Acta Derm Venereol 2002; 82: 18–20

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healthsciences

INVESTIGATIVE REPORT

Can the Immersion Time of PUVA Bath Therapy be Shortened?

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Up to now, there are only a few data available concerning the influence of bathing time on skin phototoxicity. We compared the erythemal responses of normal skin to bath PUVA with 8-methoxypsoralen (8-MOP) after 5, 10 and 20 min immersion time. Currently, 20 min is the routinely performed immersion time in many European countries, including Germany, while in other countries bathing times are shorter. The minimal phototoxic dose (MPD) following immersion times of 5 min and 10 min in a warm water bath (37°C) containing 1 mg/l 8-MOP was compared to the MPD following 20 min immersion time in a half-sided manner in a total of 24 patients. Our results revealed that an immersion time of 5 min did not yield a detectable erythema after 72 h. In contrast, both 10 and 20 min PUVA baths induced visible erythemas with a significantly higher median MPD following 10 min immersion (2.25 J/cm^2) compared to 20 min baths (1.5 J/cm^2). As an erythemal response of 8-MOP PUVA bath seems reduced after shorter immersion times, comparative studies on the clinical efficacy using shorter time regimens have to be conducted before conclusive recommendations for clinical PUVA-bathing time can be given. ***Key words: baths; photochemotherapy, time factors; psoralens; PUVA therapy.***

(Accepted December 5, 2001)

Acta Derm Venereol 2002; 82: 18–20.

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PUVA bath therapy with 8-methoxypsoralen (8-MOP) has been shown to be effective treatment for a variety of dermatoses (1, 2). PUVA bath therapy has been used increasingly in the past few years because of distinct advantages compared to peroral delivery of 8-MOP. These include a lack of systemic side effects and enhanced photosensitization with lower cumulative UVA doses.

Current practice in most countries is to apply a dilute aqueous solution of 8-MOP with concentrations of 0.5–5.0 mg/l during a 15–20 min warm water bath at 37°C (1, 3). As there are some disadvantages with PUVA bath therapy, such as longer treatment times, a need for additional staff (1) and the risk of circulation disorders due to the bathing procedure, some phototherapy centres prefer shorter immersion times down to 5 min (4). Shorter immersion times would potentially increase the convenience of PUVA bath therapy, especially for older patients or patients with circulation disorders.

It has been shown in controlled studies that the erythemal response to UVA irradiation after topical application of 8-MOP depends on bath temperature (5, 6) as well as time-lag between bath and irradiation (7–9). Up to now, different therapeutic regimens with immersion times between 5 and 30 min are being practised (4, 10). Yet only few data are available examining the influence of bathing time on skin phototoxicity. We therefore compared the erythemal responses of normal skin to bath PUVA after 5 and 10 min, respectively, with a 20 min immersion time in a dilute 8-MOP-solution.

MATERIAL AND METHODS

We recruited 24 patients with skin phototypes II ($n = 14$) and III ($n = 10$) (11) who were about to start PUVA bath photochemotherapy for inflammatory diseases of the skin, diseases such as psoriasis, lichen ruber, localized scleroderma or prurigo simplex subacuta on other parts of their body. Written informed consent was obtained from each patient. Volar aspects of their forearms were completely free of skin changes. None of them had received previous treatments with PUVA therapy and none had been taking retinoids or any other medication known to enhance cutaneous photosensitivity during the past 6 months. Patients who had received any other form of phototherapy 3 months prior to the study were excluded. No topical treatment was applied on test sites during phototesting or in the previous 4 weeks.

The skin phototype of each patient was determined, based on past history of solar-induced burning and tanning, as proposed by Fitzpatrick (11). To assess the minimal phototoxic dose (MPD), both forearms of each patient were soaked in a warm water bath of 37°C containing 1 mg/l 8 MOP (1.33 ml Meladinine 0.3%® solution by Galderma, Germany in 4 litres water). One forearm of each patient was immersed for 20 min in this solution. The manner in which the other forearm was treated was randomized for each patient according to a computer-generated plan. In one group the forearm was soaked for 5 min (group 1, $n = 12$ patients), while in a second group the forearm was soaked for 10 min (group 2, $n = 12$ patients) with an offset time of 15 and 10 min, respectively, to ensure that the end of treatment in each case was synchronized.

Immediately after bathing, 6 non-lesional template areas (2 cm^2 each) on the volar aspect of the forearm (see also Fig. 1) were irradiated with increasing doses of broadband UVA (0.5; 1.0; 1.5; 2.0; 2.5 and 3.0 J/cm^2). The irradiation equipment used was Philips TL09 fluorescent-bulbs mounted in a "PUVA 800" unit (Waldmann, Villingen-Schwenningen, Germany). These emit UVA in the 320 to 400 nm range, peaking at 355 nm with an intensity of 7.8 mW/cm^2 at 20 cm distance (measured with a calibrated UV meter (by Waldmann, Germany) at 20°C. The application of UVA doses was controlled manually by varying the exposure time using a UV dense cover material. The MPD, defined as the smallest dose of UVA to result in just detectable erythema (12), was judged visually by a single-blinded observer at 72 h after irradiation. Furthermore, the single erythema score for each test template, ranging from 0 (= no reaction) to 4 (= erythema with vesicles) and the erythema sum score (ESS)

 ISSN 0001-5555

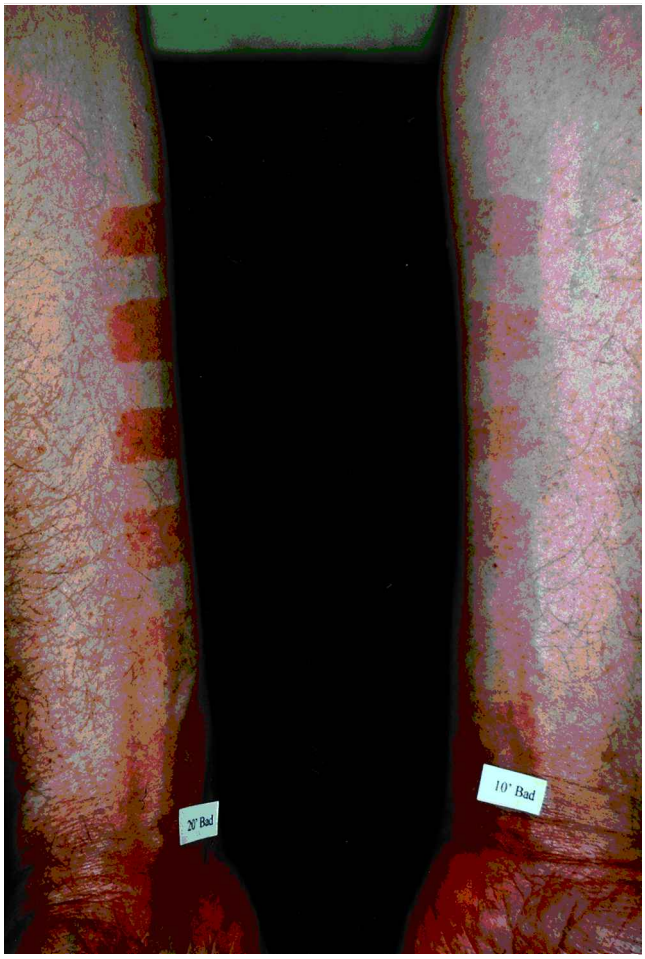

Fig. 1. Minimal phototoxic dose (MPD) of 8-MOP PUVA bath after immersion time of 10 min (left forearm) versus 20 min (right forearm): stronger erythemal response with longer bathing time (patient 8).

(13) was documented for each proband. The ESS is the sum of all single erythema scores for each individual, and is influenced both by the number of visible MPD test sites and the intensity of erythema at each site. Therefore, in contrast to the MPD, the ESS is also able to provide information on the slope of erythemal response. In general, the usage of ESS seems to be superior to plain determination of the MPD in detecting small differences in erythematous responses, as the ESS is a more sensitive evaluation parameter. An inverse relationship is anticipated between the ESS and the MPD.

Statistical analysis was performed using a Wilcoxon test with $p < 0.05$ indicating a significant result.

RESULTS

After 20 min bath water delivery of 8-MOP, the median MPD was 1.5 J/cm^2 (95% CI 1.23–2.10) in group 1 (20 min versus 5 min) and 1.5 J/cm^2 (95% CI 1.24–2.01) in group 2 (20 min versus 10 min). Immersion time of 5 min did not yield a detectable erythema in any patient of group 1. The median MPD following 10 min immersion time was 2.25 J/cm^2 (95% CI 1.75–2.75) revealing a significant difference compared to the MPD (1.5 J/cm^2) after a 20 min bath ($p = 0.005$, Figs. 1 and 2). Furthermore, there was a significant difference ($p = 0.002$) of erythema sum scores (ESS) after 10 min immersion time (median 2.5; 95% CI 1.26–4.57) compared to 20 min (median 6.5; 95% CI 4.48–8.52). Summing up the single erythema scores for each irradiation template there was a much steeper slope of erythemal response after 20 min immersion time compared to 10 min (Fig. 2).

DISCUSSION

Current practice of PUVA bath therapy in many European countries is to apply a dilute solution of 8-MOP with concentrations between 0.5 and 5.0 mg/l during a 15 to 20 min lasting warm water bath at 37°C (1). Shorter immersion times, as preferred by some centres (4), could potentially increase convenience for patients and enable a faster through-put of patients. However, so far there are very few data available comparing MPDs following different immersion times.

We were able to demonstrate that the reduction of 8-MOP immersion time in PUVA bath therapy significantly reduces erythemal response to UVA irradiation. Whereas an immersion time of 5 min did not yield any erythema within 72 h, we observed erythemal responses in 11/12 patients following 10 min immersion time after 72 h. Nevertheless, the erythemal response after 10 min was significantly reduced compared to 20 min immersion time, as reflected in a higher MPD. Furthermore, the slope of erythemal response following 20 min immersion time was much steeper than following 10 min, as demonstrated with the ESS. The reduced slope of erythemal response following 10 min immersion time may result on the one hand in a broader therapeutic window, thus reducing the risk of severe phototoxic side effects apart from being beneficial for patients with circulation disorders. However, on the other hand the efficacy of PUVA bath therapy may be decreased, resulting in higher cumulative UV doses for comparable therapeutic effects.

In summary, our data show that erythemal response after 8-MOP PUVA bath is not only dependent on

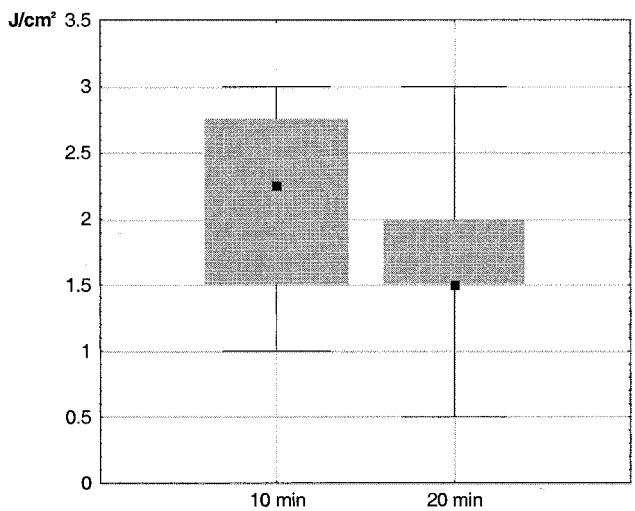

Fig. 2. Minimal phototoxic dose (MPD) of 8-MOP PUVA-bath after immersion time of 10 min versus 20 min: stronger erythemal response with longer bathing time. ⊥ Min-Max; ■ 25%–75% quartiles; ■ Median value.

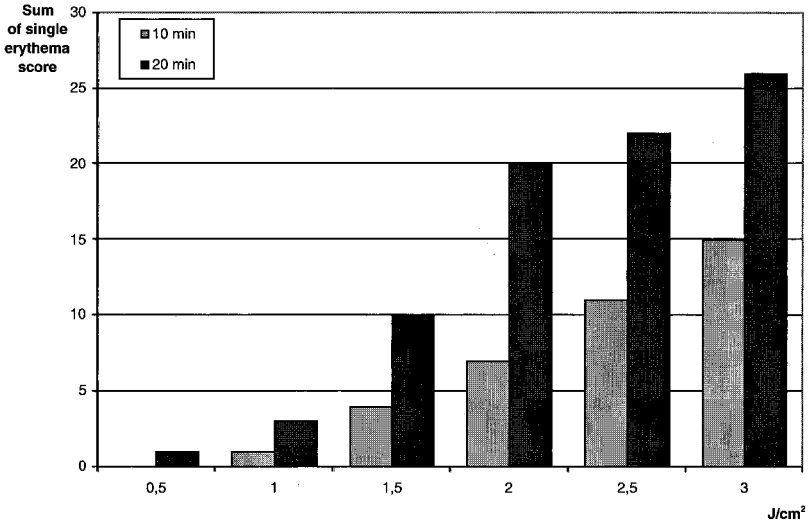

Fig. 3. Sum of the single erythema scores for each irradiation template following 10 min immersion time versus 20 min immersion time.

Table I. *Minimal phototoxic doses (MPD) and erythemal sum scores (ESS) after different immersion times*

Group 1: Erythemal response after 5 min vs. 20 min immersion time

Patient No.	MPD 5 min	MPD 20 min	ESS 5 min	ESS 20 min
1	> 3	1	0	10
2	> 3	1.5	0	7
3	> 3	1	0	12
4	> 3	2.5	0	3
5	> 3	1.5	0	8
6	> 3	1.5	0	6
7	> 3	3	0	1
8	> 3	2.5	0	4
9	> 3	2	0	6
10	> 3	3	0	2
11	> 3	2	0	5
12	> 3	1.5	0	4

Group 2: Erythemal response after 10 min vs. 20 min immersion time

Patient No.	MPD 5 min	MPD 20 min	ESS 5 min	ESS 20 min
1	3	1.5	1	7
2	2	1.5	3	7
3	2	1.5	3	7
4	1.5	1	6	12
5	1.5	1.5	4	6
6	3	2	1	6
7	2.5	2	2	3
8	1	0.5	9	13
9	1.5	1.5	6	8
10	> 3	3	0	1
11	2.5	1.5	2	7
12	3	2	1	4

8-MOP concentration and water temperature, but also strongly on immersion time. It remains to be seen whether therapeutic efficacy might decrease or whether safety of the therapeutic regimen may increase by shortening the immersion time. It also remains to be seen if higher concentrations of 8-MOP will yield comparable erythemal responses with shorter immersion time. These questions need to be targeted in further clinical trials.

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