NEWS FROM THE PIT

Arizona Poison and Drug Information Center

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sPLA2 Inhibition for the Treatment of Snakebite Envenoming

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In the United States, approximately 10,000 people are bitten by venomous snakes each year. These patients are at risk for chronic pain, functional disability, and occasionally, death. Worldwide, there are an estimated five million venomous snakebites annually, resulting in over half-a-million cases of death or permanent disability.

At present, the only direct treatment available for snakebite envenoming is antivenom, which is composed of antibodies to snake venom produced by horses or sheep inoculated with small quantities of venom from specific snake species. When there is a good match between the antivenom and the offending snake's venom and when administered soon after the bite, antivenom can significantly improve outcomes. Unfortunately, because antivenom is expensive to make and often requires refrigeration, well-matched antivenom is often not available where economic and health infrastructure resources are limited. As a result, in some places, there is no antivenom at all. Further limitations of antivenoms are that they must be given in a healthcare setting via an IV (i.e. they cannot be taken by mouth) and that large-sized antibodies are confined to the blood stream so have limited ability to neutralize snake venom toxins that have already diffused into tissues.

NEWSLETTER HIGHLIGHTS

Image 1 caption: adult Red Diamond Rattlesnake, Crotalus Ruber, from Riverside County, California

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Image 2 caption: Puff Adder, Bitis arietans, South Africa

One of the most important toxins that has been found in snake venom are a family of enzymes called secretory phospholipase A2s.

Image 3 caption: Copperhead, Agkistrodon contortrix

Recognizing the burden of snakebite and some of the limitations of existing treatments, researchers are now exploring a different approach: the use of small molecule Direct Toxin Inhibitors. This approach builds on research called proteomics – the study of proteins - applied to snake venom. Through this research, scientists have identified the toxins in the venom of many of the world's medically important venomous snakes, with the possibility that a novel therapy might be identified that would target one of these toxins.

One of the most important toxins that has been found in snake venom are a family of enzymes called secretory phospholipase A2s. Secretory phospholipase A2s (sPLA2s) are found in more than 95% of snake venoms, including all venomous snake species native to the United States. sPLA2s are also some of the most enzymatically active toxins found in snake venom and cause injuries in multiple ways through two very consistent mechanisms: 1) sPLA2s break down fats found in the body, resulting in the release of inflammatory compounds, and 2) sPLA2s have a non-enzymatic pore-forming function that damages cell membranes, disrupting cellular function. (Gutierrez 2013)

Snake venom sPLA2s are known to contribute to a number of different pathologies, including both tissue injury following bites from rattlesnakes as well as neurotoxicity following bites from elapids such as coral snakes and kraits. A more complete list of pathologies that can result from snake venom sPLA2s include:

- Weakness and paralysis, leading to respiratory failure, suffocation, and death
- Destruction of red blood cells (hemolysis), leading to anemia and kidney injury
- Alterations in the normal clotting process, leading to abnormal clotting and bleeding
- Drops in blood pressure, leading, in severe cases, to cardiovascular collapse
- Painful destruction of muscle, leading to deformities and amputation

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Based on these observations from snakebites and venoms from all over the world, developing a small molecule that can directly inhibit sPLA2 is a promising area for innovation and modernization of the treatment of snakebite that remains largely unchanged since the 19th century. A leading candidate for this role is a drug named varespladib, which appears to be a potent inhibitor of all snake venom sPLA2 enzymes and which can be formulated to be taken orally or administered through an IV. The oral formulation has been found to be stable in hot and humid climates, creating the potential for a therapy that can be used prior to hospital arrival in the U.S., as well as in low and middle-income countries with a high burden of snakebite morbidity and mortality. Varespladib was previously studied for the treatment of a variety of diseases including sepsis, arthritis, and coronary artery disease. Although varespladib was not found to be an effective treatment for these conditions, those earlier studies have provided invaluable information about the safe and appropriate dosing of the drug.

During 2022, researchers at the Arizona Poison and Drug Information Center, in collaboration with the public benefit corporation Ophirex, enrolled 12 patients bitten by rattlesnakes as part of a clinical trial comparing the efficacy of oral varespladib vs. placebo in addition to usual care, including antivenom. These data, combined with data from a variety of snake venoms from six other U.S. hospitals and six hospitals in India will be analyzed in 2023. A study of the intravenous formulation is also being planned. Through the hard work and clinical expertise of members of the Arizona Poison and Drug Information Center and the generosity of patients participating in the trial, we will soon have a better understanding of the potential of sPLA2 inhibition to treat venomous snakebites.

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Drs. Stephen Samuel (Ophirex Vice President of Clinical Medicine) and Tim Platts-Mills (Ophirex Chief Medical Officer) listen to a senior resident at a hospital in southern India present the case of a University student bitten by a common krait (July, 2022).

Central American Rattlesnake, Crotalus simun, in situ in Guanacaste Province, Costa Rica.