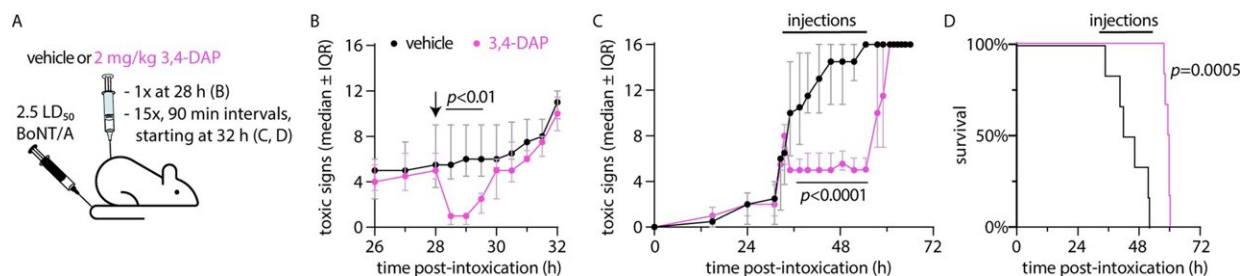


New research shows drug used to treat neuromuscular weakness could counter botulism

July 25 2022



Bolus administration of 2 mg/kg 3,4-DAP reverses clinical signs of botulism and prolongs survival. **A** Summary of experimental models. **B** Median \pm interquartile ratio (IQR) toxic signs for rats given a single injection of vehicle (black) or 3,4-DAP (pink) at 28 h after challenge with 0.44 ng/kg BoNT/A (2.5 LD₅₀ BoNT/A; n = 4 per group). Toxic signs were monitored at 30 min intervals. Arrow indicates time of injection. **(C, D)** Median \pm IQR toxic signs **(C)** and survival curves **(D)** for rats given 15 injections of vehicle (black) or 3,4-DAP (pink) at 90 min intervals, starting 32 h after challenge with 2.5 LD₅₀ BoNT/A (n = 6 per group). Black lines above graphs indicate treatment period during which injections were administered. Credit: James B. Machamer et al, *Molecular Medicine* (2022). DOI: 10.1186/s10020-022-00487-4

Wake Forest Institute for Regenerative Medicine (WFIRM) researchers are investigating a drug used to treat neuromuscular weakness as a potential treatment for botulism, a rare but serious disease.

Botulinum neurotoxins (BoNTs) are a family of bacterial poisons—the most poisonous substances known—responsible for the clinical disease known as [botulism](#). These neurotoxins act within [nerve terminals](#) to destroy proteins necessary for muscle contraction, causing paralysis that develops into respiratory arrest and can lead to death. The Centers for Disease Control (CDC) considers botulinum [neurotoxins](#) a Tier 1 agent, posing the highest risk following accidental or deliberate misuse.

The deliberate misuse aspect of the toxin is what drives the WFIRM researchers and their work to find a treatment. Currently, the only specific treatment for botulism is early administration with antitoxin. However, antitoxin is only effective if administered before prior botulism symptoms are evident. Once symptoms emerge, three out of four patients require long-term artificial ventilation for survival.

"Despite decades of effort, there are no antidotes for the life-threatening consequences of botulism. This failure is primarily because the toxin hides within the nerve terminal, where it poses a challenging target for delivery of therapeutic molecules," said corresponding author of the paper Patrick McNutt, Ph.D., who leads this research effort at WFIRM.

The researchers build on their previous work to show that administration of the FDA-approved drug 3,4-diaminopyridine (3,4-DAP) reverses botulism symptoms in a pre-clinical model. The drug is an approved treatment for Lambert Eaton Myasthenic Syndrome, an autoimmune disease caused by reduced acetylcholine release and neuromuscular weakness. Botulism paralysis is caused by reduction of [acetylcholine](#) release from motor nerve terminals to subthreshold levels required for [muscle contraction](#).

Acetylcholine is the chief chemical messenger of the parasympathetic nervous system, the part of the autonomic nervous system that contracts smooth muscles, dilates blood vessels, and slows heart rate.

For this study, recently published in *Molecular Medicine*, the researchers developed a continuous 3,4-DAP infusion model and measured dose-dependent effects on toxic signs and survival after a lethal dose of botulinum neurotoxin. They found that continuous infusion with the drug produces rapid and sustained therapeutic benefits while survival requires continuous infusion for longer than four days.

"This is the first small-molecule therapy to directly reverse toxic signs and promote survival when administered post-symptomatically after a lethal dose of botulism," said McNutt. "Our data supports the immediate clinical use of DAP in botulism patients."

The authors declare no competing interests. Additional co-authors include James B Machamer, Edwin J Vazquez-Cintron, Sean W O'Brien, Kyle E Kelly, Amber C Altvater, Kathleen T Pagarigan, Parker B Dubea and Celinia A Ondeck.

More information: James B. Machamer et al, Antidotal treatment of botulism in rats by continuous infusion with 3,4-diaminopyridine, *Molecular Medicine* (2022). [DOI: 10.1186/s10020-022-00487-4](https://doi.org/10.1186/s10020-022-00487-4)

Provided by Atrium Health Wake Forest Baptist

Citation: New research shows drug used to treat neuromuscular weakness could counter botulism (2022, July 25) retrieved 19 April 2024 from <https://medicalxpress.com/news/2022-07-drug-neuromuscular-weakness-counter-botulism.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.