NEWS FROM THE PIT

Arizona Poison and Drug Information Center

ARIZONA Poison and Drug Information Center

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Platelets and Pain

NSAIDs in Rattlesnake Envenomation

By Tyler Hoelscher, MD

Tsar Nicholas II, the last emperor of Russia, had a lot of problems in his life. One of them was that his son, Alexei, was afflicted with the "Royal Disease", hemophilia B, a genetic bleeding disorder inherited from his inbred noble lineage. At the time, hemophilia was untreatable. A bump on the road could cause internal bleeding that would put Alexei in bed for weeks with crippling pain and anemia, often near death. The Tsar's family finally found some help in the famous "Mad Monk" Grigori Rasputin, a charismatic peasant-turned mystic. While Rasputin's medical knowledge was somewhat in question, he did something that all toxicologists appreciate: discontinued all unnecessary medications.

You see, Alexei's bleeding caused severe pain, and how do you treat pain in 1910? Aspirin. Aspirin belongs to a category of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs), most of which have antiplatelet properties. Poor Alexei was bleeding because his own body lacked critical clotting proteins, and his doctors had poisoned the only other thing his body could use to stop bleeding - platelets. Rasputin convinced the Tsar's family to stop all of Alexei's medications to focus on supernatural healing, and it worked! The boy recovered. While I cannot vouch for the monk's mystical abilities, I have to admire his unwitting practice of medical toxicology.

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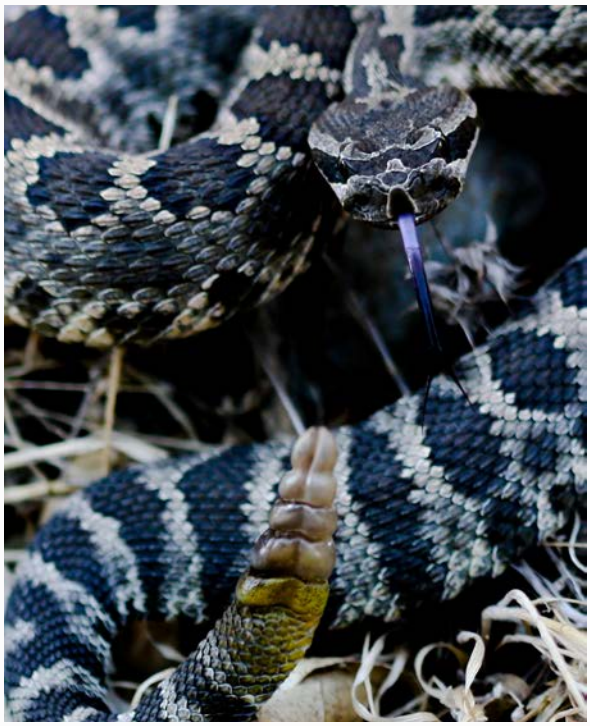
Today, NSAIDs are some of the most commonly used drugs. Aspirin is commonly used as an antiplatelet and Ibuprofen, Naproxen, Ketorolac, Meloxicam, Indomethacin, Celecoxib, and many others are used for relief of pain and inflammation. NSAIDs work by inhibiting an enzyme called cyclooxygenase (COX), which helps in creating many inflammatory markers that cause pain and swelling. One of the other molecules that require COX for synthesis is thromboxane, a chemical messenger responsible for platelet activation. NSAIDs reduce pain, reduce inflammation, and reduce platelet aggregation. If you've read a few of these newsletters already, you probably know where I'm going with this. Let's talk snakes.

Rattlesnake venom contains enzymes that inappropriately activate the body's clotting system, using platelets and clotting proteins so the body is unable to clot properly and more likely to develop bleeding. This coagulopathy is more of a laboratory concern than a clinical one, meaning that many patients develop significant clotting dysfunction, as seen in their labs, but few ever develop significant bleeding.

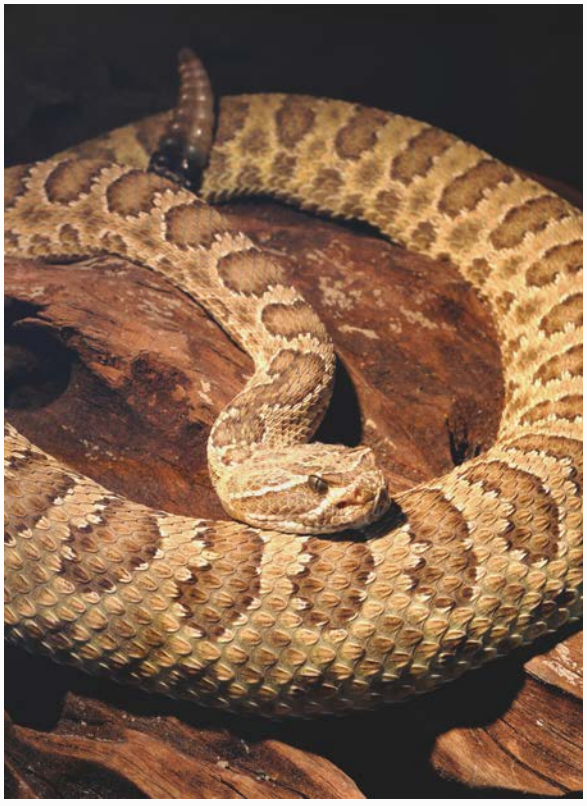
Because of this coagulopathy, we avoid other medications that can increase bleeding risk. NSAIDs can prevent platelet aggregation; therefore, they would theoretically increase the risk of bleeding and are avoided in patients with rattlesnake envenomation.

However, to date, there have been no studies on NSAIDs in rattlesnake patients. That doesn't mean a patient bitten by a snake has never received ibuprofen. It means that we don't have any research trials that say NSAIDs cause or do not cause bleeding in rattlesnake envenomation patients. Why does that matter? Pain.

Rattlesnake bites (I've been told) are very painful. Patients often complain of aching, stabbing, or burning, which is often quite severe. This should come as no surprise because in addition to hemotoxicity, which is painless, snake venom also causes neurotoxicity and cytotoxicity. Neurotoxic components of venom can directly attack nerves, causing abnormal firing, which the body may identify as numbness, tingling, or pain.



How do we treat pain with rattlesnake envenomations?



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Cytotoxicity involves the destruction of cells on the microscopic scale, essentially digesting your body. Think meat tenderizer. Intracellular components get dumped from the dead cells and, in addition to the components of the venom itself, cause significant inflammation and swelling. Inflammation and swelling are responsible for the Mickey mouse appearance of our patients' hands. Additionally, the venom seems to travel up lymphatic vessels, causing further inflammation and swelling. Patients will often complain of pain in the armpit and groin from bites on the hands and feet, which is where many lymph nodes are located.

How do we treat pain? First, antivenom. Inactivating venom can prevent progression of cytotoxic damage, but it doesn't undo what's already been done. While antivenom probably prevents worsening pain, it doesn't help with the pain the patient already feels. Acetaminophen can give some modest relief, but acetaminophen versus a tide of cell-destroying venom is often inadequate. Then let's try some NSAIDs right? Maybe some Toradol? Oh wait, platelets. Opioids it is.

That's where the current standard of care sits right now. For acute pain management we often use very high doses of opioid drugs like morphine, hydromorphone, and fentanyl. Opioids are unlikely to cause addiction in the acute setting, but can cause concern for some patients and treating physicians. For that reason, pain can often be undertreated for rattlesnake envenomations.

What should we do? Remember, only about 2% of patients develop significant bleeding. The closest thing we have to science is a study on NSAIDs given to patients bitten by copperheads (Agkistrodon contortrix), another pit viper related to rattlesnakes. The study did not show increased risk of bleeding in copperhead envenomated patients. We should take this study with a large grain of salt because copperheads are known for causing very mild hemotoxicity as compared to rattlesnakes. What have we seen? Of our 35 significant bleeds, one patient was given ibuprofen in the hospital and two patients were on daily aspirin at home.

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However, our non-bleeding patients are also not often given NSAIDs, to the tune of about 0.25-1%, so we don't have much to compare against.

Based on this evidence, we cannot form a strong recommendation. It appears unlikely that patients being treated with antivenom will be significantly harmed by NSAIDs for pain relief; however, the current standard of care would be to avoid them, and use opioids. This is likely fertile ground for more research, and perhaps there will be more to say on this topic in the future. Our next letter will cover the other side of hemotoxicity, where certain snakes actually cause blood clots!