What Bit Him: An Expert Perspective on Snake Antivenom

Announcer:
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Here’s your guest, Dr. Mark Ryan.

Dr. Ryan:
Hi, I’m Mark Ryan. I’m the Director of the Louisiana Poison Control Center. I’ve been there for 27 years. I’m also an Assistant Professor of Clinical Emergency Medicine at Louisiana State University Health Sciences Center in Shreveport, Louisiana. I always like to start these talks by asking what animal is used in the production of CroFab? Some of the answers I get back are often quite funny. The most common answer is cow. No, it’s not cow. That’s bovine. Ovine, sheep. Sheep are the host animals used to produce CroFab. CroFab is produced using the venom from four snakes native to North America. Each type of snake chosen has unique characteristics in venom composition. The snakes are collected from various areas to ensure geographic diversity in venom use to produce CroFab. The four snakes used are the western diamondback, whose hemorrhagic venom is known to cause severe coagulopathy; the Eastern Diamondback, whose hemorrhagic venom is known to cause severe coagulopathy; the Mojavi rattlesnake, whose unique Mojavi toxins cause proteolytic and hemorrhagic effects and are known to cause neurotoxicity. The Cottonmouth or Water Moccasin is a major contributor to the overall number of bites occurring each year. While it’s unusual for bites from a Cottonmouth to cause systemic effects or coagulopathy, they do cause tissue damage that could result in long term or even permanent morbidity. Inclusion of Cottonmouth venom also provides overlapping coverage for the Copperhead; a Agkistrodon contortrix. Here’s a pop quiz. A patient presents to the emergency department. How do you know what kind of snake was involved? Ask questions. What was the patient doing when the bite occurred? Were they outside reaching under a brush pile? Were they walking outside at night with no shoes on? Were they picking up what they thought was a dead snake? Don’t do that. Did they see what color the snake was? Did it have a particular pattern? Are there fang marks present? Is there blood or plasma leaking from the wound; an indicator that envenomation has occurred? It’s not necessary to know the species of a pit viper because CroFab is approved to treat all North American pit viper envenomations and is effective in adult and pediatric patients. CroFab is produced using a unique process that results in a purified mixture of antibody fragments or FABs. Here’s how it’s done. Sheep are divided into four flocks. Each flock of sheep are then immunized with the venom of one of the four snakes seen on the screen. Four flocks of
sheep, four snake venoms. After a period of time during which antibodies to the venom are produced, serum from each group of sheep is harvested. Each of the four serum batches undergo the affinity purification process separately. The whole immune globulin IgG is digested using the enzyme papain and to cleave the individual antibody fragments from the Fc portion. The Fc portion is the part which may cause allergic reactions. So removing the Fc reduces the incidence of hypersensitivity reactions. The FAB fragments are important because they bond to and neutralize circulating venom. Small individual antibody fragments are rapidly distributed throughout the body. These antibody fragments with the Fc portion removed are cleared from the body faster, decreasing the risk of hypersensitivity. At this point of the production process, the antibody fragments are further purified by using column chromatography, a process that allows for harvesting the individual antibody fragments while removing unwanted elements. At this stage, there are four monospecific antivenoms. Monospecific meaning made from the venom of a specific type of snake. Only when the four monospecific antivenoms are mixed, freeze dried, and packaged, can it be call CroFab. The product is a polyclonal antivenom, a mixture of the four monospecific antivenoms. How does it work? CroFab works by binding too and neutralizing venom. Due to the local edema that occurs around the bite site, venom can be concentrated in that area to be slowly released into circulation. CroFab is able to penetrate tissue more readily, helping to neutralize venom in the area of the actual bite. It also helps to redistribute venom toxins away from target tissues and facilitates the removal of the venom, antivenom complex from the body.

Before CroFab was approved for use by the FDA in 2000, two premarketing trials were conducted. They were named Tab1 and Tab2. Tab1 had 11 patients enrolled and Tab2, the second and pivotal trial, had 31 patients enrolled. As you can see in the charts, 41 of 42 patients in the trials achieved initial control. Initial control means that the pretreatment signs and symptoms of envenomation were arrested or improved after treatment, as judged by the investigator. 95% of patients showed a clinical response to CroFab therapy at one hour after initial control was achieved, which means that there was a sustained clinical response and initial control was not lost. A snake bite severity score was used for validation. It was compared to the investigators clinical assessment. The information gained from these trials was important because FAD antivenom was new, and at that time, many questions remained as to whether the clinical effects would be transient or sustained. While bites from one of the five subspecies of Copperhead snakes found in the U.S. are very common, Copperhead bites rarely present with coagulopathy, thrombocytopenia, or systemic effects like headache, nausea, or vomiting. Death from a Copperhead bite is extremely rare. However, there are reported cases of long term and permanent tissue damage and limb dysfunction. There were no Copperhead bite patients enrolled in either of the two initial CroFab trials because it was deemed unethical at the time given the experience with the old Wyeth antivenom. At that time, treating with antivenom was often worse than the venom effects. Recently, a placebo-controlled study was conducted to assist the recovery from limb injury in Copperhead envenomations. The study design called for patients to be randomized to receive either CroFab or placebo in a ratio of 2:1. The study authors used a patient-specific functional scale to measure the patient's level of dysfunction at various times after the bite. The patient was asked to identify three activities that they deemed to be important to them. Examples included walking up stairs, brushing one's teeth, or maybe swinging a hammer for a carpenter. It's very common following a snake bite for an affected limb or appendage to have edema occur when being used. The remedy is to stop the activity, elevate the affected area, and rest. Repeat surveys were conducted to see if improvement had occurred in the activities identified by the patient. The primary endpoint of the study was improved limb function on day 14, post-envenomation for the CroFab treated patients when compared to the placebo group. The patients who were treated with CroFab had significantly higher scores on the patient specific functional scale on day 7 and 14 post-bite. The CroFab patient showed improved limb function versus the patients who received placebo on day 14. In this study, the observed safety and the common adverse events noted were consistent with previous CroFab experience. Pain is a complaint voiced by the majority of snakebite patients. It's often described by the patient as being on the extreme end of various pain measurement tools. These patients may have pain that lasts for day or weeks. Often prompting the treating physician to prescribe opiate pain medication for an extended period. The Copperhead study showed significantly reduced opioid use in a study by patients treated with CroFab by day 14 and was sustained through day 24. You may notice an absence of CroFab treated patients using opioids on day 21 and day 24 with use again appearing on day 28. The one patient in the CroFab arm represented on day 28 on the chart, was discovered to have falsified a claim of snake bite. So his use of opioid medications was not related to venom effects. The data presented clearly shows a decreased duration of pain medication use in snake bite patients treated with CroFab. Any biological 

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product has the potential to cause reactions. Of the 42 patients enrolled in the clinical trials, 12 experienced a reaction; primarily rash, urticaria, and pruritus. Two patients developed severe allergic reactions following treatment. One of the two discontinued CroFab due to an allergic reaction. Mild reactions could be managed by stopping the CroFab infusion, treating with appropriate medications like antihistamines and steroids, and then restarting the infusion to run at a slower rate. It's important to continue the infusion if possible to bind circulating venom decreasing the possibility of long term or permanent effects. Notice that the premarketing incidence of adverse effects is much greater than the postmarketing incidence. Six of the 42 patients in the two clinical trials experienced an early serum reaction and two experienced a late serum reaction. A postmarketing retrospective study of 1,340 adult and pediatric patients who received CroFab was conducted. In this study, only 1% of patients had an acute hypersensitivity reaction and even fewer, six, or 0.4% experienced delayed hypersensitivity. Why such a large difference in pre and postmarketing data? Prior to approval, an early lot of study drug was shown to be incompletely purified, which resulted in some residual Fc remaining in the vials leading to a higher incidence of hypersensitivity reactions than observed post-approval. Subsequently, the purification process was improved, which resulted in the safety profile observed today; medically significant bleeding. Sounds very serious, and it can be. Patients envenomed can develop serious coagulopathy. Platelets and fibrinogen can be decreased to near zero and INR can be increased. A clinical picture that would suggest the possibility of bleeding is great. Late bleeding after a snake bite is feared, but thank goodness it’s an uncommon outcome. Dr. Eric Lavanos led a group that evaluated 19 published studies in an attempt to estimate the risk of medically significant bleeding. Over a thousand case records were evaluated by the group. Less than 1%, nine patients, experienced late bleeding. Five of those nine or 0.5% experienced medically significant late bleeding. Questions are often asked about antivenom use in special populations. Can it be given to a pregnant woman? It’s been shown that venom can cause placenta abruptus or miscarriage. So if a pregnant woman is showing signs of envenomation, CroFab should strongly be considered. CroFab is classified as a pregnancy category C. A very common question is, how long should the dose be reduced for a pediatric patient? The answer is none. CroFab is administered to neutralize circulating venom and no dosing alterations are required for either pediatric or geriatric patients. A concern from years ago centered around mercury. When CroFab was approved it contained thimerosal, a mercury-based preservative. Thimerosal was removed several years ago, eliminating the concern about heavy metal presence in the product. Stocking guidelines of antitoxins and hospitals. You work in a hospital that has an emergency department. You live in a state where venomous snakes are found. There are only a few states that don’t have venomous snakes. I think very north and one state out at the Pacific Ocean. If you have snakes, you should stock antivenom. The paper shown is a very good reference for many types of antidotes that hospitals should consider stocking. For CroFab, the expert consensus guidelines recommend stocking 18 vials, enough to treat one patient if your facility expects to admit the patient and provide the full course of antivenom on site. If your plan is to give the initial dose then transfer to a facility with a higher level of care, the recommendation is to stock at least 12 vials. It is important that you look at your particular hospital and the number of bites treated there each year. If you treat more bites, you should consider stocking more antivenom. If you could have multiple bite patients in a single day, more is warranted. It is also a good idea to have a plan in place to obtain more antivenom, maybe bowering from a nearby facility. A patient with severe envenomation may require more than 18 vials. When time is tissue, why risk it? CroFab has an almost two-decade history of providing quick and reliable control of envenomation effects. There is a demonstrated safety profile of low incidence of hypersensitivity reactions. CroFab can halt local effects, resolve systemic effects, and reduce coagulation abnormalities. With over 50,000 patients treated, clinicians should feel comfortable administering CroFab. If the patient has progressing envenomation effects, treat. Treat early. Time is tissue. Don't wait. Remember, CroFab will not reverse any local edema and tissue destruction that has occurred prior to treatment. Don't let venom effects get out of hand before deciding to treat. Thank you for your time.
pediatric patients with North American crotalid envenomation. The term crotalid is used to describe the Crotalinae subfamily (formerly known as Crotalidae) of venomous snakes which includes rattlesnakes, copperheads and cottonmouths/water moccasins.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Do not administer CroFab® to patients with a known history of hypersensitivity to any of its components, or to papaya or papain unless the benefits outweigh the risks and appropriate management for anaphylactic reactions is readily available.

WARNINGS AND PRECAUTIONS

Coagulopathy: In clinical trials, recurrent coagulopathy (the return of a coagulation abnormality after it has been successfully treated with antivenin), characterized by decreased fibrinogen, decreased platelets, and elevated prothrombin time, occurred in approximately half of the patients studied; one patient required re-hospitalization and additional antivenin administration. Recurrent coagulopathy may persist for 1 to 2 weeks or more. Patients who experience coagulopathy due to snakebite should be monitored for recurrent coagulopathy for up to 1 week or longer. During this period, the physician should carefully assess the need for re-treatment with CroFab® and use of any type of anticoagulant or anti-platelet drug.

Hypersensitivity Reactions: Severe hypersensitivity reactions may occur with CroFab®. In case of acute hypersensitivity reactions, including anaphylaxis and anaphylactoid reactions, discontinue infusion and institute appropriate emergency treatment. Patients allergic to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain may also have an allergic reaction to CroFab®. Follow-up all patients for signs and symptoms of delayed allergic reactions or serum sickness (e.g., rash, fever, myalgia, arthralgia).

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% of subjects) reported in the clinical studies were urticaria, rash, nausea, pruritus and back pain. Adverse reactions involving the skin and appendages (primarily rash, urticaria, and pruritus) were reported in 12 of the 42 patients. Two patients had a severe allergic reaction (severe hives and a severe rash and pruritus) following treatment and one patient discontinued CroFab® due to an allergic reaction. Recurrent coagulopathy due to envenomation and requiring additional treatment may occur.

To view the full prescribing information visit Crofab.com.

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