Synopsis of Original Research Paper

Strategic development of a photosafety evaluation system for chemicals contributing to 3Rs principle in animal experiments

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Drug-induced phototoxicity is caused by exposure to sunlight after topical and/or systemic administration of photosensitive chemicals. Both photoreactivity of chemicals and its distribution to sunlight-exposed tissues are key determinants of drug-induced phototoxicity. Recently, 3Rs principle (replacement, reduction, refinement) tends to be compliance in pharmaceutical and cosmetic industries. In this study, a new photosafety screening strategy based on the combined use of a reactive oxygen species (ROS) assay and an *in vitro* skin permeation test was developed as an alternative to animal experiments. The phototoxic risk of 6 phototoxic compounds, acridine (ACD), furosemide (FSM), hexachlorophene (HCP), 8-methoxypsoralen (MOP), norfloxacin (NFX), and promethazine (PMZ), were evaluated based on photochemical and in vitro skin deposition properties. An *in vivo* phototoxicity test in rats was undertaken to verify the prediction capacity of the proposed system. All tested compounds exhibited strong absorption in UVA/B regions, and generation of significant ROS from all tested chemicals were observed under simulated sunlight exposure. The steady-state concentration (C_{ss}) values of tested compounds in removed rat skin were estimated on the basis of the skin permeability. The C_{ss} values of ACD, FSM, HCP, MOP, NFX, and PMZ were calculated to be 69, 2.8, 57, 50, 3.2, and 59, respectively. On the basis of the ROS data and C_{ss} values of tested compounds, the phototoxic risk of tested compounds was predicted. The predicted phototoxic risk by proposed screening system (ACD > HCP > MOP > PMZ > FSM≒NFX) was mostly in agreement with the observed *in vivo* phototoxicity (ACD > HCP > MOP > FSM≒PMZ > NFX). From these findings, the phototoxic risk of tested compounds could be predicted by combined use of ROS assay and *in vitro* skin permeation test, and the new photosafety screening system would contribute to product development and animal welfare.