AI/ML AND VIRTUAL HUMAN PLATFORMS FOR THREAT AGENT HAZARD ASSESSMENT AND MEDICAL COUNTERMEASURE DISCOVERY AND DRUG DEVELOPMENT

Physiology-based Modeling To Explore Repeat Dosing Of Nasal Naloxone After Opioid Overdoses

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Opioid use is an endemic part of society with yearly increases in overdose and death rates nationally. As rates of overdose incidence increase, the use of the safe and effective reversal agent, Naloxone (specifically in the form of a nasal rescue spray) is being fielded by emergency medical technicians (EMTs) at a higher rate. Despite these deployments of rescue products, incidences of death are continuing to increase. Evidence suggests that repeated dosing of a Naloxone nasal spray (such as Narcan) is becoming more common due to the amount and type of opiate being abused and the initial dose only prolonging time-to-death without achieving resuscitation. Although there are TCCC guidelines and other strong evidence justifying the benefits of Naloxone related to opioid reversals, there are still not repeated dosing guidelines as a function of opiate substance and the substance dose the patient has taken. Goal directed dosing is promising, where respiratory markers are being used as an indication of the patient recovery but require time and understanding by the EMT. We constructed and maintain a whole-body physiology engine, BioGears, used for medical research and training simulations. This engine includes a drug dispersion and diffusion model, based on the work of Rodgers et al. (2005, 2006). The model includes both the pharmacokinetic (PK) and pharmacodynamic (PD) responses of drugs, including opiates (Morphine and Fentanyl), after intravenous injection and the effect on respiratory depression. We then expanded the drug model to include nasal deposition and administration of naloxone to investigate repeat dosing requirements for large overdoses and analyze how the two opiates may influence these requirements. By designing the model to include circulation and respiration we can investigate physiological markers and responses that may be used in goal directed therapy rescue treatments. Many opioids cause irreparable harm in high doses due to its negative effect on oxygen saturation in the blood, thus causing hypoxia. Therefore, we developed simulations which monitor oxygen saturation of the patient's blood and repeats Naloxone dosing when the saturation drops below ninety percent (approximately five percent below the lower threshold of the healthy range). Through numerous four-hour treatment scenarios where the only intervention is nasal naloxone, the data shows repeat dosing to improve survivability in fentanyl and morphine dosages up to 116.7% percent higher than with single or no dosing. In scenarios with opioid doses that still resulted in death, the time-to-death was still increased. Our simulation does not account for negative side effects that could potentially arise from these repeat dosages. We show that naloxone is highly effective at reversing respiratory symptoms of the patient and recommend dosing requirements as a function of opiate and amount administered. This can be shown through restoration of cardiovascular and respiratory baselines in addition to increasing time-to-death in higher doses. By improving time-to-death, the likelihood of emergency responders and medics to get overdosed individuals to a more appropriate care center is increased. BioGears' in situ capabilities promote a better understanding of physiology-based PK/PD medical countermeasures with full-body understanding.

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