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CASE REPORT

Hypersensitivity Reaction After Administration of Crotalidae Polyvalent Immune Fab (CroFab)

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Abstract: Crotalidae polyvalent immune Fab (CroFab) is an antivenin that is FDA approved and commonly used to treat envenomations caused by North American pit vipers. Although CroFab has been widely used since the early 2000s, hypersensitivity reactions like type I, type IV, and angioedema have been reported in the literature. We present a case of CroFab induced hypersensitivity reaction in a 41-year-old male shortly after starting CroFab infusion. Furthermore, this patient developed anaphylaxis symptoms including: difficulty breathing, oropharyngeal edema, dysphagia, wheezing, and chest tightness. This was resolved upon stopping CroFab infusion and administering epinephrine, methylprednisolone, diphenhydramine, and famotidine. The reaction occurred again when CroFab was re-introduced despite infusing it at a much slower rate. Interestingly, this patient successfully tolerated crotalidae immune F(ab′)2 (equine) antivenom (ANAVIP) upon switching him from CroFab. Hypersensitivity reactions to CroFab can be life-threatening and warrant immediate attention and treatment in a multidisciplinary setting.

Keywords: CroFab, ANAVIP, hypersensitivity reactions, anaphylaxis, snake bites

Introduction

According to the National Electronic Injury Surveillance System-All Injury Program, snakebites accounted for almost 10,000 annual visits to the emergency departments across the United States.[1] Treatment with antivenom should be given promptly to prevent progression of venom toxicity. CroFab and ANAVIP are both approved for the treatment of North American Crotalinae (rattlesnakes, copperheads and cottonmouths/water moccasins) envenomation in pediatric and adult patients. CroFab is an ovine-derived antivenom produced with venoms from 4 North American pit vipers compared to ANAVIP, which is an equine-derived antivenom produced with venoms from 2 South and Central American pit vipers. Hypersensitivity reactions to these agents have been reported in the literature and they represent a clinical challenge in treating snakebite patients. Additionally, the venom from snakebites can mimic similar reactions, which makes it difficult to identify the main culprit behind the symptoms that patients develop after antivenom administration. In 2014, a comparative randomized controlled trial showed acute serum reactions occurring in 2–3% of the patients in each group.[2] The main goal for this case report is to highlight a rare and life-threatening hypersensitivity reaction to CroFab and attempt to identify some of the potential causes for this reaction.

Case Description

This is a 41-year-old male who was brought to the emergency room (ER) after a baby rattlesnake bite to his right index finger, occurring in Santa Clarita, California. The patient presented 30 minutes after the bite with confirmatory photo of the rattlesnake. The patient placed a hair tie around his right index finger as a tourniquet prior to arrival. The snake bite measured 7.5 cm in circumference. Our patient was initially tachycardic with a heart rate (HR) of 108 beats/min and slightly hypertensive (SBP/DBP 145/94 mmHg). Patient's past medical history was only significant for hypertension. His home medication list included losartan 50 mg once daily and aspirin 81 mg once daily. Additionally, he had no documented medication/food allergies or adverse reactions. He had a puncture wound to the right index finger with numbness, mild erythema that has spread up his hand and right hand fasciculations. Marked leading edges for swelling and discoloration measured 7.5 cm proximal to the bite on right 2nd digit, 21 cm on right wrist, and 29.5 cm on right forearm. The patient also

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reported tingling of the tongue and lips. After the tourniquet was removed, the patient began to experience tingling throughout his entire body. Baseline coagulation studies obtained included prothrombin (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), platelet and fibrinogen levels were found to be all within normal limits. 6 vials of CroFab, each vial containing up to 1 gm of total protein, diluted in 250 mL normal saline bag was initiated 30 minutes after presentation, at a starting rate of 25 mL/hr for 10 minutes, which the patient tolerated without any complications. Vital signs prior to CroFab administration included HR 103 beats/min, SBP/DBP 137/94 mmHg and respiratory rate (RR) 20 breaths/min. The patient denied shortness of breath with an oxygen saturation of 95% on room air, denied dysphagia or right-hand numbness and reported improvement in pain and nausea. However, the patient continued to report localized tingling around the tongue and lips. Vital signs remained stable with CroFab administration at 25 mL/hr. About 15 minutes after increasing the rate to 250 mL/hr, our patient started experiencing shortness of breath, chest tightness, dysphagia, and oropharyngeal edema. At this time, the patient became more tachycardic (HR 121 beats/min), slightly hypertensive (SBP/DBP 146/95 mmHg) with a RR of 22 breaths/min. The patient desaturated down to 90% on room air and was placed on supplemental oxygen 2-L nasal cannula. Based on these symptoms, CroFab infusion was stopped and we initiated the anaphylaxis protocol. Patient was administered epinephrine 0.3 mg intramuscular (IM), methylprednisolone 125 mg intravenous (IV), famotidine 20 mg IV and 1-L bolus of normal saline IV, which resulted in complete resolution of his symptoms. After conducting a quick literature research by the ER Pharmacist and Physician, similar case reports were found where patients successfully tolerated CroFab infusion after decreasing the infusion rate despite developing hypersensitivity reactions.[3] Therefore, we resumed CroFab infusion 30 minutes after the infusion was previously held, with a decreased rate at 10 mL/hr. At this time, the patient stated that the numbness and tingling of the tongue and lips had subsided. Marked leading edges for swelling and discoloration increased to 8.5 cm proximal to the bite on right 2nd digit, 22 cm on right wrist, and 30.5 cm on right forearm. Shortly after reinitiating CroFab infusion, the patient again started to complain of dysphagia and oropharyngeal edema. Patient became tachycardic (HR 120 beats/min) with SBP/DBP 135/97 mmHg. CroFab infusion was stopped again and the patient was given another round of epinephrine, famotidine, and methylprednisolone with resolution of his symptoms. The patient received a total of 1920 mg (80 mL) of CroFab overall. The patient was then admitted to the Intensive Care Unit (ICU) 2.5 hours after presentation for close monitoring which included collecting coagulation studies every 1 hour for 6 hours and then every 6 hours for a total of 24 hours. The decision was then made to switch CroFab to ANAVIP for continued fasciculations to the right hand and to re-dose if swelling increases more than 2 cm, fibrinogen less than 100 and INR greater than 2. The patient successfully received 10 vials of ANAVIP, followed by an additional 4 vials per poison control recommendation secondary to the spread of a hemorrhagic blister at the site of the snake bite without developing any hypersensitivity reactions. The patient did not develop any hematologic toxicities or any further systemic toxicities throughout the hospitalization and was ultimately discharged from the ICU with the snake bite measuring 8 cm in circumference with no leading-edge progression.

Discussion

The exact mechanism of CroFab induced-hypersensitivity reactions remains unclear. Although, CroFab is generally tolerated without severe complications, there are various data about the incidence of CroFab induced hypersensitivity reactions.[4,5] In 2012 Schaeffer et al conducted a meta-analysis, which showed a very low incidence of immediate hypersensitivity reactions among 11 studies.[6] Additionally, in an observational cohort chart review, Cannon et al reported an extremely low incidence of hypersensitivity reactions, which was 5.4% among 93 patients.[7] However, some of those reactions can be life-threatening anaphylactic reactions which require prompt identification and treatment.

Although the likelihood of hypersensitivity reactions to CroFab is low, it is known that the venom itself may mimic similar reactions. Pressure immobilization is not recommended by snakebite experts for Crotalid snakebites.[8] Due to the known effects of the venom causing tissue necrosis, localizing the venom in the affected limb can lead to increase tissue damage, higher morbidity and worse long-term recovery. It is recommended that if a patient comes in with a tourniquet present, antivenom should be administered prior to gradually releasing the tourniquet to prevent the patient from receiving an instant large exposure of the venom and the byproducts of cellular destruction. Tourniquets applied in the field are rarely truly arterial tourniquets, especially if not placed by a medical professional, to be able to fully sequester the venom in that area. In our patient, the tourniquet was removed upon evaluation by the ER Physician. The patient reported to feel tingling throughout his entire body, specifically tongue, lips, hands and feet.

Table 1 Naranjo Adverse Drug Reaction Probability Scale for CroFab-Induced Hypersensitivity Reaction

Assessment Questions	Yes	No	Do Not Know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse drug reaction appear after the suspected drug was administered?	+2	0	0
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0
4. Did the adverse event reappear when the drug was re-administered?	+2	0	0
5. Are there alternative causes that could on their own have caused the reaction?	−1	0	0
6. Did the reaction reappear when a placebo was given?	0	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	0	0	0
10. Was the adverse event confirmed by any objective evidence?	0	0	0
Total score	6 = Probable		

One of the proposed mechanisms that could lead to CroFab-induced hypersensitivity reactions could be having an allergy to sheep proteins. Due to its derivation from ovine Fab immunoglobulin fragments, patients with allergies to sheep proteins may develop acute hypersensitivity reactions such as anaphylaxis or anaphylactoid reactions.[9] Furthermore, CroFab is processed with papain and may cause hypersensitivity reactions in patients who are allergic to papaya or the pineapple-enzyme bromelain. Dust mite and latex allergens share antigenic structures with papain and can potentially lead to cross allergenicity.

Finally, the oligosaccharide galactose-α−1, 3-galactose (α-Gal) which is found in multiple antivenom products, has been proposed to be a potential causative agent for immunoglobulin E (IgE)-mediated reactions to CroFab.[10] For example, Rizer et al presented a case of a 61-year-old female who developed hives after starting CroFab infusion. α-Gal IgE was detected after antibody testing, which proved that the patient had α-Gal allergy.[11] This mechanism is less likely to be what caused this reaction for our patient who tolerated ANAVIP, since ANAVIP also contains α-Gal.

We calculated a Naranjo score to determine the causality of this drug-induced reaction. A score of 6 was calculated as shown in Table 1, which indicated a probable causality, especially since our patient developed an anaphylactic reaction the second time when the causative agent, CroFab was re-administered.[12]

CroFab was initially administered 30 minutes after the initial evaluation upon arrival to the emergency room. Our patient was able to tolerate the initial CroFab infusion at 25 mL/hr for 10 minutes without any symptoms but when the infusion was increased to 250 mL/hr, the patient began to have anaphylactic reactions. The patient was treated with resolution of symptoms. CroFab was then re-initiated at 10 mL/hr. After a few minutes from re-initiation, the patient began to have anaphylactic reactions again. The decision was then made to switch to ANAVIP, as the source animal is different, which was tolerated by the patient without any complications. To our knowledge, this is the first case where a patient tolerated ANAVIP despite being allergic to CroFab.

Conclusion

CroFab is a widely used antivenom. CroFab-induced anaphylactic reactions occur at a very low rate, but can be fatal. Those reactions usually tend to resolve upon stopping CroFab infusion. Obtaining a detailed drug and food allergy history from patients can be helpful in preventing those types of reactions. Future studies are still warranted to identify the exact mechanism and risk factors for developing CroFab-induced hypersensitivity reactions.

Ethical Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient to publish the case details.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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