Phototoxicity of New Psoralen-Containing Gels and Creams Versus Bath PUVA

Peerapat Nimkulrat, MD*,
Vichit Leenutaphong, MD*, Srismorn Sudtim, BEd*

** Department of Dermatology, Siriraj Hospital, Mahidol University*

Background: *Bath-PUVA-photochemotherapy has become a useful alternative to oral PUVA therapy due to a number of advantages over systemic PUVA, for example, no ophthalmologic risk and nausea, and a lower cumulative UVA doses. However, its major disadvantage is the logistical requirement for bath tubs in practice and some patients feel uncomfortable to share the same bath with others. Topical psoralen contained preparation may be a good candidate for safe, convenient, and useful regimen in the topical PUVA therapy.*
Objectives: *The purpose of the present study was to investigate the intensity of the phototoxic response of 8-MOP bath solution to different concentrations of preparations of 8-MOP gels and creams.*
Material and Method: *Following informed consent, the test bath solution (0.375%), gels (0.0025% to 0.010%) and creams (0.0025% to 0.010%) were applied to the normal-appearing skin of the upper back of 23 volunteers who had no history of photosensitivity. The escalating UVA doses (0.25 to 7.0 J/cm2) were given 15 minutes after application of test substances. Seventy-two hours after UVA exposure minimal phototoxic doses (MPD) were defined visually and the intensity of the erythema response was also assessed by using a narrow-band spectrophotometer. The MPD and the dose-response curves for erythema response of the gels and creams were compared with those of the bath.*
Results: *There were no significant differences between the overall mean MPD of tested gels and that of bath solution ($p > 0.05$). On the contrary, the cream preparations induced phototoxic response (MPDs) to a lesser degree than bath solution and gels ($p < 0.05$). When comparing the slope of the dose-response curve for erythema of 0.0025% and 0.0100% gel to that of the bath solution, the correlation is very strong ($R^2 = 0.987$ and 0.936, respectively, $p < 0.0001$).*
Conclusion: *The present study shows that the threshold of phototoxic response of 0.0025% 8-MOP gel indicated by MPD is well correlated with those of the bath solution. The slope of the dose-response curve for erythema of this preparation also significantly corresponded to that of the bath solution. Thus, the penetration and drug delivery of 0.0025% 8-methoxypsoralen gel may be similar to 8-methoxypsoralen bath solution. This preparation may be a good candidate for a useful therapeutic modality for topical PUVA therapy, and further clinical trial should be performed.*

Keywords: *Bath PUVA, Psoralen–Containing gels, Psoralen–containing creams, Topical PUVA*

J Med Assoc Thai 2005; 88 (10): 1406-11
Full text. e-Journal: *http://www.medassocthai.org/journal*

Topical psoralen plus ultraviolet A (PUVA) using 8-methoxypsoralen (8-MOP) bath solution (bath-PUVA-photochemotherapy) is a well established and effective treatment of a variety of dermatoses. It has been widely used as an alternative to oral PUVA therapy in order to avoid ophthalmologic risks and systemic side-effects. However, bath-PUVA-photochemotherapy has disadvantages due to its requirement of bath tubs in practice. In addition, some patients feel uncomfortable to share the same bath with other patients. Cream, emulsion and gel preparations have been described as alternative modes of topical 8-MOP application. Recently, a low concentration of psoralen, parent drug of

Correspondence to : Leenutaphong V, Department of Dermatology, Siriraj Hospital, Bangkok 10700, Thailand. Phone: 0-2411-1531

8-MOP, in aqueous gel (0.0050%) was developed and photochemotherapy with this gel has been shown to be effective therapeutic modality for psoriatic patients and patients with recalcitrant dermatoses such as palmoplantar psoriasis and hyperkeratotic eczema[1]. The authors therefore investigated the intensity of phototoxic responses in terms of minimal phototoxic dose (MPD) and dose-erythematous response curve of bath solution and the different concentrations of our low-concentration preparations of 8-MOP gel and cream.

Material and Method

Preparations

Bath solution was prepared using 0.75 gram% of 8-MOP in ethanolic solution (Premedica, France) 1 ml. mixed with tap water 1 litre to make a 0.375 mg% solution. The same 8-MOP in ethanolic solution was thoroughly mixed with an aqueous gel containing Carbopol Ultreze-10 0.5% w/w, and Liquid Germall Plus as a preservative. The cream containing aminophospholipid (Ajinomoto, Japan), Carbopol Ultreze-10 0.5% w/w and Liquid Germall Plus was also used as a vehicle. The final 8-MOP concentrations of both gel and cream were 0.0025 mg%, 0.0050 mg%, and 0.0100 mg%. The preparations were stored at room temperature in an opaque bottle.

Subjects

Twenty three healthy Thai volunteers (13 males, 10 females; age range 18-69 years) were enrolled in the present study. They had no history of drug hypersensitivity, photosensitivity, or abnormal reactions to sunlight. They had no drug intake for 2 weeks. The subjects were asked not to expose themselves to ambient sunlight during the study. All were classified for skin type according to the Working Classification of Sun Reactive Skin Type introduced by Fitzpatrick[2]. Seven people were skin type III, 15 were skin type IV, and 1 were skin type V.

Radiation Sources and Dosimetry

Radiation Sources (UVA): The source of polychromatic UVA was from a high-pressure metal halide lamp (UVASUN 3000, Mutzhas, Munich, F.R.G.) that emits wavelengths between 330 nm and 460 nm without any measurable UVB. [3] The UVA irradiance was 66 mW/cm2 at a target distance of 30 cm.

Dosimetry: A UV-meter with separate UV-detectors for UVA (IL 500A radiometer, International Light Inc., U.S.A.) served to determine the UV-irradiance of the UVASUN .

MPD Measurements

After completing the consent forms, the bath solution (0.375 mg%), gels (0.0025 mg%, 0.0050 mg%, 0.0100 mg%) and creams (0.0025 mg%,0.0050 mg%, 0.0100 mg%) were applied to the normal-appearing, untanned skin of the upper back. All volunteers were exposed to UVA in doses ranging from 0.25 to 7.0 J/cm^2 on the lower back using geometric increment (dose increment factor 1.4). Seventy-two hours after UVA exposure, the erythematous response was assessed visually in terms of minimal phototoxic doses (MPD) by two experienced observers who were unaware which preparation had been applied. The MPD was defined as the smallest dose of radiation to achieve faint but easily discernible erythema

Dose-Response Angle of Erythema

The erythema of each test site were measured before and 72 h after irradiation with a reflectance spectrophotometry (Dermaspectrometer, Cortex Technology, Denmark)[4], where each measure consisted of 5 averaged measurements of each target area. This instrument irradiates the skin with a known intensity of red (655 nm) and green light (568 nm) and measures the reflexion, which gives an erythema index and melanin index related to the erythema and pigmentation of the skin. Equations for calculation of redness % and pigmentation % are built into the instrument. When the erythema index at 72 h were plotted against the log UV dose for each patient, dose-response curves for erythema were obtained (Fig. 1). Linear regression and correlation analysis were used to calculate the slope of the dose-response curve for erythema which was called dose-response angle for erythema (DRAE) and correlation between these two variables. A p-value of less than 0.05 was considered statistical significance.

Results

A Comparison of MEDs of psoralen contained gels, creams and solutions

The tested gels at all concentration induced the comparable degree of phototoxic response (MPDs) to bath solution (mean MPDs was between 2.924-3.293 J/cm^2 for gel and 2.435 J/cm^2 for bath solution, $p > 0.05$). On the contrary, the cream preparations induced phototoxic response (MPDs) in a lesser degree than bath solution and gels (mean MPDs was between: 4.446-5.522 J/cm^2 for creams, $p < 0.05$). (Table 1 There were no significant differences among different concentration of tested gels and creams ($p > 0.05$).

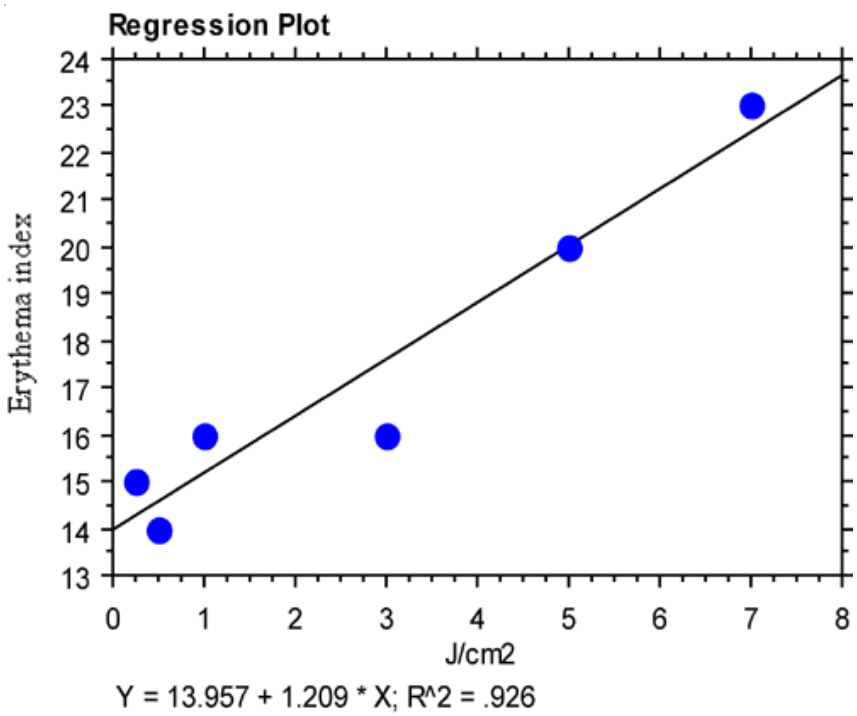

Fig. 1 The erythema index at 72 h were plotted against the log UVA dose for gel preparation for a patient. Linear regression analysis was used to calculate the slope which was called dose-response angle for erythema (DRAE)

As such, the authors chose only gel preparations to study their dose-erythematous-response curves and compared them to the gold standard of bath solution. The curves and their equations are shown in Fig. 2.

A Comparison of Dose-Response Angle of Erythema of psoralen contained gels, creams and solutions

When comparing the DRAE of 0.0025% and 0.0100% gel to that of the bath solution, the correlation was very strong (R^2 = 0.987 and 0.936, respectively, $p < 0.0001$). However, the correlation of the DRAE between the bath solution and 0.0050% gel was not strong (R2 = 0.609, $p < 0.0001$) as shown in Fig. 2.

Discussion

Local PUVA (psoralen plus ultraviolet A) therapy using 8-methoxypsoralen (8-MOP), has been

Table 1. Comparison of MEDs of psoralen contained gels, creams and solutions

Test substances	Mean MPDs ± SD (N = 23)	p-value*
Bath solution	2.435 ± 2.356	
Gels		
0.0025%	3.293 ± 2.859	0.272
0.0050%	2.924 ± 2.335	0.483
0.0100%	2.935 ± 2.399	0.479
Creams		
0.0025%	5.522 ± 2.352	<0.0001
0.0050%	4.886 ± 2.618	0.002
0.0100%	4.446 ± 2.554	0.008

* Comparing with bath solution by unpaired t - test

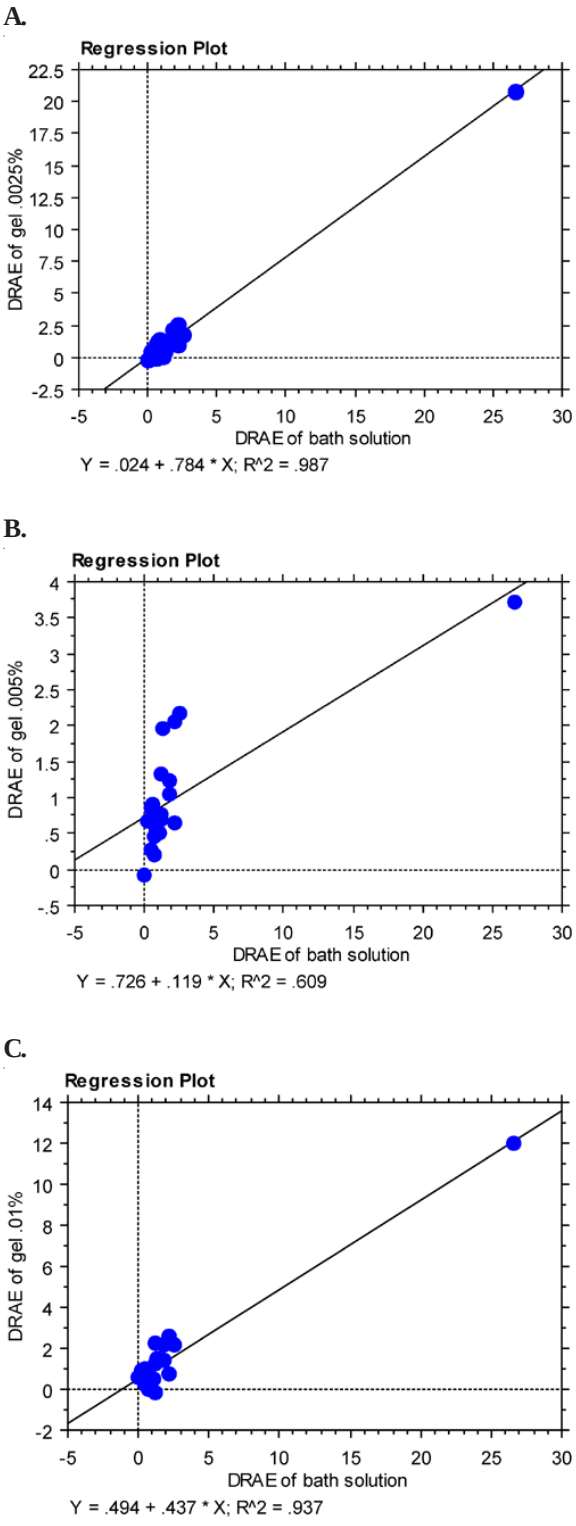

Fig. 2 Comparison of Dose-Response Angle of Erythema (DRAE) of different concentration of psoralen contained gels and bath solutions

proven to be an effective therapy for a continuously expanding range of skin disorders. There are some dermatologists who avoid the use of topical PUVA because of the risk of burning associated with its use. However, studies have shown that bath application has equal or better therapeutic efficiency and burns less easily than local application of psoralens in ointments, creams, and lotions[1]. Thus, bath delivery has become increasingly popular in recent years, both for whole-body and local therapy[5]. The major disadvantage of bath PUVA therapy is the logistical requirement for bath tubs in practice and some patients feel uncomfortable sharing the same bath with others. Other preparations may be the alternatives in these cases. Due to the fact that the commonly used concentrations of psoralen preparations other than bath solution in clinical practice are 0.05% to 0.1%, the tendency of easily burn may be reduced by lowering the concentration of the preparations. Recently, low concentration of psoralen, a parent drug of 8-MOP, in aqueous gel (0.0050%) was developed, and photochemotherapy with this gel has been shown to be effective therapeutic modality for psoriatic patients and patients with recalcitrant dermatoses such as palmoplantar psoriasis and hyperkeratotic eczema[1]. Therefore, the present study was to compare the MPD, and objective erythema intensity (dose-erythema response curve and its slope) between bath solution and tested gels and creams.

The interval between application of the psoralen in aqueous gel and UVA irradiation was relatively short, within 15 minutes, and can perhaps be further shortened[6]. The rapid penetration of the psoralen compound into the epidermis has been shown, depending on the nature of the vehicle[7]. The drug photoadducts with DNA molecules even if UVA is given as soon as the drug is applied, resulting in significant inhibition of epidermal DNA synthesis[8]. The long-term risks of topical PUVA have not yet been established, but potential advantage might be the low total UVA dose required for clearance of psoriasis. Also, the advantage of the low-concentration preparation is the avoidance of accumulation in the skin which could result in adverse erythematous reactions[1].

Minimal erythema response is widely used as an end-point for the assessment of erythema in both the clinical and research setting; however, it is somewhat subjective, and imprecise. Also, it may be surprisingly difficult to judge which site, in a series exposed to increasing doses of radiation, is the first to show "just detectable erythema". In order to overcome these problems the authors made objective reflectance

measurements of the intensity of erythema at each irradiated site, in additon to the visual assessment of minimal erythema[9].

The present study revealed that the threshold of phototoxic response (MPD) of 0.0025% and 0.0100% 8-MOP gel and bath solution are well correlated with each other. Thus, the penetration and drug delivery of 0.0025% 8-MOP gel may be similar to 8-MOP bath solution. However, lower concentration (0.0025%) gel may be safer for the patient.

The authors, therefore, propose that local PUVA therapies using bath solution and low-concentration of 0.0025% gel have comparable MPD, and erythematous response characteristics. This low-concentration psoralen contained gel (0.0025%) may be a good candidate for safe, convenient, and useful regimen in the topical PUVA therapy. Further clinical trial of the efficacy in the treatment of skin diseases and the systemic absorption when used at a higher extent should be performed. Moreover, the kinetics of photosensitivity and the stability of the product has to be demonstrated before 8-MOP cream or gel can be commercially avaiable in the market.

References

1. De Rie MA, Van Eendenburg JP, Versnick AC, Stolk LM, Bos JD, Westerhof W. A new psoralen-containing gel for topical PUVA therapy: development, and treatment results in patients with palmoplantar and plaque-type psoriasis, and hyperkeratotic eczema. Br J Dermatol 1995; 132: 964-9.
2. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988; 124: 869-71.
3. Mutzhas MF, Holzle E, Hofmann C, Plewig G. A new apparatus with high radiation energy between 320-460 nm: physical description and dermatological applications. J Invest Dermatol 1981; 76: 42-7.
4. Bjerring P, Andersen PH. Skin reflectance spectrophotometry. Photodermatol 1987; 4: 167-71.
5. Kerscher M, Lehmann P, Plewig G. [PUVA bath therapy. Indications and practical implementation]. Hautarzt 1994; 45: 526-8.
6. Danno K, Horio T, Ozaki M, Imamura S. Topical 8-methoxypsoralen photochemotherapy of psoriasis: a clinical study. Br J Dermatol 1983; 108: 519-24.
7. Kammerau B, Klebe U, Zesch A, Schaefer H. Penetration, permeation, and resorption of 8-methoxypsoralen. Comperative in vitro and in vivo studies after topical application of four standard preparations. Arch Dermatol Res 1976; 255: 31-42.
8. Danno K, Toda K, Ishida H, Horio T. Topical methoxsalen followed immediately by long-wave UV irradiation. A preliminary report on the treatment of psoriasis. Arch Dermatol 1982; 118: 471-3.
9. Diffey BL, Farr PM. Quantitative aspects of ultraviolet erythema. Clin Phys Physiol Meas 1991; 12: 311-25.

การเปรียบเทียบความสามารถในการทำให้เกิดอาการแดงจากยาทาชนิดวุ้นหรือครีมที่มีส่วนผสมของสาร psoralen เทียบกับการแช่ในสารละลายที่มี psoralen

พีรพัฒน์ นิ่มกุลรัตน์, วิชิต ลีนุตพงษ์, ศรีสมร สุทธิ์ทิม

พื้นความรู้: *ในปัจจุบันการรักษาโรคผิวหนังบางชนิดด้วยการแช่ในสารละลายที่มี psoralen แล้วฉายแสง UVA ที่เรียกว่า bath-PUVA เป็นการรักษาที่ได้ผลดีเทียบกับการรับประทานยา psoralen ก่อนฉายแสง UVA และยังมีข้อดีที่ไม่มีความเสี่ยงในการทำให้เกิดต้อกระจกที่ตา อาการคลื่นไส้อาเจียน และยังใช้ปริมาณแสงที่น้อยกว่า อย่างไรก็ตามการรักษาดังกล่าวยังมีปัญหาหลายประการเช่นจะต้องมีการใช้อ่างน้ำให้ผู้ป่วยลงแช่ซึ่งผู้ป่วยมักจะรังเกียจที่จะใช้ร่วมกัน บริหารจัดการยากและค่าใช้จ่ายสูง การรักษาด้วยยา psoralen ชนิดทาน่าจะเป็นทางออกที่ดีเพราะจะช่วยประหยัดและให้ความสะดวกได้มากกว่าการแช่*

วัตถุประสงค์: *วัตถุประสงค์ของการวิจัยเพื่อศึกษาเปรียบเทียบความสามารถในการทำให้เกิดอาการแดงจากยาทา 8-methoxypsoralen (8-MOP) ชนิดวุ้นหรือครีม ที่พัฒนาขึ้นมา เทียบกับการแช่ในสารละลายที่มีสาร 8-MOP*

วัสดุและวิธีการ: *ได้ทาสารละลาย (0.375%) วุ้น (0.0025% ถึง 0.01%) และครีม (0.0025% ถึง 0.01%) บนแผ่นหลังของผู้ป่วยจำนวน 23 รายที่ไม่มีประวัติแพ้แสง และตามด้วยการฉายแสง UVA ขนาดต่าง ๆ (0.25 ถึง 7.0 จูล/ซม^2) หลังจากนั้นทำการอ่านผล minimal phototoxic doses (MPD) ซึ่งได้แก่ตำแหน่งที่ใช้แสงน้อยที่สุด ที่เริ่มมองเห็นอาการแดงได้อย่างชัดเจน นอกจากนั้นยังประเมินความแดงด้วยเครื่อง narrow-band spectrophotometer หลังจากนั้นได้นำค่า MPD และ dose-response curves ของค่าความแดงที่วัดได้มาเทียบกันระหว่างตัวอย่างชนิดต่าง ๆ*

ผลการศึกษา: *ไม่พบความแตกต่างของค่า MPD ของวุ้นที่มีสาร psoralen เทียบกับการแช่ ($p > 0.05$) ขณะที่การทาครีมจะมีค่า MPD ต่ำกว่าวุ้นที่มีสาร psoralen และการแช่ psoralen อย่างมีนัยสำคัญ ($p < 0.05$) และเมื่อเปรียบเทียบ dose-response curves ของค่าความแดงที่วัดของวุ้นที่มีสาร psoralen กับการแช่พบมีความสัมพันธ์อย่างดีมาก ($R^2 = 0.987$ and 0.936, respectively, $p < 0.0001$)*

สรุป: *การศึกษานี้แสดงว่ายาทาชนิดวุ้นที่มีส่วนผสมของสาร 8-MOP 0.0025% ที่พัฒนาขึ้นมา มีความสามารถในการทำให้เกิดอาการแดงเท่ากับและสัมพันธ์กับการแช่ด้วยสาร 8-MOP ดังนั้นการซึมผ่านของสาร 8-MOP เมื่อยาทาชนิดวุ้นน่าจะใกล้เคียงกับการแช่ ยาดังกล่าวน่าจะถูกนำมาพิจารณาทดลองใช้ทดแทนการแช่ด้วย 8-MOP และน่าจะมีการทำการทดสอบต่อไปว่าจะใช้รักษาโรคได้หรือไม่*