

Antivenom therapy for snakebites in children: is there evidence?

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Purpose of review

A new Fab fragment antivenom (CroFab) for the treatment of crotaline envenomation, the predominant venomous snakebite in the United States, has drastically changed snakebite management since its release in December 2000. This review examines the evidence supporting the use of CroFab, with particular attention on the pediatric population.

Recent findings

The published experience with CroFab in humans consists of six studies and some case reports. These publications demonstrate that CroFab is highly efficacious in treating both the local and systemic toxic effects of crotaline envenomation. They identify an important phenomenon of recurrent or delayed toxicity in some patients. The studies report a very low incidence of acute or delayed hypersensitivity reactions to the antivenom. They suggest comparable efficacy and safety of CroFab in the pediatric population as in adults.

Summary

Based on limited data, CroFab has been shown to be a safe and efficacious antivenom for use in children as well as adults. Further studies are needed to refine our understanding of its efficacy, safety, indications, and dosing.

Keywords

antivenins, antivenoms, crotalid venom, crotaline venom, immunoglobulin fragments, pediatrics, snake bites

Introduction

More than 6600 snakebites by indigenous North American snakes were reported to US poison control centers in 2003. Of these, 696 (9%) were confirmed poisonous snakebites to children aged 0–19 [1]. The true incidence of snake envenomation to children is even higher since voluntarily reported data to poison control centers significantly underestimates the incidence of snakebites [2–4]. The incidence of snakebites varies considerably by region. Most snakebites in the United States occur in the southeastern and southwestern states; venomous snakes, however, have been identified in every state in the continental United States except Maine [3,5**]. Therefore, snake envenomation of children remains a significant disease nationally.

At least 20 venomous species of snakes are native to the United States. These are principally members of the family Viperidae, subfamily Crotalinae. These crotaline snakes, commonly called ‘pit vipers,’ include the cottonmouth, copperhead, and multiple species of rattlesnakes. Coral snakes are the only other family of poisonous snake native to the United States [3,5**]. In 2003, crotaline snakebites accounted for 97% of the reported venomous snakebites from indigenous snakes in which the species was known [1].

Crotaline venom

Crotaline venom consists of numerous proteins and peptides, most enzymatically active. These proteins damage vascular endothelium, muscle, and subcutaneous tissue at the bite site, causing tissue effects such as pain, edema, ecchymosis, and necrosis. These local tissue effects typically spread from the bite site as venom is distributed along tissue planes. Venom can also act systemically, affecting the cardiovascular, respiratory, hematologic, and nervous system. One of the most common systemic effects is a multicomponent coagulopathy, including hypofibrinogenemia, increased fibrin degradation products, prolonged prothrombin time, and thrombocytopenia. The mechanism of the crotaline venom’s coagulopathic effect is multifactorial, including direct inhibition of clotting function, breakdown of fibrin, and consumptive deficiency of clotting factors and platelets [3,5**].

Snake envenomation treatment

Traditional medical treatment for crotaline envenomation in the past consisted of supportive care, cautious use of horse serum-derived antivenom, and surgical intervention

Curr Opin Pediatr 17:234–238. © 2005 Lippincott Williams & Wilkins.

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Current Opinion in Pediatrics 2005, 17:234–238

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1040-8703

if necessary. The utility of crotaline antivenom, called ACP (antivenin [Crotalidae] Polyvalent, Wyeth-Ayerst Pharmaceuticals, Philadelphia, Pennsylvania, USA), was limited by the frequency of significant reactions. Twenty to 25% of patients receiving ACP experienced acute reactions, often severe, and more than 50% developed serum sickness [6]. A safer antivenom, Crotaline polyvalent immune Fab (ovine) antivenom (crotaline Fab; CroFab, Protherics Inc, Nashville, Tennessee, USA) was released in December 2000 and is already radically changing snakebite management. Wyeth ACP is no longer manufactured.

CroFab

CroFab is a Fab-segment-based antivenom that has been more than 15 years in the making. CroFab was designed principally to provide a safer crotaline antidote. This antivenom has significantly less serum-derived protein than ACP and lacks the highly antigenic Fc antibody fragments. CroFab is produced by injecting venom into sheep and harvesting their serum antibodies. In particular, flocks of sheep are injected with the venom of one of four crotaline species indigenous to the United States: western diamondback rattlesnake, eastern diamondback rattlesnake, Mojave rattlesnake, and the cottonmouth (water moccasin). In a process akin to the production of the Fab fragment Digoxin antidote (Digibind; Glaxo Wellcome Inc, Research Triangle Park, North Carolina, USA), serum antibodies are digested with papain to cleave their Fc portions. The Fab fragments are then recovered, purified, and pooled with Fab fragments produced in response to the other three venoms [7]. This polyvalent Fab antivenom was found to be an average of 5.2 times more potent by weight than ACP in a mouse model [8].

CroFab is administered intravenously. The Fab fragments selectively bind crotaline venom proteins, rendering them enzymatically inactive. Each crotaline species' venoms vary in their exact composition and potency [3], but are similar enough that CroFab can effectively neutralize venom from many crotaline species, including those not even included in the production process [8].

CroFab has replaced ACP as the drug of choice for crotaline envenomations. Experience with CroFab is limited, however, and therefore its indications for use, contraindications, dosing, and precautions are all evolving.

The evidence

Data-driven estimations of the antivenom's efficacy and risks are the principal considerations needed to guide its use. Ideally, the data would be generated from large, controlled clinical trials. To date, we do not have such ideal data. Currently, CroFab's efficacy and risks in humans must be evaluated from two small prerelease clinical trials [6,9] and four published postmarketing case series

[4,10–12**] totaling 114 patients. Scattered case reports provide additional insight. However, these prospective data provide significantly better data for CroFab than the only retrospective data we have for ACP.

Fortunately, the six relevant studies included comparable inclusion criteria, CroFab dosing, and outcome measures. This consistency greatly aids in comparison of results across studies and adds validity when the results are in agreement. Each relevant study almost exclusively included mild or moderate envenomations with signs of progression as defined by a generally accepted grading scale (Table 1) [7]. Lavonas *et al.* [12**] and Offerman *et al.* [4] focused on subgroups of crotaline snakebites and are unique in their exclusive inclusion of copperhead bites and children, respectively. Although most of the studies were uncontrolled case series, patients were dosed similarly in accordance with CroFab's manufacture's recommendation for four to six vials initially, repeated once as needed to gain 'initial control.' Current dosing recommendations for CroFab are as follows.

- (1) Indications for use:
 - (i) Crotaline (rattlesnake, copperhead, cottonmouth) envenomation with worsening edema or any systemic symptom including coagulopathy
- (2) Contraindications for use (relative):
 - (i) Known hypersensitivity to CroFab, papain, or papaya
- (3) Dosing:
 - (i) Intravenously infuse four to six vials of CroFab diluted in 250 ml normal saline over 1 hr
 - (ii) May adjust volume for very small child or fluid-sensitive patient
 - (iii) Initially infuse at 25–50 ml per hour for 10 min while monitoring closely for signs of acute allergic reaction
 - (iv) Observe for up to 1 hour after infusion, assessing for initial control (halted progression of edema and improvement in all aspects of systemic manifestations)
 - (v) Repeat four to six vials as needed to gain initial control
 - (vi) Scheduled follow-up doses of two vials every 6 hr for 18 hr
 - (vii) Monitor patients for delayed or recurrent toxicity requiring additional antivenom
 - (viii) Poison control centers or medical toxicologists can assist with management of individual cases

'Initial control' was consistently defined as halted progression of local tissue effects and systemic effects including coagulopathy. In each study, progression of local tissue effects (i.e., extent of edema), platelet count, prothrombin time, and fibrinogen were evaluated at regular intervals. Patients received either scheduled follow-up doses

Table 1. Definition of minimal, moderate, and severe envenomation

Envenomation category	Definition
Minimal	Swelling, pain and ecchymosis limited to the immediate bite site; Systemic signs and symptoms absent; Coagulation parameters normal with no clinical evidence of bleeding.
Moderate	Swelling pain and ecchymosis involving less than a full extremity or, if bite was sustained on the trunk, head or neck, extending less than 50 cm; Systemic signs and symptoms may be present but not life threatening, including but not limited to nausea, vomiting, oral paresthesias or unusual tastes, mild hypotension (systolic blood pressure <90 mmHg), mild tachycardia (heart rate <150), and tachypnea; Coagulation parameters may be abnormal, but no clinical evidence of bleeding present. Minor hematuria, gum bleeding and nosebleeds are allowed if they are not considered severe.
Severe	Swelling pain and ecchymosis involving more than an entire extremity or threatening the airway; Systemic signs and symptoms are markedly abnormal, including severe alteration of mental status, severe hypotension, severe tachycardia, tachypnea, or respiratory insufficiency; Coagulation parameters are abnormal, with serious bleeding or severe threat of bleeding.

Source: CroFab package insert (Protherics Inc.).

(generally two vials every 6 hr for 18 hr) or follow-up doses as need clinically. The studies all evaluated CroFab's ability to gain initial control. Other outcomes common to all relevant studies include recurrent/delayed venom toxicity as well as immediate and delayed allergic reactions to antivenom.

Table 2 lists the six relevant studies along with their principal findings. For this analysis, coagulopathy refers to

thrombocytopenia, hypofibrinogenemia, or prolonged prothrombin time. Values are considered abnormal according to each paper's reference values, which varied slightly between some authors. Other outcomes have been tallied in accordance with standardized definitions in cases in which definitions varied slightly between authors. Tallies for each outcome include only those patients in whom the outcome was reasonably assessed and the outcome was clearly discernible from the paper.

Table 2. Results of clinical trials and case series evaluating CroFab for crotaline envenomation

Author	Year of publication	Number of subjects	Age of subjects (yr)	Snake species	Initial control ^a	Initial coagulopathy
Dart <i>et al.</i> ⁹	1997	11	13–75	Crotaline (copperheads excluded)	11/11 (100%)	7/11 (64%)
Dart <i>et al.</i> ⁴	2001	31	11–76	Crotaline (copperheads excluded)	31/31 (100%)	Unreported
Ruha <i>et al.</i> ¹¹	2002	28	4–68	Rattlesnakes only	Unreported	22/28 (79%)
Offerman <i>et al.</i> ⁴	2002	12	1–13	Rattlesnakes only	11/12 (92%)	2/12 (17%)
Bush <i>et al.</i> ¹⁰	2002	15	Unreported	Rattlesnakes only	15/15 (100%)	1/15 (7%)
Lavonas <i>et al.</i> ¹²	2004	32	>3	Copperheads only	29/31 (94%)	8/30 (27%)

Author	Year of publication	Recurrent local effects ^b	Late coagulopathy ^c	Recurrent coagulopathy ^d	Acute reaction to CroFab	Serum sickness to CroFab	
Dart <i>et al.</i> ⁹	1997	2/11 (18%)	0/4 (0%)	4/6 (67%)	0/11 (0%)	0/8 (0%)	
Dart <i>et al.</i> ⁴	2001	8/31 (26%) ^e	Unreported	Unreported	6/31 (19%)	6/26 (23%)	
Ruha <i>et al.</i> ¹¹	2002	2/21 (10%)	2/6 (33%)	4/18 (22%)	0/20 (0%)	2/15 (13%)	
Offerman <i>et al.</i> ⁴	2002	1/12 (8%)	1/10 (10%)	0/2 (0%)	0/12 (0%)	0/10 (0%)	
Bush <i>et al.</i> ¹⁰	2002	3/15 (20%)	0/14 (0%)	0/1 (0%)	2/15 (13%)	0/15 (0%)	4 severe envenomation
Lavonas <i>et al.</i> ¹²	2004	6/32 (19%)	1/22 (5%)	0/1 (0%)	1/32 (3%)	1/6 (17%)	2 severe envenomation

^aInitial control = Halted progression of local tissue effects and improvement in systemic effects with initial 4–12 vials dosed per package insert.

^bRecurrent local effects = Progression of edema surrounding bite site after initially halting in response to antivenom.

^cLate coagulopathy = Coagulopathy occurring after initial normal values.

^dRecurrent coagulopathy = Coagulopathy after improvement of initial coagulopathy with CroFab.

^eIncludes 0/16 (0%) with scheduled follow-up doses.

^f1/16 (6%) when excluding patients receiving an impure lot.

Efficacy

All six studies found CroFab to be efficacious. The antivenom almost universally achieved initial control. Edema and other local effects were stabilized, but improvement with initial dosing was rare because these insults involve cellular and tissue-level damage that is not readily reversible. Resolution of local tissue effects occurred over days to weeks. In contrast, thrombocytopenia, hypofibrinogenemia, and prothrombin time prolongation all generally showed immediate improvement if not normalization.

Recurrent/delayed effects

A minority of patients had recurrent or delayed venom effects after initial control was achieved. Recurrent symptoms were much more common than delayed effects. Recurrent or delayed coagulopathy has also been reported with Crotaline envenomation treated with ACP [13]. Among competing theories, this recurrent/delayed effect is best explained by the pharmacokinetic and pharmacodynamic differences between crotaline venom and antivenom [14–16•]. Immune antivenom has a much shorter half-life than venom and therefore its clearance from the body may result in a rebounding level of unbound venom proteins. Fab antivenom is cleared much faster than ACP immunoglobulin G, explaining the apparent increased incidence of the recurrent/delayed symptoms phenomenon with the new antivenom. Recurrence of both progression of local tissue effects and coagulopathy would be expected by this theory, although recurrent local effects have never been reported with ACP. Scheduled follow-up dosing as recommended in the package insert has been shown to dramatically reduce the incidence of recurrent/delayed toxicity [6], but failures of this scheduled follow-up dosing have been reported. Recurrent/delayed coagulopathy generally responded to additional doses of CroFab but not in every case. Coagulopathy has been present up to 3 weeks after envenomation [17].

Other clinical outcomes

Current studies of CroFab have not formally examined the drug's affect on temporary or permanent functional loss. A few studies mention outcomes such as a prevented fasciotomy [12••] or partial digit amputation despite CroFab [16•], but these are presented merely as illustrations. As pointed out by Caravati [18], the risk–benefit assessment for use of CroFab may appropriately include consideration of length of hospitalization, time lost from work, chronic limb dysfunction, economic impacts, and so on. Further study is needed to investigate these considerations.

Several authors have questioned the utility of treating a 'numeric coagulopathy' [11,14,16•,19]. Hemorrhagic complications of coagulopathy were not evaluated in these studies. Significant bleeding from venom has been described [20] but is unusual and would require much larger studies to properly investigate. Although CroFab's efficacy

in treating coagulopathy has been demonstrated, the drug's role in preventing clinically significant bleeding is unproven. Inferring from coagulopathic states from other causes, isolated thrombocytopenia, hypofibrinogenemia, or prolonged prothrombin time may not carry a significant enough risk of bleeding to warrant antivenom administration [14].

Special populations

Children are underrepresented in these already small studies. The scant literature on crotaline envenomation in children suggests that children may be more likely to suffer systemic effects, presumably because of higher venom dose per body weight [21,22]. The expectation that CroFab will have efficacy in children comparable to that in adults is supported by the data from Offerman *et al.* [4]. Current understanding of venom–antivenom interaction supports the use of standard dosing in children as well as adults. 'Per kilogram' dosing is not appropriate for neutralizing antivenom because the clinical effect is more dependent on venom dose than on patient weight [4,23•].

Copperhead envenomations

CroFab has not been proven efficacious across all crotaline species, but its efficacy has been suggested by *in vitro* studies or in case reports for at least 12 species of North American crotalines [7,10]. Copperhead envenomation is particularly common and is the predominate envenomation in parts of the southeastern United States and Texas. Copperhead venom was not included in the production process for CroFab because copperhead envenomations are generally considered less severe than rattlesnake envenomations. However, serious morbidity is still common. In a recent retrospective case series, Lavonas *et al.* [12••] provide important clinical evidence that CroFab is equally as efficacious in copperhead envenomations as in other crotaline bites.

Current indications and dosing recommendations do not differ based on crotaline species. Given the slightly different natural histories of envenomations between species, however, future studies may suggest such a distinction.

Safety

CroFab was developed principally to provide a safer alternative to ACP. Similar Fab fragment antidotes such as Digibind (Glaxo Smith Kline, Oxbridge, UK) have proven to be well tolerated [24]. These six studies of CroFab demonstrate a low rate of acute allergic reaction to CroFab administration. Of the nine acute adverse reactions reported, six had classic symptoms of acute allergic reaction such as rash, pruritus, or wheezing. The remaining acute reactions were flushing with tachycardia [12] and chest pain with diaphoresis in a patient with prior myocardial infarction [10]. All patients responded to basic measures. Despite these data, care must still be taken when

administering CroFab because cases of life-threatening immediate hypersensitivity reactions have been reported [25,26].

Serum sickness from CroFab was uncommon, and all symptoms resolved completely. Symptoms were mild and included pruritus, rash, low-grade fever, and myalgias. Patients receiving CroFab should be followed for the development of serum sickness for at least 3 weeks.

Conclusion

The introduction of the new Fab fragment antivenom CroFab in 2000 is radically changing the management of most venomous snakebites in the United States. Experience and data on CroFab are limited, so our understanding of its risks and benefits are evolving. The recent literature supports its use in a range of envenomations from minimal to severe. CroFab has been shown to be highly efficacious in treating both the local and systemic toxicity of crotaline envenomation. However, delayed effects and recurrent effects have all been demonstrated. Despite its excellent safety record thus far, CroFab should be used cautiously with careful monitoring for both acute and delayed hypersensitivity reactions. Data in children are scant, but support the assumption of equal efficacy and safety as in adults. Further study is needed to assess the role of CroFab in treating crotaline envenomations, including any differences in management of bites in children, with different crotaline species, or with different clinical presentations.

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