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Short Communication on Phototoxicity Assessment: Evaluation of Skin Phototoxicity Study Using SD Rats by Transdermal and Oral Administration

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Abstract

Guinea pigs are the most frequently used animals in phototoxicity studies. However, general toxicity studies most often use Sprague-Dawley (SD) rats. To shortening of the study period and to reduce the number of animals needed for drug development, we examined whether skin phototoxicity studies could be performed using SD rats. Drugs that had previously been shown to have phototoxic potential and known phototoxic compounds were administered transdermally and orally to guinea pigs and SD rats. After administration, the animals were irradiated with UV-A and UV-B. In the result, the concordance rate of guinea pigs and SD rats was 100% in the transdermal administration study and 85% in the oral administration study. This study demonstrated that phototoxicity studies using SD rats have the same potential to detect phototoxic compounds as studies using guinea pigs.

Keywords: Phototoxicity; Guinea pig; Sprague-Dawley rats

Description

Phototoxicity is caused by exposure to a combination of a photoreactive chemical and light. It is an acute response and can result in the formation of erythema and edema. A compound that absorbs photons at any wavelength between 290 and 700 nm has the potential to be photoreactive, and therefore, can potentially cause phototoxicity [1].

In the drug development, the phototoxicity of drugs is assessed as part of standard safety screening, and typically, guinea pigs are used as an *in vivo* model [2]. The guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [3] indicate that several animal species—including guinea pigs, mice, and rats—have been used to assess drug phototoxicity, but no standardized study design has been established. The guidelines also note that phototoxicity studies must involve the collection of pharmacokinetic (PK) data because for the data to be relevant, the animals should be irradiated at approximately Tmax. In the early stage of drug development, PK data is commonly collected using mice and rats. However, if the phototoxicity study is to be carried out using guinea pigs, additional PK must be collected for guinea pigs in another trial. On the other hand, Sprague-Dawley (SD) rats are widely used in general toxicity study and PK data of SD rats is usually collected before phototoxicity assessment. Therefore it removes the need for additional PK study.

To shortening of the study period and to reduce the number of animal studies needed, we investigated the suitability of SD rats for use in phototoxicity studies [4]. In this study, drugs that had previously been shown to have phototoxic potential based on reactive oxygen species (ROS) assays [5-8] and known phototoxic compounds (8-Methoxypsoralen (8-MOP), acridin, anthracene) were administered transdermally and orally to guinea pigs and SD rats. After administration, the animals were irradiated with UV-A and UV-B. Skin reactions (erythema/eschar and edema formation) were observed and scored 24, 48, and 72 h after UV irradiation using Draize's method [9]. The skin reaction scores of individual animals were summed for each site and the mean score was calculated according to the following equation:

Mean score = Total of erythema and edema scores / Number of animals tested.

A test compound was judged to be phototoxic if the mean score of the UV-irradiated group or area was higher than that of the non-irradiated group or area at any observation period.

The skin scores recorded in the transdermal administration study are shown in Figure 1. Representative photographs of irradiated skin that had been treated with 8-MOP, acridin, anthracene, or amlodipine are shown in Figure 2. Three positive controls (8-MOP, acridine, and anthracene) were found to be phototoxic in both guinea pigs and SD rats. Aside from the positive controls, seven compounds (amlodipine, benzoyl peroxide, chlorpromazine, furosemide, ibuprofen, promethazine, and quinine) were found to be phototoxic in both guinea pigs and SD rats. A summary of the transdermal administration study is shown in Table 1. The concordance rate of guinea pigs and SD rats was 100%.

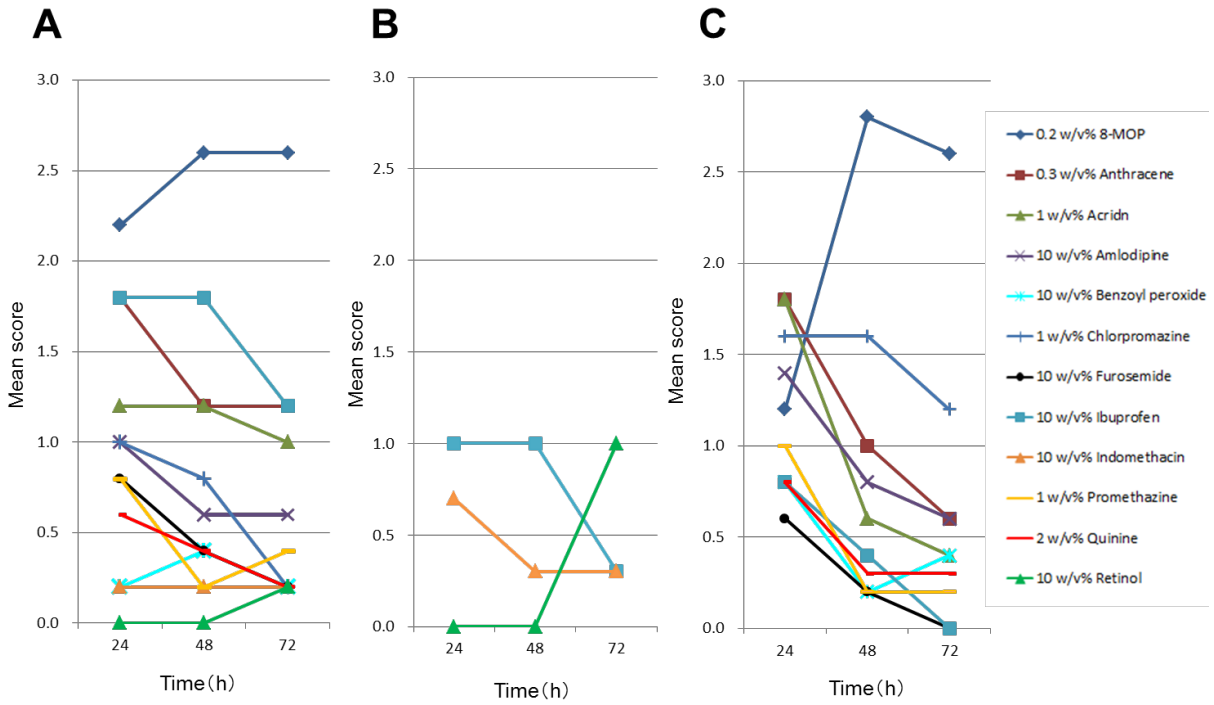

Figure 1: Plot of the Draize skin scores for the compounds tested in the transdermal administration study. (A) Guinea pigs in the irradiated group. (B) Guinea pigs in the non-irradiated group. (C) Sprague-Dawley rats in the irradiated group. Compounds with a Draize skin score of 0 at all-time points are not shown. Data of Sprague-Dawley rats in the non-irradiated group are not shown because no compounds have scores.

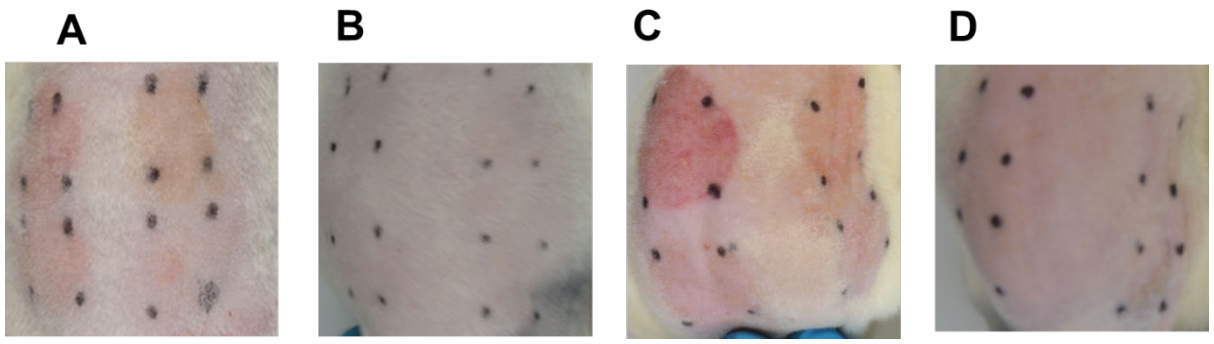

Figure 2: Photographs of the skin of guinea pigs and Sprague-Dawley rats treated with 8-methoxypsoralen, acridin, anthracene, and amlodipine 48 hours after UV-A and UV-B irradiation in the transdermal administration study. Photographs of Non-irradiated group was taken 24 hours after administration. (A) Guinea pigs in the irradiated group. (B) Guinea pigs in the non-irradiated group. (C) Sprague-Dawley rats in the irradiated group. (D) Sprague-Dawley rats in the non-irradiated group. Upper left: 0.2 w/v% 8-MOP, lower left: 0.3 w/v% Anthracene, upper right: 1.0 w/v% Acridin, lower right: 10 w/v% Amlodipine.

Compounds	Judgement		References	
	Guinea pigs	SD rats	ROS assay	Clinical reports
Phototoxic compounds				
8-MOP	Phototoxic	Phototoxic	Phototoxic[1)]	Phototoxic [2)]
Anthracene	Phototoxic	Phototoxic	N.D.	Phototoxic [3)]
Acridn	Phototoxic	Phototoxic	N.D.	Phototoxic [3)]
Drugs				
Amlodipine	Phototoxic	Phototoxic	Phototoxic[1)]	N.D.[4)]
Benzoyl peroxide	Phototoxic	Phototoxic	Phototoxic[1)]	Phototoxic[5)]
Bufexamac	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]

Chlorpromazine	Phototoxic	Phototoxic	Phototoxic[1)]	N.D.[4)]
Diclofenac	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]
Furosemide	Phototoxic	Phototoxic	Phototoxic[1)]	N.D.[4)]
Haloperidol	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]
Ibuprofen	Phototoxic	Phototoxic	Phototoxic[1)]	N.D.[4)]
Indomethacin	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]
Ketoprofen	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]
Naproxen	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]
Nifedipine	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]
Nimodipine	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.4)
Nitrendipine	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]
Piroxicam	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]
Promethazine	Phototoxic	Phototoxic	Phototoxic[1)]	N.D.[4)]
Quinine	Phototoxic	Phototoxic	Phototoxic[1)]	N.D.[4)]
Retinol	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]
Tamoxifen	Non-phototoxic	Non-phototoxic	Phototoxic[1)]	N.D.[4)]
Concordance rate*	100%22/22 compounds			

1) Data from Onoue et al., 2008 [6]; 2) Adverse drug reaction reporting, noted in the drug package insert; 3) Noted in the material safety data sheet; 4) No data with transdermal administration; 5) Data from Jeanmougin and Civatte, 1987 [12]. *Concordance rate was calculated according to the following formula: the number of compounds judged phototoxic or non-phototoxic in both guinea pigs and SD rats/total number of compounds × 100.

Table 1: Summary of the transdermal administration study.

The skin scores recorded in the oral administration study are shown in Figure 3. Representative photographs of irradiated skin of animals treated with 8-MOP is shown in Figure 4.

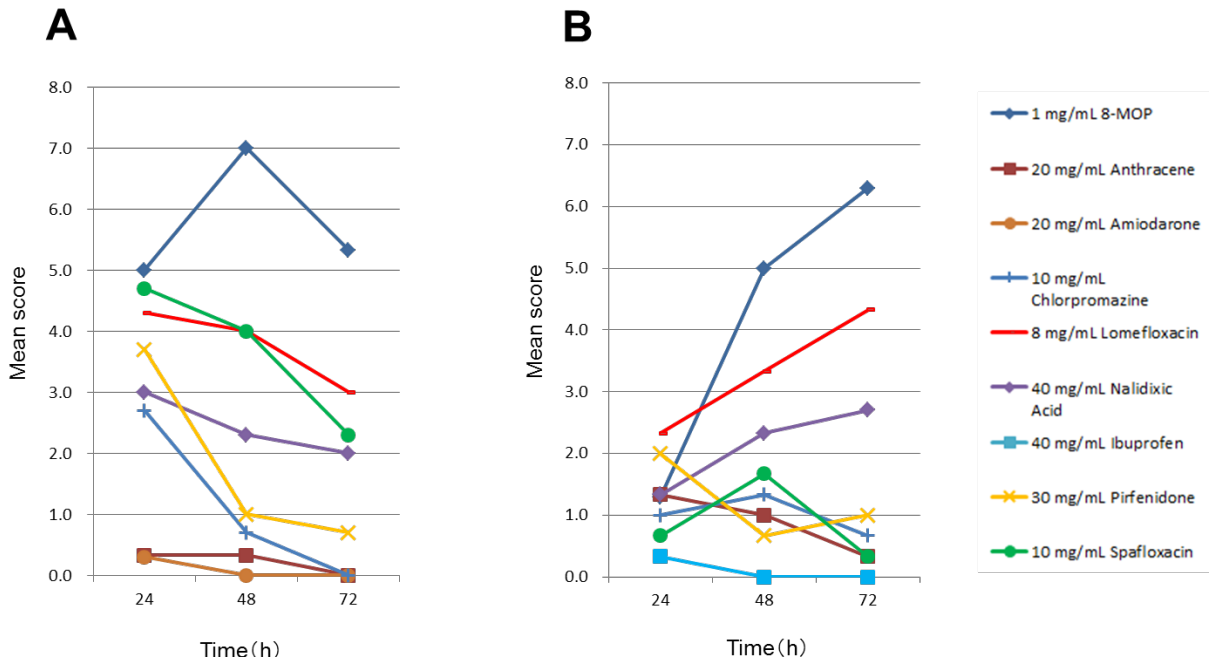

Figure 3: Plot of the Draize skin scores for the compounds tested in the oral administration study. (A) Guinea pigs in the irradiated group. (B) Sprague-Dawley rats in the irradiated group. Compounds with a Draize skin score of 0 at all time points are not shown. Data of guinea pigs and Sprague-Dawley rats in the non-irradiated group are not shown because no compounds have scores.

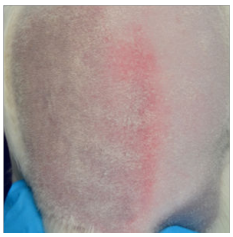

Figure 4: Photographs of guinea pig skin (A) and Sprague-Dawley rat skin (B) treated with 8-MOP in the oral administration study. The right-hand side of the back was covered with aluminum foil and therefore not irradiated.

Two positive controls (8-MOP and anthracene) were found to be phototoxic in both guinea pigs and SD rats. Apart from the positive controls, chlorpromazine, lomefloxacin, nalidixic acid, pirfenidone, and sparfloxacin were found to be phototoxic in both types of animals. Amiodarone was only phototoxic in guinea pigs, and ibuprofen was only phototoxic in SD rats.

A summary of the oral administration study is shown in Table 2. The concordance rate of guinea pigs and SD rats was 85%.

Compounds	Judgement		References	
	Guinea pigs	SD rats	ROS assay	Clinical reports
Phototoxic compounds				
8-MOP	Phototoxic	Phototoxic	Phototoxic [1)]	Phototoxic [5)]
Anthracene	Phototoxic	Phototoxic	N.D.	Phototoxic [6)]
Drugs				
Amiodarone	Phototoxic	Non-phototoxic	Phototoxic [2)]	Phototoxic [5)]
Benzoyl Peroxide	Non-phototoxic	Non-phototoxic	Phototoxic [1)]	N.D.[7)]
Chlorpromazine	Phototoxic	Phototoxic	Phototoxic [1)]	Phototoxic[5)]
Furosemide	Non-phototoxic	Non-phototoxic	Phototoxic [1)]	Phototoxic [5)]
Gatifloxacin	Non-phototoxic	Non-phototoxic	Weak phototoxic [3)]	Non-phototoxic
Ibuprofen	Non-phototoxic	Phototoxic	Phototoxic [1)]	Phototoxic [5)]
Ketoprofen	Non-phototoxic	Non-phototoxic	Phototoxic [1)]	Photoallergic [5)]
Lomefloxacin	Phototoxic	Phototoxic	Phototoxic [3)]	Phototoxic [5)]
Nalidixic Acid	Phototoxic	Phototoxic	Phototoxic [1)]	Phototoxic [5)]
Pirfenidone	Phototoxic	Phototoxic	Phototoxic [4)]	Phototoxic [5)]
Spafloxacin	Phototoxic	Phototoxic	Phototoxic [3)]	Phototoxic [5)]
Concordance rate*	85%11/13 compounds			

1) Data from Onoue et al., 2008 [6]; 2) Data from Onoue and Tsuda, 2006 [5]; 3) Data from Seto et al., 2011 [7]; 4) Data from Seto et al., 2013 [8]; 5) Adverse drug reaction reporting, noted in the drug package insert; 6) Noted in the material safety data sheet; 7) No data with oral administration. *Concordance rate was calculated according to the following formula: the number of compounds judged phototoxic or non-phototoxic in both guinea pigs and SD rats/total number of compounds × 100.

Table 2: Summary of the oral administration study.

The present study aimed to examine whether skin phototoxicity studies could be performed using SD rats instead of guinea pigs. The results confirm that phototoxicity studies using SD rats are as sensitive and specific as studies using guinea pigs.

The use of SD rats in phototoxicity studies contributes to shortening of the study period as well as 3R principles in animal experiments because it removes the need for additional PK study. Moreover, SD rats are widely used in general toxicity study, so it may be possible to incorporate phototoxicity assessments to general toxicity study. Incorporating a study into the general toxicity study is recommended by the ICH guidelines [10-12]. In a general toxicity study using SD rats, a satellite group for toxicokinetics might be used for the phototoxicity study after final blood sampling is completed. If this study can be validated, the number of animals used for the phototoxicity study can be reduced. In conclusion, the use of SD rats in phototoxicity testing is in line with the 3R principles and can speed up drug development.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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