NEWS FROM THE PIT

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History of Pitviper Antivenom in the United States

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Snakebite Burden: Simultaneously a Major Neglected Tropical Disease & Rare Disease

On a global scale, the World Health Organization has declared venomous snakebites a neglected public health problem, and a significant source of preventable morbidity and mortality. Domestically, less than 8,000 people are bitten annually in the United States. Under the 1983 Orphan Drug Act, this classifies venomous snakebites as a rare disease, which was defined as “any disease affecting less than 200,000 people in the United States”. This law came about to incentivize drug developers to research treatments for rare diseases. From a business perspective, investing in the study of rare diseases brings about concerns over profitability, given the high costs of development and the limited number of patients that will ultimately be using the treatment.

NEWSLETTER HIGHLIGHTS

Image 1: Sidewinder (*Crotalus cerastes*)

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"The physician who treats a patient with a drug and the patient recovers assumes that which is not necessarily true; that the patient recovered because of the drug, when in reality all that the physician has proved is that the drug did not kill the patient" (Fontana)

Envenomation: Inherently Challenging Disease State to Study Clinically

Despite being among the oldest sources of significant morbidity and mortality for humanity, venomous snakebites are one of the least understood diseases, and persist as a challenging public health threat to address. In large part, this is because venom is not a single toxin, but rather a collection of toxins whose composition is highly variable. The presence or absence of specific toxins varies not only between different species, but even among the same snake as it ages. Venom variation results in clinical effects that do not consistently manifest as a singular uniform disease process, complicating medical research. Instead, a broad spectrum of signs and symptoms are possible following envenomation. When a venomous snake strikes, venom is usually deposited subcutaneously. Several factors will affect the specific absorption rate, but detectable levels of venom can be found for at least 2-3 weeks, regardless of receiving antivenom. Which poses another challenge to research, as the onset of symptoms post bite can vary from within seconds to several hours later. Like most toxins, venom toxicodynamic effects are dose dependent, or in other words, the more venom deposited the worse the clinical effects are likely to be. Depending on venom composition, the clinical severity of each sign and symptom post envenomation may vary from trivial to life threatening. To date, no predictive model of the acute disease process exists for venomous snakebites, challenging researchers and leaving emergency department providers at a loss for knowing how severe the envenomation will become.

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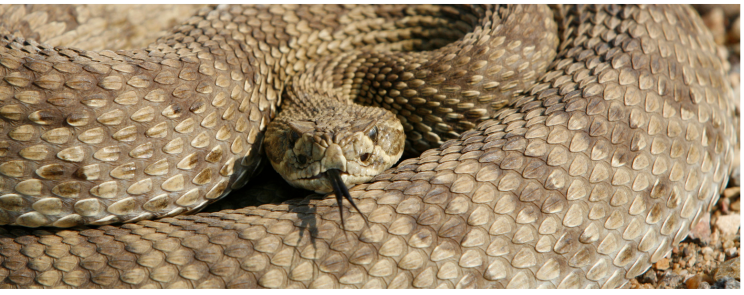
Antivenom: Overview & Mechanism of Action

Medical advances in treatment have altered our perception regarding the potential severity from pit viper envenomation. Arguably, antivenom has been credited for being the most responsible factor for decreasing mortality. In simple terms, antivenom is made by injecting venom into a host animal for the purpose of developing venom antibodies. These antibodies are later collected and purified, eventually becoming the product we refer to as antivenom. Mechanistically, antivenom is nothing more than antibodies that bind to venom components. Antibody binding can result in venom neutralization by altering the molecular structure and disrupting structure-function relationships, or by blocking enzymatic active sites. The extent and cross reactivity of this binding, as well as the relationship between binding and venom neutralization, are both areas of debate. Generally, antivenom readily neutralizes venom components responsible for coagulopathy. By contrast, the local tissue injury caused by venom will typically fail to reverse despite administering antivenom. While poor antivenom binding may be related, recognition of the various secondary effects venom has on endogenous systems provides a simpler answer as to why antivenom is routinely unable to arrest progressive tissue injury. When treatment is successful, the natural course of the envenomation becomes altered. In general, the earlier the progression of symptoms can be arrested, the less tissue injury that develops and the better the patient outcome. To better understand our modern medical practices, we are going to use this month's newsletter to take a stroll through the history of antivenom in the United States, separating periods in time by antivenom availability.



Medical Care & Mortality Rates Prior to Antivenom

Prior to the 1950's, which was when antivenom therapy became widely available, pit viper envenomation was routinely an acutely life-threatening event where simply surviving was considered a favorable outcome. Some poor outcomes can be ascribed to the "treatments" reported during this period, which included alcohol (oral/injected), strychnine, quinine, Bibron's antidote (bromine compounds), carbolic acid, enemas, cauterization, amongst many others. Sadly, reports from the period suggest that some patients, particularly children, likely died because of massive alcohol poisoning rather than envenomation. With the primary focus on survival, not much was reported in this era beyond mortality estimates and papers self-promoting various "treatments". Among what can be found, includes a 1926 report published by the United Fruit Company titled "The snakebite problem in the United States and in Central America". This report was prepared by Afranio do Amaral, a Brazilian herpetologist and Director of Antivenin Institute of America at the time. During the summer of 1925, he traveled throughout the US, especially in the south and the west to determine "how serious the snake-bite problem is in those sections". In his report, he found mortality rates ranging from 10-35% by geographic region, where the highest mortality rate and greatest incidence of bites both occurred in the southwest. In a more recent, albeit still older AzPDIC study, we reported mortality prior to antivenom and intensive care units as 5-25%, and less than 1% at the time of the study (Dart, 1992). Although the role of antivenom is widely accepted, it is important to note that other important advancements in health care such as emergency departments, EMS transportation, and critical care units, were also introduced during this time.

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1890-1953: Antivenom Origins & Prototype Generation

Before we transition to discussing times during which antivenom has been widely available, it is worth discussing the origins of antivenom. The premise for antivenom began in 1890, from the field of immunology when Emil Von Behring and Shibasaburo Kitasato developed serum therapy against diphtheria and tetanus, winning a Nobel Prize. According to historical legend, it was shortly afterwards when the French physician Albert Calmette, who was distributing vaccines against rabies and smallpox through the Pasteur Institute in Sài Gòn, would witness cases of fatal envenomation by the Indian cobra (*Naja naja*). After returning to France, Calmette would apply what was discovered with bacterial toxins, and immunize rabbits with cobra venom, ultimately producing the first cobra antivenom. Interestingly, it was also around this same time when Henry Sewall published his success developing the first rattlesnake antivenom, by inoculating pigeons. This obviously begs the unanswered question of, which of these two gentlemen deserve the honor of being remembered as the inventor of antivenom. Calmette put forth the idea that cobra antivenom may be beneficial for pit viper envenomation, although in 1909 this would be challenged. Hideyo Nogughi, a Rockefeller Institute researcher, proposed that the United States needed their own antivenom, one made specifically for North American pit vipers. Progress wouldn't start to happen until 1926, when some toxinologists would collaborate with the United Fruit Company, creating the Antivenin Institute of America. With some help from the H.K. Mulford Company, in 1927 they were able to introduce the first "North American Anti-Snake Bite Serum", Antivenin Nearctic Crotalidae. Despite being praised in medical journals at the time, the Mulford antivenom would not go on to be an overwhelming humanitarian or commercial success. Over the next 26 years the Mulford Co. developed two additional varieties of snake antivenom, Antivenin Bothropic (genus Bothrops), and Antivenin Cascabel (tropical rattlesnake).

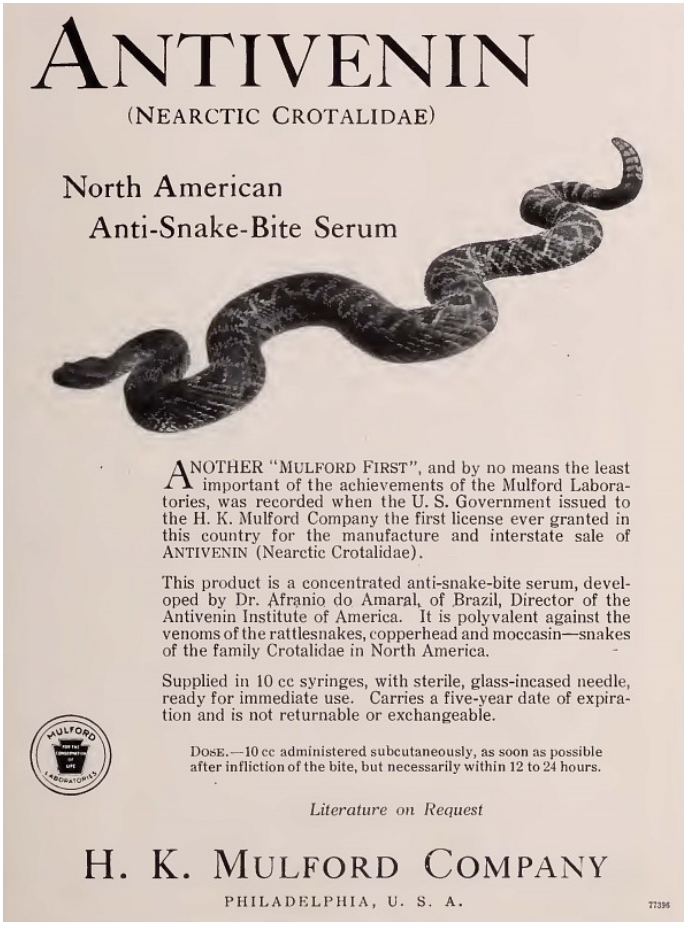

Photo above: Mulford's Antivenin advertisement. Photo courtesy of the Smithsonian Institute.

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1953-2002: Era of Wyeth® & Cautious Antivenom Administration

Shortly after its release, Wyeth® antivenom would effectively replace the Mulford antivenom. Despite increased availability, antivenom use would remain limited throughout the Wyeth® era. Primarily, this resulted from concerns regarding reported risks of life-threatening anaphylaxis (23%) and serum sickness (85%), a delayed onset flu-like syndrome. Given the drugs poor safety profile, physicians were forced to critically consider the risk to benefit ratio, before making the decision to administer antivenom. This inherently would delay treatment, allowing further venom injury to occur in the interim. During this period, acute hospital care typically lasted 2-5 days. Wyeth® antivenom was administered in 2-15 vial increments, being titrated to the total dose needed, which was determined when the advancing tissue injury arrested as well as resolution of coagulopathy. When follow-up visits were scheduled, they were 7-10 days after the bite and most patients exhibited rash, urticaria, arthralgias, and local tissue injury would still be showing signs of resolving inflammation. Clinical evidence of bleeding diathesis were usually absent and coagulation indicators, if checked at all, were believed to be mostly normal.

Photo: Mulford's Antivenin. Photo courtesy of the Smithsonian Institute.

Key Point: The Importance of Time to Antivenom

At the AzPDIC, we emphasize localized cell death and tissue necrosis caused by pit viper venom, will not be corrected, or reversed by antivenom. It is important to recognize that efficacy of antivenom relates to binding venom, where it blocks enzymatic active sites and induces conformational changes in structure that may impair some venom functions. For this to occur, antivenom needs to be given and present in the tissues, prior to venom induced injury occurring. Although antivenom binding can occur any time that antivenom and venom are both in circulation, the clinical value for patients comes from an early inactivation of venom, as a means for preventing tissue injury. International and domestic studies, as well as our own internal unpublished data detailing nearly 4,000 snakebites, have consistently supported the concept that earlier time to antivenom is associated with better outcomes. Unfortunately, the practice of waiting for symptoms to reach a "severity threshold" to justify use of antivenom still exists in practice today. The notion that it is appropriate to withhold antivenom for patients despite clear clinical evidence of envenomation, is nothing but an artifact of older practices based on risks for a treatment no longer available, having no place in current medical practice. While the financial burden of antivenom treatment does warrant consideration in select cases, withholding antivenom until tissue injury passes "x" number of joints / distance, can be equated to using the King's College Criteria to determine when to START administration of NAC in acetaminophen toxicity.

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"Physicians became more confident giving antivenom, resulting in routine rapid antivenom administration for the first time in the United States"

2000-Present: Introducing Crofab® & Redefining the Standard of Care

It would take about half a century after Wyeth® was released, for CroFab® to become available. Like what occurred after Wyeth's® release, Crofab® would go on to rapidly replace its predecessor, this time because of a vastly improved safety profile with considerably lower rates of anaphylactic reactions (4-6%) and serum sickness (8-10%). It is important to recognize just how much this improved safety profile would go on to become a game changer. Physicians became more confident giving antivenom, resulting in routine rapid antivenom administration for the first time in the United States. To follow the logic behind how Crofab® came to exist and its improved safety profile, let's look at how the two products are different. It is believed the improved safety profile with Crofab®, is primarily due to the removal of the highly immunogenic Fc portion from the whole IgG molecule. This is accomplished by digesting whole IgG molecules with papain, splintering the immunoglobulin into two independent Fab fragments, and the Fc portion which is removed during manufacturing.

Key Point: Understanding Venom Recrudesce

Although Crofab® may have provided a solution for hypersensitivity reactions and redefined the standard of care through rapid administration of antivenom, it also brought along a new and unexpected problem. Venom recrudesce was first noticed during the clinical trials, where investigators developed a hypothesis to explain its occurrence based on miss-matching pharmacokinetics between venom and antivenom. One other noteworthy difference between antivenoms is that Fab fragments have a relatively short half-life in the human body (approx. 12-23 hours), especially when compared to Wyeth® antivenom (approx. 160 hours). To understand venom recrudesce, it is important to recognize two separate concepts exist. First, the initial question about whether it occurs, and second, the question about whether it is clinically relevant. Regarding the first, we know it occurs because venom levels are detectable for weeks post envenomation, regardless of receiving antivenom. Which brings us to the unanswered second question, does it matter? While any signs or symptoms of envenomation would be expected to return during venom recrudesce, only late coagulopathy and associated bleeding events has received much attention in the published literature.

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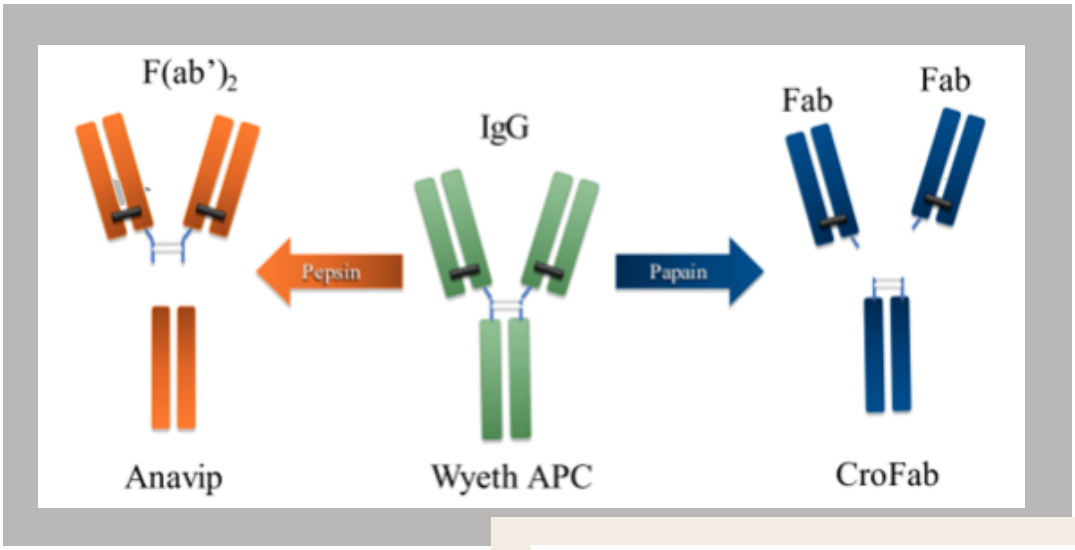
2018-Present: Introducing Anavip® & Ending Delayed/Recurrent Venom Effects?

Reminiscent of the story "Goldilocks and the Three Bears", when Anavip® was released in 2018 it was purported as the "just right" middle ground, between Crofab® and Wyeth® antivenom. Let's look at how Anavip® compares with the other two antivenoms, to understand the basis for these claims. Similar to both, whole IgG molecules are harvested from a host animal. Like Crofab®, the Fc portion is removed through an enzymatic reaction as a way to reduce hypersensitivity reactions. Unlike Crofab®, the enzyme pepsin is used which preserves the disulfide bonds of the hinge region, resulting in removing the Fc portion but leaving the singular F(ab')2 fragment, with a comparatively much longer half-life (approx. 133 hours).



Antivenom	Anavip®	Wyeth® ACP	CroFab®
Immunglobulin	$F(ab')_2$	Whole IgG	F(ab)
Enzyme Used	Pepsin	N/A	Papain
Host Animal	Horse	Horse	Sheep
FDA Approval	10/8/2018	10/1/1953	10/2/2000
Half-life (Hours)	133	≈160	12-23
Initial Vials	10	2-15	4-12
Maintenance Vials	N/A	N/A	6 over 18 hrs
Average AzPDIC Total Vials	18	17	15
Total Protein / Vial	Up to 120mg/vial	Not reported	Up to 1000mg/vial
Immunizing Species	*Bothrops asper* *Crotalus simus*	*Bothrops atrox* *Crotalus durissus* *Crotalus atrox* *Crotalus adamanteus*	*Crotalus scutalatus* *Agkistrodon piscivorus* *Crotalus atrox* *Crotalus adamanteus*

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Occam's Razor Draws Anavip® Blood……

Despite being the apparent solution to the venom recrudesce problem of Crofab®, questions remain regarding antivenom efficacy. In large part, this is because when seeking FDA approval both drugs focused on improving safety over their predecessors, Crofab® with less hypersensitivity reactions and then Anavip® with less venom recrudesce. Efficacy was determined by changing coagulopathic laboratory markers after antivenom administration. Take a moment and let this one sink in, neither currently FDA approved antivenom was studied for a single morbidity related outcome. Remember, this is for a disease state with a less than 1% mortality rate. Morbidity can be broken down in many ways, but functional recovery is arguably among the most important and is likely related to the extent of tissue injury. When considering tissue injury, and thus functional recovery, two important pharmacologic properties for antivenom stand out, the ability to penetrate the tissue (get to venom) and then bind it (inactivating venom). It is in this regard, that Crofab® has the "simple science" upper hand. Crofab® is a smaller molecule, and hypothetically should have better tissue penetration. Regarding binding, Crofab® is made from native snakes and it intuitively makes sense that Crofab® would bind better to certain venom components, this was Nogughi's reasoning back in 1909 after all. While modern studies have shown that this is not necessarily the case, at least for some Asian venom-antivenom pairings, the burden appears to be on Anavip® to overturn this "common sense".

Optimizing Antivenom: Decreasing Time to Complete Dose

With mortality rates well below 1%, the focus on morbidity is long overdue. The importance of time to antivenom may be recognized, however, the time until complete antivenom dose is rarely discussed, and likely important for morbidity related outcomes. Optimal total dosing of antivenom has never been established. Initial antivenom dosing is empirically ordered once envenomation has been diagnosed, but firm indications for subsequent doses are nearly non-existent, resulting in considerable practice variation. Ideally, minimal, and maximal effective dosing thresholds should be established for the venomous snakes of a given geographic range. For example, the average rattlesnake bite patient in AZ receives 18 vials of Anavip®, with very few receiving only 10 vials total and even less getting more than 30 vials. Considering historical data, the mechanisms driving venom induced tissue injury, and the established importance regarding time to antivenom, is there any sensible reason not to start with 20 vials of Anavip® in AZ? Similarly, with nearly all patients fully treated at 30 vials, is there a point where we should determine that a particular antivenom is simply not effective?

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On the Horizon:

As always, we are busy working away at the AzPDIC to help answer some of these clinical questions. Currently, we are working towards establishing minimum and maximum effective dosing thresholds for antivenom in our geographic coverage area. Instead of researching the time from bite until starting antivenom, we are taking it a step further and focusing on decreasing the time needed until total antivenom dose is completed.

References:

1. Dart RC, McNally JT, Spaite DW, Gustafson R: The Sequelae of Pitviper Poisoning in the United States. In Campbell JA, Brodie ED, editors: Biology of the Pitvipers, Tyler TX, 1992, Selva, pages 369-382.
2. National Museum of American History Behring Center, The Antibody Initiative-Antivenom, Smithsonian Institution, accessed 15 October 2023, <https://americanhistory.si.edu/collections/object-groups/antibody-initiative/antivenom>.