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CLINICAL RESEARCH



Incidence of allergic reactions to Crotalidae polyvalent immune Fab

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ABSTRACT

Context: The administration of Crotalidae polyvalent immune Fab (FabAV) currently requires close observation, so patients can be monitored for hypersensitivity reactions. The objective of this study was to evaluate the occurrence of hypersensitivity reactions to FabAV.

Method: This was a retrospective cohort study utilizing data from a statewide poison center database in the United States. Records of all patients envenomated by a rattlesnake and treated with FabAV between January 2002 and December 2014 were evaluated. Patients with acute hypersensitivity reactions were identified, and reactions were evaluated descriptively.

Results: A total of 1340 adult and pediatric patients received FabAV during the study period. Of these, 19 (1.4%) patients had a potential reaction to FabAV, with 10 requiring a reduction in infusion rate, but none requiring discontinuation of the antivenom. Reactions occurred during the loading dose ($n=10$), maintenance doses ($n=4$), or were delayed reactions ($n=6$). Symptoms recorded included pruritus ($n=8$), hives ($n=8$), rash ($n=7$), vomiting ($n=7$), nausea ($n=6$), dyspnea or wheezing ($n=4$), diaphoresis ($n=3$), throat irritation ($n=2$), and mild hypotension ($n=2$). One patient was given a concomitant administration of low dose epinephrine infusion until completion of the antivenom course. However, none of the reactions were considered to be life-threatening.

Conclusion: FabAV appears to be associated with a low incidence of acute hypersensitivity reactions. Patients may not require placement in a location capable of detecting and rapidly responding to hemodynamic and/or airway issues for FabAV monitoring alone.

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Introduction

Globally, snakebite envenomations are an important public health concern in many countries [1]. It is estimated that in the United States (U.S.), there are approximately 5000 venomous snakebites reported to poison centers every year [2]. Despite a very low mortality rate associated with these envenomations, the associated morbidity among survivors can be significant especially in children, elderly, and those who do not receive adequate treatment [3]. In the U.S, Crotalid envenomation is most common [4]. Clinical manifestations of this envenomation include systemic effects such as coagulopathy, as well as local progressive tissue damage, which are indications for antivenom.

Crotalid antivenom manufacturing has evolved over time. Prior to 2000, a whole immunoglobulin G antivenom was associated with a high incidence of acute hypersensitivity reactions, which included life-threatening anaphylaxis [5,6]. In 2000, the U.S. Food and Drug Administration (FDA) approved the use of Crotalidae polyvalent immune Fab (CroFab; FabAV). FabAV contains purified immunoglobulin fragments, which reduced its immunological potential. Since

then, FabAV has become the only antivenom for treatment of North American Crotalid envenomations. Hypersensitivity reactions may be acute resulting in symptoms such as hypotension or respiratory distress (e.g., Type I) or delayed resulting in symptoms such as arthralgia or fever (e.g., Type IV) that usually occur weeks after drug administration. Acute hypersensitivity reactions are of immediate concern and may be life-threatening while patients are being managed in the hospital. One randomized multicenter trial, which included 31 patients, reported a 19% incidence of acute hypersensitivity reactions with FabAV use [7]. Therefore, in some institutions in the U.S., the administration of FabAV results in the need for close monitoring of any acute hypersensitivity reactions in a location capable of detecting and rapidly responding to hemodynamic and/or airway issues (e.g., intensive care unit admission). However, in a single center retrospective study of 93 patients, the incidence of acute hypersensitivity reactions was 5.4% in those who received FabAV [8]. A more recent registry of 373 patients showed an even lower adverse event rate of 2.7% [9]. Thus, additional post-marketing surveillance is needed to determine the incidence of acute hypersensitivity reactions associated with FabAV.

Table 1. Reactions in each phase.

Reaction type	Loading dose	Maintenance dose	Delayed
Pruritus (<i>n</i> = 8)	4	1	3
Hives (<i>n</i> = 8)	6	1	1
Rash (<i>n</i> = 7)	3	1	3
Vomiting (<i>n</i> = 7)	2	3	2
Nausea (<i>n</i> = 6)	2	2	2
Dyspnea or wheezing (<i>n</i> = 4)	3	0	1
Diaphoresis (<i>n</i> = 3)	1	2	0
Throat irritation (<i>n</i> = 2)	2	0	0
Mild hypotension (<i>n</i> = 2)	1	1	0

The primary objective of this study was to determine the incidence of acute hypersensitivity reactions to FabAV using a poison control database. The secondary objective was to characterize the types and severity of hypersensitivity reactions. Based on our previous experience, we hypothesized that acute hypersensitivity reactions to FabAV are rare.

Materials and methods

Study design and setting

This was a retrospective study utilizing data from a state Poison and Drug Information Center database in the U.S. The Institutional Review Board of the University approved the study.

The poison center receives calls for the entire state with the exception of one county. Practitioners from the poison center follow up on each patient by calling the primary nurse document and advise on any potential adverse reactions. Poison center practitioners conduct several phone calls to follow-up and document patient clinical progress. Initially, the poison center recommends treatment with FabAV based on discussion with on-site staff. Subsequent calls are made before and after each dose (loading dose and each maintenance dose) of FabAV to obtain information about clinical progress as well as any reactions to FabAV. The poison center also follows up with patients twice after discharge for up to 3 months (i.e., 2 weeks and then 3 months after discharge). All of this follow-up pertaining to clinical progress and adverse events are documented in the poison center database.

Patient selection and variables

The database was queried for all patients from January 2002 to December 2014 who were envenomed by a rattlesnake and treated with FabAV who were followed by the poison center. No patients were excluded. Cases are not followed if patients were referred to a healthcare facility but did not show up, related to animals bitten by rattle snakes, related to bites outside of the State, or transferred to the other poison center in the State for the one county mentioned above. Data pertaining to the management of patients and outcomes are recorded for each case in the database. In this study, information pertaining to hypersensitivity reactions was extracted from the case records. This included the type of reaction, whether the reaction occurred during loading or

maintenance doses, and interventions required for the adverse event.

Outcomes and definitions

The primary outcome of interest was the occurrence of an acute hypersensitivity reaction. This was defined as the occurrence and documentation of any of the following symptoms after administration of FabAV: pruritic rash, urticaria, dyspnea, wheezing, nausea/vomiting, swelling (lip, tongue, throat, or any other mucous membrane), or hypotension. The poison center practitioners specifically ask about these symptoms at each phone call and these are listed as check boxes on the poison center documentation. The identification of hypersensitivity reactions was done in two stages. First, all cases with any (i.e., one or more) of the symptoms listed above were identified. These were considered to be “potential cases” requiring additional review. Second, the potential cases were reviewed in greater depth to confirm the occurrence of a hypersensitivity reaction to FabAV. Given the inherent subjectivity pertaining to the assessment of hypersensitivity reactions from case records, this second stage review was done independently by two investigators (one pharmacist and one physician). Each case was then independently categorized using the following classification system: (1) high probability (documentation in record that reaction was drug-related, or infusion rate was decreased or stopped due to the potential for a drug-related reaction), (2) medium probability (time course suggestive of possible drug-related reaction, but no change in infusion made because the reaction was considered possibly related to disease state), and (3) low probability (reaction prior to infusion or consistent with disease state rather than drug). High and medium probability reactions were defined as being potentially related to FabAV. Hypersensitivity reactions were considered to be acute if they occurred during or within 6 h of infusion. Delayed reactions were considered those occurring beyond this time frame. All delayed reactions occurred more than 1 week after infusion in this study.

Data analysis

All data were reported descriptively. Continuous variables were reported as means with standard deviations. Categorical variables were reported as percentages. Interrater reliability of hypersensitivity assessment between the two raters was tested using the kappa statistic. All analyses were conducted using STATA 13 (College Station, Texas).

Results

A total of 1340 patients were known to have received FabAV and follow-up from the poison center. There were 185 cases that were initially identified as “potential” hypersensitivity reactions for further assessment. Of these, 19 (1.4%) were determined to be as potentially related to FabAV. The mean (standard deviation) age in these patients was 42 (17) years,

and 10/19 (53%) being male. The mean (SD) number of vials used was 13 (4) vials.

Of the 19 cases, 10 were high probability, and 9 were medium probability reactions. There was 97% agreement among the raters ($\kappa = 0.82$, $p < .001$), which indicates almost perfect agreement. Approximately half (10/19) patients required reduction in the infusion rate, but none of the patients required FabAV treatment discontinuation. None of the reactions were considered to be severe or life-threatening. No patients with hypersensitivity required respiratory support.

Reactions occurred during the loading dose ($n = 10$), followed by the maintenance doses ($n = 4$), and or were delayed allergic reactions ($n = 6$). All delayed reactions occurred 1–2 weeks after FabAV administration. There was one patient who had a reaction with both loading dose (nausea/vomiting) and maintenance dose (hives). In the remaining patients, the presence of the reaction was only in one of the three phases (i.e., loading, maintenance, or delayed). The types of reactions during each phase are in Table 1. Symptoms recorded included pruritus ($n = 8$), hives ($n = 8$), rash ($n = 7$), vomiting ($n = 7$), nausea ($n = 6$), dyspnea or wheezing ($n = 4$), diaphoresis ($n = 3$), throat irritation ($n = 2$), and mild hypotension ($n = 2$). Most patients (16/19) had more than one of the above symptoms noted. Allergic reactions were managed by decreasing the infusion rate or by the administration of diphenhydramine, methylprednisolone, or ondansetron. One patient was given an epinephrine infusion until completion of the antivenom course. This patient had nausea and vomiting, with acute onset each time FabAV was initiated or restarted. The gastrointestinal distress was refractory to treatment with antiemetics, histamine antagonists, and corticosteroids. The decision was made to initiate an epinephrine infusion, which was effective in preventing any subsequent reactions.

Discussion

The key finding from this study is that the occurrence of reactions to FabAV is low (1.4%). None of the patients had life-threatening reactions or required respiratory interventions. Most of the reactions were mild and were managed by decreasing the infusion rate or provision of rescue medications such as antiemetics, antihistamines, or corticosteroids. This resulted in a resolution of reactions in all but one patient, who required an epinephrine infusion. This enabled completion of antivenom treatment in all patients. Severe reactions to FabAV have been known to occur in previous investigations and case reports [10]. Thus, although it did not occur in our study, it is possible that these can occur similar to any medication.

Acute and delayed hypersensitivity reactions can occur when animal-derived heterologous proteins are administered to humans. This is particularly true when whole immunoglobulin G antivenoms are used. For example, the use of such antivenoms has been shown to be associated with a 24% incidence of hypersensitivity reactions, as reported in an epidemiological investigation in Australia [11].

Wyeth Laboratories introduced Antivenin Crotalidae Polyvalent (ACP) in 1954. This product subsequently became the mainstay for management of crotalid envenomations. However, it was a whole immunoglobulin G equine antivenom, with 23–56% of patients developing acute reactions [5]. Close to 50 years later, the U.S. Food and Drug Administration approved FabAV. It is an ovine-derived antivenom, which is manufactured by cleaving the immunoglobulin into Fab and Fc fragments by papain [12]. The more immunogenic Fc portion is then eliminated. Thus, FabAV has a lower risk of hypersensitivity reactions. The risk of hypersensitivity with FabAV has been reported in small clinical trials and single-center studies. In one meta-analysis of 11 studies of patients who received FabAV, the incidence of immediate hypersensitivity was 8% (95% CI 5–11%) [13]. The combined estimate including serum sickness was 13% (95% CI 7–21%). When all studies were combined in this meta-analysis, there were 504 patients who received FabAV only and no other antivenom. Recent data from the North American Snakebite Registry showed that in a cohort of patients who received at least one vial of FabAV, only 10 of 273 (2.7%) had an adverse event [9]. Most events were minor (e.g., rash), and only 1.1% had severe events such as hypotension, bronchospasm, or angioedema. Our study builds upon this literature by providing safety information on a large sample of 1340 patients who received FabAV. Our findings are consistent with the North American Snakebite Registry, confirming that the risks are indeed lower than previously considered to be.

Patients may be admitted to a closely monitored setting (e.g., ICU) after a snakebite depending on the severity of their symptoms and the need for monitoring. In Hong Kong, it has been shown that up to 90% of ICU admissions after snakebites are primarily for monitoring required during antivenom administration [14]. Consensus recommendations from a panel of experts in the U.S. suggest that the first dose of FabAV should be administered in a monitored setting such as an emergency department or ICU where appropriate equipment, medications, and personnel are available to manage an airway emergency resulting from an immediate hypersensitivity reaction [15]. If there is no reaction, then patients may be transferred to a less monitored setting such as a hospital ward. However, many institutions, out of an abundance of caution require that the full treatment course should be given in a monitored setting. Out of more than a thousand patients in our study, none had respiratory compromise requiring intubation. However, these patients must also be closely monitored for coagulopathy, progression of swelling, rhabdomyolysis, and other potential clinical manifestations of envenomation. We suggest that institutions should follow the unified treatment algorithm from the consensus panel mentioned above as it pertains to monitoring of FabAV as mentioned above [15].

Our study was limited by its retrospective nature and dependence on the reporting and documentation of the adverse reactions. There is the possibility for omission of data that would underestimate the incidence of adverse reactions. However, as we mentioned in the methods,

practitioners from the poison center routinely follow up on each patient during FabAV use several times during their admission and after hospital discharge. Follow-up was done in all patients in this cohort. It is difficult to differentiate between clinical sequelae from the envenomation and those symptoms that may be attributed to FabAV administration. For example, symptoms such as nausea and vomiting may have been associated with the pain or anxiety due to envenomation rather than antivenom therapy. This may overestimate the reported incidence of the adverse drug reactions. However, we took steps to minimize the subjectivity related to assessment of these reactions by including ratings from two investigators and performing inter-rater reliability. The rating scale itself was not dichotomous but was ranked based on the potential to be a drug-related reaction. We only attempted to capture patients who had reactions to FabAV. Thus, we do not know how many patients were given prophylactic therapies that would minimize the occurrence of hypersensitivity reactions. However, based on data from a recent study, we anticipate the use of prophylactic therapies to be low [9].

Conclusions

Our findings suggest that FabAV has associated with a low incidence and mostly mild acute hypersensitivity reactions. Most patients were treated with rescue therapies such as antihistamines, antiemetics, or corticosteroids.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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