New drug combinations raise hopes of effective, locally administered snakebite treatment

December 14 2023

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New drug combinations could protect snakebite victims from the devastating, life-changing injuries caused by toxic venom, suggests

research led by Lancaster University.

Existing antivenom treatments are largely ineffective against the tissue destruction caused by the cytotoxic venomous bites of a variety of different snake species, including many vipers, such as north American rattlesnakes, African adders and Latin American lanceheads.

Antivenom is currently received intravenously when a patient arrives at hospital, at which point much of the irreversible tissue damage has been done. The bites can cause rapid destruction of skin, muscle and bone and cause permanent injuries and disfigurements, including limb loss.

However, a new study shows that a combination of repurposed small molecule drugs could inhibit specific snake venom toxins and offer the potential to be rapidly administered in the field immediately following a snakebite. The findings are published in *Nature Communications*.

Lead researcher Dr. Steven Hall, formerly of Liverpool School of Tropical Medicine and now at Lancaster University, said, "Snakebite affects millions of people yearly with upwards of 400,000 being permanently injured as a result, which is why this study is so promising. We successfully showed that combining two drugs that target just two different snake venom toxin families can almost completely inhibit the skin necrotizing activity of a wide range of geographically distinct snake species with differing venom profiles."

"Even more impressive is the fact that this reduction in necrosis remained significant even when the drugs were administered up to an hour after the envenoming event in vivo."

Promisingly, these drug combinations showed effectiveness against several snakes with drastically different venom toxin profiles, raising hopes of an effective future pan-species, pan-continental snakebite

therapy that could protect hundreds of thousands of people each year.

Professor Nicholas Casewell, Head of the Center for Snakebite Research & Interventions (CSRI) at Liverpool School of Tropical Medicine (LSTM), said, "Our findings are exciting because they show that combinations of drugs that have already been shown to be safe in human clinical trials can prevent local tissue damage caused by different snake species.

"This is important because cytotoxic snake venoms cause hundreds of thousands of cases of morbidity each year across the world. Identifying new, affordable and safer treatments for snakebite is a priority to mitigate the devastating impact caused by this neglected tropical disease."

Dr. Hall led the study of repurposed small molecule drugs 2,3-dimercapto-1-propanesulfonic acid (DMPS), marimastat, and varespladib, which target different toxins found in snake venoms.

In preclinical studies using human skin cells and animal models, rationally designed combinations of these three drugs were determined to effectively protect against the necrotic effects of venoms from genetically and geographically diverse medically important snake species—something that current antivenom treatments cannot do. While much work is still needed before these drug combinations are used in snakebite patients, the researchers hope that these findings will accelerate support for their onward development into clinical trials.

The findings follow previous research led by CSRI at LSTM, published in 2021, that showed how similar drug combinations could prevent the potentially lethal systemic effects of snakebite envenoming, including the bleeding disturbances caused by geographically diverse vipers.

More information: Steven R. Hall et al, Repurposed drugs and their combinations prevent morbidity-inducing dermonecrosis caused by diverse cytotoxic snake venoms, *Nature Communications* (2023). DOI: 10.1038/s41467-023-43510-w