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Antivenom Therapy for Snakebite

Overview of Snakebite

Venomous snakes bite several thousand people in the US each year, resulting in six deaths.[1] The incidence of venomous snakebite in Utah is 12-13 bites per year, 11 of which are from native, non-captive snakes.[2] The most common type of venomous snake in Utah is the "pit viper" or Viperidae. Snakes from the sub-family *Crotalina* represent 99% of all venomous snakebites in the US and include rattlesnakes, copperheads, and cottonmouths.[1]

Pharmacology/Toxicology of Snake Venom

The main function of snake venom is to immobilize, kill and predigest prey. This is accomplished through the effects of more than 50 enzymes and low-molecular weight peptides that have digestive, hemotoxic, and neurotoxic properties. The amount of digestive, neurotoxic, and hemotoxic components vary according to the species of snake and the geographic variables.[3] Therefore, the toxicity of the venom depends on the type of snake, geographic location and the amount of venom injected. The amount of venom injected during a snakebite is entirely controlled by the snake. In approximately 20% of snakebites no venom is injected (dry bite).[3-]

Local effects of envenomation may include pain, edema, erythema, petechiae, ecchymosis, hemorrhagic blebs and local tissue necrosis. Systemic effects may include nausea, vomiting, weakness, muscle fasciculations, diaphoresis, perioral and peripheral paresthesias, metallic taste, hypotension, rhabdomyolysis and coagulopathy. The hematologic effects are characterized by thrombocytopenia and/or hypofibrinogenemia. Progression of local and/or systemic symptoms is indicative of envenomation. Fang marks alone are not indicative of envenomation.[3]

Coaagulopathy

Coagulopathy is characterized by decreased fibrinogen, decreased platelets, and elevated prothrombin time. It occurred in approximately 75% of the envenomated patients who received CroFab®. Recurrent, persistent or late coagulopathy occurred in 53% of the patients. This is thought to be due to prolonged absorption of venom from depot sites. Furthermore, recurrent coagulopathy may persist for 1 to 2 weeks or more. The clinical significance of these abnormalities is not known. Recurrent coagulopathy occurred only in patients who experienced a coagulopathy during initial hospitalization. Monitoring for recurrent coagulopathy for one to two weeks should occur in patients with a coagulopathy at presentation. A recent retrospective study showed that Antivenin Crotalidae Polyvalent ACP (Wyeth) also carries a similar risk and incidence of recurrent coagulopathy.[6,8] Recurrent bleeding abnormalities may require additional antivenom treatment.[6] Patients should be educated concerning signs of bleeding and the importance of monitoring.

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Treatment Options

Once first-aid and supportive care have been instituted, a decision to use antivenom must be made. History is essential in this decision. Exotic snakebites may require the use of antivenom that is not commercially available in the US.[3] In the US, clinicians can locate antivenom with the help of a regional poison control center. Until recently, the only available antivenom for crotaline envenomation was ACP from Wyeth-Ayerst. In October 2000, a new antivenom, Crotalidae Polyvalent Immune Fab (CroFab®) from Protherics, Inc. was approved by the FDA for the management of patients with minimal to moderate North American rattlesnake envenomation. ACP is a mixture of venom-specific whole serum globulins (IgG) obtained from immunized horses. CroFab® is a mixture of venom-specific Fab fragments derived from sheep (similar to Digibind ®). The venom specific antibodies and Fab fragments bind the toxins in the snake venom, rendering them toxicologically inert. The body eliminates the antibody-toxin complex through the reticuloendothelial system.[5-7]

CroFab® versus ACP (Wyeth)

A comparison of the two products can be found in Table 1. Whole IgG molecules, especially of equine origin, carry the risk of anaphylaxis and serum sickness. ACP (Wyeth) is associated with a 25-50% incidence of acute allergic reaction and 50-100% incidence of serum sickness.[1] The risk of anaphylaxis and serum sickness is reduced by cleaving IgG derived from ovine sources into venom-specific Fab fragments, followed by purification. No anaphylactic reactions have occurred in patients who have received CroFab® to date. The risk of serum sickness is reduced with CroFab®. The data are limited and the possibility of anaphylaxis cannot be absolutely excluded. Appropriate precautions to treat immediate allergic reactions should be available prior to administration of either antivenom.[3-7]

(CroFab®) - Contraindications

CroFab® should not be used in patients with a known hypersensitivity to papain or papaya unless the benefits outweigh the risks. Papain, which is related to papaya, is the enzyme used in the Fab fragmentation process. Patients with known allergy to sheep protein are particularly at risk for allergic reactions.[6]

Table 1
Antivenom Products

	CroFAb®[6]	ACP (Wyeth)[5]
Animal of origin	Ovine (Sheep)	Equine (Horse)
Type of antibody	Fab fragments, affinity-purified	IgG, not well purified
Snakes venoms used in production	Four North American Crotalid species	Combination of 4 North and South American snakes
FDA Approval	**Approved for the treatment of mild to moderate envonomations from North American Crotalidae: Crotalus (rattlesnakes), Sistrurus (massasauguas or pigmy rattlesnakes), and Agkistrodon (copperhead and cottonmouth)**	**Use to counteract the toxic effects of various pit vipers including the following: Crotalus (rattlesnakes), Sistrurus (massasauguas or pigmy rattlesnakes), Agkistrodon (copperhead and cottonmouth), Bothrops (fer-de-lance) and Lachesis (bushmaster)**
Anaphylaxis	No incidences reported	Reported
Serum Sickness (Late serum rea tions	Infrequent	Frequent
Recurrent coagulopathy	Reported	Reported
Skin testing required	No	Yes
Cost	**Wholesale acquisition cost (WAC) $775/vial**	**AWP=$630.62/kit**

CroFab® Adverse Reactions

The most common adverse reactions reported in patients who received CroFab® are listed in Table 2. The majority of adverse reactions reported were mild or moderate in severity. Three patients had severe adverse reactions. One patient developed a recurrent coagulopathy requiring re-hospitalization and additional antivenom. Severe hives following treatment developed in another patient and one patient developed severe rash and pruritis several days post treatment.[6]

CroFab® Dosage and Administration

Antivenom dosage requirements depend on patient response. The recommended initial dose is 4 to 6 vials followed by a minimum one-hour observation. If "initial control" is not achieved (defined by arrest of local manifestations and return of coagulation profile and systemic signs to normal), an additional 4 to 6 vials should be repeated every hour until initial control is achieved. After initial control is achieved, it is recommended to give an additional 2-vials every 6 hours for up to three doses. In clinical trials, a maximum of 18 vials of CroFab® were used.[6] The average total dose infused in the clinical trials was 10.9 vials.[9]

CroFab® should be stored at 2-8°C. Each vial is reconstituted with 10 mL of Sterile Water for Injection USP. Reconstitution takes continuous gentle swirling for approximately 25 minutes. Further dilution with 250 mL of 0.9% Sodium Chloride USP and further mixing by gentle swirling is necessary. CroFab® should be used within 4 hours after reconstitution and dilution.[6]

Skin testing, which is required for ACP (Wyeth), is not required with CroFab®. The initial dose of CroFab® is infused intravenously over 60 minutes. The infusion should start at a rate of 25-50 mL/hour If no allergic reaction is evident, the infusion rate may be increased to 250 mL/hour. Patients should be closely monitored throughout the entire infusion.[6]

Summary

CroFab® is a new and promising treatment for mild to moderate North American Crotalid envenomation. Although allergic reaction and serum sickness cannot be dismissed, clinical studies to date have shown that CroFab® has an improved safety profile than that of ACP (Wyeth). Coagulopathic abnormalities in envenomated patients should be monitored closely as recurrence is possible for at least 2 weeks beyond envenomation.

The staff of the Utah Poison Control Center are available to consult on the management of snakebites. The UPCC has the staff and resources readily available to provide expert advice and guidelines concerning appropriate snakebite management and treatment. In addition, the UPCC collects data on exposures in Utah. Even if you do not require assistance, we would like to hear about your experience so that we can better monitor the safety profile with the new antivenom.

Table 2
Adverse reactions[6] to CroFab®

>10%	Urticaria, rash
5-10%	Pruritis, nausea, coagulation disorder
<5%	Back pain, chest pain, cellulitis, wound infection, chills, allergic reactions, serum sickness, subcutaneous nodule, hypotension, asthma, cough, increased sputum, anorexia, ecchymosis, myalgia, circumoral paresthesia, general paresthesia, nervousness.

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Public Education Materials

The UPCC is pleased to announce that Heather Foulger, MS, CHES has joined the staff as the new outreach education provider. Please contact her at (801) 585-7178 or heather.foulger@hsc.utah.edu to assist with your patient education needs. Poison prevention display boards, brochures, telephone stickers, emergency action cards, videos posters, and medicine look-a-like displays are available for checkout and purchase.

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