MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Spatiotemporal Inflammation Associated With Agent Exposure

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Chemical warfare agents (CWAs) and toxic industrial chemicals (TICs) are still some of the most feared and deadly weapons on earth, despite over a century of developing countermeasures. Additionally, newer pharmacological agents have proven to be exceedingly toxic and have the potential to be used in lethal wide-scale chemical attacks. While these agents can represent many different classes of compounds with disparate physicochemical, physiological, and pharmacological properties, a common biological response is inflammation. Investigations of cellular responses involved in a range of inflammatory processes have contributed to the advancement of treatments for a variety of morbidities. Thus, a comparative analysis of inflammatory responses following a variety of chemical agents could enhance strategies for understanding and combatting exposures. Research presented will include establishing the parameters for a comparative analysis of inflammation using fentanyl in an SKH1 mouse model to explore organ-specific, spatiotemporal inflammation. While analysis is still early, our eventual results will include 4 additional chemical agents and are expected to represent a true comparative understanding of inflammatory responses to disparate agents/exposures and ultimately enable the discovery of new universal therapeutic targets and biomarker targets for differential diagnoses.

In this study, equipotent doses were experimentally determined (Highest Non-Lethal Dose (HNLD), LD10, and LD50), followed by a two-step diagnostic process: 1) localize organ/tissue inflammation in whole animals via fluorophore- and radiolabeled inflammation probes, followed by 2) sample collection and ‘omics analyses of inflamed tissues post-exposure. Specifically, SKH1 mice were administered subcutaneous fentanyl citrate in Ringer’s solution at HNLD, LD10, or LD50 doses before data collection at 40 minutes, 6 hours, 24 hours, and 7 days post-exposure. Subjects were either analyzed for biomarkers using an immune monitoring multiplex ELISA panel, fluorescence imaged using indocyanine green (ICG), a clinical dye indicating perfusion and vascular damage, or imaged via 18F-Fluorodeoxyglucose (18F-FDG)-Positron Emission Tomography (PET) scan.

Imaging results indicated decreased brain perfusion at 40 minutes, followed by increased heart and lung perfusion up to 6 hours post-fentanyl with a return to baseline by 24 hours; further, imaging revealed decreased glucose uptake in brain and heart up to 24 hours post-dose, while the lungs recovered by 7 days. Multiplex ELISA assay determined dysregulated cytokine and chemokine concentrations in hearts and lungs through 7 days post-dose, while cortex recovered to baseline. These data show that the physiological responses to fentanyl exposure are not limited to acute respiratory depression and the impacts of a single dose are prolonged with the absence of outward symptoms. Future studies already in progress include additional chemical agents (e.g., CL, DFP, GB, HD) and will include additional ‘omics data for a complete comparison of inflammatory processes associated with acute lethal exposures in a mouse model.