Failure of Crotalidae Immune F(ab')$_2$ Equine Antivenom to Achieve Control in a Southern Pacific Rattlesnake Envenomation

Michael Levine, MD*; Hannah Spungen, MD; Anthony F. Pizon, MD

*Corresponding Author. E-mail: michaellevine@mednet.ucla.edu.

Rattlesnake envenomation can result in significant cutaneous and hematologic toxicity. While Cotalidae polyvalent immune Fab (ovine) antivenom (marketed as CroFab) was available for years, it is associated with increased late hematologic toxicity compared with its predecessor. Consequently, Crotalidae Immune F(ab')$_2$ equine antivenom [marketed as Anavip; F(ab')$_2$AV] has been recently become available. In this paper, we report a case of a 53 year-old man envenomated on his right hand by a Southern Pacific rattlesnake (*Crotalus helleri*). Edema was present, and his initial platelets were not able to be measured, prompting the administration of 10 vials of F(ab')$_2$AV. Ultimately, he received a total of 52 vials of antivenom, before his platelets peaked at 102,000/μL, 56 hours post envenomation. Within hours, his platelets began to fall again. Ultimately, his platelets reached a post-antivenom nadir of 65,000/μL. He was observed closely as an outpatient without additional antivenom, and ultimately had normalization of his platelets (211,000/μL) 20 days post envenomation. This case is one of the first cases demonstrating an inability to achieve control of the hematologic toxicity following Southern Pacific rattlesnake envenomation after treatment with F(ab')$_2$AV. [Ann Emerg Med. 2022;80:525-527.]

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2022.06.013

INTRODUCTION

Historically, North American pit viper envenomations were treated with antivenin Crotalidae polyvalent (Wyeth-Ayerst). However, because of high rates of hypersensitivity reactions, a newer, less immunogenic antivenom was sought.[1] In 2000, Crotalidae polyvalent immune Fab (ovine), marketed under the brand name CroFab (FabAV; Protherics Inc), was approved for use in the United States. Although FabAV was associated with fewer hypersensitivity reactions than its predecessor,[1,2] because of the rapid clearance of FabAV, it was quickly realized that late hematologic toxicity could occur. More recently, Crotalidae immune F(ab')$_2$ (equine), marketed under the brand name Anavip (Bioclon), was approved for use by the Food and Drug Administration. The F(ab')$_2$ antivenom, F(ab')$_2$AV, has a longer half-life and apparently reduces the late hematologic toxicity seen with FabAV. Since April 2022, both FabAV and F(ab')$_2$AV have been available for the treatment of all North American pit viper envenomations.

Hematologic toxicity is one of the hallmarks of rattlesnake envenomation and can manifest as thrombocytopenia, coagulopathy, and/or hypofibrinogenemia. Rarely, the inability to achieve control has been reported with FabAV involving other species of rattlesnakes.[2-4] In addition, the Southern Pacific rattlesnake—which is the only endemic rattlesnake in the Los Angeles, California, region—is occasionally associated with neurotoxicity, which, when reported, is difficult to treat with FabAV.[5]

F(ab')$_2$AV has been commercially available in the United States for treatment of rattlesnake envenomations since 2019. In 2022, the product received approval for the treatment of all North American pit viper envenomations, including those by the copperhead (*Agkistrodon contortrix*). Despite some studies suggesting that most patients treated with F(ab')$_2$AV require only a single dose of the antivenom without subsequent maintenance dosing,[6] other data have suggested that patients often require multiple doses of F(ab')$_2$AV.[7,8] Failure to achieve adequate control of thrombocytopenia with F(ab')$_2$AV has not been previously reported. However, we report the case of a patient with a Southern Pacific rattlesnake envenomation that caused severe thrombocytopenia, who failed to respond adequately to F(ab')$_2$AV.

CASE REPORT

A 53-year-old, right-handed man with a history of hypertension, hypercholesterolemia, and diabetes presented to the emergency department approximately 2 hours after

receiving a bite on the right ring finger by a Southern Pacific rattlesnake (*Crotalus helleri*). The patient had immediate pain and edema of the hand, which extended to the forearm. The patient had no reported use of antiplatelets or anticoagulants prior to the envenomation.

On arrival to the emergency department, he was noted to have edema of the right hand, prompting the administration of 10 vials of F(ab')$_2$AV prior to the initial laboratory results being reported. The laboratory results subsequently demonstrated a prothrombin time of 13.7 seconds (normal, 11.8 to 14.4 seconds), with an international normalized ratio of 1.07. The fibrinogen level was 316 mg/dL (normal, 215 to 450 mg/dL). The laboratory was not able to report his quantitative platelet count because of "fibrin interference." After receiving the initial 10 vials of F(ab')$_2$AV, repeat laboratory assessments revealed a platelet count of 54,000/μL (normal, 160,000 to 360,000/μL). An additional dose of F(ab')$_2$AV was administered (Figure). Prior to receiving the second dose of the antivenom, an additional platelet count returned at 29,000/μL. Because of persistent thrombocytopenia (Figure) and increasing edema of the right forearm, an additional dose of 6 vials of F(ab')$_2$AV was administered. Over his first 34 hours after the envenomation, the patient received a total of 52 vials of F(ab')$_2$AV. The repeated dosing was largely driven by refractory thrombocytopenia. Of note, the patient's platelet count reached a maximum of 102,000/μL 56 hours after the envenomation but then began falling again. However, 60.5 hours after the envenomation, his platelet count was 80,000/μL (Figure). Despite ongoing thrombocytopenia, he received no additional further antivenom and was discharged home approximately 74 hours after the envenomation.

The first outpatient laboratory studies, obtained 92 hours after the envenomation, revealed a platelet count of 65,000/μL. The patient did not receive any additional antivenom and was followed up clinically as an outpatient. He was followed up over the next approximately 2 weeks as an outpatient. Twenty days after the envenomation, repeat laboratory studies revealed a platelet count of 211,000/μL. All other coagulation parameters were normal, although the patient had persistent edema in the hand and some difficulty making a full fist.

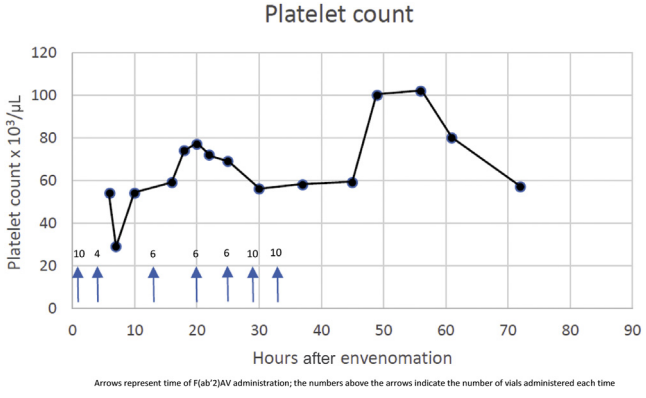

Figure. Platelet count per unit time. The arrows represent the time of F(ab')$_2$AV administration; the numbers above the arrows indicate the number of vials administered each time.

DISCUSSION

In recent years, F(ab')$_2$AV has emerged as an alternative to FabAV. Although *C helleri* envenomations were included in the original study comparing FabAV and F(ab')$_2$AV that led to approval by the Food and Drug Administration, the number of patients envenomated by *C helleri* were few.[8]

The Southern Pacific rattlesnake is the only native venomous snake in the Los Angeles area, and as such, the patient could have only been bitten by this species; however, there is significant variation in the venom of *C helleri* even within a relatively small geographic range.[9-12] Furthermore, F(ab')$_2$AV has shown variable neutralizing responses in in vitro studies involving this rattlesnake.[10,13] Thus, F(ab')$_2$AV may not be effective against the venom of a particular species of *C helleri*.

Patients who experience a rattlesnake envenomation can experience late hematologic toxicity.[4,14] Such toxicity can include either delayed toxicity (no evidence of hematologic toxicity during the index hospitalization but then develop thrombocytopenia or coagulopathy on follow-up) or recurrence (initial hematologic toxicity that resolves with an antivenom but recurs later). Because the patient had early thrombocytopenia and never achieved normal platelet counts during the initial hospitalization, this case did not present with late hematologic toxicity, but rather presented with thrombocytopenia resistant to antivenom therapy. Thrombocytopenia occurring within the first 24 hours of an envenomation needs to be aggressively treated with an antivenom. However, late hematologic toxicity is quite different and, although potentially dangerous, does warrant a different treatment. In the absence of bleeding, late hematologic toxicity typically does not require retreatment with an antivenom unless the platelet count is less than 25,000/μL or less than 50,000/μL with concurrent coagulopathy.[15]

This case report has several limitations. First, it was impossible to know with certitude the species of the snake. However, given that *C helleri* is the only rattlesnake in this area, it is highly probable that the patient was envenomated by this species. Second, the typical control dose of

F(ab')$_2$AV is 10 vials. The patient received an initial dose of 10 vials, but several of the subsequent doses were less. Therefore, it is possible that control was not fully achieved because of some smaller doses of the antivenom. However, we believe that this was less likely because the patient did get several doses of 10 vials of the antivenom. Furthermore, the patient received a large total quantity of the antivenom, and given the long half-life of F(ab')$_2$AV, it is unlikely that the smaller aliquots resulted in the inability to fully achieve control.

In addition, we did not know the patient's baseline platelet count. Given that thrombocytopenia resolved after 2 weeks, we believe that it is unlikely that the patient had baseline thrombocytopenia. We cannot state based on this case report whether F(ab')$_2$AV is less effective (eg, the antivenom does not bind) or whether there is cross-neutralization of the venom. However, clinicians need to be aware that some patients envenomated by *C helleri* may not respond to F(ab')$_2$AV as expected.

SUMMARY

In conclusion, this case of *C helleri* envenomation involved severe thrombocytopenia that appeared to be refractory to the new F(ab')$_2$AV. More research is needed to determine the effectiveness of F(ab')$_2$AV in the treatment of envenomations by the Southern Pacific rattlesnake and determine whether interspecies variation exists in the response to these antivenoms.

Supervising editor: Lewis S. Nelson, MD. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Department of Emergency Medicine (Levine, Spungen), University of California, Los Angeles, California; Division of Medical Toxicology (Pizon), Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

Author contributions: All authors attest to meeting the four ICMJE.org authorship criteria:(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Michael Levine takes responsibility for the paper as a whole.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

REFERENCES

1. Ruha AM, Curry SC, Beuhler M, et al. Initial postmarketing experience with Crotalidae polyvalent immune Fab for treatment of rattlesnake envenomation. *Ann Emerg Med*. 2002;39:609-615.
2. Pizon AF, Ruha AM. Antivenom for North American Venomous Snakes (Crotaline and Elapids). In: Hoffman RS, et al, eds. *Goldfrank's Toxicologic Emergencies*. 11th Ed. New York: McGraw-Hill; 2019:1627-1632.
3. Offerman SR, Barry JD, Schneir A, et al. Biphasic rattlesnake venom-induced thrombocytopenia. *J Emerg Med*. 2003;24:289-293.
4. Miller AD, Young MC, DeMott MC, et al. Recurrent coagulopathy and thrombocytopenia in children treated with crotalidae polyvalent immune fab: a case series. *Pediatr Emerg Care*. 2010;26:576-582.
5. Richardson WH, Goto CS, Gutglass DJ, et al. Rattlesnake envenomation with neurotoxicity refractory to treatment with crotaline Fab antivenom. *Clin Toxicol (Phila)*. 2007;45:472-475.
6. Mascarenas DN, Fullerton L, Smolinske SC, et al. Comparison of F(ab') 2 and Fab antivenoms in rattlesnake envenomation: first year's post-marketing experience with F(ab')2 in New Mexico. *Toxicon*. 2020;186:42-45.
7. Ruha AM, Padilla-Jones A, Canning J, et al. Early experience with crotalidae immune F(ab′)2 antivenom to treat Arizona rattlesnake envenomations. *J Med Toxicol*. 2022;18:38-42.
8. Bush SP, Ruha AM, Seifert SA, et al. Comparison of F(ab′)2 versus Fab antivenom for pit viper envenomation: a prospective, blinded, multicenter, randomized clinical trial. *Clin Toxicol (Phila)*. 2015;53:37-45.
9. Sunagar K, Undheim EA, Scheib H, et al. Intraspecific venom variation in the medically significant Southern Pacific rattlesnake (*Crotalus organus helleri*): biodiscovery, clinical, and evolutionary implications. *J Proteomics*. 2014;99:68-83.
10. Jurado JD, Rael ED, Lieb CS, et al. Complement inactivating proteins and intraspecies venom variation in *Crotalus oreganus helleri*. *Toxicon*. 2007;49:339-350.
11. Salazar AM, Guerrero B, Cantu B, et al. Venom variation in hemostasis of the Southern Pacific rattlesnake (*Crotalus oreganus helleri*): isolation of hellerase. *Comp Biochem Physiol C Toxicol Pharmacol*. 2009;149:307-316.
12. French WJ, Hayes WK, Bush SP, et al. Mojave toxin in venom of *Crotalus helleri* (Southern Pacific rattlesnake): molecular and geographic characterization. *Toxicon*. 2004;44:781-791.
13. Galán JA, Sánchez EE, Rodríguez-Acosta A, et al. Neutralization of venoms from two Southern Pacific rattlesnakes (*Crotalus helleri*) with commercial antivenoms and endothermic animal sera. *Toxicon*. 2004;43:791-799.
14. Ruha AM, Curry SC, Albrecht C, et al. Late hematologic toxicity following treatment of rattlesnake envenomation with crotalidae polyvalent immune Fab antivenom. *Toxicon*. 2011;57:53-59.
15. Ruha AM. Rattlesnakes and other North American crotalids. In: Brent J, ed. *Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient*. 2nd ed. Springer Nature; 2017:2503-2526.