

Snake Bite Envenomation in Illinois:

Scope of Problem and Issues of Antivenin Stocking and Procurement

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Introduction:

The Illinois Poison Center (IPC) has received several inquiries regarding the availability of snake antivenin products and suggested guidelines for adequate stock quantities. This article presents information regarding the incidence and epidemiology of snakebites in Illinois; a brief overview of the toxicity and medical management of symptomatic snake envenomation; and a discussion of current antivenin stocking recommendations, along with strategies for hospital preparedness. As snakes are currently in cold weather hibernation, now is an opportune time for hospitals to prepare for the 2003 snake bite season.

Background:

There are thirty species of poisonous snakes native to North America. Most are members of the newly-classified Viperidae family, subfamily Crotalinae family, which include the rattlesnakes, copperhead and water moccasins. These are also known as "pit vipers" due to the presence of a pit-like depression of the skin behind the nostril, which acts as a heat-sensing organ. Also, there is the presence of a pair of hollow fangs that project the toxic venom into the prey, which are shed and replaced periodically. Other common characteristics include eyes that have vertical elliptical pupils and, in the case of rattlesnakes, a hard keratin rattler at the tail.

According to the Illinois Department of Natural Resources, four members of the Crotalinae family are endogenous to Illinois. They are the copperhead (*Agkistrodon contortrix*), the timber rattler (*Crotalus horridus*), the water moccasin (*Agkistrodon piscivorus*) and the eastern massasauga (*Sistrurus catenatus*). The copperhead, timber rattler and water moccasin inhabit the southern one-third of the state, while the eastern massauga lives in scattered locations within the counties of Madison, Clinton, Piatt, Knox, Warren, Will, Cook and Lake. These venomous snakes are not aggressive and tend to bite people only when stepped on, picked up or cornered. It is important to note that even recently killed snakes may still deliver a venomous bite. Venomous snake bites have also been reported to the IPC because of collectors keeping illegal exotic specimens imported from overseas, or crotalines not native to Illinois. For instance, a

September 2002 news media report revealed the break-up and arrest of a ring of illegal reptile vendors in an unincorporated area of Streamwood, Illinois. Included among the reptiles seized were two timber rattlesnakes and three copperhead snakes. Also, in December 2001, an arrest in Will County resulted in a seizure of one monacled albino cobra and 10 other venomous snakes.

Incidence and Epidemiology:

Approximately 6,000-8,000 venomous snakebites occur each year in the United States. Most occur in the southern or western states. Deaths are rare, ranging from five to 15 deaths per year. Approximately 20 percent of bites are considered to be “dry bites,” where a bite has occurred but no venom has been injected into the victim. Most bites occur between the months of May and October. Children, intoxicated individuals, snake handlers and collectors are frequent victims. Over half of the bites occur while the individual is purposely handling a known venomous snake.

A retrospective review of all snakebites reported to the IPC was undertaken for the 34-month period from January 1, 2000 through October 31, 2002. A total of 241 cases were identified. The vast majority of these cases were from non-venomous snakes, such as the common garter snake (*Thamnophis sirtalis*), a black rat snake (*Elaphe obsoleta*), and a corn snake (*Elaphe guttata*), in which these bites resulted in minimal wounds. Forty-eight (20 percent) calls involved bites from pythons and boa constrictors, which are non-venomous bites; however, these snakes’ can inflict extremely painful bite injuries. A total of 13 (5.4 percent) cases involved bites from a crotaline snake in Illinois. Five of these patients did not receive any antivenin product and were managed with only conservative measures. Eight patients received Wyeth antivenin crotalidae polyvalent (ACP) product, however, two patients experienced immediate anaphylaxis and administration of the antivenin was discontinued. Of the remaining six cases the median number of vials given was 10, with a range of five to 20 vials. One patient was transferred to an out-of-state tertiary care institution where a total of 18 vials of CroFab® was administered.

In our series of 13 crotaline envenomations, all patients were male. The median age was 36 years old (range 16 to 78 years). Eleven of these cases were reported between the months of May through October, which is the peak time period in which most bites occur. Five of thirteen cases (38 percent) occurred within a residential dwelling. In two of the exposures, symptoms occurred when coming in contact with the fangs of a dead rattlesnake. Eight victims were bitten as results of attempting to handle,

move or give water to the snake. All patients were evaluated in emergency departments with ten out of the 13 victims being admitted for further treatment and observation.

The most common crotaline envenomation in Illinois involved copperheads (five out of 13). One bite each from a timber rattlesnake and an eastern massauga were also reported. In two cases where the exact identity of the crotaline was unknown, local signs, symptoms and hypotension in one case, and the presence of snake “rattles” in another, were evidence of species from this family of snakes. It should be pointed out that in three out of the eight cases where antivenin was administered and one case where no antivenin was given, the snake implicated was not native to Illinois. These included a western diamondback (*Crotalus atrox*), tiger rattlesnake (*Crotalus tigris*), Colorado sidewinder (*Crotalus cerastes*), and an unknown Colorado rattlesnake. Additionally, in December 2001, the IPC was consulted regarding a patient who was bitten by an African gaboon viper (*Bitis gabonica*), one of the most highly toxic snakes in the world. The IPC coordinated procurement of antivenin using state police from two states and securing Samir® vaccine that was stocked in two large zoos with exotic reptile houses. These incidents point to a growing problem of illegal sales of highly toxic, exotic reptiles and the need for hospitals to be prepared with contingency plans to handle these rare-poisoning events.

The following table summarizes the eight crotaline envenomations where antivenin was administered:

Table 1: Snake and Envenomation Cases Reported to IPC

Type of Snake	Signs and Symptoms	No. of vials used	Circumstances
Western Diamondback	-swelling/pain from hand to axilla -sinus tachycardia	20 ACP	-pet snake: cleaning cage
Timber Rattlesnake	-swelling/pain from hand to elbow -hypotension, paresthesias, ecchymosis, anxiety, diaphoretic, thrombocytopenia -anaphylaxis: respiratory distress and urticaria	20 ACP	-“amateur herpetologist” snake watching in woods
Colorado Desert Sidewinder	-swelling/severe pain from hand to shoulder -mild paresthesias	10 ACP	-pet snake: cleaning cage
Copperhead	-swelling of hand -mild cellulitis -anaphylaxis: respiratory distress	1 ACP	-tried to move snake

Copperhead	-swelling of hand -vomiting, mild bleeding, ecchymosis, diaphoretic, sinus tachycardia, hypotensive	5 ACP	-moving/collecting rocks
Rattlesnake (unknown)	-swelling from hand to elbow -erythema, numbness, pain, hypotensive	11 ACP	-catches snakes often in backyard
Eastern Massasauga	-swelling/pain of finger -elevated CPK levels -hemorrhagic bullae -headache, arm/chest tenderness	9 ACP	-tried to move snake with stick
Arizona Tiger Rattler	-local pain, redness, bleeding -CPK 16,000 -PT 120 -fibrinogen <20 -anaphylaxis from ACP	1 ACP 18 CroFab – out of state hospital	-playing with dead snake transported in a cooler

Clinical Effects and Management:

Crotaline venom is a complex mixture of various proteins, peptides, lipids, carbohydrates and enzymes and contains RNAase and DNAase, kinins, leukotrienes, histamine, phospholipase, serotonin, hyaluronidase, acetylcholinesterase, collagenase, and metallic ions. Crotaline envenomations are associated with a variety of local tissue effects and generalized systemic complications.

Local tissue effects at the bite site include pain, edema, erythema, occasional local bleeding, ecchymosis, bleb formation, tissue necrosis, lymphangitis, and sloughing. Compartment syndrome requiring fasciotomy is uncommon.

Systemic signs and symptoms may include hypotension, shock, respiratory failure, mental status changes, weakness, light-headedness, diaphoresis, paresthesias, taste changes, nausea, vomiting and diarrhea. Coagulopathy may occur with ecchymosis, purpura, petechiae as well as laboratory evidence of thrombocytopenia, prolongation of PT and PTT, decreased fibrinogen and/or elevated fibrin split products.

All patients with crotaline envenomation should be evaluated in a health care facility as soon as possible. Immobilization of the affected limb, positioned at a level lower than the heart, is recommended. Do not apply ice, heat, oral suctioning, tight tourniquets, electric shocks or make incisions to the bite site. In the emergency department, obtain and monitor vital signs, EKG, CBC, PT/PTT, urinalysis, electrolytes, CPK, fibrinogen, fibrin-split products, as well as a type and cross. Tetanus prophylaxis should be given if indicated. Provide good wound and supportive care. Administer

intravenous crystalloid fluids and begin vassopressors for hypotension if necessary. Broad spectrum antibiotics may be considered if evidence of infection develops. Blood products may be necessary in patients with severe coagulopathy.

Crotaline antivenin is considered the mainstay of therapy for moderate and severe snakebite envenomation. Two products are currently available in the U.S. to treat crotaline envenomation. They are Antivenin (Crotalidae) Polyvalent by Wyeth Labs (equine origin) and Crotalidae Polyvalent Immune Fab, CroFab® manufactured by Protherics Inc. and marketed by Savage Labs (ovine origin). Indications for antivenin administration include evidence of coagulopathy, systemic venom effects or progression of local tissue injury. Administration of the antivenin early in the course of envenomation has been proven most effective. Moderate envenomations may require initial doses of 10 to 20 vials of ACP, while severe envenomations may require 20 or more vials. Using CroFab®, moderate envenomations require 10 to 12 vials (4-6 vials initially, followed by 2 vials every 3 hours for 3 doses), while severe envenomations may require 18 or more vials. Antivenin dosing is generally continued until control of local, systemic and coagulation abnormalities has been established.

Since ACP is of equine origin, allergic reactions including urticaria, delayed serum sickness and life-threatening anaphylaxis may occur. The product literature advises a skin test prior to antivenin administration. The product must be administered in a critical care setting with prompt administration of epinephrine, antihistamines and steroids for hypersensitivity reactions. The potential for serious allergic reactions to the CroFab® product is less likely to occur. Skin testing is not necessary; however, administration in a critical care setting is advised. The sheep derived CroFab® product is comprised of a purified Fab fragment with the Fc fragments being removed, while the horse derived ACP contains whole IgG antibodies and is only partially purified.

In the February 2001 *Annals of Emergency Medicine*, the potential for hypersensitivity reactions of both antivenin products was compared. A review of past retrospective series of the ACP product showed hypersensitivity incidence rates ranging from 23 percent to 56 percent. Although no published cases can be cited in the literature, the authors are aware of three deaths due to ACP-induced anaphylaxis. In research trials, the overall incidence rate of adverse reactions to CroFab® was six out of 42 patients (14.3 percent). This included four cases of urticaria and two cases of urticaria and bronchospasm in patients with known reactive airway disease. Anaphylaxis has not been reported with CroFab®, however experience is too limited to

conclude that anaphylaxis will not occur. Most cases regarding CroFab® were mild to moderate in presentation, while the most severe cases were treated with typical measures.

Serum sickness is a common complication of ACP, with reported incidence rates as high as 75 percent to 86 percent. In contrast, the incidence of serum sickness from CroFab® in early trials was reported to be six out of 38 patients (16 percent). Later trials using more highly purified products report a lower incident rate of five percent.

Snake bites by copperheads usually result in mild to moderate envenomations. Treating such envenomations with the ACP product is a difficult clinical decision, as treatment may not warrant the risk of serious life-threatening anaphylactoid reactions. Early CroFab® trials did not include copperhead bites; therefore, efficacy and safety of this product for the treatment of bites from this species were unclear. At the September 2002 North American Congress of Clinical Toxicology (NACCT), a multi-center observational case series of 23 symptomatic patients envenomated by copperheads and treated with CroFab® was presented. Most patients had moderate signs of envenomation. In 19 of these patients, progression of swelling was completely halted within one hour of the antivenin infusion and did not reoccur. The mean antivenin dose for initial control was 4.4 vials (range 2-8 vials). One patient developed delayed coagulopathy that appeared to respond to repeated administration of CroFab®. One patient experienced a mild rash and wheezing that resolved without treatment. The authors concluded that it was reasonable to treat victims with progressive swelling due to copperhead snakebites with CroFab®.

Antivenin Shortage:

CroFab® received FDA approval on October 2, 2000. On March 20, 2002, Protherics Inc., of Savage Laboratories, announced a potential shortage of CroFab® antivenin for the 2002 snakebite season. The shortage was a result of a short-term problem with the production process. On August 13, 2002, Savage Labs announced the release of 2,718 vials of CroFab®, which represented the fourth shipment of CroFab® this year. Hospitals who were in short supply could call the Rocky Mountain Poison Control Center CroFab® Medical Line at 1-877-377-3784, who provided a list of nearby hospitals that may have CroFab®. Savage Labs could be contacted at 1-800-231-0206 regarding supplies of CroFab®.

ACP was introduced by Wyeth Labs in 1954. It was reported that Wyeth Labs had discontinued the production of its ACP product in January 2001, but had later

resumed the manufacturing process. Until the shortage was alleviated, Wyeth distributed product to end-users only. In an emergency situation, hospitals were able to obtain 10 vials of ACP by calling Wyeth Labs at 1-800-666-7248 (after hours: 1-610-971-5400).

In early November 2002, a representative of Savage Labs stated that a shipment of Crofab® would be available for distribution in late November. At the same time, a Wyeth Labs representative stated that ACP would be available to distributors in spring 2003.

According to the 2002 Drug Topics Red Book, the average wholesale price (AWP) of ACP is \$585.58 per vial. The AWP for Crofab® is \$1,937.50 for a two vial kit. Keep in mind that these prices were published before these two product shortages were announced and therefore are subject to change.

According to their respective manufactures, the shelf life after manufacture of ACP is 60 months and that of Crofab® is 30 months.

Antidote Survey:

Between fall 2001 and spring 2002, the IPC conducted a survey of antidote stocking in Illinois hospitals. Pharmacies were queried regarding the numbers of vials of ACP and CroFab® in pharmacy inventory. The results from 163 responding hospitals are summarized and found in Table 2. It is important to note that this data was compiled prior to the announced product shortages this year.

Table 2: Crotalinae Antivenin Stocks in 163 Illinois Hospitals

Product/Manufacturer	Antivenin (Crotalidae) Polyvalent					
	Wyeth Labs					
Number of Vials	0	1-4	5-9	10-14	15-19	20 +
Number of Hospitals	105	37	14	6	0	10

Product/Manufacturer	Crotalidae Polyvalent Immune Fab, CroFab®			
	Protherics			
Number of Vials	0	1-4	4-6	7 +
Number of Hospitals	160	2	0	1

Strategies for Antivenin Preparedness:

Snake envenomation in Illinois is an uncommon, yet potentially critical poisoning event requiring immediate medical intervention in an emergency department and rapid procurement of sufficient amounts of antivenin products. Hospitals located in areas of the state where bites by native crotalines are endemic especially should be prepared to manage these events. Institutions in larger urban environments should have plans to manage envenomations caused by non-native or native snakes kept as pets. Recall that in 36 percent (five out of 14) of snakebites reported to the IPC, non-native or exotic snake species were implicated. Occasionally snake bite victims are transferred to larger or tertiary care medical centers long distances from the original incident site.

Since it is neither reasonable nor cost effective for every hospital in the state to inventory large stocks of these rarely used and expensive products, a few antidote procurement strategies include:

1. Local health system pharmacist associations may initiate and implement an antivenin sharing/borrowing plan in a given region of the state.
2. If no such association exists in a particular locality, pharmacy managers or pharmacy and therapeutic committee members should network with neighboring institutions to develop policies and procedures for a sharing/borrowing plan.
3. Emergency department managers of smaller rural or community hospitals should consult with their tertiary care institutions and decide where critically envenomated patients would be transferred to assure antivenin preparedness.
4. The IPC maintains the results of confidential antidote surveys and can assist in the location of antivenin stock, if notified.
5. Pharmacy managers of hospitals located near zoos that include reptile houses may make arrangements for antivenin sharing/borrowing with the zoo's reptile curator.
6. There is currently a national shortage of antivenin. Until the problem is resolved, it is suggested that hospital pharmacy staff not discard outdated products. Consideration may be made to administer expired products to seriously envenomated patients if no other source is available in a reasonable time frame.

In answer to the question 'How much is enough?', there are no state, federal or accreditation agency mandates for minimal stock quantities of antidotes. As a general rule, the IPC recommends having enough antidote on hand to start an initial adult dose. This would therefore entail stocking either 10 vials of ACP or 4-6 vials of CroFab®. This is only enough for initial treatment, so plans for rapid mobilization of more products should be in place in the event more is necessary.

Readers may obtain a free copy of the Illinois Poison Center Antidote List which include suggestions for stocking 27 poison antidotes by calling the IPC at 1-800-222-1222 (option 3 on the menu).

The IPC is the only certified, regional poison center in Illinois, serving more than 12 million residents in 102 counties – 24 hours a day, 365 days a year – via a national, toll-free number, 1-800-222-1222. Calling the toll-free hot line will connect callers with their designated local poison center at any time, from anywhere in the U.S.; all calls placed in Illinois are routed to the IPC. Staffed by pharmacists, physicians, nurses and poison information providers, the IPC provides poison prevention information and treatment advice to the public and health care professionals on alcohol or drug misuse, medication problems, bites and stings, occupational accidents and other poisonings.

The IPC is a program of the Metropolitan Chicago Healthcare Council, an association of more than 130 hospitals and health care organizations working together to improve the quality of health care services.