NEWS FROM THE PIT

Arizona Poison and Drug Information Center

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Fashionably Late

The AzPDIC Experience with Late Coagulopathies in Rattlesnake Envenomations

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You've seen this scene a thousand times. Someone out in the middle of the desert gets bitten by a snake and their companions have to suck out the venom before certain death hits. By now, you probably know that sucking on the wound does no good and the right answer is antivenom. But does that truly solve all of our patient's problems?

When dealing with rattlesnake envenomations, we typically think of three toxic effects: 1) cytotoxicity, which is responsible for local swelling (aka the reason the patient's hands look like Mickey Mouse gloves), 2) neurotoxicity, which can cause muscle paralysis, dyspnea, and fasciculations (we will be discussing more on the reality of this down the road), and 3) hemotoxicity, which impairs the clotting process.

You can pretty much look at a patient and determine if the first two toxicities mentioned are having an effect. The patient certainly can tell and instinctively knows they need to be cautious. Hemotoxicity is different! For this, we rely on lab work, specifically Hgb/Hct, platelets, fibrinogen, and PT/INR. During the hospitalization, we give antivenom and watch these values normalize and freezeframe high-five each other as we discharge another patient saved from harm's way. But not so fast! There are human venonemia studies proving that serum venom levels rise again days after the hospitalization is over.

NEWSLETTER HIGHLIGHTS

Fashionably Late

Continued from page 1

This is the cause for late coagulopathies, which can happen in two ways: a recurrent or delayed fashion. Recurrent coagulopathies are coagulopathies that present initially, resolve with antivenom, then come back after the patient is discharged. Delayed coagulopathies are ones that never arise during the initial hospitalization, but occur after antivenom is given and the patient has been discharged.

Furthermore, coagulopathies are also broken down by thrombocytopenia (<150,000/uL) or hypofibrinogenemia (<150 mg/dL). So, if we're concerned enough about venom effects to hospitalize these patients initially, shouldn't we be just as concerned when they come back after the patients leave? This is the question we looked to answer and is what we'll be talking about over the new few issues of this newsletter. The first part of that answer starts with determining the extent that late coagulopathies even happen.

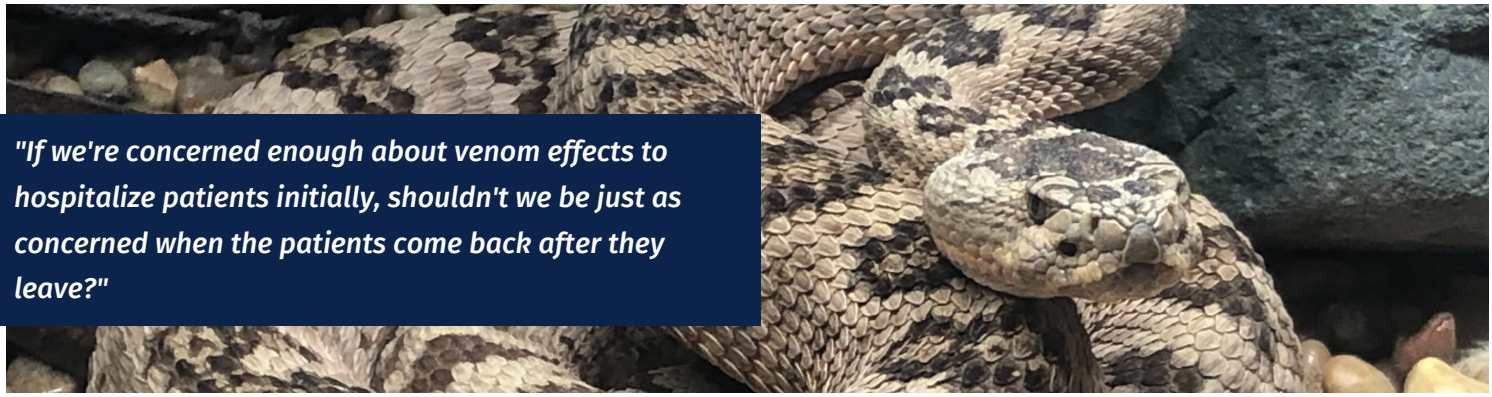
The AzPDIC looked at all our rattlesnake envenomations from 2018-2020 that received antivenom and outpatient lab monitoring. Of these 522 cases, 302 patients met our inclusion criteria and 73 of those (24%) had a late coagulopathy, which occurred an average of seven days post-envenomation. It's not quite that simple to say one in four patients develop a late coagulopathy because of the antivenom factor.

There are two pit viper antivenoms on the market: CroFab and ANAVIP. The big difference between the two are the snakes used to make the antivenom and the molecular weights used.

If you've heard any toxicologist talk about treating rattlesnake bites, you'll hear them utter the phrase, "pharmacokinetic mismatch" (we're obligated to say this at least once per bite, or we lose our credentials). The idea here is that venom is a huge molecule that distributes into tissues and stays around much longer than antivenom. CroFab has a molecular weight of 50 kDa, while ANAVIP's is around 110 kDa. This size difference leads to ANAVIP's longer half-life (133 hours vs. 23 hours), which would suggest better coverage against late coagulopathies.

When we looked at late coagulopathies by antivenom, this logic checked out. Approximately 36% of all patients treated with CroFab developed a late coagulopathy, while only 10% developed one with ANAVIP. Not only did CroFab have a higher rate of late coagulopathies, but the severity was also worse, as the mean drop in platelets and fibrinogen were much steeper with CroFab than ANAVIP (see Tables 1-3).

What's really interesting is that no patient treated with ANAVIP in our study developed a late hypofibrinogenemia. We commonly see an initial thrombocytopenia that immediately bounces back after antivenom. We know we can't make hundreds of thousands of platelets in an hour, so there's something weird happening there whether the platelets are clumping together or being sequestered. The fibrinogen drop is real, meaning true consumption through thrombin-like enzymes takes much longer to recover.



"If we're concerned enough about venom effects to hospitalize patients initially, shouldn't we be just as concerned when the patients come back after they leave?"

Fashionably Late

Continued from page 2

The fact that late thrombocytopenias happen with ANAVIP proves that venom effects can recur, but the fibrinogen remaining steady suggests there is superior coverage, although it may not be simply due to a longer half-life.

Based on what we found, late coagulopathies occur with either antivenom, but are more frequent and severe with CroFab.

This tells us there is still a need for outpatient monitoring (which the AzPDIC coordinates for all patients we're consulted on) no matter the antivenom used based on the lab values.

The true question that remains is: what is the clinical significance of this? We don't treat the numbers, we treat the patients. What we are ultimately looking for is the risk of clinically significant bleeding.

Stay tuned for the next issue, where we dive past the lab values and look more into the outcomes!

Table 1. Demographics

	Fab AV* (n=54)	F(ab')2 AV** (n=13)
Mean Age	43.2 ± 23.31	55.2 ± 17.16
Median Age	47.5	64
Sex		
Male	35 (65%)	9 (69%)
Female	19 (35%)	4 (31%)
Baseline platelet count	194.3 ± 89.6	181.4 ± 50.64
Baseline fibrinogen level	251.2 ± 97.04	290 ± 85.08

*CroFab ** ANAVIP

Table 2. Coagulopathy Breakdown

	Fab AV (n=54)	F(ab')2 AV (n=13)
Late Coagulopathy		
Recurrent	23 (43%)	7 (54%)
Delayed	31 (57%)	6 (46%)
Days to Onset	8.1 ± 2.42	
Coagulopathy Type (At Onset)		
Thrombocytopenia only	16 (30%)	13 (100%)‡
Hypofibrinogenemia only	32 (59%)	0‡
Both	6 (11%)	0
Mean Platelet at Onset (Thrombocytopenic patients)	103.89 ± 31.44	131.49 ± 15.45‡
Mean Platelet Nadir (Thrombocytopenic patients)	89.05 ± 28.76	129.13 ± 19.79‡
Mean Fibrinogen at Onset (Hypofibrinogenemic patients)	73.02 ± 40.7	N/A
Mean Fibrinogen Nadir (Hypofibrinogenemic patients)	65.25 ± 39.04	N/A

‡ p-value <0.01

Table 3. Severe Coagulopathy

	Fab AV (n=54)	F(ab')2 AV (n=13)
Severe Thrombocytopenia (<100,000/uL)	17 (31%)	2 (15%)
Severe Hypofibrinogenemia (<100 mg/dL)	32 (59%)	0‡
Mean Platelet Nadir	70.86 ± 18.76	86.5 ± 12.5
Mean Fibrinogen Nadir	46.19 ± 15.48	N/A