Initial postmarketing experience with crotalidae polyvalent immune Fab for treatment of rattlesnake envenomation.

Anne-Michelle Ruha

Steven C Curry

Michael Beuhler

Kenneth D. Katz MD
Lehigh Valley Health Network, kenneth_d.katz@lvhn.org

Daniel E Brooks

See next page for additional authors

Published In/Presented At

Ruha AM, Curry SC, Beuhler M, Katz K, Brooks DE, Graeme KA, Wallace K, Gerkin R, Lovecchio F, Wax P, Selden B. Initial postmarketing experience with crotalidae polyvalent immune Fab for treatment of rattlesnake envenomation. Ann Emerg Med. 2002 Jun;39(6):609-15. doi: 10.1067/mem.2002.123698.

Initial Postmarketing Experience With Crotalidae Polyvalent Immune Fab for Treatment of Rattlesnake Envenomation

Anne-Michelle Ruha, MD
Steven C. Curry, MD
Michael Beuhler, MD
Ken Katz, MD
Daniel E. Brooks, MD
Kimberlie A. Graeme, MD
Kevin Wallace, MD
Richard Gerkin, MD
Frank LoVecchio, MD
Paul Wax, MD
Brad Selden, MD

From the Department of Medical Toxicology, Good Samaritan Regional Medical Center, Phoenix, AZ.

Author contributions are provided at the end of this article.

Received for publication August 20, 2001. Revisions received November 1, 2001; December 5, 2001; and January 31, 2002. Accepted for publication February 11, 2002.

Address for reprints: *Anne-Michelle Ruha, MD, 925 East McDowell Road, 2nd Floor, Phoenix, AZ 85006; 602-239-2342; E-mail Michelle.Ruha@bannerhealth.com.*

0196-0644/2002/$35.00 + 0
47/1/123698
doi:10.1067/mem.2002.123698

See editorial, p. 648.

Study objective: We describe our postmarketing experience with patients receiving Crotalidae polyvalent immune Fab (CroFab; FabAV) antivenom for treatment of rattlesnake envenomation.

Methods: The charts of 28 patients admitted between March 1 and September 9, 2001, with rattlesnake envenomation and treated with FabAV were reviewed for demographic information, time until antivenom treatment, laboratory findings, evidence of hypersensitivity reaction, length of hospital stay, and readmission to the hospital.

Results: All patients had swelling, 20 patients had elevated prothrombin times (>14 seconds), 12 patients had low fibrinogen levels (<170 mg/dL), and 6 patients had thrombocytopenia (platelet count <120,000/mm^3) on presentation. The total dose of FabAV ranged from 10 to 47 vials per patient. Hypofibrinogenemia was resistant to FabAV in some patients. On follow-up, recurrence of coagulopathy was detected in 3 patients, and recurrence of thrombocytopenia was detected in 1 patient. Two patients demonstrated delayed-onset severe thrombocytopenia. Recurrence or delayed-onset toxicity might have been underestimated because of incomplete follow-up in some patients. No acute hypersensitivity reactions occurred. Two patients reported mild symptoms of possible serum sickness on follow-up.

Conclusion: FabAV effectively controlled the effects of envenomation; however, initial control of coagulopathy was difficult to achieve in some cases, and recurrence or delayed-onset hematotoxicity was common. When initially managing hematotoxicity, a trend toward normalization of laboratory values might be a more reasonable end point for FabAV treatment than attainment of normal reference values in nonbleeding patients.

[Ruha A-M, Curry SC, Beuhler M, Katz K, Brooks DE, Graeme KA, Wallace K, Gerkin R, LoVecchio F, Wax P, Selden B. Initial postmarketing experience with Crotalidae polyvalent immune Fab for treatment of rattlesnake envenomation. *Ann Emerg Med.* June 2002;39:609-615.]

INTRODUCTION

Treatment of rattlesnake envenomation has traditionally been done with Wyeth Crotalidae Polyvalent antivenom, a horse serum preparation that often produces immediate and delayed-onset hypersensitivity reactions. Concern for development of a severe hypersensitivity reaction occasionally precludes treatment with Wyeth antivenom.[1] Recent US Food and Drug Administration approval of Crotalidae polyvalent immune Fab (CroFab; FabAV) provides a potentially safer treatment for rattlesnake envenomation. FabAV is a relatively pure and specific Fab immunoglobulin product made in sheep and contains less than 3% Fc fragment, making it less immunogenic.[2] Each vial of FabAV contains up to 1 g of total protein. FabAV is expected to produce fewer hypersensitivity reactions. The incidence of acute anaphylactoid-anaphylactic reactions and serum sickness in clinical trials was 14.3% and 16%, respectively. This was higher than expected as a result of incomplete purification of one lot of antivenom.[2] The true incidence of hypersensitivity reactions associated with FabAV in clinical use is unknown at this time.

FabAV has been studied in 2 premarketing clinical trials, the first comprising 11 patients, and the second comprising 31 patients. Children younger than 10 years of age were excluded. The maximum dose of FabAV administered to any patient was 18 vials.[2,3] A concerning phenomenon observed during these trials was recurrence of local and hematologic effects after initial improvement.[4]

On the basis of previous studies, patients are considered at risk for recurrence if they exhibit hematologic abnormalities during the first 36 hours after envenomation, and it has been recommended that these patients be reassessed every 48 hours after the last dose of antivenom until coagulation values and platelet counts are stable or improving for several days.[5] In initial trials, patients without coagulopathy or thrombocytopenia during initial treatment did not demonstrate recurrence on follow-up. This group of patients is considered to be at low risk for recurrence, but follow-up within 5 days of treatment is still recommended.[5]

Postmarketing clinical experience with this new therapy has not been published to date. We report our initial experience with the use of FabAV in patients admitted to our tertiary referral center.

MATERIALS AND METHODS

We reviewed the medical records of 28 consecutive patients who were admitted to our toxicology service and treated with FabAV between March 1, 2001, and September 9, 2001. Exemption from institutional review board review was granted for this series. The information extracted from each record included demographic information, time of envenomation, time until antivenom treatment, laboratory abnormalities, and type of snake involved. At our center, the treating physician completes a standard data collection form during and after the care of all patients bitten by a rattlesnake. This form contains information pertaining to patient demographics, bite site, time of bite, times and results of laboratory studies, antivenom dosing, progression of swelling, and adverse reactions. All forms were completed by the authors and reviewed by 2 authors (AMR, SCC), and all information was checked for accuracy by means of comparison with the medical record (no discrepancies were found). None of our patients were able to identify the specific species of rattlesnake by which they were envenomated. The rattlesnake species responsible for most envenomations in our patients are the western diamondback *(Crotalus atrox)* and Mojave *(C scutulatus)*. However, we also encounter envenomations by other rattlesnakes: blacktail *(C molossus)*, speckled *(C mitchelli)*, sidewinder *(C cerastes)*, faded midget *(C viridis decolor)*, and others.

The decision to use antivenom was made after documentation of continued proximal swelling, coagulopathy, or thrombocytopenia. Our initial dosing guidelines were generally based on the package insert. The manufacturer recommends that an initial dose of 4 to 6 vials of FabAV be administered intravenously over 1 hour and that additional doses be given, as needed, to achieve control of the envenomation. "Control" was defined by the manufacturer as complete arrest of local manifestations and return of coagulation study results, platelet counts, and systemic signs to normal. After control is achieved, the manufacturer recommends another 2 vials every 6 hours for 3 additional doses to prevent recurrence. Additional 2-vial doses might be administered as necessary on the basis of clinical course.

On arrival to our facility, patients were evaluated for progressive swelling of the extremity, coagulopathy (prothrombin time [PT] >14 seconds or plasma fibrinogen <170 mg/dL), and thrombocytopenia (platelet count

<120,000/mm^3). These values are outside of the normal reference range for our laboratory and are consistent with definitions used previously.[1] An initial FabAV dose of 4 to 8 vials was administered over 1 hour, and the same parameters were reevaluated 1 hour later. Additional doses of 4 to 8 vials were given again over 1 hour in an attempt to achieve control. After treating our first few patients, it became apparent that control of coagulopathy was not achieved in all individuals with severe coagulopathy, despite use of large amounts of antivenom. We revised our definition of control as clear improvement in coagulation parameters rather than a full return to normal reference values. After control was achieved, patients then received 2 vials of FabAV over 1 hour every 6 hours for at least 3 doses (maintenance doses). Laboratory parameters were checked approximately 24 hours after the third maintenance dose when possible. Initially, only patients who presented with coagulopathy or thrombocytopenia were instructed to return in 48 to 72 hours after antivenom administration for repeat clinical and laboratory evaluation. We noted delayed-onset hematologic toxicity in some patients who did not demonstrate coagulopathy or thrombocytopenia on presentation. Therefore, we began instructing all patients to return for 48- to 72-hour follow-up. Recurrence was defined as an increase in swelling proximally or worsening thrombocytopenia or coagulopathy greater than 24 hours after completion of maintenance FabAV dosing.

All patients were observed closely for hypersensitivity reactions. Telephone follow-up was obtained for all patients for 21 days to detect serum sickness. Serum sickness was defined as rash, pruritus, fever, myalgias, and arthralgias, with onset occurring at least 3 days after initial administration of antivenom.

RESULTS

Patients' ages ranged from 4 to 68 years. Demographics and envenomation treatment characteristics are shown in Table 1.

All patients demonstrated progressive distal-to-proximal swelling of the involved extremity on initial presentation (Table 2). Most patients (16/28 [57%]) achieved control of swelling with 4 to 6 vials of FabAV, but others required repeated control doses to stop the progression of swelling. One patient with a foot bite experienced new groin tenderness more than 24 hours after control administration, which is suggestive of continued lymphatic spread of venom.

Twenty patients had elevated PTs (range 14 to >60 seconds; Table 2). Improvement followed administration of FabAV in all cases; however, 16 (80%) patients required more than 10 vials to gain control (ie, improvement) of this parameter. Twelve patients had hypofibrinogenemia (range <15 to 167 mg/dL). All improved after FabAV treatment; however, 8 (67%) of these patients required more than 10 vials to raise fibrinogen levels.

Six of 28 patients had thrombocytopenia (platelet range 2,000 to 107,000/mm^3). Platelets increased to normal levels after 6 to 10 vials of antivenom in 5 of 6 patients. The sixth patient received 20 vials before normalization of platelet count.

Follow-up laboratory results were obtained greater than 24 hours after the last dose of FabAV in 21 of 28 patients. Two patients followed up with their personal physicians, and results were unavailable to us. Two early patients had mild envenomation without significant hematologic abnormalities during hospitalization, and further laboratory evaluation was not performed. Three patients underwent follow-up studies less than 24 hours after the final dose of FabAV. Overall, 6 (28.5%) of 21 patients demonstrated either recurrence or delayed onset of venom effects. Four patients were readmitted to the hospital, 1 had the initial hospital stay extended, and 1 was lost to further follow-up. Details concerning patient age, site of envenomation, FabAV dosing, and hematologic parameters are found in Table 3.

Four of the 22 patients with coagulopathy were lost to follow-up. Three of the remaining 18 patients with coagulopathy had recurrence on reevaluation, all with a PT of greater than 60 seconds and plasma fibrinogen levels of less than 30 mg/dL (Table 3). Two of the patients with coagulopathic recurrence had marked coagulopathy and

Table 1.
Demographics and envenomation treatment characteristics in 28 patients treated with antivenom.

Characteristic	No.	%
Patients		
Male	24	86
Female	4	14
Children (<10 y)	3	11
Location of bite		
Upper extremity	24	86
Lower extremity	4	14
Mean time from envenomation to first dose of FabAV, h	4 (range 1.75–7.5)	
Mean No. of vials received on first admission	16 (range 10–28)	
Mean length of initial hospital stay, d	4.2 (range 2–10)	
Mean length of hospital stay for readmission, d	4.5 (range 3–8)	

hypofibrinogenemia during their initial treatment course. The third patient had only mild elevation in PT (PT of 15.3 seconds) and mild hypofibrinogenemia (fibrinogen level of 118 mg/dL) during his initial hospitalization.

All patients with coagulopathic recurrence were readmitted, and the first 2 patients (patients 1 and 2; Table 3) received repeat treatment with 19 and 12 vials of FabAV, respectively. Each responded with only moderate increases in fibrinogen concentration. Because of the resistance of coagulopathy to retreatment in these patients, we subsequently elected not to treat recurrence of coagulopathy in the absence of bleeding but chose rather to observe these patients in the hospital until their coagulation status improved.

Our third patient, with an unmeasurable fibrinogen level and prolonged PT on a follow-up visit (patient 3; Table 3), was readmitted for observation without further FabAV treatment. He had a seizure disorder and was employed in construction of high-rise buildings. On hospital day 8 of the second admission, his fibrinogen level became measurable (18 mg/dL), but the coagulopathy did not resolve until 17 days after the bite. He had demonstrated mild coagulopathy during his initial admission.

Three patients demonstrated thrombocytopenia on follow-up evaluation. One patient (patient 4; Table 3) had recurrence of thrombocytopenia, with platelet count decreasing from 173,000/mm^3 14 hours after the last antivenom administration to 100,000/mm^3 67 hours after the last antivenom administration. This patient was lost to further follow-up. Two patients (patients 5 and 6; Table 3) never exhibited thrombocytopenia on initial presentation but were discovered on follow-up examinations to have severe thrombocytopenia. The first patient (patient 5) received follow-up 55 hours after the last antivenom infusion (76 hours after envenomation) and had a normal PT, platelet count, and fibrinogen concentration at that visit. He was followed up by telephone several days later to check for bleeding, which he denied. Ten days after the envenomation, the patient presented with a history of rectal bleeding for 2 days, and a platelet count of 15,000/mm^3 was discovered. His hemoglobin level had not decreased significantly since his initial presentation, and it remained stable during the second hospitalization. He was retreated with 18 vials of FabAV, which was temporally associated with a slow, gradual rise in platelet count (Table 3). Blood products were not administered, and the patient had no further bleeding.

The second patient with delayed-onset thrombocytopenia (patient 6; Table 3) was a 4-year-old child with autism. His platelet count decreased at 33 hours after treatment and continued to decline for 7 days after completion of antivenom administration, reaching a nadir of 17,000/mm^3. Hospitalization was extended until the thrombocytopenia improved. The patient did not experience bleeding.

Two patients exhibited recurrent swelling on follow-up evaluation. One patient (patient 2; Table 3) had increased swelling 4 days after final antivenom dosing. This patient had a lower extremity envenomation, and it is possible this swelling was partly caused by dependent edema. The second patient (patient 5; Table 3) had mildly increased swelling and tenderness of the envenomated upper extremity approximately 1 week after FabAV treatment.

Delayed onset or recurrence of venom toxicity was not found in 15 patients. However, some patients might have experienced recurrent or delayed coagulopathy or thrombocytopenia but were missed as a result of limited follow-up. Detailed laboratory data for 22 patients not reported in Table 3 are available from the authors.

No acute anaphylactic or anaphylactoid reactions were observed. Two patients reported mild symptoms consistent with serum sickness. A 51-year-old woman who received 14 vials of FabAV reported a pruritic rash and low-grade fever that began 6 days after FabAV administration. These symptoms resolved within 2 days and were self-treated only with oral diphenhydramine. The second patient was a 42-year-old man who received 18 vials of FabAV. He experienced pruritus and low-grade fever without rash beginning 14 days after FabAV administration but was lost to follow-up.

Table 2.
Frequency of initial, recurrent, and delayed venom effects.

Venom Effect	No. of Patients (%)	No. of Patients With Recurrence (%)*	No. of Patients With Delayed-Onset Toxicity
Local swelling	28/28 (100)	2/21 (9)	0
Coagulopathy			
PT >14.0 s	20/28 (71)	3/16 (19)	0
Fibrinogen <170 mg/dL	12/27† (44)	3/11 (27)	0
Thrombocytopenia (platelets <120,000/mm^3)	6/28 (21)	1/6 (17)	2/15‡ (13)

*The denominator reflects the number of patients with the venom effect that were available for follow-up.
†The fibrinogen level was not determined in 1 patient before treatment.
‡No evidence of thrombocytopenia during initial hospital admission.

Table 3.
Detailed laboratory test results and antivenom dosing in patients who demonstrated recurrence or delayed-onset hematotoxicity after treatment with FabAV.

Patient No.	Age, y	Bite Site	Time After Bite, h	Total No. of Vials Already Received	Time Until Antivenom Started, h	PT, s	Fibrinogen Level, mg/dL	Platelet Count, 1,000/mm^3
1	68	Hand	1.5	0		14.9	20	2
			7.5	6	5	>60	<15	176
			13	12		>60	<15	9
			19	18		16	49	192
			21.5	22		15	63	195
			39.5	26		13.3	128	170
			60	28		12.6	225	165
			113	28		>100	<30	130
			128.5	34		>60	<15	165
			133	40		30.6	23	163
			140.5	44		17.9	55	190
			147.5	45		16.2	75	187
			153.5	46		13.8	90	165
			181.5	47		12.6	169	165
			257	47		10.1	215	141
2	58	Foot	2	0		11.8	285	73
			6.5	6	4	25.7	32	223
			11	12		18.7	44	213
			16.5	16		15.6	77	198
			37.5	22		12.8	319	157
			50.5	22			478	160
			60.5	22		12.1	466	152
			140	22		>60	<15	202
			148.5	26		>60	<15	224
			152.5	30		30.5	19	207
			157.5	32		23.8	39	—
			183.5	34		13.5	84	228
			236.5	34		11.2	159	292
3	27	Hand	1.5	0		12.2	226	212
			5.5	5	3	13.9	118	246
			10.5	10		15.3	141	245
			15.5	12		13.1	151	222
			37.5	18		12.2	261	220
			89	18		>100	<15	231
			97	18		>60	<15	—
			107*	18		>60	<15	—
			251	18		>60	18	—
			299	18		>100	43	205
			371	18		11.7	90	269
4	39	Hand	1.5	0		14.4	—	78
			3	0		17.6	236	71
			7.5	6	4	18.1	197	—
			19.5	10		—	—	126
			46	16		14.5	228	173
			98.5	16		14.3	278	100†
5	56	Hand	1	0		11.3	321	181
			8	6	1.5	13	274	223
			23	12		12.8	337	227
			29	12		12.6	414	224
			76	12		10	607	139
			234	12		12.7	422	15
			240	18		—	—	17
			249	24		—	—	31
			264.5	30		—	—	50
			287	30		—	—	77
			340	30		—	—	206

Continued on p. 614.

Table 3 continued.
Detailed laboratory test results and antivenom dosing in patients who demonstrated recurrence or delayed-onset hematotoxicity after treatment with FabAV.

Patient No.	Age, y	Bite Site	Time After Bite, h	Total No. of Vials Already Received	Time Until Antivenom Started, h	PT, s	Fibrinogen Level, mg/dL	Platelet Count, 1,000/mm^3
6	4	Hand	3	0		19.2	—	280
			8	18	3	16.2	165	306
			34	24		12.1	264	207
			58.5	24		13.0	280	88
			84.5	24		12.4	310	61
			106.5	24		12.1	269	60
			131.5	24		12.8	257	53
			159	24		12.2	226	44
			179.5	24		12.4	295	17
			203	24		12.7	248	18
			231.5	24		—	—	31

*Values for PT and fibrinogen remained unchanged on numerous rechecks between 107 and 251 hours and are not shown.
†Lost to follow-up.

Three children (ages 4, 4, and 9 years) received up to 24 vials of FabAV without adverse effects. Two presented with coagulopathy but without thrombocytopenia. On follow-up, one of these patients exhibited delayed thrombocytopenia (patient 6; Table 3). Another had normal coagulation and platelet studies. The third child had normal laboratory values on presentation and was lost to follow-up.

Mean initial hospital stay was 4.2 days. This was caused by a combination of factors, including maintenance infusion of FabAV for 18 hours after attainment of control and monitoring of persistently abnormal hematologic study results. One patient underwent a fasciotomy and remained in the hospital for 8 days. The indication for fasciotomy was apparent before receiving FabAV. The 4 patients who were readmitted to the hospital for recurrence experienced additional stays ranging from 3 to 8 days, with their total hospital stay (initial admission plus readmission) averaging 7.7 days.

DISCUSSION

Our experience with FabAV provides information that allows us to draw some preliminary conclusions. First, severe coagulopathy might be resistant to FabAV. Hypofibrinogenemia and PT prolongation in patients experiencing rattlesnake bites only rarely result from disseminated intravascular coagulation[6] and instead usually represent a relatively benign state that does not result in spontaneous bleeding. This coagulopathy results from the action of thrombin-like enzymes, fibrinolysins, and other proteins affecting coagulation that are found in rattlesnake venoms.[6] Giving large doses of FabAV to nonbleeding patients for treatment of isolated coagulopathy might be unnecessary. The recurrence of coagulopathy further suggests the futile and unnecessary costs of treatment. Observation might be all that is warranted in the absence of active bleeding. This has been our practice for years in nonbleeding patients with coagulopathy who could not safely be treated with the Wyeth product. Unfortunately, this approach prolongs hospitalization time.

Second, it is evident that initial masking of hematologic abnormalities occurs during treatment, making it impossible to predict which patients will experience coagulopathy or thrombocytopenia on follow-up. Compliance with outpatient follow-up is problematic in some patients who sustain rattlesnake envenomations. However, every effort should be made to repeat coagulation studies within 2 to 3 days after treatment with FabAV. Even if results are normal, a trend toward coagulopathy or thrombocytopenia warrants continued daily reevaluation until it halts or reverses. We emphasize that, although we documented recurrence or delayed onset of venom-induced hematologic toxicity in 6 (21%) of 28 patients, this might underestimate the true frequency given incomplete follow-up in all patients.

If FabAV is not used to correct laboratory coagulation abnormalities in nonbleeding patients, then the total number of vials needed per patient might decline. The increased expense associated with FabAV use is offset by

what appears to be a much lower rate of immediate hypersensitivity reaction and serum sickness, which reduces morbidity and might offer treatment to patients with relative contraindications to Wyeth antivenom. We have administered up to 47 vials of FabAV to one patient without any evidence of immediate or late hypersensitivity reactions.

Although our report represents a relatively large number of patients treated with FabAV from a single center, a weakness of our report is that it does not comprise a blinded comparative trial between FabAV and other treatments. Furthermore, our experience might not pertain to patients envenomated by snakes found in other areas.

Until further observations are reported, we consider all patients treated with FabAV to be at risk for recurrence or delayed onset of coagulopathy, thrombocytopenia, and bleeding complications. The optimal protocol for FabAV administration has not been determined. Initial control of coagulopathy might be difficult to achieve, and recurrence is common. When managing coagulopathy and thrombocytopenia, a trend toward normalization of laboratory values might be a more reasonable end point for FabAV treatment than actual attainment of normal reference values. Additionally, although anaphylactoid reactions appear to be infrequent, clinicians should continue to anticipate and prepare for their occurrence in patients receiving FabAV.

Author contributions: AMR and SCC cared for patients, collected data, and primarily prepared the manuscript. MB, KK, DEB, KAG, KW, RG, FL, PW, and BS cared for patients, collected data, and provided editorial review of and made changes to the manuscript. AMR and SCC take responsibility for the paper as a whole.

REFERENCES

1. Tanen DA, Ruha AM, Graeme KA, et al. Epidemiology and hospital course of rattlesnake envenomations care for at a tertiary referral center in central Arizona. *Acad Emerg Med.* 2001;8:177-182.

2. Dart RC, McNally J. Efficacy, safety, and use of snake antivenoms in the United States. *Ann Emerg Med.* 2001;37:181-188.

3. CroFab Crotalidae polyvalent immune Fab (ovine) [package insert]. Nashville, TN: Protherics Inc; October 2000

4. Seifert SA, Boyer LB. Recurrence phenomena after immunoglobulin therapy for snake envenomations: part 1. Pharmacokinetics and pharmacodynamics of immunoglobulin antivenoms and related antibodies. *Ann Emerg Med.* 2001;37:189-195.

5. Boyer LB, Seifert SA, Cain JS. Recurrence phenomena after immunoglobulin therapy for snake envenomations: part 2. Guidelines for clinical management with Crotaline Fab antivenom. *Ann Emerg Med.* 2001;37:196-201.

6. Holstege CP, Miller MB, Wermuth M, et al. Crotalid snake envenomation. *Crit Care Clin.* 1997;13:889-921.