Recognition and Management of Medication Excipient Reactivity in Patients With Mast Cell Activation Syndrome

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ABSTRACT

Mast cell activation syndrome (MCAS) is a complex disorder hallmarked by chronic multisystem inflammatory, allergic and growth dystrophic phenomena caused by inappropriate mast cell activation. MCAS has been estimated to affect as many as 17% of the population with a severity ranging from mild to life-threatening. MCAS patients are more sensitive than the average person to chemicals in the environment, including the nondrug ("inactive") ingredients (excipients) in medications and supplements. Excipient reactivity may explain unusual side effects to medications health professionals often find puzzling, such as the patient who appears intolerant of prednisone, acetaminophen, levothyroxine, or a vitamin. We present a series of patients with MCAS to illustrate important points regarding excipient reactivity which may be useful in everyday practice.

Key Indexing Terms: Excipient; Mast cell activation syndrome; Postural tachycardia syndrome; Chemical sensitivity; Ehlers-Danlos syndrome. **[Am J Med Sci 2019;357(6):507–511.]**

INTRODUCTION

Mast cells are primitive cells of the immune system which act as "sentinels," present in all tissues but standing guard most prominently at the body's environmental interfaces, e.g. the skin, the gastrointestinal tract, the respiratory tract and the genitourinary tract. Unlike lymphocytes, which have great specificity, mast cells use nonspecific chemical mediators as their dominant mechanism of attack against foreign invaders (e.g. parasites). More than 200 different mast cell mediators have been identified, including histamine, tryptase, heparin, prostaglandins and leukotrienes. Mast cell activation syndrome (MCAS) is a newly described, complex multisystem disorder. The first case report was published in 2007,[1] and the first proposals for diagnostic criteria were published in 2010 and 2011.[2,3] Unlike allergies, which involve specific IgE-mediated activation of mast cells, mast cells in MCAS are activated inappropriately by specific and nonspecific triggers, such as positive or negative emotional or physical stress, extremes of temperature or temperature or barometric pressure change, environmental chemicals, alcohol, high histamine foods, odors, physical stimuli (e.g. pressure from a tourniquet), drugs and the nondrug ingredients (excipients) in medication products. Since mast cells are present in all organs, and since their chemical mediators enter the bloodstream, inappropriate mast cell activation can produce a large number of signs and symptoms that may vary and occur in a fluctuating pattern, often creating a complex clinical picture. Like most diseases, MCAS exists on a spectrum, ranging from very mild to extremely severe, and it has been estimated to affect up to 17% of the population.[4]

Symptoms of MCAS may be acute and/or chronic. Skin flushing, itching, fleeting rashes and hives are very common, but not all patients have grossly obvious cutaneous manifestations. Other common symptoms include bone, muscle, joint and/or neuropathic pain; paresthesias; gastroesophageal reflux; abdominal pain; nausea/vomiting; bowel motility issues (gastroparesis and/or diarrhea alternating with constipation); presyncope/syncope; heart rate and/or blood pressure lability; chest pain; dyspnea (often subtle, typically described as an occasional brief inability to take a deep breath); unexplained weight loss or gain (which may be significant); anxiety; depression; mood lability; cognitive dysfunction; sleep disturbance; lethargy; fatigue; malaise; fevers; night sweats; headache and vertigo.[5] Many patients experience mast cell "flares" or "spells," but more severely affected patients also have chronic symptoms due to constitutive mediator release aside from mediator release related to aberrant reactivity. Prior to adulthood, patients with MCAS often initially enjoy symptom-free intervals interspersed amongst symptomatic periods. Over time, symptom-free intervals shorten, and finally symptoms become chronic with an intensity which fluctuates, but with an overall trend toward steadily increasing severity. An increase in disease severity often follows major stress. Mast cells are also intimately involved in growth regulation, and patients with MCAS often have cysts in 1 or more organs, poor wound healing,

or other signs of dysregulated tissue growth. Patients with MCAS have often experienced a lifetime of multi-system unwellness with broad themes of inflammation, allergy and disordered growth. For most MCAS patients, signs of the disease first emerge in childhood (median age at symptom onset is 9 years), but there is an average delay in diagnosis of MCAS of 30 years.[5] In one evolving model, MCAS increasingly is being suspected to arise proximately from mutations in one or more mast cell regulatory genes, and these mutations – usually somatic, heterozygous and multiple – themselves likely emerge due to complex interactions among other mutations which are germline (i.e., inborn) and both genetic and epigenetic.[6,7] Stressor-induced cytokine storms, too, may significantly impact these interactions and the development of the consequent somatic mutations (that is, mutations which are acquired, not inborn, but often beginning relatively early in life). MCAS may also occur secondary to an underlying allergic, infectious, immunodeficiency or an autoimmune disorder.

In some sense, patients with more severe forms of MCAS may be akin to "canaries in the coal mine." Coal miners used to bring caged canaries into the mines with them, knowing that canaries are particularly sensitive to methane and carbon monoxide gases. Thus, if the canaries died, these dangerous gases were reaching dangerous levels and the mine needed to be evacuated to avoid human death. Like the canaries, MCAS patients are unusually sensitive to environmental chemicals. These include not only chemicals in processed foods, cleaning and personal care products but also the inactive ingredients in medications and supplements. Medication intolerances are very common in patients with MCAS,[8] so much so that a long list of "allergies" can be used as a diagnostic clue to the possible presence of underlying MCAS. While there are some drugs (i.e., "active ingredients") which may trigger activation of both normal and abnormal mast cells in some people, excipient reactivity is a much more common reason for medication intolerance in patients with MCAS. Active pharmaceutical agents which can trigger MCAS in some patients due to their mast cell activating properties include: morphine, codeine and other opiates, vancomycin and certain other antibiotics, nonsteroidal anti-inflammatory agents and aspirin in some patients (in other patients, these agents act as mast cell inhibitors), some anesthetic agents, angiotensin converting enzyme inhibitors and radiographic dyes.

According to the Collins English dictionary, an excipient is "a substance, such as sugar or gum, used to prepare a drug so it is suitable to administer." Excipient ingredients in medications are supposed to be "inert" and "safe," but they may cause problematic reactivity in MCAS and other patients,[9] including anaphylaxis. Almost all medications and supplements contain one or more excipients, including compounded medications. Commonly used classes of excipient ingredients, their intended purposes and examples are summarized in Table 1. Often excipients make up the bulk of the final medication product. There are currently over 1000 different excipients used in pharmaceutical products. In the past, excipients were of natural origin, e.g. wheat, sugar, corn or minerals. Today, with the use of complex drug formulations and delivery systems, excipients which may be more toxic are used frequently.[9] The severity of excipient reactivity in MCAS patients varies from patient to patient and, in the authors' experience, seems to correlate generally with the overall severity of the MCAS. (No formal scales or systems for measuring excipient reactivity have been established, though the Quick Environmental Exposure and Sensitivity Inventory tool [https://www.ncbi.nlm.nih.gov/pubmed/10416289] may be the closest

Table 1. Excipients and their function.

Excipient type	Purpose	Examples
Anti-adherents, lubricants, glidants	Prevent tablets from sticking together	Magnesium stearate, stearic acid, talc, silica, magnesium carbonate
Antimicrobial agents	Reduce the risk of infectious contamination	Benzyl alcohol, phenol, methylparaben
Binders, fillers	Bind ingredients and give volume to tablets when the active ingredient is present in very small amounts	Microcrystalline cellulose, lactose, sucrose, starches, sorbitol, gelatin, polyethylene glycol
Coatings	Protect the tablet or capsule ingredients from deterioration and make tablets easier to swallow	Shellac, gelatin
Dyes	Improve the identification of medications and improve the "aesthetic look" of medications	FD&C red #5, FD&C yellow #10, FD&C blue #2, ferric oxide red, ferric oxide yellow
Flavorings, sweeteners	Used to mask unpleasant tasting active ingredients and improve the likelihood the patient (especially kids) will complete the prescribed course of therapy	Sucralose, xylitol
Preservatives	Increase the shelf-life of the medication; reduce risk of infectious contamination	Methyl paraben, citric acid, retinol palmitate
Solubilizing agents	Solubilize the active ingredient	Alcohols, acetone, glycerol, EDTA, polysorbate 80
Disintegrants	Expand and dissolve when wet, causing the tablet to break apart in the digestive tract, releasing the active ingredient for absorption	Crospovidone, croscarmellose, sodium starch glycolate

Abbreviations: EDTA, ethylenediaminetetraacetic acid; FD&C, United States Federal Food, Drug, and Cosmetic Act.

yet.) Occasional MCAS patients are so reactive that their medications must be compounded in an ultraclean compounding facility to prevent contamination with even trace amounts of excipients to which they are reactive. A complete list of excipient ingredients known by the manufacturer to be present in each United States Food and Drug Administration medication product approved for sale in the United States is provided on the FDA's "Daily Med" website: https://dailymed.nlm.nih.gov/dailymed/. Daily Med is an invaluable resource for not only patients with MCAS but also their physicians and pharmacists. The differential diagnosis of multiple medication intolerances includes pharmacogenomic polymorphisms, but excipient reactivity usually presents quickly (within the first few doses), whereas toxicity due to excessive drug accumulation from a poor-metabolizing pharmacogenomic polymorphism usually does not emerge until at least a few weeks after initiation of treatment.

CASE PRESENTATIONS

Patient #1

A 50-year-old female with long-standing multisystem problems that began in childhood (including neuropsychiatric issues, recurrent unexplained syncope, episodic severe lethargy, cognitive dysfunction, frequent chest pain, night sweats, prominent gastrointestinal symptoms, fleeting rashes, severe fatigue and malaise) was diagnosed with MCAS. In addition to a consistent clinical phenotype, she was found to have an elevated serum prostaglandin D2 level on 2 separate occasions, and testing for other conditions which might account for some or all of her symptoms was negative. She experienced meaningful clinical improvement and had been stable for several months on a medication regimen which included ranitidine, cetirizine and oral cromolyn. She returned, however, with a several week decline, noting increasing malaise, gastrointestinal symptoms and rashes. When asked, "What changed?" she was adamant that there had not been any new medications, supplements, personal care or cleaning products or dietary changes. It turned out, however, that she had gotten her carbamazepine refilled shortly before onset of the decline. She had been taking this medication for 20 years, but with the most recent refill, the pharmacy gave her a formulation of the drug from a different manufacturer which contained sodium lauryl sulfate. Her carbamazepine was switched back to the original manufacturer without this excipient and she quickly returned to her prior baseline.

What We Can Learn From Patient #1

- Excipient reactivity may not be noticed immediately by the patient.
- While some excipients cause acute symptoms within minutes to an hour, ranging from anaphylaxis to headache, flushing, anxiety, etc., others may cause a more insidious decline.
- MCAS patients should review all medications on the FDA's Daily Med website before picking them up from the pharmacy to be sure there has not been a change in manufacturer and to be sure there are no excipients to which they have previously reacted.
- It is helpful for MCAS patients to make a spreadsheet of the excipients from medication and supplement products they know they tolerate versus products they know they do not tolerate.
- Because there are multiple excipients in most medications and supplements, using clues from tolerated and not-tolerated agents can help determine culprit excipient or excipients.

Patient #2

An 18-year-old man with hypermobile Ehlers-Danlos syndrome and disabling postural tachycardia syndrome was diagnosed with MCAS by a consistent clinical history, absence of any other evident diagnoses better accounting for the full range and duration of his problems and findings, and an elevated serum prostaglandin D2 and 24-hour urine *N*-methylhistamine. His functional ability improved significantly by gaining understanding of mast cell and autonomic disease triggers and by using salt, fluids, twice daily cetirizine and cannabis, a recognized mast cell inhibitor via mast-cell-surface cannabinoid receptors. After starting college, he reported increasing headaches and insomnia, and he wanted to resume nortriptyline, which he took in the past with improvement in these symptoms. He had stopped it previously because despite helping his headaches and insomnia, it "made me feel weird." A review of the excipients present in the particular formulation of nortriptyline he took in the past was notable for benzyl alcohol (he was extremely sensitive to alcohol, with acute onset of symptoms with minimal ingestion) and 5 different FD&C dyes. He was switched to a different formulation of nortriptyline which did not contain benzyl alcohol, and the dye-containing capsule was discarded, emptying the contents into yogurt or applesauce. This resulted in even better improvement in his headaches and insomnia, and he did not "feel weird" when he took it.

What We Can Learn From Patient #2

- Patients can have a mixed response to medication products, i.e., improvement in certain symptoms due to the active ingredient, but worsening of other symptoms, negation of the benefit of the active ingredient, or even emergence of new symptoms due to reactivity to one or more excipients.
- FD&C dyes are very common triggers in MCAS patients: In the authors' experience, red dyes seem to be the most poorly tolerated, followed closely by yellow and then blue. Often the dyes are contained in the

capsule, and for some (but not all) capsule-contained medications, the capsule can be opened and its contents consumed *sans* capsule.
- Not all colored pills contain FD&C dyes. Some contain ferric oxide red or yellow which tend to be well tolerated by most MCAS patients.
- Not all apparently uncolored (i.e., white) pills are free of dyes.
- Alcohols are also common triggers in MCAS patients, e.g. benzyl alcohol, polyvinyl alcohol.
- When considering the possibility of excipient reactivity in MCAS patients, dyes and alcohols are good places to start.
- It is also important to avoid culprit excipients in foods as well as personal care and cleaning products in patients who are reactive, e.g., shampoos and toothpastes may contain dyes.

Patient #3

A 24-year-old man was diagnosed with severe MCAS (elevated 24-hour urine and serum prostaglandin D2, elevated 24-hour urine *N*-methylhistamine). This diagnosis explained his years-long history of severe mood lability (diagnosed as atypical bipolar disorder), headaches, fatigue, anxiety, arrhythmias and dysautonomia.

During one of the many emergency department visits for his severe symptoms, he had been given lorazepam, which resulted in significant improvement in many of his symptoms. There are inhibitory receptors for benzodiazepines on the surface of mast cells and benzodiazepines inhibit mast cell activation in many patients. He was started on clonazepam by his psychiatrist with significant, but incomplete improvement. It was noted that the clonazepam contained yellow dye. A new prescription was ordered as "no dyes," but he worsened significantly. The new formulation he was given was for orally disintegrating tablets, which contained sodium lauryl sulfate, crospovidone, talc and aspartame, all of which have caused problematic reactivity in some MCAS patients. He was switched to 2 mg dye-free clonazepam tablets (from the same manufacturer as the original 0.5 mg tablets) and had an even better response than with the original prescription.

What We Can Learn From Patient #3

- Patients can have more than one problematic excipient.
- While dyes and alcohols are a good place to start, other excipients which have been problematic in some MCAS patients include sodium lauryl sulfate, artificial sweeteners, talc, polyethylene glycol, magnesium stearate, shellac, povidone, crospovidone and sodium hydroxide.
- Some MCAS patients even react to usually very well-tolerated ingredients, e.g. microcrystalline cellulose, gelatin.
- Different strengths/dosages of medications produced by the same manufacturer may have different excipients, especially dyes, so that a patient may distinguish between different strengths of the medication more easily, e.g. the patient using 2 different strengths of warfarin.

Patient #4

A 63-year-old woman with thrombotic antiphospholipid syndrome and secondary MCAS (positive serum prostaglandin D2 on 2 separate occasions) had experienced many years of medication intolerances so severe that she regularly traveled overseas to get certain formulations of heparin and warfarin. She was intolerant of hydroxychloroquine, an important treatment in the management of the fatigue and arthralgias she experienced from antiphospholipid syndrome. Hydroxychloroquine caused rapid-onset hives, flushing and malaise, which are unusual side effects of this drug. A trial of hydroxychloroquine compounded by a distant pharmacy in microcrystalline cellulose was well tolerated. When she needed a refill, it was compounded with the same "recipe" at a local pharmacy and she again developed side effects. Cellulose is a ubiquitous plant-based product, but different plants make slightly different forms of cellulose. Investigation found that the source of microcrystalline cellulose used by the local pharmacy was cotton and the source used by the distant pharmacy was wood. She has used the distant pharmacy ever since and has tolerated the hydroxychloroquine well. It has resulted in significant improvement in her fatigue and arthralgias.

What We Can Learn From Patient #4

- Although idiosyncratic drug reactions are always possible, signs or symptoms that are not typical side effects of a particular active ingredient, e.g. hives or headache from steroids or headaches, abdominal pain or suicidal ideation from montelukast, raise possibilities of not only excipient reactions but also occult MCAS.
- Some MCAS patients react to usually well-tolerated ingredients.
- Compounding pharmacies can be invaluable for severely reactive patients to help determine whether a reaction is directed against the active ingredient or a particular excipient.

Patient #5

A 14-year-old girl with hypermobile Ehlers-Danlos syndrome and postural tachycardia syndrome was diagnosed with MCAS based on an elevated 24-hour urine *N*-methylhistamine on 2 separate occasions. She had a severe flare of musculoskeletal pain in her back after excessive physical activity. Disc herniation, Tarlov cyst, fracture and other conditions were ruled out. Her pain

was severe and refractory, and she underwent trigger point injections. The injections made her pain acutely worse and also caused hives and flushing. Investigation found that the steroid and local anesthetic agent used in the injection both contained alcohol. She underwent repeat injection with alcohol-free agents, which resulted in rapid clinical improvement.

What We Can Learn From Patient #5

- Problematic excipients may also be present in parenteral medications.
- Certain formulations of lidocaine and ropivacaine do not contain alcohol.
- Certain formulations of betamethasone do not contain alcohol.
- Multidose medication vials (e.g., nasal sprays, eyedrops) must contain a preservative, and many MCAS patients react to these preservatives.
- Due to different excipients, a patient may tolerate an oral formulation of a medication but not the parenteral formulation or vice versa. For example, a patient may do well with oral lorazepam (benzodiazepines act as mast cell inhibitors in most patients) but not intravenous lorazepam, as all intravenous formulations of lorazepam presently available in the United States are stabilized with alcohol, which commonly is a mast cell activator.
- A patient may also tolerate one brand of preservative-free intravenous diphenhydramine or oral cromolyn but not another brand even though each only contains the active drug and sterile water with no apparent excipients. These patients may be reacting either to an ingredient contained in the material of the vial itself which leeches into the drug, or a contaminant may get into the product during the manufacturing process, or the water supply used may be sterile but not necessarily completely pure. Publicly available reports from the FDA's pharmaceutical manufacturing plant inspectors document many reports of multiple drug quality manufacturing issues, such as gross particulate contamination of certain manufactured lots of certain intravenous drugs.
- Parental medications and their excipients are included in the DailyMed database.

CONCLUSIONS

Though difficult to learn to recognize due to the extreme complexity of its pathobiology and its extreme clinical heterogeneity, MCAS appears to be common, and medication excipient reactivity is a common problem in MCAS patients. Reactivity to FD&C dyes and alcohols are the most common, but some MCAS patients react to usually well-tolerated excipients, including those which are used by compounders. An excipient reaction in an MCAS patient should be suspected if different responses are seen to different formulations of the same drug, if atypical "side effects" are seen (e.g., hives or headache from steroids), or if there is a reaction to a medication that a patient tolerated well previously. Different excipients may result in different signs/symptoms, and excipient reactions may present acutely or more insidiously. It also should be kept in mind that reactions may be mixed, i.e., benefit from the active ingredient but worsening from the excipient. We recommend that when a culprit excipient is identified, it should be added to the patient's allergy list, rather than listing the medication, but since most modern electronic medical record and electronic pharmacy systems feature drug–allergy interaction checking but not excipient–allergy interaction checking, manual review of medication ingredient lists should be performed by both pharmacists and patients. We encourage US patients to learn how to use the Daily Med database and to take ownership of knowing what excipients are present in all of their medications and supplements.

AUTHOR CONTRIBUTIONS

J.R.S. conceived of the article, wrote the initial draft, and contributed to the editing. L.B.A. contributed significantly to the editing of the article.

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Submitted January 6, 2019; accepted March 15, 2019.

Conflicts of interest: The author has no financial or other conflicts of interest to disclose.

Source of funding: None

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