NEWS FROM THE PIT

Arizona Poison and Drug Information Center

ARIZONA
Poison and Drug
Information Center
1-800-222-1222

Better Late Than Never

Does Time to Antivenom Matter?

By Geoffrey Smelski, PharmD, DABAT

Today, we are going to discuss clinical relevance regarding the timing of antivenom (AV) administration following rattlesnake envenoming in the United States. Since the 1950's when rattlesnake AV first became widely available, this has been a bit of a controversial topic. From a scientific perspective, it is always hard to show that you truly prevented something from happening. This challenge becomes compounded when you factor in venom variability and our inability to analyze venom composition at the bedside. As a result, we fall a touch short when it comes to meeting evidenced based medical standards. For some, this lack of rigorous science behind medical practices is enough to be highly skeptical, and rightfully so.

Afterall, it wasn't that long ago that patients were being given strychnine, ethanol, or electricity to "treat" envenoming. Indeed, the higher pediatric mortality rates that have historically been reported, were likely related to complications from massive doses of ethanol. While there are some general perceptions regarding the benefits from AV that have remained consistent across the years, other ideas have shifted as our understanding of envenoming has evolved. In our discussion today, I will attempt to organize the scientific evidence behind the topic in a way that is easy to follow as well as illustrates the current limitations of our understanding. Most of the concepts discussed here could be applied to a variety of envenoming situations, however the details provided will be specific for rattlesnake envenoming and concepts may not always translate to envenoming elsewhere.

NEWSLETTER HIGHLIGHTS

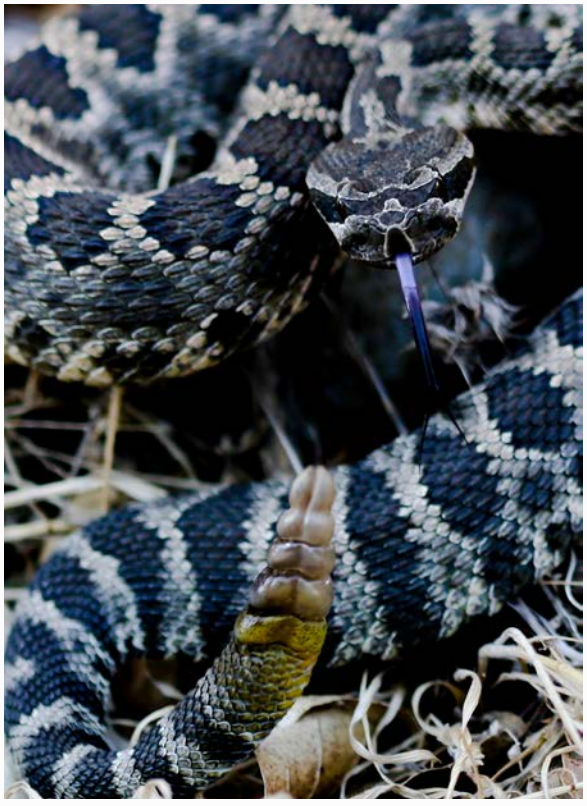
Better Late Than Never

Continued from page 1

.Additionally, my personal experience is restricted to managing rattlesnake envenoming within the state of Arizona and clinical findings described may vary in different geographic locations. There, got the disclaimer out of the way, now let's start this discussion by establishing what you should expect to get by giving antivenom in the first place. I mean seriously, getting AV paired with an ICU stay is not cheap, shouldn't we know what we are getting for all those healthcare dollars?

There is only one thing that AV consistently does well, and that is that it resolves the coagulopathy problem. Specifically, it resolves the problem of defibrination. Mechanistically, venom is depleting our pool of fibrinogen, regardless of whether it is forming a clot, getting directly degraded, or simply generating poorly crosslinked strands that are then getting rapidly degraded, the clinical result of defibrination is present. If you give an adequate dose of AV, this process will stop, and synthesis of fibrinogen will eventually yield normal fibrinogen levels. If you are treating a patient and the process of defibrination is continuing, you should really consider giving more AV because it is likely that the dose of antivenom is insufficient.

I find trending fibrinogen levels as an excellent surrogate for venom levels...



In the over 2,000 rattlesnake envenoming cases that I have personally reviewed, I am not aware of a single case of hypofibrinogenemia that received multiple doses of AV without an acute resolution. I mention acute resolution because late coagulopathy is its own complication and even patients receiving a large amount of AV initially, may go on to develop a late coagulopathy. In my personal practice, I find trending fibrinogen levels as an excellent surrogate for venom levels and thus useful in making the determination of clinically obtaining or losing "control" of an envenoming. In some yet to be published work looking into predictive models, we looked at every patient that presented with undetectably low fibrinogen, who received antivenom, and then had a consistent rise in fibrinogen levels that never dipped below 150 mg/dL again.

Better Late Than Never

Continued from page 2

The mean rate of recovery from the time of the first detectable fibrinogen level until the first level above 150 mg/dL was then calculated. A rate of 8 mg/dL/hr was found, with a rather small range of 6-9 mg/dL/hr across all patients. There are several limitations with this method that are currently being further worked out, notably it is less useful in predicting the patient's course for those that are not starting from undetectably low levels as well as looking at the rate of synthesis when above 150 mg/dL. Despite the limitations, when patients have a fibrinogen less than 150 mg/dL the rate of recovery can be calculated between lab draws.

Again, in my personal practice, If the recovery rate is below 6 mg/dL/hr it prompts a thorough assessment for other markers of active envenoming due to insufficient AV dose. This, along with knowing the average number of antivenom vials patients are receiving, has been helpful in differentiating loss of initial control from the natural redistribution edema course. For those looking for a more formal discussion of these concepts, a manuscript is in the works. Until then, keep in mind that this method only works because venom is consistently leading to low fibrinogen levels and AV is very effective at stopping it.

It is worth mentioning that AV is also reliably contributing to the resolution of any bleeding that may be occurring. Hemorrhage, however, requires some level of tissue injury to be present, or as I like to say there must be a hole to be leaking out of.

Simply developing thin blood on its own, acutely speaking, is not going to lead to a clinically significant hemorrhage. AV is not going to plug any holes on its own nor is it going to replace the lost hemoglobin when your patients become anemic. Your clinical takeaway from this is that if you have a patient actively experiencing significant bleeding, make sure to give them AV but also make sure to treat their bleeding when needed, because AV alone will not always be enough. Several of our past newsletters have addressed bleeding, including discussion on treatment. My advice is to simply look at hemoglobin levels and replete as you would any other trauma patient in the ED with those levels, just make sure you are also giving AV.

Next, we should touch on some things that AV may, or may not be doing. Platelet levels are at the top of this list for me. Sometimes they are low when the patient comes in, you give AV, and the levels shoot up at a rate that is way beyond what we normally synthesize. Sometimes, the exact opposite occurs, they are normal, you give AV, and they drop down and stay low. You can investigate the discussion regarding platelet aggregating effects from venom, or you can take my word on it that venom can be both pro- and anti- platelet aggregating. Whichever effect your patient is experiencing, it may or may not then get reversed with AV.

In my personal practice, if the recovery rate is below 6mg/dL/hr it prompts a thorough assessment for other markers of active envenoming due to insuffiencient AV dose

Better Late Than Never

Continued from page 3

Further muddying the water, platelets can simply be destroyed by multiple mechanisms, over differing timelines, which will then take days to resynthesize. And of course, we also have patients with normal or low platelet levels, who after AV, continue to have the same levels. In fact, if you can think of a pattern for increasing or decreasing platelet levels over time, I probably have a group of patients that exhibited it. Clinical takeaway, low levels in a patient without a history of thrombocytopenia are a marker of venom and an indication to give AV. Outside of that, I do not find them terribly helpful once the decision to give AV has been made. At incredibly low platelet levels, a risk of significant spontaneous hemorrhage has been well described outside the setting of rattlesnake envenoming. A key factor to remember is that this risk typically comes from patients with baseline thrombocytopenia due to the impaired synthesis of platelets. For example, bleeding events and thrombocytopenia in chemotherapy patients are commonly looked at. Acute thrombocytopenia in an otherwise healthy patient, would not be expected to carry the same level of bleeding risk.

Neurotoxicity is another area of uncertainty. There are case reports of rapid symptom reversal following AV as well as cases where the symptoms persisted. I have read several cases where reasonable doses of AV failed to reverse the symptoms based on what the authors reported. There are also cases where the timing of AV suggests that AV aided with the resolution of symptoms, all though it is impossible to know that the symptoms would not have resolved on their own without AV. Thankfully, severe neurotoxicity is very rare and neurotoxic symptoms are almost never the sole factor being considered when deciding the need for additional AV. The one case where this may come up, is with regards to pain control. We have given AV for pain control numerous times with no clear results because analgesics were also being administered. It is possible, that a neurotoxin is mediating pain signaling. It is also possible, that said neurotoxin is not being neutralized by AV.

Neurotoxicity is another area of uncertainty.

Better Late Than Never

Continued from page 4

While I do not have benchtop literature mapping this mechanism out, I can say that anecdotally a small number of patients receive large doses of IV opioids with minimal improvement in pain. During my fellowship training, I treated a young teenager with scheduled doses of IV hydromorphone (plus oxycodone prn) that should have put any opioid naïve patient into complete respiratory failure. Despite these doses, she clearly exhibited numerous signs of inadequate pain control. Eventually I added IV lorazepam which took the edge off, although she continued to have considerable pain throughout her hospital stay and after discharge. Since this dramatic case, I have paid more attention to pain control and give IV midazolam/lorazepam for patients reporting severe pain without improvement from a couple doses of IV opioids.

The last thing I will touch on today regarding antivenom efficacy, because after all this newsletter is supposed to be about time to AV…., is whether AV impacts local tissue damage. And to answer this critical question, all I can say is that ……. the jury is still out on this one. Oh, and it is also likely the most important question that needs to be answered because local tissue damage seems like it should correlate with functional recovery and a major component of snakebite morbidity. Remember that mortality from snakebites is very low, so wouldn't it be nice to know if your six-figure hospital bill was expected to improve your chances of recovery?

We think so, but we are realistically years away from compiling enough compelling evidence to help answer this question. Now that we have covered what you can reliably expect from AV vs what you may or may not get from it, let's get back to the original topic.

Everyone in medicine knows that clinical decisions need to be made off limited evidence, perhaps none know this better than toxicologists. So, let's talk about how to approach the situation of risk vs benefit for AV in the setting of a rattlesnake envenoming, and layer in how time to AV impacts it. First off, we know that there is a time at which AV is no longer of benefit. I mean, if you have a patient that was bitten 3 years ago and they still haven't received AV, they are probably good at this point. On the other hand, we have this mantra in emergency medicine that gets repeated, "Time is Tissue", and this is a rather good mantra to have. It fits well in the field of toxicology as most of our "antidotes" are preventing problems, not actually reversing them.

We know that AV is not going to stimulate your regenerative process following an envenoming, and so the question becomes can AV prevent tissue damage? The simple answer to this is yes, it can. If you look at animal models where AV is given, then the animal is injected with venom, a variety of complications can be minimized or outright prevented.

Venom is typically given through a needle, and not from a natural snakebite.

Better Late Than Never

Continued from page 5

That's great, except that I don't have a time machine to go back and pre-administer AV before the bite occurred. Also, if I did have a time machine, why wouldn't I just go back and yell out something like "hey watch out". Anyways, the next thing we need to consider is the time from venom deposition until the maximal amount of venom effects has occurred. And this is the piece that is missing, especially in the setting of giving AV. Bear in mind that venom levels can be detected for several weeks following a bite, even long after your favorite F(ab')2 or Fab fragments have been eliminated. What we do know is that some effects happen very rapidly, and that nothing short of prior antivenom will prevent them. One example that comes to mind is a study that injected lethal doses of venom into the tips of rat tails and then in 1-2 minutes amputated the tail, the rats still died. Animal studies show that even waiting 5 or 10 minutes to give AV after injecting venom will dramatically reduce the impact AV has, although some benefit is usually still observed. However, animal models do not translate to human effects.

Venom is typically given through a needle, and not from a natural snakebite. Also, humans are considerably larger than study animals and our size is one of our greatest defenses against the toxicity venom induces. Global clinical effects observed in smaller animals are typically far more dramatic, which makes sense from an evolution standpoint, considering that immobilizing prey is beneficial for the snake feeding. Simply speaking, snakes didn't evolve their venom for thousands of years so that they could feed on humans.

So, let's summarize what we know and discuss the application of everything. We know that AV works for stopping the defibrination from venom, and we know that this helps with regards to any bleeding complications that may come up. We also know that the benefits of this can be seen at any point in the envenomation because we synthesize fibrinogen on a time scale of hours, so low or down trending fibrinogen almost always equals active venom effects. If you give AV even as late as 2 weeks after the bite occurred, this effect is expected to be reversed. So, for this it is easy, if you have any bleeding or hypofibrinogenemia, there is a realistic potential for benefit from AV. The clinical significance of that bleeding is for another discussion, but here today, we can say that AV would be expected to improve it.

Better Late Than Never

Continued from page 6

We also know that AV can limit local tissue damage, but its effects are reduced as time gets further from the time of bite. The window of time where AV can prevent tissue damage, and thus likely limiting morbidity, may be rather small. In fact, the window of time may be impractically small even with first world EMS services and resources. However, the possibility does remain that early AV may limit tissue damage, even if it's a few hours out. Internationally, a delay to AV greater than 4 or 6 hours (depending on the study) has been shown to be a risk factor for increased mortality.

This doesn't translate well to patients with first world resources, but it does provide evidence that time to AV has some potential impact on outcomes. Notably, secondary complications such as infections are another common risk factor for mortality in numerous international studies. It is possible that these patients experiencing a delay to AV may additionally be septic upon arrival, whereby earlier AV without antibiotics would not have changed the outcome.

We are now firmly planted in the gray zone of the unknown, welcome! The best that I can do is share how I navigate these waters. In my opinion, if a patient ends up receiving AV, it was in their best interest to have received that AV as rapidly as possible. There is a point in time where benefits are lost, but if the patient is going to be incurring the costs of AV treatment, they should get the best chance possible at reducing their morbidity and that will come with rapid AV administration.

At the AzPDIC we do not follow the practice of grading envenomations and withholding treatment of "minor" rattlesnake bites, once a rattlesnake envenoming has been diagnosed, the rapid administration of AV is recommended. It is important to remember that this low threshold to administer AV needs to be judiciously balanced with the considerable financial harm that would come from treating something like a cactus prick with AV.

At the AzPDIC we do not follow the practice of grading envenomations and witholding treatment of "minor" rattlesnake bites....