anesthetic management of children with mastocytosis is in general agreement with reports in the literature and suggests that when needed, agents such as opioids and muscle relaxants can be used. However, one should consider the details of the patient's history, be cognizant that potential serious anesthesia-related adverse events may occur, and treatment for those events should be readily available. Further, we suggest that routine preoperative drug testing is unnecessary and baseline serum tryptase levels are valuable for the diagnosis of intraoperative events.

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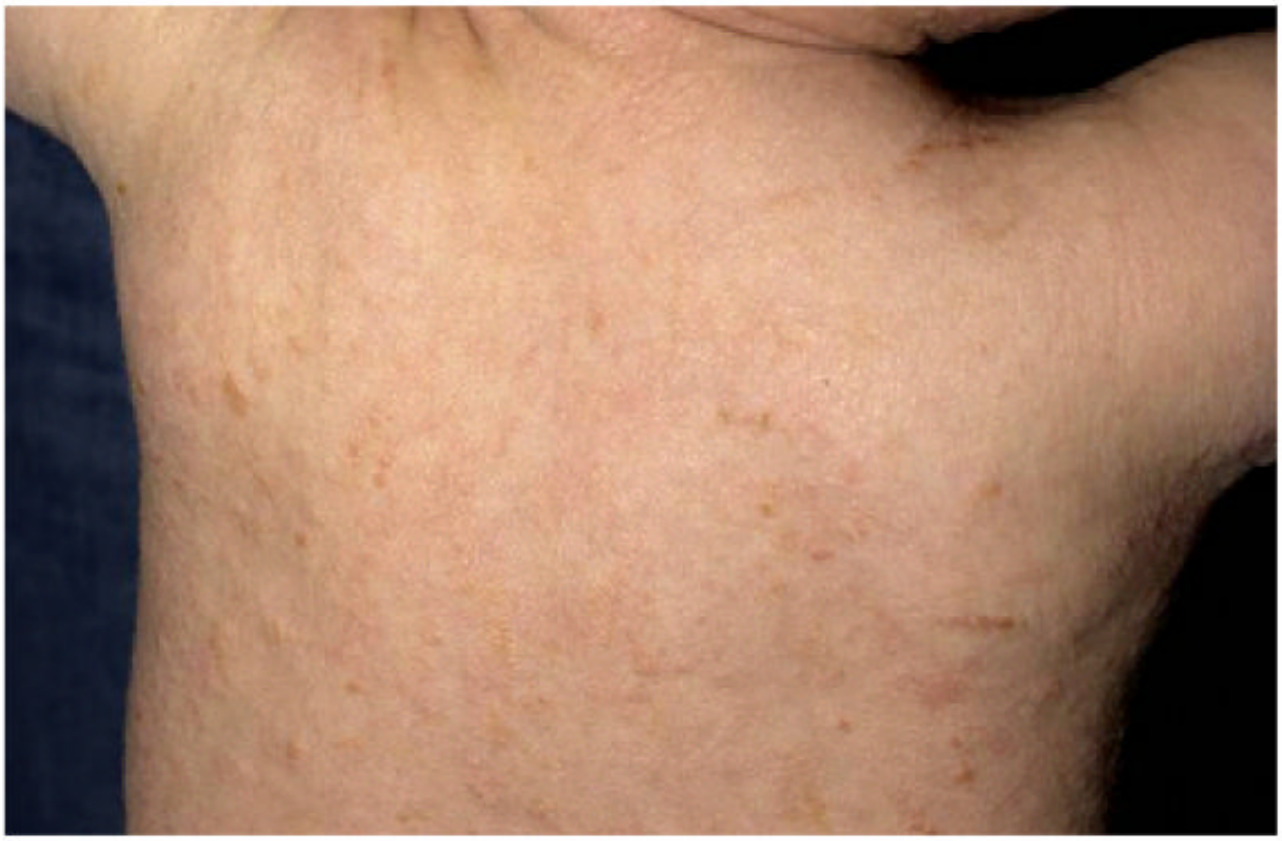

Figure 1. Diffuse Cutaneous Mastocytosis

An infant with Diffuse Cutaneous Mastocytosis. The skin is diffusely infiltrated with mast cells demonstrating a peau d' orange appearance without distinct uritcaria pigmentosa lesions.

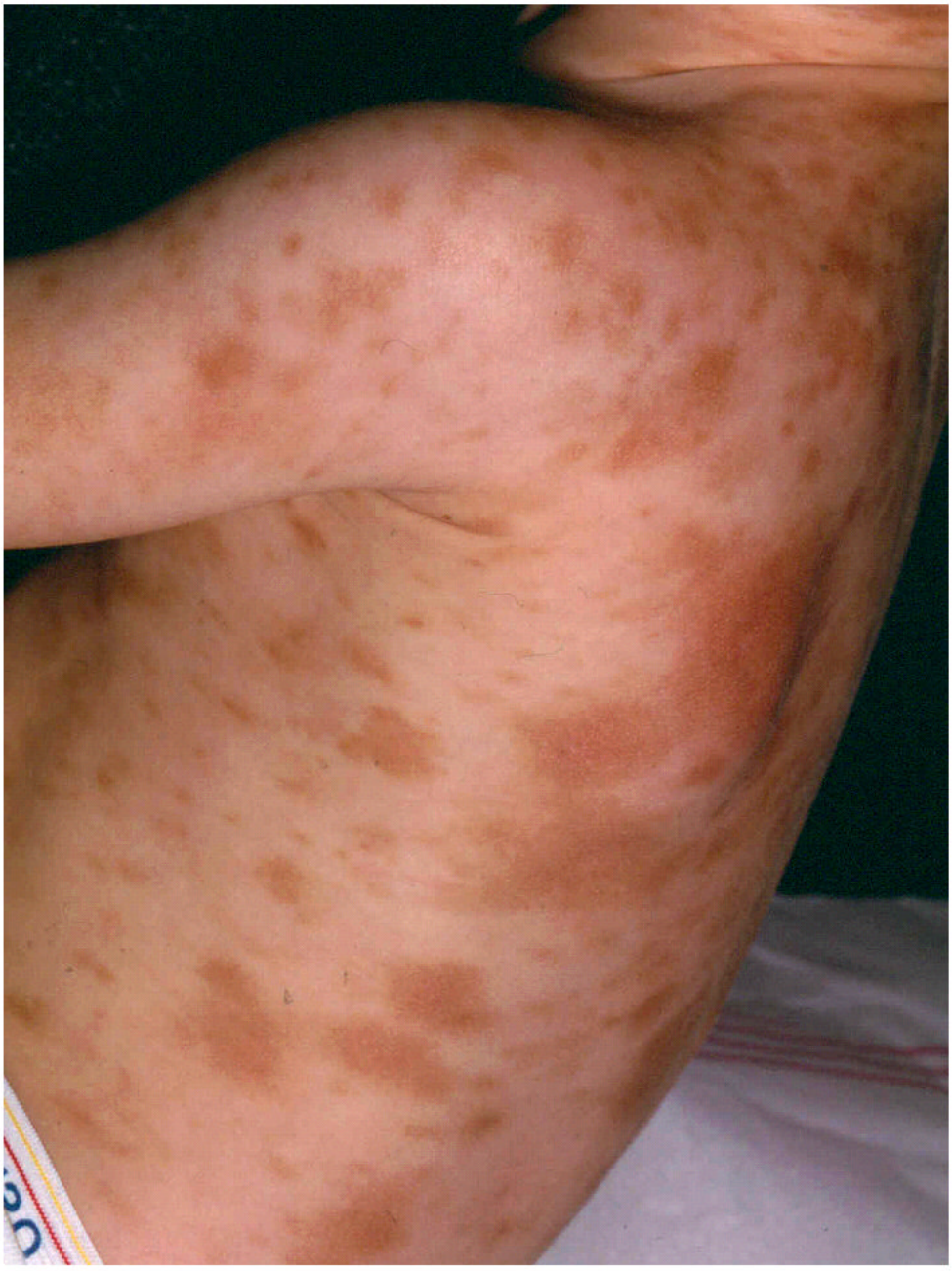

Figure 2. Urticaria Pigmentosa

A child with Urtcaria Pigmentosa demonstrating typical lesions seen in patients with cutaneous mastocytosis. The lesions are varied in size and reddish-brown in color on a background of normal appearing skin.

Table 1

World Health Organization Consensus Classification on Mastocytosis [1]

Variant Term	Abbreviation	Sub variants
Cutaneous Mastocytosis	CM	Urticaria Pigmentosa (UP)
		Maculopapular CM (MPCM)
		Diffuse CM (DCM)
		Mastocytoma of Skin (MAST)
Indolent Systemic Mastocytosis	ISM	Smoldering SM
		Isolated bone marrow mastocytosis
Systemic Mastocytosis with an	SM-AHNMD	SM-AML
Associated Clonal Hematologic		SM-MDS
Non-Mast Cell Lineage Disease		SM-MPD
		SM-CMML
		SM-NHL
Aggressive Systemic Mastocytosis	ASM	
Mast Cell Leukemia	MCL	Aleukemic MCL
Mast Cell Sarcoma		
Extracutaneous Mastocytoma		

[1] adapted from reference 10

Table 2

Demographics and Serum Tryptase Levels in Patients with Pediatric Mastocytosis

Patient	Diagnosis	Gender	Age of onset (months)	Age at first procedure (years)	Serum Tryptase (normal <20 ng/ml)
1	MPCM	F	2	2.0	7
2	MPCM	M	Birth	6.0	6
3	UP	M	Birth	1.6	8
4	UP	M	3	20.0	5
5	UP	F	Birth	6.1	5
6	UP	M	Birth	9.2	2
7	UP	F	3	1.0	27
8	UP	M	12	3.2	5
9	DCM	M	4	1.3	74
10	DCM	M	3	0.8	167
11	DCM	M	9	4.2	5
12	DCM	F	4	3.4	18
13	DCM	M	Birth	7.3	126
14	ISM	F	1	5.6	109
15	ISM	M	6	1.9	22
16	ISM	M	5	14.8	45
17	ISM	M	3	2.9	54
18	ISM	F	Birth	2.4	348
19	ISM	F	Birth	3.2	238
20	ISM	M	Birth	0.5	124
21	ISM	M	Birth	1.0	440
22	MAST	M	3	20.3	21

MPCM = Maculopapular Cutaneous Mastocytosis; UP = Urticaria Pigmentosa;

DCM = Diffuse Cutaneous Mastocytosis; ISM = Indolent Systemic Mastocytosis;

MAST = Mastocytoma.

Table 3

Pre-Operative Symptom Frequency and Post-Operative Adverse Reactions.

Signs & Symptoms	Number of Patients (%)	Intra-Op or Post-Op Adverse Reaction (%)
Cutaneous		
Flushing	19 (86)[1]	2 (9)
Pruritus	17 (77)	0
Blistering	4 (18)	0
Gastrointestinal		
N/V/ Diarrhea	10 (45)	4[1] (18)
Abdominal pain	9 (41)	0
Hepatosplenomegaly	5 (23)	--
GERD	5 (23)	0
PUD	2 (9)	0
Neurological		
Headache	5 (23)	0
Cardiovascular		
Hypotension	0 (0)	0
Syncope	3 (14)	0
Anaphylaxis	1 (5)	0

Total number of patients = 22

[1] *All 4 patients had nausea and vomiting only*.

GERD = Gastroesophageal Reflux Disease

PUD = Peptic Ulcer Disease

Table 4

Anesthetic management of patients with pediatric-onset mastocytosis*

Patient	Age	Surgical time	Anesthetic time	Antihistamine	Procedure	Drugs used perioperatively			Adverse events
						Pre	Intra	Post	
1	2	15	30		skin biopsy and bone marrow biopsy and aspirate	midazolam	sodium thiopental, lidocaine, ketamine		none
2a	12	90	120	diphenhydramine ranitidine	EGD, colonoscopy	midazolam	propofol, isoflurane		none
2b	13	25	50		bone marrow biopsy		midazolam, ketamine	acetaminophen	none
3	13	30	45		bone marrow biopsy and aspirate		lidocaine, bupivacaine, isoflurane, sevoflurane, nitrous oxide	fentanyl	vomiting
4	4	30	48		bone marrow biopsy and aspirate		lidocaine, sevoflurane, nitrous oxide, fentanyl	ondansetron	flushing
5a	0.9	15	48		bone marrow biopsy and aspirate	fentanyl, midazolam		fentanyl	none
5b	3	70	85		EGD	midazolam	sevoflurane		none
6a	1	15	30		bilateral myringotomy tubes		sevoflurane, nitrous oxide	acetaminophen	none
6b	5	54	63	diphenhydramine ranitidine	cardiac catheterization		lidocaine, midazolam heparin	acetaminophen	none
7a	0.6	30	45		bone marrow biopsy and aspirate		lidocaine, chloral hydrate		none
7b	19	60	75		bone marrow biopsy and aspirate	midazolam	lidocaine, propofol, fentanyl, ephedrine	fentanyl, acetaminophen	none
8	20	105	125		laproscopic cholecystectomy	midazolam	propofol, rocuronium, fentanyl, ondansetron, neostigmine, glycopyrrolate	acetaminophen, hydrocodone	vomiting
9	1	35	65		bone marrow biopsy and aspirate		lidocaine, sevoflurane nitrous oxide, propofol		none
10	6	18	27		bone marrow biopsy and aspirate	midazolam	prilocaine, ketamine		none
11	9	75	90		CT guided spleen biopsy	midazolam	lidocaine, propofol, isoflurane, vercuronium, fentanyl, neostigmine, glycopyrrolate		none

Patient	Age	Surgical time	Anesthetic time	Antihistamine	Procedure	Drugs used perioperatively			Adverse events
						Pre	Intra	Post	
12	0.8	20	40	hydroxyzine ranitidine	bone marrow biopsy and aspirate		lidocaine, sevoflurane, nitrous oxide	acetaminophen, fentanyl	none
13	20	15	20		bone marrow biopsy and aspirate		lidocaine, midazolam, fentanyl		none
14	4	30	40	ranitidine	bilateral myringotomy tubes and adenoidectomy	midazolam methylpred -nisone	sevoflurane, propofol	ondansetron, acetaminophen, fentanyl	vomiting
15	3	40	55	hydroxyzine diphenhydramine ranitidine	bone marrow and skin biopsy		atropine, sevoflurane, nitrous oxide		none
16	1	30	55	diphenhydramine ranitidine	bone marrow biopsy and aspirate	midazolam	lidocaine, propofol, ketamine	acetaminophen, ibuprofen	vomiting
17	13	30	45	cetirizine ranitidine	bone marrow biopsy and aspirate	midazolam	lidocaine, propofol. sevoflurane, isoflurane, nitrous oxide	fentanyl	none
18	2	20	30		bone marrow biopsy and aspirate	midazolam	isoflurane, sevoflurane, nitrous oxide, fentanyl		none
19a	2	23	38		bone marrow biopsy and aspirate	midazolam	atropine, ketamine, midazolam		none
19b	9	40	55		bone marrow biopsy and aspirate		lidocaine, nitrous oxide,fentanyl sevoflurane, isoflurane,		flushing
20	3	30	45		bone marrow biopsy and EGD		lidocaine, sevoflurane, fentanyl isoflurane, nitrous oxide		none
21	3	20	30	hydroxyzine cetirizine ranitidine	bone marrow biopsy and aspirate		lidocaine, chloral hydrate		none
22a	7	120	135		dental rehabilitation	midazolam	lidocaine, propofol, vecuronium, sodium thiopental	fentanyl	none
22b	14	45	50		EGD	midazolam	propofol, isoflurane, nitrous oxide, fentanyl succinylcholine, cisatracurium		none
22c	16	340	360	cetirizine	otoplasty and bone marrow biopsy and aspitrate	ceftriaxone	lidocaine, propofol, isoflurane, nitrous oxide, cisatracurium, fetanyl	diphenhydramine	none

Patient	Age	Surgical time	Anesthetic time	Antihistamine	Procedure	Drugs used perioperatively			Adverse events
						Pre	Intra	Post	
							ondansetron		

*Age, in years and anesthetic and surgicaltimes in minutes. EGD= esophagogastroduodenoscopy.