Title

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CLINICAL VIGNETTE

Importance of Serum Tryptase for Evaluation of Perioperative Anaphylaxis

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A 69-year old female on hemodialysis, was admitted for deceased donor kidney transplant and developed perioperative anaphylaxis during kidney transplant surgery. Her other problems included hypertrophic obstructive cardiomyopathy status post alcohol ablation, diastolic heart failure 9LVEF 65-70%), and complete AV heart block post status pacemaker placement, hypertension, and Diabetes Mellitus Type II. The evening before surgery, she received hemodialysis with 1L fluid removal. The morning of surgery, her home antihypertensive medications were held (nifedipine, clonidine, losartan, spironolactone, hydralazine) and her blood pressure was recorded at 190/80. She was taken to the Operating Room (OR) at 9am and following induction of anesthesia and intubation (Midazolam, propofol, cisatracurium, fentanyl, lidocaine), she received cefazolin 1g IV, had placement of latex Foley urinary catheter after skin cleaning with Betadine, and instillation of bacitracin to the bladder, which is standard procedure prior to kidney transplantation. In the midst of multiple medications being administered, her previously hypertensive blood pressure had declined to 80/37. The kidney transplant operation was aborted, and she required 11 minutes of cardiopulmonary resuscitation. Transthoracic echocardio-gram revealed concentric hypertrophy of the left ventricle with low filling volumes which improved after resuscitation with 1L NS and 4 bottles of albumin. She was transferred to the MICU for further evaluation and treatment of hypotensive shock.

Operating Room Course

Time	Medications administered, resulting signs and symptoms
8:54am	Arrived in OR, received Midazolam 1mg IV, BP 199/87.
9:23am	Induction of anesthesia and intubation with propofol 90mg, cisatracurium 6mg, fentanyl 25mcg, and lidocaine 60mg IV. BP 190/83.
9:40 am	received Ancef(cefazolin) 2g IV
9:47am	BP 88/37, with continued decline.
9:49am	progressive hypotension BP 70/70 despite phenylephrine. Chest compressions initiated, given code doses of epinephrine 1mg IV x2
10:00am	chest compressions stopped, continued volume resuscitation with total 1L NS and albumin x4. Latex Foley urinary catheter removed.
10:03am	Serum tryptase level drawn
10:17am	TEE performed, revealed evidence of hypovolemia. Patient transferred to MICU requiring pressor support.

Severity of Periprocedural Allergic Hypersensitivity Reactions

Grade	Symptoms
I	Cutaneous signs only (erythema, urticaria, angioedema)
II	Measurable but non-life-threatening symptoms: cutaneous signs, hypotension, tachycardia, and/or respiratory symptoms (cough bronchospasm or difficulty ventilating)
III	Life-threatening symptoms: cardiovascular collapse, tachycardia or bradycardia, arrhythmias or severe bronchospasm
IV	Cardiac and/or respiratory arrest

Adapted from Table 1 of Iammatteo et. al.[1]

The incidence of perioperative hypersensitivity reactions ranges from 1 in 385 to 1 in 20,000 procedures. Hemodynamically significant anaphylaxis occurs at a rate of 1 in 8,400 perioperative cases with the associated mortality rate ranging from 3 to 9%.[1] Anaphylaxis is a severe multisystem allergic hypersensitivity reaction which can be caused by IgE mediated and non- IgE mediated processes.[2] It can be graded based on severity (Table 1) and is difficult to diagnose clinically, as it can mimic other processes and have variable patterns of organ involvement.[1] Perioperative and intraoperative anaphylaxis can be even more difficult to evaluate due to dramatic physiological shifts, and the inability of a surgical patient to communicate the early signs and symptoms of anaphylaxis. Additionally, the number of medications used in anesthesia and surgery, coupled with the patient's inability to provide a history adds to the complexity of identifying the culprit antigen. However, anaphylaxis is a clinical diagnosis and treatment should not await confirmation of the diagnosis. A careful review of the drug administration record, operative notes and laboratory evaluation to confirm anaphylaxis is important in the retrospective assessment to establish that the patient had anaphylaxis and aides in subsequent evaluation to identify the culprit antigen. The most critical aspect of perioperative anaphylaxis evaluation is the blood samples for measurement of mast cell and basophil degranulation and serum tryptase level. Tryptase is a serine protease released from predominantly mast cells which contain approximately 500 times more tryptase than basophils during an allergic hypersensitivity reaction and anaphylaxis.[3,4] Normal levels of serum tryptase range from 1 to 11.4 ng/mL.

When evaluating patients with anaphylaxis, serum tryptase level measurement is advised and should be taken as soon as

possible after symptom onset. Three timed serial measurements can be helpful in determining whether the episode was due to anaphylaxis. "British guidelines explicitly recommend that serial blood samples for acute serum tryptase should be taken as soon as possible after the onset of symptoms and at 1 to 2 hours following symptoms onset and a baseline sample at least 24 hours after the episode."[5] The timing reflects the 2hour half-life of tryptase, where the peak is 1 to 2 hours after symptom onset and the return to baseline is 6-8 hours after symptom onset. Stone et al reports that tryptase can remain elevated at 50% above baseline for up to 10 hours.[6] There is no international consensus criteria for elevation or a percentage change from baseline that corresponds to an elevated level, although ≥ 11.4ng/mL is frequently cited. Other values include serum tryptase ≥2 + 1.2 x baseline tryptase levels.[7] Elevated serum tryptase is highly suggestive of anaphylaxis, though a normal tryptase does not rule out anaphylaxis. Tryptase elevations are more likely to be found in cases of anaphylaxis due to medications, stinging insect venoms, and reactions involving hypotension. Previous studies reported that patients normotensive during anaphylaxis and those with food-induced anaphylaxis do not show an elevation in serum tryptase as often as other causes of anaphylaxis, while the presence of hypotension predicts a higher serum tryptase level.[8,9] The presence of hypotension significantly increases the probability of having levels of acute serum tryptase ≥ 11.4ng/Ml. Mertes et al reported "high levels of acute serum tryptase in patients developing severe cardiovascular perioperative anaphylaxis during general anesthesia."[10] Buka et al obtained serum tryptase in 141 cases (33 percent) at a mean time period of 4.75 hours after onset of symptoms and again after resolution in 23 cases. A serum tryptase above 12.4 ng/mL showed high specificity (88 percent) and positive predictive value (0.93) and low sensitivity (28 percent) and negative predictive values (0.17). British guidelines recommend acute serum tryptase measurements in children, and in cases of drug induced, venom induced or idiopathic anaphylaxis.[5] Acute serum tryptase often take several days to result and are not typically available to clinicians until >72hours after ordering the test. Additionally, the presence of an elevated serum tryptase does not identify the mechanism of the reaction as IgE mediated or non- IgE mediated.

Following a perioperative allergic hypersensitivity reaction, comprehensive skin testing to all perioperative agents along with specific IgE to latex has variable ability to identify the causative agents ranging from 18-91%.[1] Medication skin tests are performed using the skin test guidelines jointly published by the European Network for Drug Allergy (ENDA) and the European Academy of Allergy and Clinical Immunology (EAACI) drug allergy interest groups, which specify non irritating concentrations for NMBAs, induction agents, opiates and local anesthetics.[11] Medication skin tests can be considered if the mechanism of action is suspected to be IgE mediated. However, skin testing is of no benefit in the evaluation of anaphylaxis due to a non-IgE mediated mechanism. Furthermore, the timing of skin test must be 4-8 weeks after anaphylaxis due to the risk of false negatives. False negatives on skin test performed sooner than 4-6 weeks after anaphylaxis may occur due to time needed for basophils and mast cells to replenish their cells with allergic mediators expended during the anaphylaxis event. This post anaphylaxis period of 4-8 weeks is called the refractory period. Recent U.S studies cited the most common identifiable cause of perioperative allergic hypersensitivity as antibiotics, while most European studies identified neuromuscular blocking agents (NMBAs) as the most likely cause.[1] In general, NMBAs are known causes of immediate hypersensitivity reactions during anesthesia with high cross reactivity among agents. A 2017 retrospective study sought to identify causative agents of periprocedural hypersensitivity reactions in 34 patients and identified the most common causative class of medications was induction agents (midazolam, etomidate, ketamine and propofol) followed by cefazolin.[1] Testing for IgE mediated hypersensitivity to antibiotics is very limited. There are no validated allergy skin or blood tests available to evaluate the likelihood of an IgE mediated reaction to any drug other than select penicillin related as the sensitivity and specificity of IgE mediated testing to antibiotics is not known. To evaluate the likelihood of an IgE mediated hypersensitivity reaction to a non-penicillin antibiotic, a graded dose challenge can be utilized in the appropriate circumstance. To determine if a patient is allergic to any drug other than penicillin, amoxicillin or cefazolin, the patient would have to be given the medications in increasing amounts over hours and observed for evidence of an IgE mediated reaction.

We determined that our patient needed skin testing to cefazolin, propofol and rocuronium as anesthesiology expressed a desire to use rocuronium or vecuronium for her planned kidney transplant. Her testing included serum tryptase with in 4hours of allergic hypersensitivity symptoms/anaphylaxis, a baseline serum tryptase after hospital discharge, latex specific IgE as there is no available validated skin test to evaluate for IgE mediated latex allergic hypersensitivity. In addition to skin testing for cefazolin antibiotic, neuromuscular blocking agent rocuronium and induction agent propofol no sooner than 4-8 weeks following anaphylaxis. Results showed serum latex IgE negative, serum tryptase elevated at 176 *ug/L* at the time of anaphylaxis with a slow decline 3 and 6 hours after and a baseline serum tryptase of 6.4 *ug/L*. The perioperative skin test results were positive to cefazolin, which was subsequently avoided. The patient tolerated subsequent anesthesia and had a successful renal transplant.

Labs

Component *Latest Ref Rng & Units*	
Latex (k82) IgE *<=0.34 kU/L*	<0.10

Serum tryptase measurements

Component *Latest Ref Rng & Units*	At the time of anaphylaxis	3 hours post anaphylaxis	6 hours post anaphylaxis	28hours post anaphylaxis	4 months post anaphylaxis
	10:00 AM	1:00 PM	4:00 PM	2:00PM	12:00PM
Tryptase *<=10.9 ug/L*	176.0 (H)	69.0 (H)	49.8 (H)	9.3	6.4

Skin test

Intraoperative/perioperative Anaphylaxis Skin Testing:

	Skin Prick	**Intradermal**
Rocuronium (10mg/ml)	Prick: 0/3mm; intradermal 0/5mm	
Propofol (10mg/ml)	Prick: 0/3mm; intradermal 0/3mm	
Cefazolin (100mg/ml)	**Prick 5/5mm; intradermal: 8/24mm**	
Histamine control	Prick: 7/25mm; intradermal: 16/45mm	
Sterile water control	Prick: 0/3mm; intradermal 0/3mm	

This case illustrates the importance of serum tryptase in the assessment of perioperative anaphylaxis. Due to limitations of IgE mediated hypersensitivity testing, serum tryptase can be invaluable in establishing that a patient with multiple medical had anaphylaxis as opposed to a mimicker of anaphylaxis such as a cardiac, pulmonary or other medical disease. Acute serum tryptase (drawn within 1-2 hours of allergic hypersensitivity symptoms) has a high specificity and positive predictive value, low sensitivity and negative predicative value in the diagnosis of perioperative anaphylaxis. Serial measurements, after the onset of symptoms, at 1 to 2 hours following symptoms onset and a baseline sample at least 24 hours after the episode is helpful in the assessment of anaphylaxis, albeit impractical in outpatient anaphylaxis. Furthermore, the presence of hypotension is a significant predictor of serum tryptase ≥ 11.4ng/mL and serum tryptase should be obtained in all suspected cases of medication induced drug hypersensitivity reactions.

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