LOCALIZING CHEMICAL AND BIOLOGICAL THREAT DETECTION

Clinical Biomarkers Of Acute Toxicity Induced By Mustard Vesicant Exposure In The Ocular Tissue

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Background: Sulfur mustard (SM) is a notorious chemical warfare agent, infamously known as the king of battle gases. It is a bifunctional alkylating agent that causes extensive ocular damage owing to eyes being highly aqueous in nature. SM-caused extensive ocular injuries and sudden vision impairment could be most debilitating for soldiers and civilians alike. Though corneal injuries following SM exposure have been studied, their overall in-depth clinical assessments are lacking.

Objective: To determine the biomarkers of acute ocular injuries upon mustard vesicant exposure utilizing non-invasive clinical assessments. Since SM use is highly regulated, nitrogen mustard (NM), also a bifunctional alkylating agent with similar toxicity properties and widely used laboratory prototype of SM, was used in the current study.

Methods: Studies were performed utilizing two NM exposure times utilizing male New Zealand White rabbits. The right eye of the animals was exposed to 1% NM for either 2 min (low) or 5 min (high) and the left eyes served as saline (vehicle) exposed controls for the respective durations. General animal behavior was recorded daily, and the assessments of clinical parameters using ocular imaging (pattern electroretinogram [PERG], optical coherence tomography, slit lamp imaging, and digital imaging) and vitals were performed at day 3, 5 and 7 post NM exposure.

Results: The data indicated that NM exposure caused an increase in corneal opacity, corneal ulceration, corneal neovascularization (NV), iris NV, conjunctivitis, and eyelid notching at both NM exposure durations, compared to controls. A significant and marked increase in corneal opacity, corneal ulceration and conjunctivitis was observed at day 3, 5 and 7 post both NM exposure time points. NV in the cornea and iris was also observed as early as day 3 post NM exposure. A significant increase in eyelid notching was also observed at day 3 post NM exposure, which decreased as a function of time in both NM exposure durations. General animal behavior was also monitored including level of squinting, ocular edema, and general face expression, where an increased squinting and ocular swelling were observed in the initial days after NM exposure. The squinting, edema and face grimace occurred in a duration of NM exposure manner and decreased as a function of time. Other behavioral aspects, such as movement, eating/drinking, feces/urine output and weight were also monitored and found to be normal throughout the study period. PERG analysis of the voltage in the retinal ganglions showed that there was decreased voltage particularly with the higher duration NM exposure, indicating impaired nerve/electrical activity in the visual context.

Conclusion and Implication: The outcomes indicate that mustard vesicant exposure causes ocular damage that can be assessed using non-invasive clinical parameters; notably, corneal opacity/ulceration, NV in the cornea and iris, conjunctivitis, and PERG measurements indicated ocular mustard insults as early as 3 days post-exposure. Furthermore, our results suggest that these biomarkers could provide the knowledgebase needed for the development of non-invasive detection capability and aid in the development of countermeasures in future.

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