BiPS as a Countermeasure for Vesicant-Induced Injury in Mouse Ear Skin

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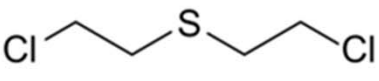
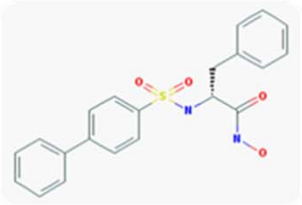
Sulfur mustard (SM) is a bi-functional alkylating chemical warfare agent. It is important to develop countermeasures to aid in promoting SM induced skin wound healing. During SM skin injury, MMP-9 degrades the basement membrane at the dermal-epidermal junction, resulting in skin separation, blister formation, and a strong inflammatory response. The present study tests MMP-2/MMP-9 inhibitor, (2R)-[(4-Biphenylylsulfonyl)amino]-N-hydroxy-3-phenylpropionamide (BiPS) a widely used anti-inflammatory compound, using the mouse ear vesicant model (MEVM). The inner ear skin was directly exposed to SM (0.08 mg) with or without BiPS (25 mM) treatment. Animals were divided into four groups including untreated, BiPS only, SM only, and SM with BiPS. Punch biopsies were taken at 1, 3, and 7 days post-exposure. The degree of hyperplasia and epidermal thickness of the skin was measured as an index of edema and inflammation. In addition, dermal thickness and relative skin weights were measured. For inner ear, the epidermal thickness of SM only samples extensively increased 170 % compared to naïve at 3 days and remained elevated at 7 days, With BiPS treatment, the epidermal thickness showed 25% reduction in SM+BiPS samples compared to SM only samples by 72 hr. Results of the outer ear skin thickness were similar but less dramatic than the inner ear. Skin exposed to SM had peak thickness at 3 days; similar data observed in ear weight and dermal thickness measurement. The thickening of the epidermis was not limited to only the treated side (inner ear) suggesting that it is either caused by systemic effects or SM is able to penetrate through the cartilage to induce skin damage on the outer ear. Overall, BiPS appeared to improve the hyperplasia and decrease epidermal thickness significantly across the SM treated samples. Further studies will help to elucidate the therapeutic effect of BiPS on SM induced skin wound repair. Supported by NIH U54AR055073, P30ES005022, and R25ES020721.





0.08mg SM + 25mM BiPS

Mouse ear vesicant model (MEVM)
Application to inner surface of ear

1day
3day
7day

Punch biopsies post-exposure

- 4 groups
  - Naïve
  - BiPS-only
  - SM-only
  - SM+BiPS