A diagnostic workup of perioperative anaphylaxis reveals a selective type 1 hypersensitivity to cefazolin

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Abstract: Anaphylaxis in the operating room although infrequent can be potentially fatal.[1] The diagnosis of perioperative anaphylaxis is complex due to a multitude of factors. Firstly, patients under anesthesia cannot verbalize their complaints, the anesthetic agents themselves can alter vital parameters (e.g. heart rate and blood pressure) and cutaneous signs in a completely draped patient may be missed.[2] Secondly, the differential diagnosis of intraoperative anaphylaxis is wide. Conditions such as asthma exacerbation, arrhythmia, hemorrhage, angioedema, mastocytosis, acute myocardial infarction, drug overdose, pericardial tamponade, pulmonary edema, pulmonary embolus, sepsis, tension pneumothorax, vasovagal reaction, venous air embolism, laryngospasm, blood transfusion reaction and malignant hyperthermia need to be considered.[3] Thirdly, the diagnostic workup is challenging due to the multiple medications administered and other exposures encountered such as latex and chlorhexidene. However, through a timely allergy consultation and a systematic approach, identification of the culprit agent and safe alternatives can be established to prevent future occurrences as illustrated in the case below.

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Report of Case

A 21-year-old man with a diagnosis of an atrial septal defect (ASD) and an associated mitral valve prolapse was scheduled to undergo an ASD device closure.

The patient had no history of asthma, allergic rhinitis, dermatitis, food or previous history of drug allergy. He had no known history of latex allergy. He had no previous operations and he was unsure of antibiotic use in the past. He was commenced on aspirin 5 days prior to the procedure.

Physical examination on table revealed a patient who was afebrile, blood pressure 120/70 mm Hg, pulse rate of 85 beats per min, an oxygen saturation of 99% on inspired oxygen of 100%. Anesthesia was induced with administration of propofol, lignocaine and rocuronium. He was intubated and ventilated. Ten minutes post intubation, the patient was given intravenous cefazolin for surgical prophylaxis. Within 5 minutes he was noted to be hypotensive associated with increased airway pressures.

He had periorbital edema, lip swelling and generalized flushing. There were no rhonchi on auscultation. He was promptly treated with intravenous epinephrine, fluid boluses, hydrocortisone, and promethazine. His blood pressure responded and the operation proceeded. No serum tryptase was taken.

Postoperatively he was kept on a tailing dose of prednisolone, cetirizine and was monitored for any late reaction.

The patient returned to the allergy clinic 8 weeks post his anaphylactic reaction for prick and intradermal skin tests and these were performed in accordance with published guidelines[4] on the volar surface of the forearm The penicilloyl polylysine (Diater, Madrid Spain) and minor determinant mixture (Diater) were diluted and tested according to the manufacturers' instructions. A positive prick test was defined as a wheal greater than 3mm than the negative control. The prick and intradermal skin tests were all negative except to the positive control histamine (concentration of 10mg/ml with a 5mm weal and flare) and cefazolin , at a concentration of 1mg/ml with a 7mm weal and flare. Prick and intradermal tests were read after 15 min. For those reagents with negative skin tests, challenges were undertaken if feasible. Oral challenges to penicillin V, amoxicillin-clauvulanic acid and cefuroxime were performed to a cumulative dose (500mg, 625mg and 500mg) respectively. Each challenge was performed on different days. Increasing doses (starting with 0.01 of the daily therapeutic dose were administered in 30 minute intervals until the cumulative total therapeutic dose was reached). The patient did not react to any of the oral challenges. Chlorhexidene and latex challenges were

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negative.

Table 1: Prick, intradermal and challenge tests

REAGENT	PRICK TEST	PRICK TEST RESULT	ID TEST	ID RESULT	CHALLENGE
NMBA					
Atracurium	1mg/ml	negative	0.01mg/ml	negative	ND
Rocuronium	10mg/ml	negative	0.05mg/ml	negative	ND
Pancuronium	2mg/ml	negative	0.2mg/ml	negative	ND
Suxamethonium	10mg/ml	negative	0.1mg/ml	negative	ND
Hypnotics					
Propofol	10mg/ml	negative	1 mg/ml	negative	ND
Local Anesthetic					
Lidocaine	10mg/ml	negative	1mg/ml	negative	ND
Latex		negative	–	ND	negative
Chlorhexidene	0.5mg/ml	negative	–	negative	negative
Antibiotics					
Benzylpenicilloyl poly-L-lisine	0.04mg/ml	negative	0.04mg/ml	negative	ND
Minor determinant mixture*	0.5mg/ml	negative	0.5mg/ml	negative	ND
Phenoxymethypenicillin	ND	–	ND	–	negative
Amoxicillin clauvulanic acid	25mg/ml	negative	25mg/ml	negative	negative
Cefazolin	100mg/ml	negative	1mg/ml	positive	ND
Cefuroxime	ND	–	ND	–	negative

ID intradermal

ND Not done

NMBA Neuromuscular blocking agents

*Contains sodium benzylpenicillin, benzylpenicilloic acid, sodium benzylpenicilloate

Discussion

Any suspected hypersensitivity reaction during anesthesia must be extensively investigated to confirm the nature of the reaction, to identify the responsible drug, to study cross-reactivities of related drugs and to provide recommendations for future anesthetic procedures.[2] A methodical approach and knowledge of the likelihood of causal agents is imperative. The most recent epidemiological French survey[5] suggests NMBAs still represent the most frequently involved substances (47.4%), followed by latex (20%) and then antibiotics (18%). This recent literature shows an epidemiological change in the relative contribution of causal agents with an increase in antibiotic allergy compared to previous reports.

In our patient, the time of onset, the nature of the reaction and the positive intradermal test to cefazolin strongly suggests that he had an IgE-mediated hypersensitivity to cefazolin.

More perioperative cefazolin use has resulted in an increased risk of cefazolin-associated reactions.[6-10]

From a large database of cefazolin IgE-mediated hypersensitivity,[9] the authors have implicated the R1 side chain as playing an essential role in IgE mediated reactions to cefazolin. However, no clear rule was determined to predict cross reactivity with other β lactams. The majority of their patients did tolerate amoxicillin and several other cephalosporins. Likewise our patient demonstrated a selective hypersensitivity to cefazolin but was able to tolerate penicillin V, amoxicillin-clauvunate acid and cefuroxime. This suggests that his reaction was caused by a selective hypersensitivity to the side chain determinant rather than to the betalactam ring. Hence he was asked to avoid cefazolin in future and a medical alert card was issued.

This case illustrates that the diagnostic workup of perioperative anaphylaxis must be comprehensive and knowledge of the emerging culprits such as antibiotics is useful.

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