

Crotalidae Polyvalent Immune Fab

In Patients with North American Crotaline Envenomation

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Abstract

Crotalidae polyvalent immune Fab is an antivenom comprising purified, sheep-derived, Fab IgG fragments and is indicated for use in patients with North American crotaline envenomation. Crotalidae polyvalent immune Fab is produced using four North American snake venoms: *Crotalus atrox*, *Crotalus adamanteus*, *Crotalus scutulatus*, and *Agkistrodon piscivorus*.

Intravenous crotalidae polyvalent immune Fab was effective in patients aged ≥ 10 years who had minimal or moderate envenomation by a North American crotaline, who presented within 6 hours of the snakebite, and who had progression of the envenomation syndrome, according to the results of two prospective trials. One trial was a noncomparative, multicenter pilot study and the other trial was a randomized, open-label, multicenter trial in which patients received scheduled or 'as needed' administration of crotalidae polyvalent immune Fab after initial control had been achieved.

A prospective, postmarketing trial demonstrated the efficacy of crotalidae polyvalent immune Fab in confirmed *Crotalus viridis helleri* envenomation (indicating cross-protection against a venom not used in its production).

Results of these prospective trials are supported by the findings of additional (mainly retrospective) studies demonstrating the efficacy of crotalidae polyvalent immune Fab in patients with crotaline envenomation, including patients with severe envenomation, pediatric patients, and patients with symptoms of neurotoxicity.

Despite treatment with crotalidae polyvalent immune Fab, patients may experience delayed-onset or recurrent venom effects (e.g. coagulopathy).

Intravenous crotalidae polyvalent immune Fab was generally well tolerated; acute hypersensitivity reactions (e.g. urticaria, rash, pruritus) were the most commonly occurring adverse event.

Features and properties of crotalidae polyvalent immune Fab (CroFab®)

Indication

Management of patients with North American crotaline envenomation

Mechanism of action

Binds and neutralizes venom toxins

Description

Purified, lyophilized, nonpyrogenic preparation comprising venom-specific, sheep-derived, Fab IgG fragments

Minimum potency per vial for each venom component (mouse LD ₅₀ neutralizing units)	<i>Crotalus atrox</i> : ≥ 1270 <i>Crotalus adamanteus</i> : ≥ 420 <i>Crotalus scutulatus</i> : ≥ 5570 <i>Agkistrodon piscivorus</i> : ≥ 780
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Dosage and administration

Route of administration	Intravenous
To achieve initial control	Four- to six-vial dose; if initial control not achieved within ≈ 1 h, additional dose of four to six vials should be repeated until initial control is achieved
Subsequent dosing	Two-vial doses every 6 h for up to 18 h

Most commonly occurring adverse events

Acute hypersensitivity reactions (e.g. urticaria, rash, pruritus)

Approximately 8000 venomous snakebites occur each year in the US, resulting in five to six deaths annually.^[1] The majority of venomous snakes indigenous to the US belong to the subfamily Crotalinae (e.g. rattlesnakes, copperheads, and cottonmouths).^[1] The manifestations of crotaline envenomation vary (depending on such factors as the species of snake, the location of the bite, and the amount of venom injected), and range from no apparent clinical effects through to life-threatening effects.^[1,2] The main toxicities associated with crotaline envenomation include local symptoms at the bite site (e.g. pain, edema, ecchymosis), hematologic toxicity (e.g. coagulopathy, defibrination, thrombocytopenia), neurotoxicity (e.g. weakness, paresthesias, fasciculations), and other systemic effects (e.g. hypotension, tachycardia, vomiting).^[1,2] Even after successful initial treatment, patients with crotaline envenomation may develop delayed or recurrent venom effects (particularly hematologic effects) several days (or even several weeks) later.^[3-5] Some patients experience long-term sequelae (e.g. limb disfigurement).^[6]

US guidelines for the management of North American snake envenomation recommend the prompt use of sufficient amounts of antivenom in conjunction with aggressive supportive care.^[1] Given that fatal crotaline bites are not common, the main benefits of antivenom therapy relate to a reduction in morbidity (e.g. arresting tissue destruction, reversing coagulopathy, improving patient comfort, and reducing analgesic requirements).^[7]

In the US, crotaline envenomation used to be treated with an equine-derived whole-antibody IgG antivenom (hereafter described as equine-derived antivenom) that, although effective, was associated with high rates of anaphylaxis and serum sickness.^[4,8] This equine-derived antivenom is no longer being manufactured; therefore, the only antivenom currently available for crotaline envenomation is crotalidae polyvalent immune Fab (CroFab®), a sheep-derived antivenom that comprises purified Fab IgG fragments.^[4,8,9] Crotalidae polyvalent immune Fab was initially approved in the US in 2000 for the management of patients with minimal to moderate North American crotaline envenomation;^[8] however, this indication was recently expanded to include all severities of North American crotaline envenomation.^[9] Expert consensus guidelines recommend that all US hospitals providing emergency care should stock crotalidae polyvalent immune Fab.^[10]

This article reviews the therapeutic efficacy and tolerability of crotalidae polyvalent immune Fab in the management of patients with North American crotaline envenomation, as well as summarizing its pharmacologic properties. The taxonomic and common names of snakes mentioned in this article are shown in table I.

Medical literature (including published and unpublished data) on the use of crotalidae polyvalent immune Fab in

patients with North American crotaline envenomation was identified by searching databases since 1996 (including MEDLINE, EMBASE, and in-house AdisBase), bibliographies from published literature, clinical trial registries/databases, and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug. Searches were last updated 14 February 2011.

1. Pharmacologic Profile

This section provides a description of crotalidae polyvalent immune Fab, along with an overview of its mechanism of action, activity in animal studies, and pharmacokinetic profile (although data concerning the pharmacokinetics of the antivenom are limited).

Description

- Crotalidae polyvalent immune Fab comprises venom-specific, sheep-derived, Fab IgG fragments.^[9] This purified, lyophilized, nonpyrogenic preparation is obtained from the blood of healthy sheep inoculated with one of the following four North American snake venoms: *Crotalus atrox*; *Crotalus adamanteus*; *Crotalus scutulatus*; and *Agkistrodon piscivorus*.^[9]
- To prepare each monospecific antivenom, IgG is fractionated from the ovine serum and digested with papain in order to isolate the venom-specific Fab fragments and eliminate the

Table I. Taxonomic and common names of snakes mentioned in this article

Taxonomic name	Common name/s
<i>Agkistrodon contortrix</i>	Copperhead
<i>Agkistrodon contortrix contortrix</i>	Southern copperhead
<i>Agkistrodon piscivorus</i> ^a	Cottonmouth; water moccasin
<i>Crotalus adamanteus</i> ^a	Eastern diamondback rattlesnake
<i>Crotalus atrox</i> ^a	Western diamondback rattlesnake
<i>Crotalus horridus atricaudatus</i>	Canebrake rattlesnake
<i>Crotalus horridus horridus</i>	Timber rattlesnake
<i>Crotalus mitchellii pyrrhus</i>	Southwestern speckled rattlesnake
<i>Crotalus molossus molossus</i>	Northern blacktailed rattlesnake
<i>Crotalus ruber ruber</i>	Red diamond rattlesnake
<i>Crotalus scutulatus</i> ^a	Mojave rattlesnake
<i>Crotalus viridis helleri</i>	Southern Pacific rattlesnake
<i>Sistrurus miliarius barbouri</i>	Southeastern pygmy rattlesnake; Florida ground rattlesnake

a Venom from this snake is used in the production of crotalidae polyvalent immune Fab.

immunogenic Fc portion of the antibody.^[9,11] Following ion exchange and affinity chromatography purification, the four different monospecific antivenoms are then mixed.^[9]

- In each vial of crotalidae polyvalent immune Fab, the minimum number of mouse LD₅₀ neutralizing units of *C. atrox*, *C. adamanteus*, *C. scutulatus*, and *A. piscivorus* is 1270, 420, 5570, and 780, respectively. One neutralizing unit is defined as the amount of mixed monospecific Fab proteins needed to neutralize one LD₅₀ of each venom component (LD₅₀ equates to the amount of venom that would be lethal in 50% of mice).^[9]

Mechanism of Action

- Crotaline venom comprises dozens of components (with differing molecular weights and activities), meaning that its dynamics and kinetics are complex.^[12,13] Although the exact composition of crotaline venom varies (depending on factors such as the species and nutritional status of the snake), it contains numerous proteins and peptides, most of which are enzymatically active.^[1,5,8]
- Venom enzymes disrupt connective tissue (facilitating the distribution of toxins from the envenomation site), release mediators of inflammation, and cause cell lysis and necrosis.^[8,14] Fibrinolysins, thrombin-like enzymes, and nonspecific proteases contained in venom contribute to coagulopathy, and other venom components inhibit presynaptic acetylcholine release (causing muscle paralysis) or interfere with calcium binding on the nerve membrane (causing muscle fasciculations).^[8]
- The precise mechanisms underlying certain venom effects, such as venom-induced thrombocytopenia, remain unclear.^[15] Possible mechanisms explaining venom-induced thrombocytopenia include platelet aggregation, platelet sequestration at the venom injection site, or decreased platelet production.^[4,15] For example, crotalocytin, a serine protease isolated from *Crotalus horridus horridus* venom, caused platelet aggregation and activation *in vitro*.^[16,17] It has been suggested that venom-induced platelet aggregation is implicated in early thrombocytopenia, with platelet sequestration involved in delayed thrombocytopenia.^[15]
- Crotalidae polyvalent immune Fab binds and neutralizes venom toxins, facilitating the redistribution of these toxins away from target tissues and their subsequent elimination.^[9] For example, crotalidae polyvalent immune Fab may ameliorate the early phase of venom-induced thrombocytopenia by binding the venom proteins that cause platelet aggregation.^[15] This highlights the need for early administration of adequate doses of crotalidae polyvalent immune Fab (section 4), in order to prevent clinical deterioration and avoid systemic coagulation abnormalities.^[9]
- The complex and dynamic relationship between crotalidae polyvalent immune Fab, the crotaline venom components,

and the complex formed by the antivenom and the venom determines the therapeutic effect.^[8,13] The dynamic nature of this relationship may also partly explain the delayed or recurrent venom effects seen in some patients. For example, dissociation of some venom components from the antivenom may occur and may contribute to delayed or recurrent venom effects,^[3,11,13] although data from a closely analogous situation involving a digoxin-specific Fab product suggest the rate of dissociation of the complex formed by the Fab and digoxin is too slow to account for the observed recurrence phenomenon.^[13]

- Moreover, differences between the dynamics and kinetics of crotalidae polyvalent immune Fab and those of the crotaline venom components may also contribute to the development of delayed or recurrent venom effects.^[3,4,13] For example, there may be prolonged absorption of venom components from the envenomation site and, given that the clearance of unbound crotalidae polyvalent immune Fab is faster than the absorption and clearance of some of the crotaline venom components, repeat administration may be needed in order to avoid or treat the recurrence of venom effects.^[3,9,13]

Animal Studies

- In a murine lethality model, crotalidae polyvalent immune Fab neutralized the venom of ten clinically important North American snakes.^[18] The dose of crotalidae polyvalent immune Fab per kg of mouse bodyweight needed to protect 50% of mice against the lethal effect of venom was 39.2 mg against *C. atrox*, 22.7 mg against *C. adamanteus*, 4.9 mg against *C. scutulatus*, 21.9 mg against *A. piscivorus*, 12.7 mg against *Crotalus horridus atricaudatus*, 849.8 mg against *Crotalus viridis helleri*, 217.7 mg against *Crotalus molossus molossus*, 35.9 mg against *Agkistrodon contortrix contortrix*, 70.1 mg against *Sistrurus miliarius barbouri*, and 81.2 mg against *C. horridus horridus*.^[18]
- Thus, good cross-protection was generally seen against venoms not used in the production of crotalidae polyvalent immune Fab.^[9,18]
- In this murine model, crotalidae polyvalent immune Fab was 3.1–9.6 times more potent than equine-derived antivenom against nine of these venoms (a potency ratio could not be determined for *C. viridis helleri* because only 67% protection from lethality was seen with the equine-derived antivenom).^[18]

Pharmacokinetic Profile

- In patients with crotaline envenomation, crotalidae polyvalent immune Fab had a distribution half-life of 2.5–2.7 hours, a volume of distribution of 110 mL/kg, and a terminal elimination

half-life of 18 hours.^[13] Although unbound crotalidae polyvalent immune Fab may be eliminated renally, the complexes formed between the antivenom and some of the venom components may be too large for renal elimination.^[13]

2. Therapeutic Efficacy

The main focus of this section is the results of prospective trials examining the use of intravenous crotalidae polyvalent immune Fab in the management of patients with North American crotaline envenomation.^[6,11,19] Additional data from mainly retrospective analyses (including data specifically relating to severe envenomation, pediatric patients, and neurotoxicity) are also briefly discussed.^[20-26]

Prospective Trials

Prospective trials included an early noncomparative pilot study,^[11] a randomized trial comparing two regimens of crotalidae polyvalent immune Fab (scheduled or 'as needed' ad-

ministration of crotalidae polyvalent immune Fab following initial control),^[6] and a noncomparative, observational, postmarketing study.^[19] The pilot^[11] and randomized^[6] trials included patients with minimal or moderate envenomation with a North American crotaline; although patients with *A. contortrix* envenomation were excluded from these trials,^[6,11] it should be noted that crotalidae polyvalent immune Fab was subsequently approved for use in all crotaline snakebites.^[9] The observational study^[19] included patients with crotaline envenomation of any severity (most of the patients had *C. viridis helleri* envenomation). The trials included patients aged ≥ 10 years^[6,11] or patients of any age.^[19] Additional information regarding study design details (including selected inclusion and exclusion criteria), crotalidae polyvalent immune Fab regimens, and patient characteristics at baseline are shown in table II.

Pilot Study

- Crotalidae polyvalent immune Fab was effective in patients with moderate North American crotaline envenomation,

Table II. Details of prospective trials examining the efficacy of intravenous crotalidae polyvalent immune Fab (FabAV) in patients (pts) with North American crotaline envenomation. Trials comprised a randomized, open-label, multicenter trial^[6] comparing two regimens of FabAV, a noncomparative, multicenter pilot study,^[11] and a noncomparative, single-center, observational, postmarketing study^[19]

Parameter	Pilot study ^{[11]a}	Randomized trial ^{[6]b}		Observational study ^{[19]c}
		scheduled admin	'as needed' admin	
No. of pts	11	15	16	15
Mean age (range) [y]	41.3 (13–75)	34.9 (11–70)	39.6 (15–76)	NR
No. of patients with minimal or moderate envenomation ^d	Minimal: 0 Moderate: 11	Minimal: 2 Moderate: 13	Minimal: 0 Moderate: 16	NR
Inclusion criteria	Age ≥ 10 y; minimal or moderate envenomation ^d by a North American crotaline; presentation within 6 h of the snakebite; progression of the envenomation syndrome			Pts of any age with a rattlesnake bite ^e
Selected exclusion criteria	Severe crotaline envenomation; ^d <i>Agkistrodon contortrix</i> envenomation; lack of progression			Snake identification inconclusive; pt received equine-derived antivenom
Efficacy endpoint	Snakebite Severity Score ^f (primary efficacy endpoint)			Snakebite Severity Score ^f

a Pts received one or two four-vial doses of FabAV, depending on response.

b Pts received 6 or 12 vials of FabAV to achieve initial control (defined as the cessation of progression of local effects, systemic effects, and coagulopathy). FabAV was then administered on a scheduled basis (two vials every 6 h for a total of three doses) or on an 'as-needed' basis (in two-vial increments).

c Pts generally received 6–12 vials of FabAV to achieve initial control, with most pts subsequently receiving two vials every 6 h for a total of three doses.

d Minimal envenomation defined as swelling, pain, and ecchymosis limited to the immediate bite site; systemic signs and symptoms absent; coagulation parameters normal with no evidence of bleeding. Moderate envenomation defined as swelling, pain, and ecchymosis involving less than a full extremity or extending <50 cm if sustained on the trunk, head, or neck; systemic signs and symptoms may be present, but not life threatening; coagulation parameters may be abnormal, but no evidence of bleeding. Severe envenomation defined as swelling, pain, and ecchymosis involving more than an entire extremity or threatening the airway; systemic signs and symptoms markedly abnormal; coagulation parameters abnormal with serious bleeding or severe threat of bleeding.

e Nine pts were bitten by *Crotalus viridis helleri*, four pts were bitten by *Crotalus scutulatus*, and one pt each was bitten by *Crotalus mitchellii pyrrhus* or *Crotalus ruber ruber*.

f The total Snakebite Severity Score ranges from 0 to 20.^[2] Efficacy was defined as no further increase in the Snakebite Severity Score.

admin = administration; NR = not reported.

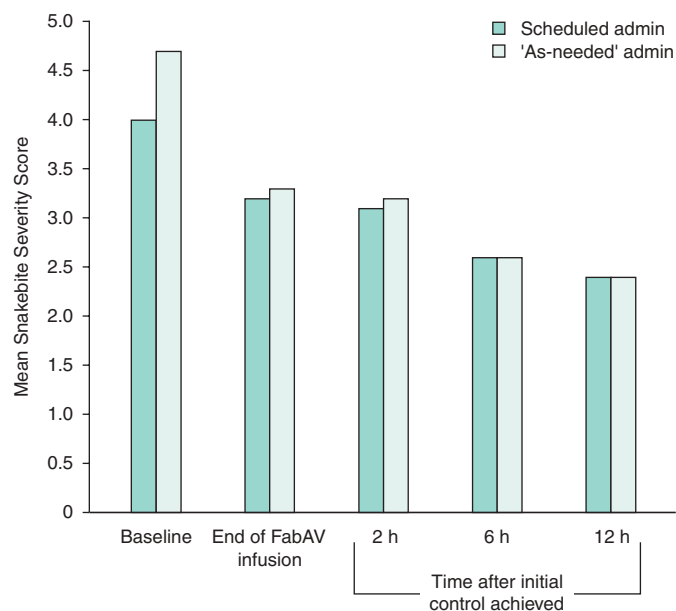


Fig. 1. Efficacy of intravenous crotalidae polyvalent immune Fab (FabAV) in patients (pts) with minimal or moderate envenomation with a North American crotaline. Results of a randomized, open-label, multicenter trial in which pts received 6 or 12 vials of FabAV to achieve initial control, after which they received FabAV on a scheduled basis (two vials every 6 h for a total of three doses) or on an 'as-needed' basis (in two-vial increments).^[6] Shown are the Snakebite Severity Scores (primary endpoint) at various timepoints. **admin**=administration.

according to the results of the pilot study.^[11] The mean Snakebite Severity Score decreased from 3.9 at baseline to 3.3 at the end of the crotalidae polyvalent immune Fab infusion, and 3.0, 2.6, and 2.6 at 1, 4, and 12 hours after the infusion, respectively. In addition, the investigators considered that all patients were clinically improved after treatment with crotalidae polyvalent immune Fab.^[11]

- One patient had recurrent coagulopathy on day 14 that resolved without further treatment, one patient had recurrence of prothrombin time prolongation on day 7 (resolved by day 14), and three patients had recurrent hypofibrinogenemia at follow-up visits on days 7 or 14.^[11]

Randomized Trial

- Both scheduled and 'as needed' administration of crotalidae polyvalent immune Fab were effective in patients with minimal or moderate envenomation with a North American crotaline.^[6] The mean Snakebite Severity Score decreased in both treatment groups, with no significant between-group differences (figure 1).^[6]
- None of the patients in the scheduled treatment group required additional crotalidae polyvalent immune Fab.^[6] Eight

of 16 patients (50%) in the 'as needed' treatment group required additional doses of crotalidae polyvalent immune Fab for recurrence of local venom effects during the first 12 hours (two additional vials of crotalidae polyvalent immune Fab resulted in successful resolution of each local recurrence episode). Overall, there was no significant difference between scheduled and 'as needed' treatment in the total amount of crotalidae polyvalent immune Fab administered (mean 13.0 vs 11.1 vials).^[6]

- The manufacturer's prescribing information^[9] reports that in this trial,^[6] significantly fewer patients receiving scheduled rather than 'as needed' treatment with crotalidae polyvalent immune Fab had abnormal platelet levels at follow-up (14% vs 56%; $p=0.04$). Abnormal fibrinogen levels at follow-up were seen in 14% of patients receiving scheduled crotalidae polyvalent immune Fab and 44% of patients receiving 'as needed' crotalidae polyvalent immune Fab.^[9]

Observational Study

- According to the results of the observational study, crotalidae polyvalent immune Fab was effective in confirmed *C. viridis helleri* envenomation, thereby demonstrating cross-protection against a venom not used in its production.^[19] In all nine patients bitten by *C. viridis helleri* who received crotalidae polyvalent immune Fab, the Snakebite Severity Score improved or remained the same for at least 6 hours. Median Snakebite Severity Scores were 4 at baseline and 3, 3, 2, and 2 at 6, 12, 18, and 24 hours, respectively. A mean 7.2 vials was needed to achieve initial control. Two patients experienced local recurrence despite the use of maintenance doses at 6, 12, and 18 hours.^[19]
- Among the four patients bitten by *C. scutulatus*, median Snakebite Severity Scores were 5 at baseline and 1.5, 1, 1, and 1 at 6, 12, 18, and 24 hours, respectively.^[19] Snakebite Severity Scores also decreased over time in the patient bitten by *Crotalus mitchellii pyrrhus* and the patient bitten by *Crotalus ruber ruber*.^[19]

Additional Data

Severe Envenomation

A retrospective, multicenter study examined the efficacy of crotalidae polyvalent immune Fab in 28 patients with severe crotaline envenomation.^[20] The primary endpoint was the change in the modified Snakebite Severity Score (in the modified version, the total score ranges from 0 to 6, with a score of 5 or 6 indicating severe envenomation).^[20]

- Crotalidae polyvalent immune Fab was effective in patients with severe crotaline envenomation.^[20] Median modified Snakebite Severity Scores were 5 prior to the administration of crotalidae polyvalent immune Fab and 1 at both the time of initial control (or after administration of the last loading dose) and at the final clinical assessment.^[20]
- Initial control was achieved in 16 of 28 patients (57%).^[20] Among the patients achieving initial control, recurrence of venom effects (e.g. recurrent local tissue effects or asymptomatic coagulopathy) occurred in 5 of 16 patients (31%) and delayed-onset venom effects occurred in 1 of 16 patients (6%).^[20]

Pediatric Patients

In terms of data specifically relating to the use of crotalidae polyvalent immune Fab in pediatric patients, results are available from a retrospective, single-center study (involving 24 patients aged 1.9–13 years [average age 7.3 years]),^[22] and from a study in which data were collected prospectively at one center and retrospectively at a second center (involving 12 patients aged 14 months to 13 years [mean age 6.9 years]).^[21]

- Crotalidae polyvalent immune Fab halted progression of local venom effects in pediatric patients with crotaline envenomation.^[22] Control of local swelling was achieved with a single four- to six-vial dose of crotalidae polyvalent immune Fab in 14 of 24 patients (58%). In total, a mean 12.3 vials of crotalidae polyvalent immune Fab was administered per patient. Twenty-three patients developed coagulopathy or thrombocytopenia during hospitalization; none required administration of blood products.^[22]
- Within 24 hours of crotalidae polyvalent immune Fab administration, Snakebite Severity Scores had stabilized or improved in all 12 pediatric patients with rattlesnake envenomation (scores ranged from 2 to 9 on presentation [mean score of 5] and from 1 to 3 at 24 hours [mean score of 1.8]).^[21] Each patient received between 4 and 22 vials of crotalidae polyvalent immune Fab (mean 12.7 vials per patient). Abnormal coagulation laboratory parameters were seen in two patients on presentation; these abnormalities resolved following treatment with crotalidae polyvalent immune Fab.^[21]

Neurotoxicity

A case series of three adults reported the effects of crotalidae polyvalent immune Fab on symptoms of neurotoxicity following rattlesnake envenomation (two cases of *C. atrox* envenomation and one case of *C. scutulatus* envenomation).^[23] Patients developed neurologic symptoms including fasciculations, weakness, and paresthesias, as well as other symptoms of crotaline envenomation.

- Crotalidae polyvalent immune Fab rapidly reversed symptoms of neurotoxicity in all three patients.^[23] For example, in one patient, fasciculations resolved within 15 minutes of crotalidae polyvalent immune Fab administration (with no recurrence of symptoms). In a second patient, fasciculations diminished by 90% with the first six-vial dose of crotalidae polyvalent immune Fab and completed resolved with the second six-vial dose.^[23]

Other Retrospective Analyses

Three retrospective studies (conducted through a single medical toxicology service^[24,25] or poison center^[26]) examined the efficacy of crotalidae polyvalent immune Fab in patients with rattlesnake envenomation (n=28^[24] and 66^[25]) or *A. contortrix* envenomation (n=32).^[26] One analysis specifically examined late hematologic toxicity following treatment; the first follow-up visit occurred a mean 4 days after the last dose of crotalidae polyvalent immune Fab.^[25]

- Initial control of swelling was achieved with a single dose of four to six vials of crotalidae polyvalent immune Fab in 16 of 28 patients (57%) with rattlesnake envenomation, while others required additional doses.^[24] All of the patients with prolonged prothrombin times (n=20) or hypofibrinogenemia (n=12) at presentation showed improvement after treatment with crotalidae polyvalent immune Fab, although the majority of patients needed more than ten vials to achieve control of envenomation. Recurrence or delayed onset of venom effects was seen in 6 of 21 patients (29%).^[24]
- At follow-up, two patients had recurrent swelling, three had recurrent coagulopathy, one had recurrent thrombocytopenia, and two had delayed-onset thrombocytopenia; three patients received further treatment with crotalidae polyvalent immune Fab.^[24]
- Late hematologic toxicity was reported in 21 of 66 patients (32%) with rattlesnake envenomation who initially received treatment with crotalidae polyvalent immune Fab (18 patients experienced recurrent hematologic toxicity and 3 experienced delayed hematologic toxicity).^[25] Late coagulopathy was seen in 9 patients (14%), late hypofibrinogenemia was seen in 13 patients (20%), and late thrombocytopenia was seen in 8 patients (12%). Five patients (8%) had severe late hematologic toxicity, although only one patient (with late thrombocytopenia) required retreatment with crotalidae polyvalent immune Fab.^[25]
- Following *A. contortrix* envenomation, 28 of 32 patients (88%) had a rapid initial response to crotalidae polyvalent immune Fab therapy (median time to achieve initial control of 1 hour).^[26] Early recurrent swelling occurred in 4 of 32 patients (13%), with 2 of the remaining 28 patients (7%) experiencing

late recurrent swelling. One of the patients with late recurrent swelling developed delayed defibrination syndrome, which improved with additional crotalidae polyvalent immune Fab and fresh frozen plasma.^[26]

3. Tolerability

Data regarding the tolerability of intravenous crotalidae polyvalent immune Fab in patients with crotaline envenomation were obtained from the randomized trial^[6] discussed in section 2 and from retrospective studies.^[20,27] The tolerability analysis of the retrospective study^[20] in patients with severe crotaline envenomation (see section 2) also included 181 patients with minimal to moderate envenomation (total safety population of 247). A second retrospective analysis included 93 patients who received intravenous crotalidae polyvalent immune Fab (mean dose 12 vials) for rattlesnake envenomation.^[27]

- Treatment with intravenous crotalidae polyvalent immune Fab was generally well tolerated. Acute hypersensitivity reactions occurred during infusion in 6 of 31 patients (19%) receiving crotalidae polyvalent immune Fab in the randomized trial.^[6] Four patients had mild, transient urticaria and two patients (both of whom had a history of reactive airway disease) had moderate allergic reactions (cough and urticaria in one patient and hives, dyspnea, and wheezing in the other patient). Two patients with mild urticaria required no treatment and all other patients responded to treatment with histamine H₁ receptor antagonists, H₂ receptor antagonists, corticosteroids, and/or albuterol (salbutamol).^[6]
- Of the 26 evaluable patients at the 14-day follow-up, six (23%) developed serum sickness (symptoms included pruritus, rash, arthralgia, anorexia, hives, and/or urticaria).^[6] Two cases of mild serum sickness resolved spontaneously and two cases each of moderate and severe serum sickness required treatment with H₁ receptor antagonists and corticosteroids. Five of the six affected patients were found to have received a batch of crotalidae polyvalent immune Fab that contained excess Fc fragments (a new purification step was subsequently introduced to the manufacturing process).^[6]
- In the retrospective analyses, acute hypersensitivity reactions occurred in 15 of 247 patients (6%)^[20] and 5 of 93 patients (5%)^[27] who received crotalidae polyvalent immune Fab. However, in the latter study, it was not clear if the reaction was related to crotalidae polyvalent immune Fab administration or some other factor (e.g. administration of opioids for pain management) in three patients.^[27]
- Patients generally responded to slowing or discontinuing the crotalidae polyvalent immune Fab infusion or to treatment with

H₁ receptor antagonists, H₂ receptor antagonists, corticosteroids, albuterol, and/or epinephrine (adrenaline),^[20,27] apart from one patient who had a serious acute hypersensitivity reaction and required cricothyroidotomy for airway edema.^[20] Three other patients in this study also experienced serious acute hypersensitivity reactions.^[20] Serum sickness was reported in 2 of the 41 patients (5%) who were followed up for ≥6 days after the last dose of crotalidae polyvalent immune Fab.^[20]

4. Dosage and Administration

US prescribing information recommends that treatment with intravenous crotalidae polyvalent immune Fab should start as soon as possible after the crotaline snakebite in patients with signs of progressive envenomation, in order to prevent clinical deterioration and avoid systemic coagulation abnormalities (section 1).^[9] Clinical trial results demonstrated that crotalidae polyvalent immune Fab was effective when administered within 6 hours of the snakebite.^[9]

The crotalidae polyvalent immune Fab dosage needed to achieve initial control is contingent on the response of the individual patient and may vary depending on the severity of the envenomation syndrome (initial control is defined as the complete arrest of local manifestations and the return of systemic signs and coagulation tests to normal). The recommended initial dose of crotalidae polyvalent immune Fab is four to six vials.^[9] After administration of the first dose, patients should be observed for up to 1 hour to ascertain if initial control has been achieved. If initial control has not been achieved, an additional crotalidae polyvalent immune Fab dose of four to six vials should be repeated until initial control is attained.

Once initial control is achieved, it is recommended that two-vial doses of crotalidae polyvalent immune Fab be administered every 6 hours for up to 18 hours. Additional two-vial doses may then be administered at the discretion of the treating physician, based on the clinical course of the patient.^[9] Dosage adjustments are not required in pediatric patients.^[9]

Because of the risk of delayed or recurrent hematologic abnormalities, it has been suggested that following discharge, all patients receive close outpatient monitoring for at least 1 week, and that all patients be screened for late thrombocytopenia, hypofibrinogenemia, and coagulopathy ≈2–3 days after crotalidae polyvalent immune Fab treatment.^[8,25,28]

Local prescribing information should be consulted for further information regarding the preparation and administration of crotalidae polyvalent immune Fab, as well as for information concerning contraindications, warnings, and precautions.

5. Crotalidae Polyvalent Immune Fab: Current Status

Crotalidae polyvalent immune Fab is approved in the US for use in the management of patients with North American crotaline envenomation.

Intravenous crotalidae polyvalent immune Fab is effective in patients with minimal, moderate, or severe crotaline envenomation, halting the progression of local venom effects and ameliorating hematologic and other systemic abnormalities of envenomation. Despite treatment, patients may experience delayed-onset or recurrent venom effects (e.g. coagulopathy). Intravenous crotalidae polyvalent immune Fab is generally well tolerated, with acute hypersensitivity reactions being the most commonly occurring adverse event.

Acknowledgments and Disclosures

The manuscript was reviewed by: **R.C. Dart**, Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, Colorado, USA; **A.-M. Ruha**, Department of Medical Toxicology, Banner Good Samaritan Medical Center, Phoenix, Arizona, USA.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

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