Toxicology in Vitro 28 (2014) 515–523

Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

Intra-/inter-laboratory validation study on reactive oxygen species assay for chemical photosafety evaluation using two different solar simulators

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ARTICLE INFO

Article history:
Received 25 September 2013
Accepted 14 November 2013
Available online 30 December 2013

Keywords:
Phototoxicity
Photoreactivity
Reactive oxygen species
Validation
Inter-laboratory precision

ABSTRACT

A previous multi-center validation study demonstrated high transferability and reliability of reactive oxygen species (ROS) assay for photosafety evaluation. The present validation study was undertaken to verify further the applicability of different solar simulators and assay performance. In 7 participating laboratories, 2 standards and 42 coded chemicals, including 23 phototoxins and 19 non-phototoxic drugs/chemicals, were assessed by the ROS assay using two different solar simulators (Atlas Suntest CPS series, 3 labs; and Seric SXL-2500V2, 4 labs). Irradiation conditions could be optimized using quinine and sulisobenzone as positive and negative standards to offer consistent assay outcomes. In both solar simulators, the intra- and inter-day precisions (coefficient of variation; CV) for quinine were found to be below 10%. The inter-laboratory CV for quinine averaged 15.4% (Atlas Suntest CPS) and 13.2% (Seric SXL-2500V2) for singlet oxygen and 17.0% (Atlas Suntest CPS) and 7.1% (Seric SXL-2500V2) for superoxide, suggesting high inter-laboratory reproducibility even though different solar simulators were employed for the ROS assay. In the ROS assay on 42 coded chemicals, some chemicals (ca. 19–29%) were unevaluable because of limited solubility and spectral interference. Although several false positives appeared with positive predictivity of ca. 76–92% (Atlas Suntest CPS) and ca. 75–84% (Seric SXL-2500V2), there were no false negative predictions in both solar simulators. A multi-center validation study on the ROS assay demonstrated satisfactory transferability, accuracy, precision, and predictivity, as well as the availability of other solar simulators.

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1. Introduction

Drug-induced phototoxicity can appear in light-exposed tissues, elicited by topical or systemic application of drugs and exposure to sunlight or artificial light (Moore, 2002). Several classes of pharmaceutics cause phototoxic reactions in skin and/or eyes (Moore, 1998, 2002), including photoirritant, photoallergic, and photogenotoxic events (Epstein, 1983). Although drug-induced phototoxicity might not be a life-threatening side effect in most cases, phototoxicity has a major impact on quality of life and therapeutic compliance/outcomes. With the aim of reducing and

Abbreviations: 3T3 NRU PT, 3T3 neutral red uptake phototoxicity test; 8-MOP, 8-methoxypsoralen; CV, coefficient of variation; ECVAM, Europe Center for the Validation of Alternative Methods; GLP, Good Laboratory Practice; ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods; JaCVAM, Japanese Center for the Validation of Alternative Methods; KoCVAM, Korean Center for the Validation of Alternative Methods; OECD, Organisation for Economic Co-operation and Development; PABA, *p*-aminobenzoic acid; ROS, reactive oxygen species; SDS, sodium dodecyl sulfate; UV, ultraviolet; VIS light, visible light; VMT, Validation Management Team; ZEBET, International Centre for Documentation and Evaluation of Alternative Methods to Animal Experiments.

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http://dx.doi.org/10.1016/j.tiv.2013.11.014
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preventing phototoxicity, increasing attention has been drawn to hazard identification and risk management upon photosafety assessment of pharmaceutical products. A number of *in vitro* methodologies have been developed for photosafety assessment over the past few years. Guidance on the photosafety testing of medicinal products was established by regulatory agencies in the US and EU in the early 2000s (Seto et al., 2012), and the recent issuance of the draft ICH S10 photosafety guidance document also provided a detailed framework and guidance for photosafety evaluation of pharmaceutical substances and products (ICH, 2013). These guidelines describe photosafety assessment strategies on the basis of photochemical and photobiochemical properties, and *in vivo* pharmacokinetic behavior (EMEA/CPMP, 2002; FDA/CDER, 2002; OECD, 2004).

Previously, a reactive oxygen species (ROS) assay was developed for the photosafety assessment of pharmaceutical substances (Onoue et al., 2008b; Onoue and Tsuda, 2006), in which the generation of ROS such as singlet oxygen and superoxide from photoirradiated chemicals was monitored. The photo-excited phototoxins tend to generate ROS, triggering phototoxic events in the light-exposed tissues (Brendler-Schwaab et al., 2004; Epstein and Wintroub, 1985), and the photobiochemical responses of phototoxins could provide a rationale for the use of ROS assay in photosafety assessment. A multi-center validation study was previously carried out to establish and validate a standard protocol for the ROS assay, supervised by the Japanese Center for the Validation of Alternative Methods (JaCVAM) (Onoue et al., 2013). Outcomes from the validation study were indicative of the satisfactory transferability, inter-laboratory variability, and predictivity of the ROS assay, and these findings provided sufficient support for the ROS assay as an alternative method for photosafety assessment. However, the ROS assay in the previous validation study was conducted in only one solar simulator (Atlas Suntest CPS series), so the applicability of other solar simulators to the ROS assay has never been elucidated.

The present study was designed to validate a standard protocol for the ROS assay using different solar simulators, under the supervision of the Japanese Center for the Validation of Alternative Methods (JaCVAM) throughout the work. Since a UVA light source has been widely employed for the 3T3 neutral red uptake phototoxicity test (3T3 NRU PT) (Spielmann et al., 1994b), the present validation study focused on the compatibility of another solar simulator (Seric SXL-2500V2) commonly used for 3T3 NRU PT as an alternative to the Atlas Suntest series. In accordance with the previous study design, inter- and intra-laboratory validation studies were carried out to assess the transferability, assay precision, and predictive capacity of the ROS assay using 2 standard chemicals and 42 coded chemicals, including 23 phototoxins and 19 non-phototoxic drugs/chemicals.

2. Materials and methods

2.1. General conditions of the study

The validation study was coordinated as reported previously (Onoue et al., 2013). Briefly, the Validation Management Team (VMT) was organized under the JaCVAM, and the roles of the VMT were to design the study, to guide and facilitate the validation process, to evaluate the results and, on the basis of these, render subsequent decisions during the progress of the study, and to analyze the outcomes from the studies. The VMT was comprised of the trial coordinator, assistant trial coordinator, chemical management group, data analysis group, quality assurance group, and representatives of participating laboratories. The validation study and the quality assurance were carried out in the spirit of Good Laboratory Practice (GLP), although not all the participating laboratories routinely worked under GLP certification in accordance with the protocol provided by the VMT. All raw data and the data analysis sheet were pre-checked for quality in each laboratory and then reviewed by the quality assurance group of the VMT.

2.2. Participating laboratories

The seven participating laboratories are as follows: Laboratory 1 (Lab#1), Mitsubishi Tanabe Pharma Corporation, Safety Research Laboratories; Laboratory 2 (Lab#2), Food and Drug Safety Center, Hatano Research Institute; Laboratory 3 (Lab#3, lead laboratory), University of Shizuoka, School of Pharmaceutical Sciences; Laboratory 4 (Lab#4), Asahi Kasei Pharma Corporation, Pharmaceuticals Research Center; Laboratory 5 (Lab#5), ASKA Pharmaceutical Co., Ltd., Safety Research Department; Laboratory 6 (Lab#6), Shionogi & Co., Ltd., Drug Developmental Research Laboratories; and Laboratory 7 (Lab#7), Taisho Pharmaceutical Co., Ltd., Pharmaceutical Technology Laboratories.

2.3. Chemicals and reagents

As reported previously, chemicals for the validation study were selected by the chemical management group of the VMT in cooperation with Dr. Manfred Liebsch (ZEBET), Europe Center for the Validation of Alternative Methods (ECVAM), Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), and Korean Center for the Validation of Alternative Methods (KoCVAM). According to the reported *in vitro*/*in vivo* photosafety information and clinical observations (Durbize et al., 2003; Moore, 2002; Motley and Reynolds, 1989; Onoue et al., 2010; Peters and Holzhutter, 2002; Portes et al., 2002; Spielmann, 1994; Spielmann et al., 1994a, 1998a,b, 1995; Trevisi et al., 1994) and in-house assay results from *in vitro* 3T3 NRU PT, 2 standard chemicals and 42 test chemicals, including 23 phototoxins and 19 non-phototoxic drugs/chemicals, were selected (Table 1).

Quinine (**1**), chlorpromazine HCl (**6**), fenofibrate (**8**), ketoprofen (**10**), 6-methylcoumarin (**11**), nalidixic acid (**13**), norfloxacin (**15**), ofloxacin (**16**), piroxicam (**17**), promethazine HCl (**18**), anthracene (**21**), rose bengal (**25**), aspirin (**26**), benzocaine (**27**), erythromycin (**28**), phenytoin (**29**), penicillin G (**30**), cinnamic acid (**34**), L-histidine (**36**), 2-(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol (octrizole, **38**), octyl methacrylate (**39**), *p*-aminobenzoic acid (PABA, **42**), sodium dodecyl sulfate (SDS, **43**), $NaH_2PO_4{\cdot}2H_2O$, $Na_2HPO_4{\cdot}12H_2O$, dimethyl sulfoxide (DMSO), *p*-nitrosodimethylaniline, imidazole, and nitroblue tetrazolium (NBT) were obtained from Wako Pure Chemical Industries (Osaka, Japan). Doxycycline HCl (**7**) and nalidixic acid (Na salt) (**14**) were bought from MP Biomedicals (Irvine, CA, USA). Rosiglitazone (**19**) and methylbenzylidene camphor (**37**) were purchased from Enzo Life Sciences International (Farmingdale, NY, USA) and Alfa Aesar (Ward Hill, MA, USA), respectively. Sulisobenzone (**2**), acridine HCl (**4**), furosemide (**9**), 8-methoxypsoralen (**12**), avobenzone (**22**), hexachlorophene (**24**), octyl methoxycinnamate (**40**), and octyl salicylate (**41**) were purchased from Tokyo Chemical Industry (Tokyo, Japan). Acridine (**3**), amiodarone HCl (**5**), 6-methylcoumarin (**11**), tetracycline (**20**), bithionol (**23**), 2-*tert*-butyl-6-(5-chloro-2*H*-benzotriazol-2-yl)-4-methylphenol (bumetrizole, **31**), camphor sulfonic acid (**32**), chlorhexidine (**33**), 2-(2-hydroxy-5-methylphenyl)benzotriazole (drometrizole, **35**), and 2-(2*H*-benzotriazol-2-yl)-6-dodecyl-4-methylphenol (UV-571, **44**) were purchased from Sigma–Aldrich Japan (Tokyo, Japan). A quartz reaction container for high-throughput ROS assay (Onoue et al., 2008a) was constructed by Ozawa Science (Aichi, Japan).

Each chemical for the validation study was supplied from the VMT to participating laboratories. Quinine (**1**), a positive control, and sulisobenzone (**2**), a negative control, were uncoded, and the

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