COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Optimizing Drug Delivery To The Respiratory Tract Using In Silico Models

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In theater, warfighters need access to rapidly deployable medical countermeasures targeted to the site of injury. To this end, researchers have been turning towards inhalable countermeasures that can act as rapid pre- or post-exposure prophylaxis for targeted drug delivery in the upper and lower respiratory tract. These devices can be highly efficient, protective, easy to deploy, and lightweight – reducing the overall cost, risk, and weight of warfighter carry. Ensuring the safety of warfighters and preserving the integrity of the mission requires fast-response interventions. For this presentation, Applied Research Associates (ARA) will highlight the need for in silico models that can be iteratively developed to inform pre-clinical and clinical studies and optimize drug delivery to elicit therapeutic outcomes. We will highlight one recent application of this science, discussing how modeling and experimentation has been able to work in tandem in the development of novel prophylactics that counter the onset of high-altitude pulmonary edema (HAPE) within hours after rapid transport to high elevations. Similar to deployment of countermeasures in a CB-impacted environment, medical countermeasure treatment for HAPE requires optimal particle size distribution and concentration of the aerosolized drug to target affected sites within the pulmonary region. Otherwise, over- or under-dosing may lead to adverse side effects or inadequate therapeutic responses. For this effort, we utilized mathematical modeling to aid in drug formulation and delivery by determining the fate of inhaled drugs in HAPE patients. Modeling efforts included construction of realistic lung geometries in humans and laboratory animals, drug formulation based on physicochemical properties of the compound, and development of a mathematical model to study transport and deposition of aerosolized drug particles in the lungs. For prophylactics that remain in particulate phase and are inhaled via normal breathing, our predictions showed that at normal breathing only 7% of generated particles reached and deposited in the pulmonary regions of the rat lung, which were the target sites for drug delivery. We were also able to show the peak deposition to occur for particles near 2 micrometers in rats. In humans and via oral breathing, about 15% of particles deposited in the pulmonary region for particle sizes around . In general, optimal delivery size of particles depends on physicochemical properties of the prophylactics and drug inhalation profile, which can be determined for the scenario of interest. In conclusion, modeling as a part of experimental design can be used to show the ideal delivery platform for desired application of drug as well as an understanding of how to extrapolate results from animal models to humans.

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