

Severe Adverse Drug Reaction Following Crotalidae Polyvalent Immune Fab (Ovine) Administration for Copperhead Snakebite

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Abstract

Objective: To present the case of a severe anaphylactic/anaphylactoid reaction to Crotalidae Polyvalent Immune Fab (Ovine) in a patient bitten by a copperhead snake. **Case Summary:** A 68-year-old man presented with progressive envenomation after receiving a copperhead snakebite on each hand. Crotalinae Fab antivenom was administered. While the initial and only dose was partially infusing, the patient developed an adverse drug reaction (ADR) of urticaria and hypotension, which resolved with cessation of the infusion, recurred with resumption of the infusion, and ultimately was completed with supportive care. An additional episode of hypotension, urticaria, and angioedema occurred shortly after antivenom therapy completion. Epinephrine was administered, resolving the reaction with complete patient recovery. The event received a Naranjo score of 10, indicating a definite ADR. **Discussion:** Treating copperhead snakebites with antivenom is a matter of debate. Concern over adverse events and cost induce some physicians to manage copperhead bites without antivenom because they are generally milder in severity. **Conclusion:** As demonstrated in this case, severe ADR can occur with Crotalinae Fab antivenom, and its efficacy for copperhead envenoming needs to be better established via placebo-controlled, randomized trials.

Keywords

Crotalidae polyvalent immune Fab, CroFab, antivenom, copperhead, anaphylactic reaction, adverse drug reaction

Introduction

The vast majority of snakebites in our region of North Carolina occur after copperhead exposures, where subspecies intergrades include *Agkistrodon contortrix contortrix* (southern copperhead) *x A c mokasen* (northern copperhead). Whether copperhead (*A contortrix*) snakebites should be treated with antivenom is a matter of debate.^{1–4} Among the venomous snakes in the United States, copperheads have less toxic venom and generally produce a less-severe envenomation⁵ than other *Crotalinae* (pit viper), such as rattlesnakes or cottonmouths. Because a copperhead bite is often a self-limited injury, some endorse withholding antivenom from patients with confirmed copperhead bites, except for “a very small percentage” that progress to severe.¹ Purified Fab antivenom is safer in terms of immune reactions relative to its whole immunoglobulin G predecessor.⁶ Adverse drug reactions (ADRs) still occur at a rate of approximately 8% according to the best-available recent evidence, but severe reactions are rare.⁷ We report a case of severe acute serum reaction to Fab antivenom in a patient with copperhead envenomation.

Methods

This is a report of an illustrative case of an ADR managed in our emergency department and hospital at a teaching facility. Because of the extreme rarity of the reaction, a literature review going back as far as 1997 (when this particular antivenom was introduced) of comparable cases is included. The antivenom used in this case was Crotalidae Polyvalent Immune Fab (Ovine), CroFab (BTG International Inc, West Conshohocken, PA 19428), which will hereafter be referred to as *Crotalinae Fab antivenom*. The senior

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Figure 1. Copperhead bites to bilateral upper extremities; photo by the senior author with patient consent.

author confirmed the snake identification from a photograph on an iPhone.

Patient Case

A 68-year-old man was bitten by a copperhead while mowing his lawn. The patient was bitten twice, once on his dominant left hand as he tried to brush the snake toward the woods, and a second time on his right hand as he swatted the snake in retaliation. The patient had a past medical history of hypertension on an angiotensin-converting enzyme inhibitor (enalapril) and allergies to arthropod stings (local pruritus). Because of this sensitivity, the patient self-administered diphenhydramine 50 mg after the envenomation and sought immediate medical care by calling 911 within minutes of the bite.

On presentation to the emergency department, signs of progressive envenoming were observed. Tenderness and swelling had advanced 12 cm along each arm (Figure 1). The patient's platelet count dropped from 225 000 to 163 000 platelets/ μ L, and his fibrinogen level increased from 285 to 344 mg/dL over the course of 3 hours. On presentation, his blood pressure and heart rate were stable at 113/68 mm Hg and 74 bpm, respectively. It was determined that he was a candidate for antivenom because of the progression of local swelling, pain, and ecchymosis extending from the bite site and a downward trend in platelet count.

An initial dose of Crotalinae Fab antivenom 6 vials (250 mL total) intravenous (IV) was ordered. The infusion was slowly administered at a rate of 50 mL/h during the first 10 minutes. The patient tolerated this initial infusion rate, and as a result, the infusion was increased to a rate of 250 mL/h. But 10 minutes after increasing the rate, the patient began to have sudden-onset, new urticaria and hypotension



Figure 2. Truncal urticaria; photo by the senior author with patient consent.

(systolic blood pressure of 94 mm Hg). The infusion was stopped, and 1 L of normal saline, diphenhydramine 25 mg IV, famotidine 40 mg IV, and methylprednisolone 125 mg IV were administered. Urticaria cleared and blood pressure normalized 10 minutes later. The risks versus benefits and alternatives of the antivenom treatment were again reviewed with the patient. Despite the ADR, the patient desired to proceed. The remainder of the infusion was given, although urticaria and mild hypotension (not less than systolic blood pressure 90 mm Hg) returned. However, it was tolerable to the patient and care providers until shortly after completing the Crotalinae Fab antivenom infusion, when the patient developed a significant episode of hypotension (systolic blood pressure decreasing to approximately 60 mm Hg); abdominal pruritus, which rapidly progressed to urticaria; and pronounced angioedema of the tongue (Figures 2 and 3). The patient's tongue tripled in size over 10 minutes, but no stridor or wheezing was observed. A subcutaneous dose of epinephrine 0.3 mg was administered. During the next 10 minutes, the tongue stopped swelling and subsequently reduced to about double in size. The patient's systolic blood pressure improved to approximately 100 mm Hg. The patient began to verbalize his convalescence, and his color improved. After therapy completion, the patient reported that his hands were less tight, painful, and tender. Objectively, the patient's hands were less swollen. He was admitted to the intensive care unit, but no further adverse events were noted. By early the next morning, all signs of

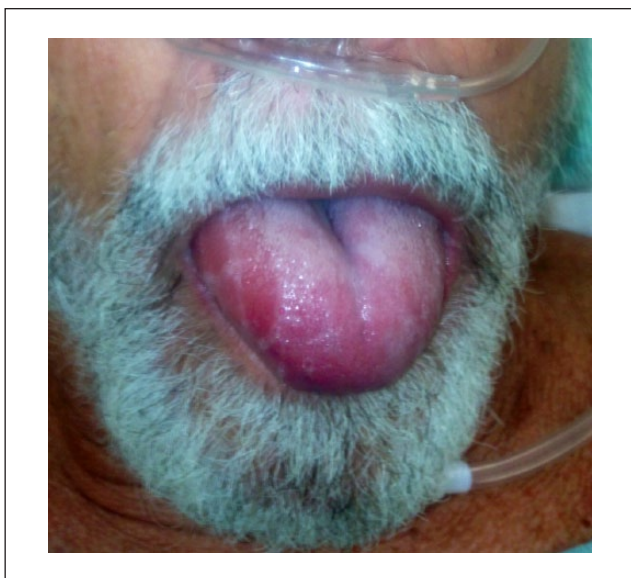


Figure 3. Rapidly progressive angioedema to the tongue; photo by the senior author with patient consent.

an anaphylactic or any ADR had resolved. In total, this reaction received a score of 10 on the Naranjo ADR probability scale (calculated below), indicating a definite drug reaction.⁸ This case was reported to the manufacturer. Of note, no other concomitant medications were given prior to the reaction.

Interest in the case was piqued because it was a second consecutive ADR to Crotalinae Fab antivenom after a copperhead bite at our medical center. The initial case has been submitted for publication elsewhere.

Naranjo ADR Probability Scale

1. Are there previous conclusive reports on this reaction? Yes, +1.
2. Did the adverse events appear after the suspected drug was given? Yes, +2.
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? Yes, +1.
4. Did the adverse reaction appear when the drug was readministered? Yes, +2.
5. Are there alternative causes that could have caused the reaction? No, +2.
6. Did the reaction reappear when a placebo was given? Not done, 0.
7. Was the drug detected in any body fluid in toxic concentrations? Not done, 0.
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? Yes, +1.
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? No, 0.

10. Was the adverse event confirmed by any objective evidence? Yes, +1.

Discussion

Crotalinae Fab antivenom is generally considered safer in terms of immune reactions (compared with the previously available product) because of its purified fragment-antigen-binding (Fab) formulation, where allergenic Fc fragments are removed from whole immunoglobulins via papain digestion and affinity purification.⁹ The tolerability of Crotalinae Fab antivenom, as perceived by the medical community, has been followed by increased use of antivenom in copperhead bite patients. Before the introduction of Crotalinae Fab antivenom in 2000, there were a total of 3911 snake bites reported to the National Poison Center Database System. Of those 3911 snake bites, 743 (19%) bites were treated with antivenom. After Crotalinae Fab antivenom became available, there were a total of 4974 snake bites reported to the National Poison Center Database System in 2007. Of those 4974 snake bites, 1617 (32.5%) bites were treated with antivenom, and the rate of treating copperhead bites with antivenom rose from 9.8% to 35.8%—a difference of 26% ($P < 0.001$).¹⁰

Although safer, Crotalinae Fab antivenom is not a completely benign treatment. The initial rate of hypersensitivity reactions was reported as 17%, as found in the results of trials that brought the product to market. However, it was later determined that some of these hypersensitivity cases were the result of incomplete purification, where allergenic Fc fragments were present in the Fab formulation. Improvements have been made to the manufacturing process, resulting in a more purified product with much lower rates of hypersensitivity.¹¹ However, a few notable immune reactions have been documented.

Current Literature Review

Only a few reported cases of hypersensitivity reactions to purified Fab antivenom exist. Most involve antivenom for the treatment of rattlesnake, as opposed to copperhead, bites, and most resolve with brief supportive therapy, often allowing continued treatment with antivenom. Cannon et al¹² retrospectively reported a series of 5 hypersensitivity events to Crotalinae Fab antivenom between 2000 and 2004 after rattlesnake envenomation. First, the series included a 91-year-old woman who developed erythema, wheezing, and hypotension during the infusion of antivenom. The patient was treated with diphenhydramine, methylprednisolone, albuterol, and hydroxyzine. Her infusion was completed, and then, the patient experienced angioedema of her tongue and lip without airway compromise. She was administered ranitidine, methylprednisolone, and an epinephrine infusion. Second, a 25-year-old man developed wheezing on examination after the antivenom was administered. His

wheezing was treated with albuterol, promethazine, and prednisone. The patient received an additional 6 vials of antivenom, which resulted in pruritis. Hydroxyzine and diphenhydramine were given in response, leading to complete resolution of symptoms. The third case involved a 28-year-old man who developed a diffuse erythematous rash during the infusion of Crotalinae Fab antivenom, which resolved with the administration of diphenhydramine. The patient was able to tolerate 2 additional vials of Crotalinae Fab antivenom. The fourth case involved a 38-year-old man who developed compartment syndrome, hypotension (systolic blood pressure 81 mm Hg), and rigors in response to Crotalinae Fab antivenom. He was treated with hydroxyzine, and the rate of the Crotalinae Fab antivenom infusion was decreased, resolving all symptoms. It was unclear whether the patient's rigors were directly related to the antivenom because of retrospective limitations. The fifth case described a 78-year-old woman who was administered antivenom with hydromorphone. She developed pruritus during her first dose of Crotalinae Fab antivenom, which resolved without treatment. A second dose of antivenom was administered, and she developed mild pruritus and a sore throat for which she was treated with hydroxyzine. A third dose was given, which resulted in pruritus and redness on her back and right side. These symptoms also resolved with the administration of hydroxyzine and dexamethasone. In this fifth case, it was uncertain whether these adverse reactions were solely the result of Crotalinae Fab antivenom or some histamine-mediated reaction from coadministration of hydromorphone during the antivenom infusion.⁶ These 5 reported reactions to Crotalinae Fab antivenom were limited in severity and responded favorably to symptomatic treatment, and repeated doses of antivenom were tolerated as required. The authors discuss the probability that these specific reactions were the result of contaminated batches of purified antivenom with allergenic Fc fragments during the initial introduction of Crotalinae Fab antivenom to the market.⁵

Clark et al¹¹ describe an anaphylactic reaction to Crotalinae Fab antivenom after a rattlesnake bite, which took place in 2001. A 36-year-old man displayed symptoms of urticaria, angioedema, wheezing, congestion, flushing, and oxygen desaturation during an antivenom infusion. The patient was treated with diphenhydramine, famotidine, epinephrine, and albuterol, which resolved all his symptoms. The antivenom infusion was resumed and completed, and the patient was able to tolerate a second infusion. Similar to the case review by Cannon et al,¹² this hypersensitivity reaction was attributed to contaminated batches of antivenom with Fc fragments.

Holstege et al¹³ reported a hypersensitivity reaction to Crotalinae Fab antivenom in a 16-year-old boy. Antivenom was given in response to a copperhead snake bite, and the initial 6 vials were infused at a rate of 10 mL/h.

Approximately 50 minutes into the infusion, the rate of administration was rapidly increased to 650 mL/h. The patient developed pruritus, facial and periorbital edema, shortness of breath, and tachycardia. Hydroxyzine, famotidine, methylprednisolone, and normal saline were administered, and the rate of antivenom infusion was decreased to 250 mL/h. All symptoms resolved without recurrence, suggesting that this particular case was possibly a rapid infusion-related reaction and not a hypersensitivity reaction to Crotalinae Fab antivenom itself.¹³

Other than the aforementioned cases, we could find only 1 other published severe ADR attributed to Crotalinae Fab antivenom in the United States since 1997.¹⁴ A 71-year-old woman reportedly fully arrested "within seconds of infusion" of Crotalinae Fab antivenom. Unfortunately, this case report is published in abstract form only. The author presented this abstract in a live forum and added that concomitant medications (eg, pain medication) were given but was not able to provide further details on direct questioning. A causal relationship between the antivenom and ADR is questionable. Of note, this previous case involved a patient bitten by a copperhead.

In these reported immune reactions to Crotalinae Fab antivenom, it may be argued that these examples were the result of either contaminated early batches of antivenom or infusion-related reactions. However, the manufacturer's pharmacovigilance and quality assurance team conducted an investigation of the current ADR and our previous one, and the conclusion was that there was no evidence of any quality event (no issues found with the Crotalinae Fab antivenom used). Also, the manufacturer's drug safety review found no evidence of an overall change in severity or frequency of allergic reactions, and they continuously monitor this for trends. Therefore, our patient case report demonstrates that ADRs can occur, even when fully standardized Crotalinae Fab antivenom is given according to prescribing instructions.

None of the previously reported cases was documented photographically. Our report is limited in rigor and detail because it is a retrospective look at a single case. It is possible that the patient's premedication with diphenhydramine could have affected the patient's response to venom and/or antivenom. We feel that this is unlikely because of the temporality of the ADR. Additionally, the patient's symptoms could have been attributable to the envenomation; however, this is unlikely because severe symptoms, such as shock, are rare after copperhead envenomation.

Conclusion

Despite being safer in terms of immune reactions than its whole IgG predecessor, Crotalinae Fab antivenom administration can still be associated with serious adverse events. This case, describing a significant acute serum reaction to

Crotalinae Fab antivenom, underscores one reason for the controversy involving antivenom use for copperhead envenomations. More study is needed to determine the efficacy and safety of Crotalinae Fab antivenom therapy for copperhead envenoming. Because serious adverse events can occur with Fab antivenom, its efficacy for copperhead envenomation needs to be better established via placebo-controlled, randomized trials (which are in progress now).¹⁵ Additionally, alternative antivenoms, such as F(ab')₂, should be examined in the context of copperhead envenomation.¹⁶

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MRL and SHB have nothing to disclose. SPB reports receiving remuneration for educational presentations related to the medical management of venomous bites from BTG international Inc. No other potential conflicts of interest relevant to this article were reported.

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References

1. Walker JP, Morrison RL. Current management of copperhead snakebite. *J Am Coll Surg*. 2011;212:470-474.
2. Bebart VS, Morrissey R, Mirkin D. Antivenom use for copperhead envenomations. *J Am Coll Surg*. 2011;213:692-693.
3. Caravati EM. Copperhead bites and Crotalidae polyvalent immune Fab (ovine): routine use requires evidence of improved outcomes. *Ann Emerg Med*. 2004;43:207-208.
4. Lavonas EJ, Ruha A, Banner W, et al. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. *BMC Emerg Med*. 2011;11:2-15.
5. Stolz U, Shirazi F, Walter CM, McNally J. Epidemiology of the reported severity of copperhead (*Agkistrodon contortrix*) snakebite. *South Med J*. 2012;105:313-320.
6. Dart RC, McNally J. Efficacy, safety, and use of snake antivenoms in the United States. *Ann Emerg Med*. 2001;37:181-195.
7. Schaeffer TH, Khatri V, Reifler LM, Lavonas EJ. Incidence of immediate hypersensitivity reaction and serum sickness following administration of Crotalidae polyvalent immune Fab antivenom: a meta-analysis. *Acad Emerg Med*. 2012;19:121-131. <http://www.ncbi.nlm.nih.gov/pubmed/22320362>. Accessed September 30, 2014.
8. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245.
9. Adukauskienė D, Varanauskienė E, Adukauskaitė A. Venomous snakebites. *Medicina (Kaunas)*. 2011;47:461-467.
10. Spiller HA, Bosse GM, Ryan ML. Use of antivenom for snakebites reported to United States poison centers. *Am J Emerg Med*. 2010;28:780-785.
11. Clark RF, McKinney PE, Chase PB, Walter FG. Immediate and delayed allergic reactions to Crotalidae polyvalent immune Fab (ovine) antivenom. *Ann Emerg Med*. 2002;39:671-676.
12. Cannon R, Ruha AM, Kashani J. Acute hypersensitivity reactions associated with administration of Crotalidae polyvalent immune Fab antivenom. *Ann Emerg Med*. 2008;51:407-411. doi:10.1016/j.annemergmed.2007.09.036.
13. Holstege CP, Wu J, Baer AB. Immediate hypersensitivity reaction associated with the rapid infusion of Crotalidae polyvalent immune Fab (ovine). *Ann Emerg Med*. 2002;39:677-679.
14. Gross GA, Gross OAP. Acute hypersensitivity reaction following administration of Crotalidae polyvalent immune Fab antivenom: a case report [abstract 251]. *Toxicon*. 2012;60:225.
15. BTG International Inc. A randomized, double-blind, placebo-controlled study comparing Crotalinae Fab antivenom versus placebo with rescue treatment for copperhead snake envenomation (copperhead RCT). <http://clinicaltrials.gov/ct2/show/NCT01864200?term=copperhead&rank=1>. Accessed September 30, 2014.
16. Instituto Bioclon S.A. de C.V. A comparison of Crotalinae (Pit Viper) equine immune F(ab)₂ antivenom (Anavip) and Crotalidae polyvalent immune Fab, ovine antivenom (CroFab) in the treatment of pit viper envenomation. <http://clinicaltrials.gov/ct2/show/NCT00868309?term=anavip&rank=2>. Accessed September 30, 2014.