

TOXIN MEDICAL COUNTERMEASURES - DEVELOPMENT OF NOVEL, BROAD-SPECTRUM COUNTERMEASURES FOR TOXIN EXPOSURE

Evaluation Of The Ability To Prevent Renarcotization After Carfentanil Challenge In Canines

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Background: Weaponized, ultra-potent opioids pose a significant threat to warfighters, especially in remote deployments where access to medical care is limited. Current antidotes (e.g., naloxone) are effective for immediate reversal of opioid effects but do not offer prolonged protection, leading to potential renarcotization where symptoms can reoccur hours after treatment. Renarcotization often demands repeated doses of naloxone and continual observation. High-dose naloxone and nalmefene can extend protection beyond standard naloxone but fail to provide sufficient coverage over the necessary duration. There is therefore an urgent need for a long-acting antidote to reverse opioid poisoning and provide extended protection from renarcotization. **Purpose:** The research purpose is to develop a long-acting antidote capable of sustaining protection against opioid poisoning and renarcotization, addressing the critical need for prolonged care in battlefield and far forward deployments.

Objective: The objective is to demonstrate the efficacy of CP216, a new naloxone formulation, in extending protection against synthetic opioid poisoning in animal models. **Research Rationale:** Due to the short metabolic half-life of current antidotes, there is a pressing need for a solution that can protect Warfighters for extended periods without repeated dosing and constant monitoring.

Relationship to Other Areas: This research builds on previous studies of opioid antagonists and controlled-release pharmaceuticals, incorporating advanced drug delivery systems like microparticles to enhance the duration and efficacy of antidote action. **Methods:** The research involved multiple studies including:

- Pharmacokinetic Studies to assess the duration of naloxone levels in plasma post-administration of CP216.
- Efficacy Studies comparing recovery and protection periods between canines treated with CP216 and a control group after carfentanil challenge.
- Prophylaxis Study to evaluate the preventive capabilities of CP216 against opioid poisoning.

Preliminary Results: In efficacy studies, canines treated with CP216 showed sustained protection for 8 hours without additional naloxone doses, in contrast to the control group that remained lethargic and required repeated rescue naloxone, constant monitoring, and thermal support. Opioid poisoning indicators, including respiratory rate, heart rate, blood oxygen levels, core body temperature, and general affect, showed favorable responses to CP216 administration. Pharmacokinetic studies confirmed extended naloxone plasma levels for 20 hours, and a dose-response curve was established for carfentanil renarcotization. The Prophylaxis Study demonstrated efficacy of naloxone-encapsulating microparticles (MP-NLX) within CP216 as a prophylaxis against carfentanil challenge. Canines pre-treated with MP-NLX remained alert and maintained vital parameters for more than 8 hours post carfentanil challenge, underscoring MP-NLX's potential as a prophylactic treatment to prevent opioid poisoning. **Preliminary Conclusions:** CP216 represents a significant advancement in the development of synthetic-opioid antidotes, and shows promise as a long-acting antidote, providing extended protection against renarcotization without the need for frequent medical intervention in opioid poisoning scenarios. CP216 also has the potential for prophylaxis against opioid poisoning. **Impact to the DTRA JSTO Mission and the Joint Force:** The development of CP216 aligns with the DTRA JSTO mission to enhance the resilience and survivability of the Joint Force by providing effective medical countermeasures against chemical threats, thereby improving operational effectiveness and warfighter safety in environments at high risk for opioid exposure.

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