

REPURPOSING TO SPEED CHEMICAL AND BIOLOGICAL MEDICAL COUNTERMEASURE DISCOVERY AND DEVELOPMENT

A Non-human Primate Model Of Carfentanil Overdose: Rescue Treatments That Completely Prevent Renarcotization

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We established a physiological and overt intoxication model using African green monkeys (*Chlorocebus aethiops sabeus*) and a high dose of injected carfentanil. Intoxication is rapid and rescue is typically required within 10 minutes. Naloxone, administered at a 10 mg human-equivalent dose (HED; 0.355 mg/kg), is immediately effective but is limited by its short duration of action. Specifically, animals typically return to a state of severe respiratory depression within about 2.5 hours, necessitating further medical intervention. Therefore, we studied two novel medical countermeasures: nalmefene and CS-1131. Nalmefene is a mu-opioid antagonist with high affinity and a much longer duration of action, but little is known about its efficacy against carfentanil. Therefore, we covered a range of doses from 3.2-32 mg estimated HED (based upon allometric scaling) through both the intramuscular and intranasal routes. CS-1131 is a novel opioid scavenger (licensed by Clear Scientific, Inc) capable of binding carfentanil stoichiometrically, inactivating the synthetic opioid, and then eliminating the scavenger-opioid complex through renal excretion. Results show that both countermeasures were superior to naloxone alone and exhibited dose-dependent efficacy. This research provides strong proof-of-concept and sets the stage for additional studies of longer-lasting opioid antagonists administered through various routes, and for the further development, characterization, and refinement of novel opioid scavenger molecules. This non-human primate model can be utilized to study potent synthetic opioids, new analogues, and other novel countermeasures in a way that yields predictive results to support human clinical trials.

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