

Crotalidae Polyvalent Immune Fab: A Guide to Its Use in North American Crotaline Envenomation

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Abstract

Intravenous crotalidae polyvalent immune Fab (CroFab®) is effective in patients with minimal, moderate or severe crotaline envenomation, halting the progression of local venom effects and ameliorating haematological 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.

What is the rationale for developing the drug?

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, 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, oedema, ecchymosis), haematological toxicity (e.g. coagulopathy, defibrination, thrombocytopenia), neurotoxicity (e.g. weakness, paraesthesias, 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 haematological effects) several days (or even several weeks) later.^[3-5] Some patients experience long-term sequelae (e.g. limb disfigurement).^[6]

In the US, the only antivenom currently available for crotaline envenomation is crotalidae polyvalent immune Fab (CroFab®) [table I].^[7]

How does the drug work?

Crotalidae polyvalent immune Fab comprises venom-specific, sheep-derived, Fab IgG fragments.^[8] This purified, lyophilized, non-pyrogenic preparation is obtained from the blood of healthy

Table 1. Adis Evaluation

What are the key clinical benefits and limitations of crotalidae polyvalent immune Fab (CroFab®)?

Clinical benefits

Effective in patients with minimal, moderate or severe North American crotaline envenomation
Halts the progression of local venom effects
Ameliorates haematological and other systemic abnormalities of envenomation
Generally well tolerated

Limitations

Despite treatment, patients may experience delayed-onset or recurrent venom effects (e.g. coagulopathy)
Hypersensitivity reactions may occur

sheep inoculated with one of the following four North American snake venoms: *Crotalus atrox* (Western diamondback rattlesnake), *Crotalus adamanteus* (Eastern diamondback rattlesnake), *Crotalus scutulatus* (Mojave rattlesnake) and *Agkistrodon piscivorus* (cottonmouth or water moccasin).^[8] To prepare each monospecific anti-venom, IgG is fractionated from the sheep serum and digested with papain in order to isolate the venom-specific Fab fragments and eliminate the immunogenic Fc portion of the antibody.^[8,9] Following purification, the four different monospecific antivenoms are then mixed.^[8] In animal studies, good cross-protection was generally seen against venoms not used in the production of crotalidae polyvalent immune Fab.^[8,10]

Crotaline venom comprises dozens of components, meaning that its dynamics and kinetics are complex.^[11,12] Crotalidae polyvalent immune Fab binds and neutralizes venom toxins, facilitating the redistribution of these toxins away from target tissues and their subsequent elimination.^[8] For example, crotalidae polyvalent immune Fab may ameliorate the early phase of venom-induced thrombocytopenia by binding the venom

proteins that cause platelet aggregation.^[13] This highlights the need for early administration of adequate doses of antivenom, in order to prevent clinical deterioration and avoid systemic coagulation abnormalities.^[8]

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.^[12,14] The dynamic nature of this relationship may also partly explain the delayed or recurrent venom effects seen in some patients. 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.^[3,8,12]

How should it be used?

Crotalidae polyvalent immune Fab is indicated in the management of patients with North

Table II. Prescribing summary of intravenous crotalidae polyvalent immune Fab (CroFab [®]) in patients with North American crotaline envenomation in the US ^[6]	
What is its approved indication?	
Management of patients with North American crotaline envenomation (all severities)	
Early use (within 6 h of snakebite) advised to prevent clinical deterioration and occurrence of systemic coagulation abnormalities	
Which venoms are used in its production?	
Minimum potency per vial for each venom component (mouse LD ₅₀ neutralizing units)	<i>Crotalus atrox</i> (Western diamondback rattlesnake): ≥1270 <i>Crotalus adamanteus</i> (Eastern diamondback rattlesnake): ≥420 <i>Crotalus scutulatus</i> (Mojave rattlesnake): ≥5570 <i>Agkistrodon piscivorus</i> (cottonmouth or water moccasin): ≥780
How should it be administered?	
To achieve initial control	Four- to six-vial dose If initial control not achieved within ≈1 h, an additional dose of four to six vials should be repeated until initial control is achieved (i.e. dose contingent on patient response) No dosage adjustment needed in paediatric patients
Subsequent dosing	Two-vial doses every 6 h for up to 18 h
How is it available and how should it be stored?	
Availability	Each vial contains up to 1 g of lyophilized total protein and a maximum of 0.03 mg of mercury
Storage	Refrigerate at 2–8°C (36–46°F); do not freeze Use within 4 h of reconstitution
What are the contraindications to its use?	
Known history of hypersensitivity to papaya or papain unless the benefits outweigh the risks and appropriate management for anaphylactic reactions is readily available	
Are there any precautions regarding its use?	
Recurrent coagulopathy may occur and may persist for ≥ 1–2 wk	
Severe hypersensitivity reactions (including anaphylaxis and anaphylactoid reactions) may occur	

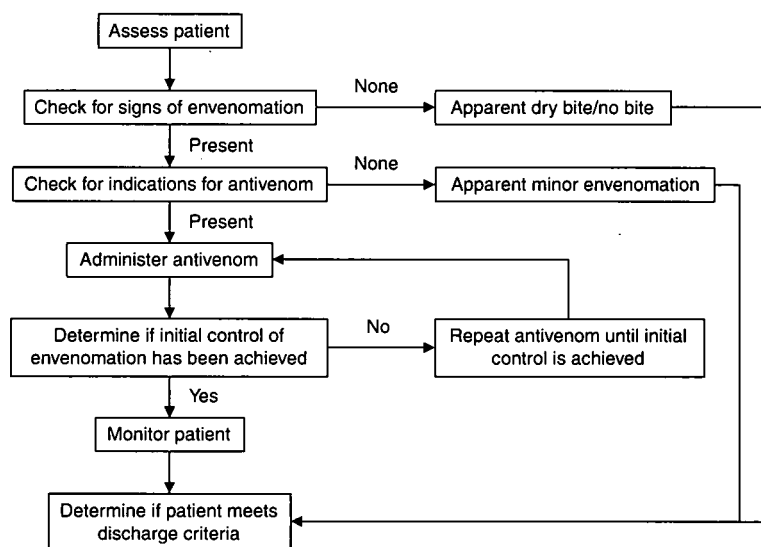


Fig. 1. Treatment algorithm for the management of crotaline envenomation with crotalidae polyvalent immune Fab, as suggested by Lavonas et al.^[15]

American crotaline envenomation (see table II for a summary of the US prescribing information).^[8]

US experts have developed a treatment algorithm for the management of crotaline snakebite with crotalidae polyvalent immune Fab (figure 1).^[15] Following initial assessment and a check for signs of envenomation, patients should be assessed to see if administration of crotalidae polyvalent immune Fab is indicated (i.e. presence of swelling that is more than minimal and is progressing; elevated prothrombin time, decreased fibrinogen levels or platelets; or any systemic signs).^[15]

Crotalidae polyvalent immune Fab dosing should be titrated to the clinical response; repeat administration of antivenom may be needed if initial control of envenomation is not achieved.^[15] Patients should then be monitored and the need for maintenance antivenom therapy assessed (maintenance therapy may not be needed in patients with minor envenomation or in facilities where close observation by a physician expert is available). Discharge criteria include no progression of any venom effects during the specified observation period, and no unfavourable trends in prothrombin time, fibrinogen levels or platelets.^[15]

After discharge, among patients who received antivenom, those bitten by copperhead snakes

should be followed up as required, whereas those bitten by other crotalines should have repeat laboratory parameters (prothrombin time, fibrinogen levels, platelets, haemoglobin) measured on days 2–3 and on days 5–7, and then as required.^[15]

Certain treatments should be avoided in crotaline envenomation, including cutting or suctioning of the wound; application of a tourniquet or ice; use of NSAIDs, prophylactic antibacterials, prophylactic fasciotomy or corticosteroids (except for in the treatment of allergic phenomena); and the routine use of blood products.^[15]

It is recommended that physician-experts be consulted in the following high-risk clinical situations: life-threatening envenomation, hard-to-control envenomation, recurrence or delayed-onset of venom effects, allergic reactions to antivenom, if transfusion is considered, uncommon clinical situations and complicated wound issues.^[15]

What is its therapeutic efficacy in minimal to moderate envenomation ...

Two trials examined the use of intravenous crotalidae polyvalent immune Fab in the management of patients aged ≥ 10 years with North American crotaline envenomation.^[6,9] The primary

endpoint of these trials was the Snakebite Severity Score, which ranges from 0 to 20; efficacy was defined as no further increase in this score. Although patients with *Agkistrodon contortrix* (copperhead) envenomation were excluded from these trials,^[6,9] crotalidae polyvalent immune Fab was subsequently approved for use in all crotaline snakebites.^[8]

Crotalidae polyvalent immune Fab was effective in patients with moderate North American crotaline envenomation, according to the results of a noncomparative pilot study (n=11).^[9] The mean Snakebite Severity Score decreased from 3.9 at baseline to 3.3 at the end of the antivenom infusion, and 3.0, 2.6 and 2.6 at 1, 4 and 12 hours after the infusion, respectively. The investigators considered all patients to be clinically improved after treatment with crotalidae polyvalent immune Fab.^[9] 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.^[9]

Both scheduled and 'as-needed' administration of crotalidae polyvalent immune Fab following initial control were effective in a randomized trial in 31 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 2).^[6] None of the patients in the scheduled treatment group required additional crotalidae polyvalent immune Fab.^[6] Half of the patients in the 'as-needed' treatment group required additional doses of antivenom for recurrence of local venom effects during the first 12 hours (with two additional vials resulting 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 antivenom administered (mean 13.0 vs 11.1 vials).^[6] According to the manufacturer's prescribing information,^[8] significantly fewer patients receiving scheduled rather than 'as-needed' treatment with crotalidae polyvalent immune Fab had ab-

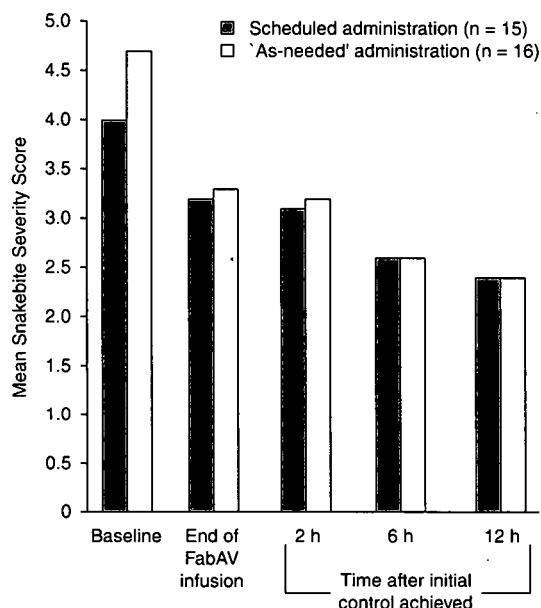


Fig. 2. Efficacy of intravenous crotalidae polyvalent immune Fab in patients with minimal or moderate envenomation with a North American crotaline. Snakebite Severity Score (primary endpoint) at various timepoints in a randomized, open-label, multicentre trial in which patients received 6 or 12 vials of crotalidae polyvalent immune Fab to achieve initial control, after which they received antivenom 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] **FabAV** = crotalidae polyvalent immune Fab.

normal platelet levels at follow-up (14% vs 56%; $p=0.04$). Abnormal fibrinogen levels at follow-up were seen in 14% versus 44% of patients receiving scheduled versus 'as-needed' antivenom.^[8]

... and other patient groups?

A non-comparative, observational, postmarketing study included patients of any age with crotaline envenomation of any severity; patients had been bitten by *Crotalus viridis helleri* (Southern Pacific rattlesnake) [n=9], *C. scutulatus* (n=4), *Crotalus mitchellii pyrrhus* (Southwestern speckled rattlesnake) [n=1] or *Crotalus ruber ruber* (Red diamond rattlesnake) [n=1].^[16] Crotalidae polyvalent immune Fab was effective in confirmed *C. viridis helleri* envenomation of any severity, thereby demonstrating cross-protection against a venom not used in its production.^[16] In patients bitten by *C. viridis helleri*, the median

Snakebite Severity Scores were 4 at baseline and 3, 3, 2 and 2 at 6, 12, 18 and 24 hours, respectively. A mean of 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.^[16] Snakebite Severity Scores also decreased over time in patients bitten by *C. scutulatus*, *C. mitchellii pyrrhus* or *C. ruber ruber*.^[16]

Crotalidae polyvalent immune Fab was effective in 28 patients with severe crotaline envenomation, according to the results of a retrospective, multicentre study,^[17] and rapidly reversed symptoms of neurotoxicity (e.g. fasciculations, weakness and paraesthesias) in three patients with rattlesnake envenomation.^[18] In addition, crotalidae polyvalent immune Fab halted progression of local venom effects in paediatric patients with crotaline envenomation in a retrospective, single-centre study,^[19] and Snakebite Severity Scores had stabilized or improved in all 12 paediatric patients with rattlesnake envenomation within 24 hours of crotalidae polyvalent immune Fab administration in another study.^[20]

What is its tolerability profile?

Treatment with intravenous crotalidae polyvalent immune Fab was generally well tolerated. The most commonly occurring adverse events included urticaria and rash, with patients experiencing early or late serum reactions.^[8]

For example, acute hypersensitivity reactions occurred during infusion in 6 of 31 patients (19%) with minimal or moderate crotaline envenomation who received 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, dyspnoea 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 salbutamol (albuterol).^[6]

In a retrospective analysis involving 247 patients with minimal to severe crotaline envenomation who received crotalidae polyvalent immune Fab,

15 patients (6%) had acute hypersensitivity reactions.^[17] Patients generally responded to slowing or discontinuing the crotalidae polyvalent immune Fab infusion and/or treatment with antihistamines and corticosteroids,^[17] apart from one patient who had a serious acute hypersensitivity reaction and required cricothyroidotomy for airway oedema.^[17] Three other patients in this study also experienced serious acute hypersensitivity reactions.^[17] 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.^[17]

Data from 11 studies in which patients received crotalidae polyvalent immune Fab were used to calculate combined estimates for the incidence of immediate hypersensitivity (8%; 95% CI 5, 11) and serum sickness (13%; 95% CI 7, 21).^[21]

What is its current positioning?

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 haematological 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.

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