



Prevalence of Acute Hypersensitivity Reactions in Pediatric Patients Receiving Crotalidae Polyvalent Immune Fab

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Abstract

Introduction Studies of acute hypersensitivity reactions in pediatric populations receiving Crotalidae Polyvalent Immune Fab (CPIF) are complicated by small size, wide age ranges, and diverse definitions of such reactions.

Methods This is a retrospective chart review of patients aged 13 years or younger treated with CPIF for Crotalid envenomation from November 2006 to 2016. The primary outcome was the presence of an acute hypersensitivity reaction to CPIF and was defined as the development of any of the following symptoms within 3 hours of initiation of CPIF infusion: urticaria, wheezing or respiratory distress, angioedema, hypotension, nausea, and/or vomiting. Demographics, CPIF dose to control and total dose, bite location, level of care, and length of stay were also recorded.

Results Thirty-four patients were ultimately treated with CPIF. Ages ranged from 10 months to 13 years. Twenty-one patients (60%) were male, 24 (70.6%) were admitted to the ICU, and the median length of stay was 2 days with a range of 1–11 days. Zero patients developed an acute hypersensitivity reaction to CPIF.

Conclusion Acute hypersensitivity reactions to CPIF did not occur in this cohort. Such reactions are rare with the use of CPIF in pediatric patients.

Keywords Hypersensitivity reaction · Pediatric · Antivenom · Crotalid

Introduction

Antivenom has become the mainstay of treatment for Crotalid envenomation. Until recently Crotalidae Polyvalent Immune Fab (CPIF) was the only available antivenom (other than the older Wyeth whole IgG antivenom). While there is now more than one option for the treatment of Crotalid envenomation, CPIF is the only FDA-approved antivenom for the treatment of copperhead and cottonmouth envenomation [1, 2]. Of identified species, copperhead and cottonmouth snakes make up approximately 26% of all snake envenomations in the

USA compared with 25% for rattlesnakes [3]. As such CPIF will likely continue to play a role in the management of these envenomations. CPIF is an ovine-derived polyclonal Fab fragment. Use of Fab fragments, which have the more immunogenic Fc portion of the antibody removed, is thought to reduce the risk of acute hypersensitivity reactions and serum sickness that complicated the use of the previous whole IgG antivenom produced by Wyeth. According to the CPIF package insert, 6/42 or 14% of patients developed what was described as early serum reactions, although the specific time frame was not delineated [1]. Fourteen percent is an improvement over the 20–25% reported with whole IgG yet is higher than our anecdotal experience [4]. Post-marketing studies of the pediatric population have been performed. These studies were limited by relatively small sample size and in one the inclusion of at least one patient aged 20 (further breakdown was not provided making it unclear how many pediatric patients were treated) [5–7]. To that end, we aimed to assess the prevalence of acute hypersensitivity reactions in patients aged 13 or younger receiving CPIF for Crotalid envenomation.

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Table 1 Demographic and descriptive statistics, *n* (%).

Total patients	34
Age (mean, years)	4.9
Sex (male)	21 (60)
Bite site	
RUE	7 (21)
LUE	11 (32)
RLE	6 (18)
LLE	9 (26)
ABD	1 (3)
LOS (mean, days)	2.9
LOC	
ICU	24 (70.6)
IMU	2 (5.9)
Med/Surg	7 (20.6)
Transferred	1 (2.9)
Time to CPIF (mean, min)	170
Total Vials CPIF (mean)	10.9
Vials to control (mean)	6.9
Acute hypersensitivity rxn.	0(0)
Delayed/recurrent thrombocytopenia	6 [#] (18)
Delayed/recurrent hypofibrinogenemia	2* (5.9)

LOS length of stay, LOC level of care, ICU intensive care unit, IMU intermediate care unit, RUE right upper extremity, LUE left upper extremity, RLE right lower extremity, LLE left lower extremity, ABD abdomen, *1 unknown, [#] 1 unknown

Methods

This is a retrospective chart review of all consecutive patients aged 13 years or younger suffering Crotalid envenomation and receiving CPIF from November 2006 to November 2016 at a tertiary care children's hospital. Three investigators abstracted the data from the electronic medical record (EMR). Patients were identified in the EMR with a specific query for the administration of CPIF. No other inclusion or exclusion criteria were used. Our primary outcome was the presence of acute hypersensitivity reactions to CPIF. The criteria used to define an acute hypersensitivity reaction included the presence of any of the following within 3 hours of initiation of CPIF infusion: urticaria, wheezing, respiratory distress, angioedema, hypotension, nausea, and/or vomiting. Time since last CPIF administration was also recorded. Secondary outcomes and demographic data obtained are shown in Table 1. Stabilization was defined as arrest of local

tissue damage and improvement or stabilization of hematologic parameters (platelet count, fibrinogen) for 6 hours without the need for further antivenom similar to a previous study [6]. If no specific comments were found in the medical record with respect to stabilization of local tissue damage, stabilization was deemed present if no further vials of antivenom were given for a 6-hour period. IRB approval for the study was obtained.

Results

Thirty-four patients were treated with CPIF for Crotalid envenomation during the 10-year study period. Average age was 4.9 years with a range of 10 months to 13 years. Twenty-one of 34 patients (60%) were male. Average time from envenomation to CPIF administration was 170 minutes with a median of 120 minutes. Average and median doses of CPIF for initial control were 6.9 and 6 vials, respectively. Total average and median doses of CPIF were 10.6 and 10 vials, respectively. Most patients were admitted to the critical care unit (24 or 70.6%), and the mean and median length of stay were 2.9 and 2 days, respectively, with a range of 1–11 days. The bite site was the left upper extremity (LUE) in 11 cases (32%), right upper extremity (RUE) in 7 (21%), left lower extremity (LLE) in 9 (26%), right lower extremity (RLE) in 6 (18%), and the abdomen in a single case (3%) (see Table 1). Results for hematologic parameters can be found in Table 2. No patients in our cohort developed an acute hypersensitivity reaction to CPIF.

Discussion

In sum, three prior studies in the pediatric population found that a total of 6/118 or 5.1% of patients developed a reaction to CPIF [5–7]. The terminology used to describe these reactions is different in each study and includes adverse drug reaction, allergic reaction, and hypersensitivity reaction. Only 2 of these studies also examined patients younger than or equal to 13 years of age and found no acute reactions in a total of 36 patients [5, 6]. One of these studies by Pizon et al. was retrospective, included 24 patients, and did not specify criteria for the diagnosis of “acute allergic reactions” (the term used in this specific paper). The other study by Offerman et al. included data from 12 patients collected both prospectively and

Table 2 Hematologic parameters.

	Initial	Discharge	Nadir
Mean platelets $\times 10^9/l$ (range)	<u>219 (21–391)</u>	<u>235 (39–399)</u>	<u>163 (6–320)</u>
Mean fibrinogen mg/dl (range)	<u>234 (61–334)</u>	<u>272 (153–419)</u>	<u>192* (< 45–302)</u>

*1 unmeasurable (< 45) not used in calculation of mean value

retrospectively, with no patients having a “hypersensitivity reaction” (again the terminology used in this paper), and again without specifying criteria for the diagnosis of such reactions. The only study, by Farrar et al., to report any patients having an “adverse drug reaction” (paper-specific terminology) was retrospective and included 82 patients, 6 of whom (7.3%) had an adverse drug reaction. The patients ranged in age from 5 to 16, and the reactions included pruritis in 2, urticaria in one, cough and wheezing in 2 with one of these 2 also having restlessness and periorbital edema, and a final patient with rash and facial swelling. All reactions were reported to have occurred during the initial CPIF infusion. While the criteria, for what constituted an adverse drug reaction, were not documented, rash, urticaria, respiratory distress, wheezing, and hypotension were specifically mentioned as being of interest. This study was conducted at a children’s hospital but included one patient aged 20 based on the range reported. A further breakdown of patients’ ages was not supplied, but 2 of the patients with adverse drug reactions were older than 13 [7].

In 3 studies not focused on children, 6/70 patients, or 8.6%, developed an acute reaction to CPIF [4, 8, 9]. Two of these studies included 4 patients aged 13 or less, and none of these patients developed an acute reaction to CPIF [8, 9]. The third study had patients ranging in age from 11 to 76 but no further breakdown, and while 6/31 (19%) had an acute reaction to CPIF, the ages of these patients were not mentioned [4]. Reactions in this study included isolated urticaria in 4; cough and urticaria in one; and hives, dyspnea, and wheezing in the final patient [4]. Like the studies in children, various terminologies were used, sometimes even within the same paper, to refer to reactions related to CPIF. In only one study was the criteria for such reactions described, and this was not particularly specific (any apparent adverse response occurring within in 2 hours of the infusion of CPIF) [4].

Limitations

Our study is limited by its retrospective nature and the difficulty this brings in assessing the presence of an acute hypersensitivity reaction based on documentation in the electronic medical record. Although we used several trained data abstractors, we did not calculate a kappa value for inter-rater reliability bringing into question the consistency of our data extraction. Finally, while our sample size is larger than other studies, it is still relatively small, thus limiting conclusions drawn for relatively rare events such as acute hypersensitivity reactions to CPIF.

Conclusion

We had zero patients meet our definition of an acute hypersensitivity reaction. Comparison of the prevalence of acute

hypersensitivity reactions in our study to others is challenging given the disparate terms used and lack of pre-specified criteria in many studies. Despite these varying definitions, our findings are consistent with prior studies which did not have any acute hypersensitivity, allergic, or other related reactions to CPIF. It is unlikely that no patients would ever have an acute hypersensitivity reaction to this antivenom (or any drug for that matter), so the real prevalence likely lies somewhere between these studies showing no reactions and the two studies with a prevalence of 7% and 19%.

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Compliance with Ethical Standards

Conflict of Interest None.

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