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Comparison of F(ab')$_2$ and Fab antivenoms in rattlesnake envenomation: First year's post-marketing experience with F(ab')$_2$ in New Mexico

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ABSTRACT

Two antivenoms are available for rattlesnake envenomations in the U.S., Fab (CroFab®, BTG, UK), and F(ab')$_2$ (Anavip®, Bioclon, Mexico) antivenom (AV) with F(ab')$_2$AV released in October 2018. The F(ab')$_2$AV Phase 3 comparative clinical trial demonstrated similar efficacy in treating venom-caused hematologic toxicity, similar rates of Types I and III hypersensitivity reactions, and a lower rate of recurrent hematological effects than FabAV. We hypothesized that a post-marketing, comparative study of effectiveness and rates of hypersensitivity reactions in treating rattlesnake envenomations in New Mexico would demonstrate similar outcomes.

Patients eligible for the study presented to a New Mexico healthcare facility between May and October 2019 and were known/suspected to have a rattlesnake bite. Exclusion criteria for antivenom comparison were those with a dry bite, lost to follow-up, or late presentation. All cases were included for patient/bite demographics, initial local control, hematological control, number of maintenance/control doses, development of persistent, recurrent or late-, new-onset hematologic effects, and hypersensitivity reactions. We used Fisher's exact tests for analysis and 0.05 cutoff to determine significance.

There were 54 rattlesnake-bitten patients in New Mexico with 17 excluded for comparison of antivenom because of dry bites, loss to follow-up, and one case of late presentation. Thirty-seven patients remained for comparative analysis between F(ab')$_2$AV (n = 11) and FabAV (n = 26). There were no significant demographic differences between F(ab')$_2$ and Fab-treated patients. No patient had a Type I hypersensitivity reaction. No rescue doses were given. The rate of recurrent, persistent or late-, new-onset of hematologic effects was 0% with F(ab')$_2$AV and 29% with FabAV. No patient was readmitted. No patient had bleeding complications. Type III hypersensitivity reactions were similar between F(ab')$_2$AV (36%) and FabAV (25%).

The results of our study are consistent with the Phase 3 clinical comparative trial and indicate no significant differences in safety or effectiveness between FabAV and F(ab')$_2$AV. F(ab')$_2$AV offers the advantages of not requiring maintenance doses and may have a lower rate of late hematologic effects in treating rattlesnake envenomations.

1. Introduction

The majority of venomous snakebites in North America belong to the subfamily Crotalinae and the Agkistrodon genus. Nearly 5000 venomous snakebites are reported in the United States (U.S.) each year, with an average of 5–6 deaths annually (Cardwell, 2011) (Corbett and Clark, 2017). Rattlesnakes, a member of the Crotalinae subfamily, are responsible for the majority of U.S. snakebite fatalities (Seifert et al., 2009). The majority of rattlesnake bites occur in the Southwest, particularly in Texas, New Mexico, Arizona, and California (Cardwell, 2011) (Corbett and Clark, 2017). During the 2018 snakebite season, 72 cases of rattlesnake bites were reported to the New Mexico Poison and Drug Information Center (UNM News Service, 2019).

Morbidity and mortality secondary to venomous snakebites have declined since the introduction of antivenom. Antivenom is essential for reducing local venom effects at the bite site, hematologic abnormalities, and overall systemic effects (Dart and McNally, 2001). A new antivenom may have a role in Crotalinae envenomations in regards to unresolved issues with Fab antivenom, such as the need for maintenance dosing following initial control, and persistent, recurrent, or late-, new-onset of

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hematological abnormalities (Boyer et al., 2013).

There are now two antivenoms (AV) available to treat rattlesnake envenomations in the U.S., Fab (CroFab®, BTG, UK) and F(ab')$_2$ (Anavip®, Bioclon, Mexico). The F(ab')$_2$AV Phase 3 comparative clinical trial demonstrated similar efficacy in treating venom-caused hematologic toxicity, similar rates of Type I and Type III hypersensitivity reactions, and a lower rate of recurrent hematological effects compared to patients treated with FabAV. Both antivenoms produced apparent control of progression of local effects, and patients treated with the F(ab')$_2$AV did not require maintenance dosing. There was no need for additional dosing for recurrent local or hematological effects with either antivenom (Bush et al., 2015). Following the clinical trial, the FDA approved F(ab')$_2$ antivenom for use against all North American rattlesnake envenomations.

The goals of this study were first to compare initial local and hematologic control between Fab and F(ab')$_2$ antivenoms in the 2019 New Mexican sample of rattlesnake envenomations. Second, we wanted to determine the need for maintenance dosing for F(ab')$_2$AV. Third, we aimed to determine rates of Type I and Type III hypersensitivity reactions for both antivenoms. Finally, we wanted to determine the rate of persistent, recurrent or late-, new-onset hematologic effects with F(ab')$_2$AV and FabAV in our rattlesnake/patient population. Our hypotheses were that F(ab')$_2$AV would produce equal control of local injury without the need for maintenance doses, equal acute control of hematologic effects with a lower rate of persistent, recurrent, or late-, new-onset of hematological effects, and equal rates of Type I and Type III hypersensitivity reactions compared to Fab antivenom in the first-year's post-marketing experience in New Mexico.

2. Materials and methods

We performed an observational study using 100% sampling of a statewide reporting of rattlesnake bites between May 1, 2019 and October 10, 2019 disclosed to the New Mexico Poison and Drug Information Center (NMPDIC). Patients and healthcare providers alike called the NMPDIC to report possible rattlesnake bites and to seek guidance on medical management. These calls were answered by a licensed pharmacist who had undergone training outlined by the American Association of Poison Control Centers (2017), with consultation and review by a board-certified medical toxicologist.

The indications for recommending antivenom included a witnessed snakebite and/or suspicion for a snakebite plus the presence of either local or systemic envenomation. Local symptoms of pain, swelling, bruising, bleeding, erythema, or blisters at the bite site with proximal progression of edema were a sufficient, independent indication. Hematological effects including an abnormal platelet count, low fibrinogen, or prolonged INR were also independent indications. If antivenom was indicated, the choice of antivenom was determined by the initial healthcare provider, with additional input and guidance from the NMPDIC. All patients were managed consistent with manufacturer-recommended antivenom dosing protocols.

All reports of snakebite were recorded and saved in the NMPDIC database. Two trained abstractors obtained the following information after each case closure: patient demographics, bite site, signs of envenomation, antivenom administration, control (no further progression/worsening) of local symptoms and signs, antivenom maintenance and rescue dosing, hematologic studies, including initial, in-hospital, and post-discharge laboratory tests, adverse events, and Type I and Type III hypersensitivity reactions. Type I hypersensitivity reactions are immediate allergic reactions, whereas Type III hypersensitivity reactions, also known as serum sickness, lead to an inflammatory response that can present later in the clinical course. Poison specialists at the NMPDIC conducted a phone interview for hypersensitivity Type III reactions at approximately 21 days post-envenomation. A patient scored positively if they affirmed any signs or symptoms of Type III hypersensitivity reactions including fever, hives, rash, itching, joint or muscle pain, malaise, hypotension, or hematuria between 5 and 21 days post-rattlesnake bite.

The number of cases in the region during our study period determined the sample size. All rattlesnake bite cases reported to the NMPDIC were included for overall patient and bite demographics, regardless of whether or not antivenom was received during the clinical course. For the purposes of antivenom comparison, we excluded those that did not receive any antivenom. This group consisted of patients lost to follow-up, those who presented late to a healthcare facility (more than 24 h after envenomation), and dry bites.

Rescue doses of antivenom were given for patients with persistent, late, or new-onset hematologic abnormalities. We defined these hematologic abnormalities (laboratory studies) based on Seifert et al. (2011), in which hematologic recurrence was any value that was abnormal within 12 h of envenomation, became normal, and then returned to abnormal four or more days post-envenomation. Persistent hematologic abnormality was any value that was abnormal within 12 h of envenomation and did not return to normal four or more days post-envenomation. Finally, late, new-onset hematologic abnormalities were those in which there was never an abnormality in the acute phase of envenomation (36–48 h post-envenomation) and then became abnormal four or more days post-envenomation.

Analytic statistics compared the bivariate predictor variable (Fab versus F(ab')$_2$ antivenom) and outcome variables measuring effectiveness (initial local control, maintenance dosing, and need, if any, for rescue dosing), hematologic effects (initial rates, persistence, recurrence, and/or late-new onset), and hypersensitivity reactions Type I and III. All data were analyzed using the Fisher's exact test and a 0.05 alpha error cutoff to determine significance. Our study was approved by the Institutional Review Board (IRB). This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

3. Results

There were 54 patients in our study with a median age of 51 years and a range of 16 months–86 years. Males (n = 40; 74%) outnumbered females (n = 14; 26%). Twenty-seven bites (50%) involved the upper extremity, 26 bites (48%) involved the lower extremity, and 1 bite (2%) involved the trunk.

We excluded 17 patients (31% of our total sample) in the comparative antivenom analyses: 10 patients had a dry bite and 1 patient presented > 24 h post-envenomation; none were treated with antivenom. An additional six patients were transferred out-of-state and lost to follow-up leaving a sample of 37 patients for antivenom comparison.

Of the remaining patients, 11 (30%) received exclusively F(ab')$_2$AV and 26 (70%) received only FabAV. There were no significant demographic differences between F(ab')$_2$ and Fab-treated patients (Table 1).

The number of control doses and initial and recurrent, persistent or late, new-onset of hematological effects is given in Table 2. No patients received rescue doses (additional antivenom doses needed to treat hematologic abnormalities) with either antivenom.

With FabAV, the rate of recurrent, persistent or late hematologic abnormalities was 29% overall and 41% in those with an initial hematologic abnormality. No patient in either group was readmitted or had bleeding complications.

No patient had an immediate allergic reaction in either group. Of patients who were reached for follow-up at approximately 21 days post envenomation, the number reporting symptoms consistent with a Type III hypersensitivity reaction with F(ab')$_2$ and FabAV are shown in Table 3. All Type III hypersensitivity reactions were mild.

4. Discussion

The results of our comparative analysis of F(ab')$_2$ and Fab

Table 1
Patient demographics, F(ab')$_2$AV v. FabAV groups.

N = 37	F(AB')$_2$ N (%)	FAB N (%)	p-value
	11	26	
GENDER			0.27
MALE	7 (64)	21 (81)	
FEMALE	4 (36)	5 (19)	
AGE			0.077
MEAN	33.8	49.1	
MEDIAN	25	53	
RANGE (YRS)	1.3–73	7–77	
BITE SITE			0.89
UPPER EXTREMITY	5 (45)	12 (46)	
LOWER EXTREMITY	6 (55)	13 (50)	

Not all patients had data in all categories.

Table 2
Antivenom dosing and hematological effects, F(ab')$_2$AV v. FabAV groups.

N = 37	F(AB')$_2$ N (%)	FAB N (%)	p-value
	11	26	
CONTROL DOSES[a]			0.30
1	7 (64)	20 (80)	
2	4 (36)	5 (20)	
INITIAL HEMATOLOGIC EFFECTS			0.28
Yes	8 (73)	14 (54)	
No	3 (27)	12 (46)	
RECURRENT/PERSISTENT/LATE-, NEW ONSET HEMATOLOGICAL ABNORMALITIES			0.072
Yes	0 (0)	7 (29)	
No	11 (100)	17 (71)	

Not all patients had data in all categories.
[a] Control doses consist of multiple vials of antivenom based on manufacturer guidelines.

Table 3
Type I and Type III hypersensitivity reactions, F(ab')$_2$AV v. FabAV groups.

N = 37	F(AB')$_2$ N (%)	FAB N (%)	p-value
	11	26	
Type I Hypersensitivity Reaction			1
Yes	0 (0)	0 (0)	
No	11 (100)	26 (100)	
Type III Hypersensitivity Reaction			0.68
Yes	4 (36)	5 (25)	
No	7 (64)	15 (75)	

Not all patients had data in all categories.

antivenoms in New Mexico are consistent with the F(ab')$_2$AV Phase 3 comparative clinical trial results. F(ab')$_2$ antivenom in our population was effective in managing the local and hematological effects of rattlesnake envenomation.

Our study also showed that maintenance dosing is not needed with F(ab')$_2$ antivenom and that rescue doses are not likely to be needed in their absence, similar to the Phase 3 clinical trial. Because of recurrence of local effects in some patients who receive Fab antivenom (Dart et al., 2001), the current recommendation is to routinely administer maintenance doses during the first 24 h (BTG International Inc, 2018). F(ab')$_2$ antivenom appears to not require maintenance dosing compared to Fab antivenom, which reduces concern for recurrence of local effects, though larger studies are required to confirm this.

In our study, F(ab')$_2$ antivenom had a zero frequency of persistent, recurrent, or late-, new-onset of hematologic abnormalities, and this was not true for Fab antivenom. This finding is consistent with the Phase 3 clinical trial (Seifert et al., 2011). Persistent, recurrent, or late-, new-onset hematological abnormalities are an important aspect of envenomation treatment and post-discharge monitoring and management. Late hematological effects can be severe and cause clinical bleeding (Fazelat et al., 2008) (Miller et al., 2010) (Moore et al., 2019) (O'Brien et al., 2009) and, in one case, intracranial hemorrhage and death (Kitchens and Eskin, 2008). In the F(ab')$_2$AV comparative clinical trial, 30% of Fab-treated patients developed persistent, recurrent or late-, new-onset of hematological abnormalities, while only 8% of the F(ab')$_2$-treated patients did so (Bush et al., 2015). In a previous study of 66 rattlesnake envenomated patients treated with FabAV, recurrent, persistent, or late-, new-onset of hematologic abnormalities occurred in 32% overall, and 50% of those with an initial hematological abnormality (Ruha et al., 2011). In another study, 18% of 60 Fab-treated rattlesnake envenomations and 50% of those with an initial hematological abnormality developed persistent, recurrent or late-, new-onset of hematologic abnormalities (Seifert et al., 2011). In all of these studies, these effects were seen primarily post-discharge. In our study, 29% of all patients, and 47% of those with an initial hematological abnormality in the Fab-treated group had persistent, recurrent, or late-, new-onset of hematological abnormalities, while none of the F(ab')$_2$-treated patients did so.

Our study found similar rates of Type III hypersensitivity reactions between F(ab')$_2$ and Fab antivenoms. There was an overall higher rate of Type III hypersensitivity reactions in this study (36% for F(ab')$_2$ and 25% for FabAV) compared with prior studies, where rates have ranged from 2.5% to 9% (Bush et al., 2015) (Dart et al., 1997). Our findings of a higher rate of Type III hypersensitivity reactions may be secondary to our 21-day, structured interview methodology and liberal attribution of a Type III hypersensitivity reaction to any patient reporting one of the included symptoms or signs. However, consistent with previous studies, all Type III hypersensitivity reactions were mild and did not require further medical evaluation or prescription medications (Boyer et al., 2013) (Bush et al., 2015). Finally, no patient developed any Type I hypersensitivity reactions with either antivenom, making both antivenoms safe for use in our region.

5. Limitations

The study was conducted in a single state and at a single poison center. National Poisoning Data System (NPDS) data have certain limitations. Not all cases are reported to poison centers. Data were acquired second-hand and some data fields were incomplete for some patients. Patients may be lost to follow-up. The small sample size affected the study's power. In this first year of experience with F(ab')$_2$AV, only a few hospitals in New Mexico stocked that antivenom. Since the University of New Mexico Hospital was one institution that carried F(ab')$_2$ antivenom, and pediatric patients were more likely to be transferred to this facility, our patient age distribution may be skewed by such transfers. Additionally, these pediatric patients' sex ratio tended to be less biased towards males. It is unclear what elements of bias this may have introduced. A separate age and sex-matched analysis of patients treated with FabAV in prior years (data not presented) did not demonstrate any outcome differences from the F(ab')$_2$ antivenom group.

6. Conclusions

Our experience is consistent with that found in the F(ab')$_2$ antivenom versus Fab antivenom comparative clinical trial. The control of local effects and hematological effects of Fab and F(ab')$_2$ antivenoms were similar. None of the F(ab')$_2$-treated patients required maintenance doses or required rescue antivenom. There were no persistent, new-, late-onset, or recurrent hematologic effects with F(ab')$_2$ antivenom. There were no Type I hypersensitivity reactions with either group. F(ab')$_2$ and Fab antivenom had similar rates of Type III hypersensitivity reactions.

We conclude that F(ab')$_2$ antivenom is safe and effective for rattlesnake envenomations in our region and offers some clinical advantages over Fab antivenom. Future research with a larger number of F(ab')$_2$-treated patients is needed to confirm our findings.

Ethical statement

All authors have abided by the statement of ethical standards for manuscripts submitted to *Toxicon*. Our study was approved by the Institutional Review Board (IRB) through the University of New Mexico Health Sciences Center (UNM HSC) with the approval number/ID of 19–607.

CRediT authorship contribution statement

D.N. Mascarenas: Conceptualization, Investigation, Visualization, Writing - original draft, Project administration. **L. Fullerton:** Formal analysis, Methodology, Validation, Writing - review & editing. **S.C. Smolinske:** Writing - review & editing. **B.J. Warrick:** Writing - review & editing. **S.A. Seifert:** Supervision, Investigation, Data curation, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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