NEWS FROM THE PIT

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Keeping Thin

Antiplatelets and Anticoagulants in Rattlesnake Envenomation

By Tyler Hoelscher, MD

In the 1920's a disturbing phenomenon was discovered on several Northern US and Canadian farms: cattle were being found dead in their barns. A cow would undergo a simple procedure, such as a horn removal, and several hours later would be found dead in a massive puddle of its own blood. Other cattle would be found dead without any identifiable cause of bleeding. It took decades to discover the cause, but in the 1940's the murderer was identified. Rather, there were two culprits: mold and sweet clover. Fungus growing on feed made from sweet clover chemically altered molecules in the plant, called phytocoumarins, into a molecule called dicoumarol, which inhibited the cows' ability to stop bleeding, causing them to die from massive hemorrhages.

Now I want you, the reader, to put yourself into the shoes of the scientists at the University of Wisconsin who discovered this molecule, and guess how they decided to make use of their discovery. Really think on it. Now, was your answer to use small doses of the drug to prevent and treat embolic illnesses like stroke, deep vein thrombosis, and pulmonary embolism? Did you think to use it to thin the blood around newly invented mechanical heart valves to dramatically lengthen the lives of patients with valvular disease? Did you think of creating the first oral anticoagulant medication that would change medicine forever? If that's what you thought they would do, then you're wrong. They used it to kill rats.

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Tongue-in-cheek history aside, all of these things eventually became true of a new drug called warfarin, which turned into one of the most prescribed medications in the world. As time has passed, other anticoagulants have been discovered, including novel oral anticoagulants (NOACs) which have further changed medicine. Unlike warfarin, they do not require close monitoring of patients' level of anticoagulation. In addition to anticoagulant drugs, antiplatelet agents like aspirin and clopidogrel are also very commonly used, and both categories, anticoagulants and antiplatelets, save lives and prevent countless strokes and heart attacks every year. They also present their own set of challenges, especially for patients bitten by rattlesnakes.

As previously discussed, rattlesnake venom causes coagulopathy, meaning it prevents blood from clotting, which in bad cases can cause severe bleeding. You can imagine that patients who are already anticoagulated from medication have an even higher risk of bleeding than the average rattlesnake patient. The best literature behind these patients that we currently have comes from our colleagues in Phoenix, who studied the risk of bleeding as it compares between patients taking anticoagulant and/or antiplatelet drugs versus neither. Patients taking anticoagulants/antiplatelet drugs showed a significantly increased risk of bleeding both during the initial admission and after discharge, when some patients developed late coagulopathies. Since this study, which was performed in 2013, new challenges have also presented.

As I discuss how we take care of these patients, I want you to picture a set of scales. On one side of the scales sits the risk of bleeding, and on the other side sits the risk of embolic and thrombotic events. What are those? Well, in any patient on an anticoagulant or antiplatelet drug, there is a reason why that drug was started. The most common reason to be on an anticoagulant is a heart rhythm called atrial fibrillation, which can result in large blood clots being sent into the brain, causing strokes. Patients with histories of blood clots in other places, like the lungs or veins in the legs, are also frequently started on anticoagulants. Patients with mechanical heart valves also need to be anticoagulated or risk a stroke.

Patients are usually started on antiplatelet drugs when they've had some type of disease from plaques in the arteries, like heart attacks, strokes, or peripheral artery disease. So, it is our job to balance this imaginary scale between bleeding and the patient's risk of whatever disease they are taking the medications for. After all, if my patient is bitten by a snake and then has a massive stroke because I took them off warfarin, I really haven't done any good.

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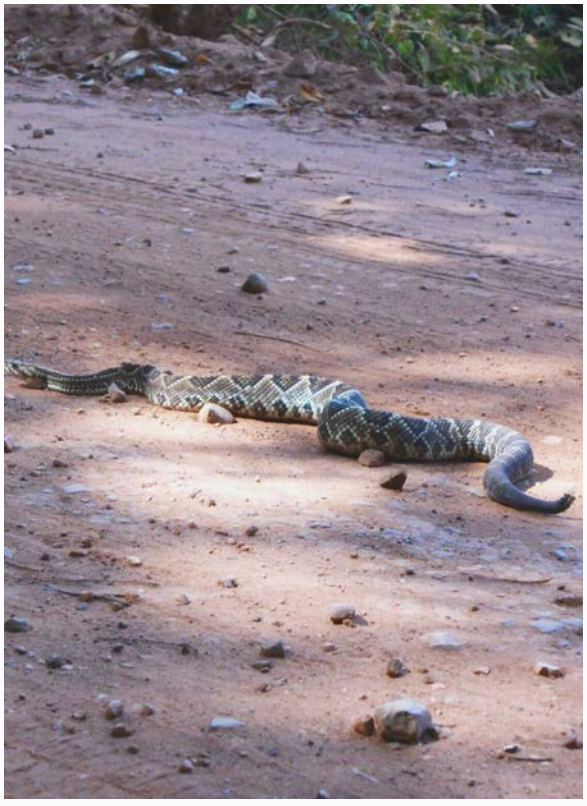

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Before I get to the tricky parts of anticoagulated snakebite patients, I'll just briefly touch on the parts we understand. During initial hospitalization, rattlesnake-envenomated patients are typically taken off all their anticoagulant and antiplatelet medication when they arrive at the hospital. The rates of recurrent embolic or thrombotic disease during the initial admission are low enough that patients are generally safe to remain off those medications. But for how long?

Warfarin has a very narrow therapeutic window, meaning it's easy to take too little and risk having a stroke, or to take too much, and become supratherapeutic. In other words, risk bleeding like one of those poor cows. To handle this, patients on warfarin have frequent doctor's visits to check their INR, a lab value that gives an approximation of how anticoagulated a patient is. Given the high rates of supratherapeutic warfarin, patients are usually taken off of warfarin after a rattlesnake bite until they have multiple follow-up visits to confirm that they don't develop a delayed coagulopathy.

Next are the NOACs like Eliquis and Xarelto. We in medicine love these drugs because they make it much easier to anticoagulate a patient. However, we don't have studies involving NOAC patients bitten by rattlesnakes, so we consider each patient on a case-by-case basis. For my patient with a mechanical heart valve who's had multiple strokes before, I would probably keep them on a NOAC. For my 86 year-old racecar driver with afib, I would probably stay off those meds for the time being.

The last tricky part is tackling the risk of late bleeding with ANAVIP. Like we mentioned in a previous letter, since ANAVIP contains much larger antibody fragments, it stays in the body much longer, and we see fewer late coagulopathies. That means in our patients who get ANAVIP, those imaginary clot vs bleed scales might be swinging in the direction of the clots, so those patients might need to be restarted on their anticoagulant or antiplatelet sooner. It's difficult to address this topic because once again, we don't have studies to support these statements, yet we have to treat these patients.

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The last thing to mention is what to do when you have a bleeding snakebite patient who is on one of these drugs. While this can be a life-threatening situation, it actually isn't a very difficult decision to make from the toxicologist's perspective. In these cases we can forget about mitigating risks of thrombotic and embolic events and do everything we can to stop that bleed, similar to the bleeding patients I spoke about in the last newsletter. In these cases we must reverse their anticoagulation and resuscitate with blood products as needed - just don't forget the antivenom.

What has the AzPDIC seen? Among our 35 severe bleeds from the last 2000 patients, two were on aspirin, one on warfarin, and one on Eliquis. Further work is currently being done to quantify the risk we can attribute to anticoagulants and antiplatelets, so you'll be hearing more from us in the future. All in all, patients on anticoagulants and antiplatelets show how toxicology remains a developing field, and how we have to move quickly to keep up with the pace of medical advances.

In the meantime, if your grandma on Eliquis meets an unfriendly snake, a toxicologist is only ever a phone call away. Stay tuned for our next newsletter for a deeper dive specifically into non-steroidal anti-inflammatory drugs and how they can affect rattlesnake envenomations.

A Note From The Editor

By Geoffrey Smelski, PharmD DABAT

Dr. Hoelscher uses figurative scales to illustrate the balance of hemostasis between clotting and bleeding. With this in mind, a rattlesnake bite in Arizona would create an acute disturbance that pushes the scales towards bleeding. How much “weight” is added to the scale on the side of bleeding is hard to assess with our current tools. Labs will routinely indicate a significant impairment (sometimes both undetectable platelets & fibrinogen) that does not match what we observe clinically because the patient may not be bleeding. In most patients it will be appropriate to hold their home anticoagulation/antiplatelet medications while giving antivenom to obtain initial control.

This brings us to the second “tipping of the scales,” in that at some point the antivenom will have neutralized the venom and the patient will be regenerating the clotting components lost to the venom. Thus, the scales will tip to the side of clotting as they return to their baseline health. Deciding when to restart any home anticoagulant or antiplatelet requires balancing patient specific factors along with the potential third tipping of the scales: any rattlesnake bite may develop a late coagulopathy. As of right now, we do not have any definitive way to predict who will or will not develop one. Obviously, if the coagulopathy returns and the patient has restarted their home medications, the scales would then be pushed farther back in the direction of bleeding again.

The following are some thoughts on how to navigate these murky waters. In most patients, minor bleeding will be of less concern than the patient developing a clot because their home meds were held. Start with a thorough patient-specific assessment of the risk for bleeding as well as clotting. Then, consider their ability to self-monitor for signs of bleeding and their ability to return to healthcare. I mention this because I once had a patient in their 80’s, who had been on warfarin for 30+ years due to 2x unprovoked DVT’s, that now lived alone in a trailer in the middle of the desert, about 2 hours from the nearest “hospital”. Decide which risk (clot vs. bleed) is the “lesser evil” for your patient and establish a clear plan on monitoring with the patient. Venom can have effects for 2-3 weeks post bite in patients, although significant clinical effects are mostly (but not always) seen in the first few days.

As always, patient specific advice from a trained toxicologist is available 24/7/365 through your local poison center. If for any reason your local toxicologist on call is not familiar with managing rattlesnake bites, we are always happy to assist and can be reached at the Arizona Poison and Drug Information Center in Tucson, AZ.