

Etiology of 8-Methoxypsoralen Phototoxicity in Mouse Skin is Dependent on Vehicle, Exposure Time and Administration Site.

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ABSTRACT

We have characterized the effects of dermal exposure of 8-Methoxypsoralen (8-MOP) plus UVA light on different mice strains, comparing dosing site (ears vs. dorsal skin), time post-dosing, and solvent vehicle. We observed delayed time-dependent photoirritation in mouse ears, as well as dose- and time-dependent phototoxic effects of 8-MOP on depilated dorsal mouse skin in Balb/c, Swiss Webster and SKH-1 mice. Swiss Webster mice were most variable and least sensitive and predictive. SKH-1 hairless mice were slightly more sensitive than depilated Balb/c mice, but these two strains were equally predictive of 8-MOP-induced phototoxicity. Dimethylsulfoxide (DMSO) proved to be a superior vehicle in all respects when compared to acetone, which severely attenuated the phototoxic responses. Use of DMSO as the vehicle consistently produced sensitive (down to 0.01% 8-MOP) and reproducible photoirritation.

METHODS AND MATERIALS

- Swiss Webster, SKH-1 and Balb/c mice ordered from Ace Animals, Boyertown, PA, or Jackson Laboratories
- Hair was removed 24-48 hours prior to dosing by clipping with an electric clipper (and some mice then depilated with Nair®)
- Honle solar simulator with UVB cutoff filter used for UVA irradiation (99.7% UVA; 0.3% UVB)
 - Distance from Solar Simulator and duration of irradiation to produce 10 J/cm² of UVA
- The prototypical patent phototoxin (8-Methoxypsoralen, 8-MOP), a commonly used as a positive control in photobiology assay was used in all experiments
- Doses of 8-MOP applied to dorsal skin or ear (25 ml) in various vehicles, at concentrations between 0.01% and 1.0%
- Dose applied, allowed to sit for 40-45 minutes, and wiped off with wet gauze
- Ear swelling (edema) measured, erythema graded as per modified Draize score

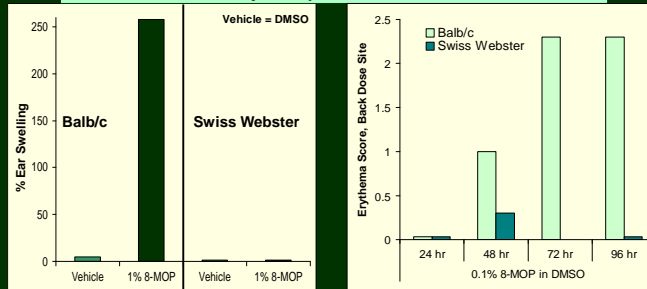
RESULTS

Initially, it was difficult to elicit a phototoxic response to 8-MOP in the clipped dorsal skin of Swiss Webster mice, using acetone vehicle. A change to Balb/c mice using DMSO as vehicle produced measurable responses, which became significant only when the Balb/c mouse skin was depilated after clipping, and the observations were extended post 48 hours until at least 72 hours. Based on the reproducible results in denuded skin, Balb/c to SKH-1 mouse strains were compared for sensitivity to 8-MOP phototoxicity. Once the Balb/c mice were denuded, and DMSO was used as the vehicle (acetone proved a poor vehicle) there was no biologically significant difference in the induction of erythema in Balb/c when compared to SKH-1 mice.

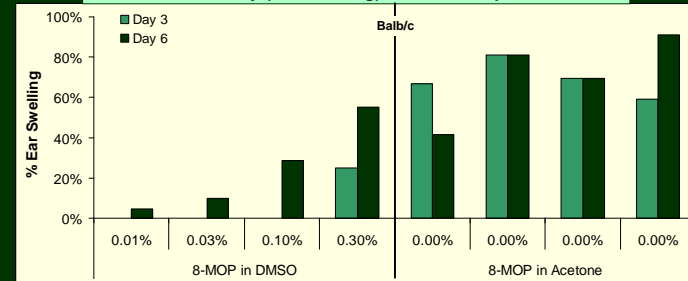
CONCLUSIONS

- The dorsal skin and ear (dorsal auricle) of the Balb/c and SKH-1 mice are useful test systems for phototoxicity assays.
- DMSO, in contrast to Acetone, is a superior vehicle for dermal dosing (topical administration) of the benchmark positive control phototoxin, 8-Methoxypsoralen.
- The Swiss Webster mouse is not a sensitive model for dermal phototoxicity assays.
- Depilation (short chemical denuding) of the dorsal skin of Balb/c and SKH-1 mice produces a sensitive and responsive dosing site, comparable to the mouse ear.
- Unexpectedly, a longer time course of 72 hours (to as much as 5-7 days) is necessary to observe the full elicitation of both erythema (skin redness) and edema (ear swelling). Shorter time points of 1, 4, or 24 hours were of little use.

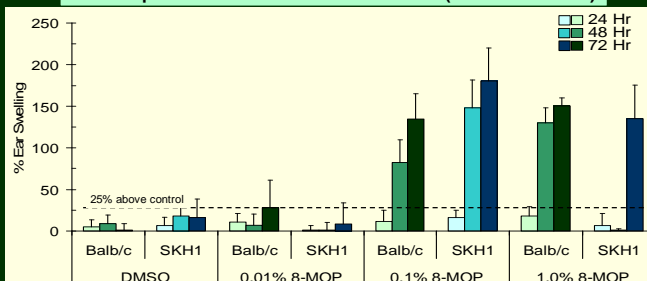
Phototoxicity is Dependent on Mouse Strain



Phototoxicity (Ear Swelling) is Vehicle Dependent



Dose-Dependent 8-MOP-Induced Ear Edema (Balb/c vs. SKH-1)



Dorsal Skin – Draize Erythema Score – Time Course

