Turbo-PUVA: Dihydroxyacetone-Enhanced Photochemotherapy for Psoriasis

A Pilot Study

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Background: Dihydroxyacetone (DHA), a colorless sugar in "sunless" tanning lotions, binds to stratum corneum to form a UV-A–protective brown pigment. Bound DHA polymer is shed faster from hyperproliferative skin sites such as psoriatic plaques. We tested the hypothesis that selective shedding of DHA pigment during psoralen–UV-A (PUVA) treatment of psoriasis may allow higher UV-A doses, thus accelerating clearing while protecting uninvolved skin. Concurrent use of lactic acid was investigated as an aid in removing scale and residual DHA from psoriatic plaques.

Observations: Thirty psoriatic patients with more than 20% body surface area involvement were recruited. The 6 PUVA study groups were (1) standard American style, (2) American style plus lactic acid, (3) DHA-PUVA or "topical ultraviolet-resisting barrier to optimize PUVA" (Turbo-PUVA), (4) Turbo-PUVA with lactic acid, (5) European style, and (6) European style plus DHA. Combinations of lactic acid and European-style treatment were not studied. Each subject received up to 30 oral PUVA treatments twice weekly 3 days apart. The DHA-PUVA groups used 15% DHA lotion twice weekly. Lactic acid groups used 7% lotion daily except on treatment days. Psoriasis area and severity index scores were recorded weekly. Turbo-PUVA allowed higher UV-A exposures with minimal burns, showed faster clearing, and required fewer treatments for 90% clearing (P<.001).

Conclusions: Protection of uninvolved skin by DHA during PUVA treatment allows higher UV-A exposures to be tolerated, demonstrates faster clearing, and requires fewer treatments to clear psoriasis. By reducing the total body dose received, Turbo-PUVA may also reduce long-term risks.

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SORALEN–UV-A (PUVA) therapy is a highly effective treatment with acute (erythema, pruritus) and chronic (skin cancer, photoaging) adverse effects. Retinoids or methotrexate given in combination with PUVA reduce the total fluence and the number of treatments needed for remission,1,3 while adding other risks. In general, phototoxicity of uninvolved skin limits the aggressiveness (tolerance) for PUVA therapy.

Dihydroxyacetone (DHA) is the colorless 3-carbon sugar present in most "sunless" tanning products.1 Dihydroxyacetone covalently binds to stratum corneum proteins, then polymerizes by the Maillard reaction to form a brown pigment that simulates a suntan. This color is lost by corneocyte sloughing.4,5 Dihydroxyacetone offers 2- to 5-fold protection against UV-A.4,5 Concentrations of DHA up to 15% provide up to 10-fold protection against PUVA-induced erythema, depending on concentration.8 Bound DHA is also shed faster from psoriatic plaques than from uninvolved skin, the differential in DHA staining of psoriatic vs uninvolved skin being greatest at 72 hours.8 Therefore, we chose 72 hours in this pilot study as the interval between application of DHA and PUVA administration. By preferentially protecting uninvolved skin, DHA may allow higher UV-A doses to be tolerated and delivered to the psoriatic plaques, perhaps accelerating clearing.

Diffuse reflectance spectroscopy (DRS) measurements can be used to accurately predict phototoxic protection factors as determined by standard light-testing procedures,9 eliminating the need to determine traditional minimal phototoxic doses (MPDs) repeatedly during a treatment course. Protection factor at 350 nm was determined to be equal to the square root of the ratio of 350-nm light
SUBJECTS AND METHODS

Thirty adult volunteers of all skin types with stable plaque-type psoriasis involving at least 20% body surface area were recruited. Institutional approval was obtained. Unstable psoriasis, pregnant and lactating women, those who had used topical steroids within the previous 2 weeks or phototherapy of any kind within the last 2 months, and those taking photosensitizing medications were excluded. Pustular and erythrodermic psoriatic subjects were not enrolled. All volunteers were sequentially assigned to 6 different groups, each receiving twice-weekly PUVA treatments 72 hours apart. All were allowed to use only petroleum jelly as an emollient, if needed.

All DHA groups applied a 15% DHA lotion (Estée-Lauder, Melville, NY) twice weekly to the whole body except the face, groin, and a small test area of uninvolved skin, typically in the axilla. The latter area served as a control site to evaluate the extent of photoprotection achieved in DHA-treated areas. The DHA was applied only during the first 3 weeks of treatment. Effectively, this requirement meant that each DHA group subject applied the self-tanning lotion only 6 times. These subjects were instructed how to make even application of the DHA lotion, using disposable gloves to avoid palmar staining. The DHA was always applied approximately 12 hours after a PUVA treatment, about 2½ days before the next PUVA treatment. A typical DHA schedule was, for example, PUVA treatment Monday morning, DHA application Monday evening, PUVA treatment Thursday, followed by another DHA application on Friday morning. Those groups using 7% lactic acid (Estée-Lauder) applied it daily except for treatment days, to the whole body except face and groin.

The starting UV-A treatment dose for all non-DHA subjects was 75% of the baseline MPD. For DHA groups, the starting dose was 0.75 (MPD × protection factor; see below). Maximum doses achieved were 22 J/cm² for all American-style and European-style groups, while DHA groups were arbitrarily limited to a maximum of 32 J/cm², a practical level set in part by the light source irradiation, for a maximum exposure time of about 40 minutes.

For all treatment groups, liquid 8-methoxypsoralen capsules were given at 0.5 mg/kg orally, 1 hour before light treatment with a UV-A light cabinet (model V4472-IV; Ultralite Enterprises, Lawrenceville, Ga) having 38 fluorescent light bulbs (F42T12-BL; National Biologic Corporation, Cleveland, Ohio). Irradiance measured with a 325-to 385-nm UV-A detector (International Light IL-1700, Newburyport, Mass) was 14 mW/cm². The MPDs were determined with a 0.6 × 0.9 m (2 × 3 ft) UV-A light panel (Ultralite Enterprises) with optical output spectrum identical to that of the treatment unit.

The 6 study groups (Table 1) were (1) standard American-style PUVA (UV-A increments of 0.5-1.5 J/cm² per treatment), (2) American-style PUVA plus lactic acid, (3) DHA-PUVA or Turbo-PUVA, (4) DHA-PUVA with lactic acid or Turbo-PUVA with lactic acid, (5) European-style PUVA (UV-A increments based on serial phototesting), and (6) European-style PUVA plus DHA. Combinations of lactic acid and European-style treatment were not studied because data analysis after the first 4 groups completed enrollment revealed that the lactic acid had no apparent effect. All subjects continued in treatment until clearing, defined as a 90% reduction in baseline psoriasis area and severity index (PASI) score, or until 30 treatments, whichever came first. Increments of UV-A treatment dose varied between groups. For European-style PUVA groups, increases were based on standard assessment of the MPD, determined during the course of PUVA.11 American-style PUVA groups received increments of 0.5 to 1.5 J/cm² per treatment unless PUVA-induced erythema was present, in which case no increment was given. Increments in the DHA-PUVA groups were based on DRS-derived protection factors at 350 nm. This was performed because of the theoretical concerns that DHA staining could be variable and unpredictable. Diffuse reflectance spectroscopy was performed by aligning and synchronously scanning the excitation and emission wavelengths of a fluorescence spectrophotometer equipped with a bifurcated fiber bundle (Sunscreen Machine, Spex Inc, Edison, NJ) held in contact with the skin. Protection factor was defined as the square root of the ratio of skin reflectance at 350 nm for unstained normal skin relative to DHA-stained normal skin. Reflectance spectra were consistently measured in the same DHA-protected and DHA-treated skin sites to determine the protection factor, and UV-A dose increments were given as prior dose × protection factor if there was no erythema.

In all groups, any PUVA treatment causing mild transient erythema resulted in the patient’s receiving the same dose as on the last visit. If moderate erythema occurred and persisted, the next treatment was withheld.

At each visit, photographs were taken. Weekly PASI scores were recorded as well as the number of treatments to clearance.12 Also noted were the UV-A dose increments, DHA protection factors, the number of individuals in each group who had clearing by 6, 12, 18, 24, and 30 treatments, and any subjective responses. The Fisher exact test was used to evaluate statistical significance of data between the 6 groups.

Twenty-four subjects completed the pilot study. Six individuals, 1 from each group, had dropped from the study for personal reasons; 4 developed conflicting commitments and 2 changed jobs. Thus, only 4 subjects successfully completed the study in each group. There were 16 men and 8 women with a mean age of 47.3 years (range, 24-67 years). There were 9 with skin type I, 5 with skin type II, 6 with skin type IV, 2 with skin type V, and 2 with skin type VI. All subjects had involvement of 20%
Among the 6 treatment groups, the Turbo-PUVA group showed the fastest rate of clearing, followed by the European-style groups. The European-style PUVA group showed 90% clearing in 1 subject after each of 12, 18, 24, and 30 treatments. One subject with skin type II experienced a moderate PUVA strip burn at treatment 12, which he related to a change in his manner of standing in the light unit. He ultimately showed more than 70% clearing by treatment 30. Two subjects in the European-style PUVA plus DHA group experienced minor localized burns associated with shifting of placement of undergarments during phototherapy. Three of 4 subjects in this group had clearing by treatment 30.

The American-style PUVA group had the lowest rate of clearing. Only 1 subject showed greater than 90% clearing by treatment 30. The other 3 subjects reached a mean of 75% clearing by treatment 30, the termination point. There were 2 subjects with mild burns, 1 on the hands and 1 on the flanks and the buttocks, occurring at 12 and 15 J/cm², respectively. For the American-style PUVA plus lactic acid group, only 1 subject had clearing by treatment 30, and the other 3 had a mean of 75% clearing.

to 40% total body surface area. Each group had at least 1 subject with skin type II and 1 with skin type III.

For each group, the number of subjects whose psoriasis was clear by a given treatment is shown in Table 2. Among the 6 treatment groups, the Turbo-PUVA group showed the fastest and greatest degree of clearing of psoriasis at all time periods. This group also needed the least number of treatments for 90% clearing. Doses as high as 32 J/cm² were safely reached in this group. There was 1 case of moderate patchy truncal burning at a dose of 24.3 J/cm² on the fifth treatment, even though the same skin type II patient had tolerated the 22-J/cm² dose well on the previous treatment. This burn coincided with the subject’s premature discontinuation of DHA after the fourth treatment, simply because he forgot to use it. Three of 4 subjects in this group had clearing by treatment 30. The other 3 had a mean of 75% clearing.

The Turbo-PUVA plus lactic acid group showed the second best response, with all 4 subjects having clearance by treatment 24. One subject in this group experienced a moderately severe, nonblistering burn in patches on the buttocks, from the first treatment given after DHA application had stopped. The same patient had a history of easy burning from traditional American-style PUVA, and all previous treatments had failed, including systemic methotrexate.

The increments used in the Turbo-PUVA groups were much greater than those routinely given. For example, 1 subject in the Turbo-PUVA group received doses of 4.5, 10.0, 14.0, and 20.0 J/cm² for the first 4 treatments while another received doses of 8.0, 16.0, 24.0 and 30.0 J/cm² without any complications. The mean UV-A increments for the Turbo-PUVA group were 6.75, 6.25, 6.0, and 4.0 J/cm² for the first 4 increments. As per protocol, the American-style increments were 0.5 to 1.5 J/cm². The corresponding mean European-style group increments were 4.5, 3.1, 1.75, and 1.0 J/cm². Despite the high UV-A fluence and large increments given for Turbo-PUVA, the regimen was well tolerated because of photoprotection by DHA.

In general, subjects using DHA stated that they enjoyed the immediate “tan” that they received. Generally, subjects with skin type V and VI did not notice a significant change in their skin color with DHA use, but 1 subject disliked the trace orange color he perceived in the first 3 weeks of the study. Some subjects complained about the smell of the lactic acid lotion. There were no irritant or allergic reactions associated with use of either the DHA or lactic acid. Compliance was excellent with the exception of the 1 subject from the Turbo-PUVA group who forgot to use the DHA once, and developed erythema on the subsequent treatment.

The 2 Turbo-PUVA groups showed the fastest rate of clearing, followed by the European-style groups. The European-style PUVA group showed 90% clearing in 1 subject after each of 12, 18, 24, and 30 treatments. One subject with skin type II experienced a moderate PUVA strip burn at treatment 12, which he related to a change in his manner of standing in the light unit. He ultimately showed more than 70% clearing by treatment 30. Two subjects in the European-style PUVA plus DHA group experienced minor localized burns associated with shifting of placement of undergarments during phototherapy. Three of 4 subjects in this group had clearing by treatment 30.

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\[\text{Table 1. PUVA Study Groups and Their Parameters}^{*}\]

<table>
<thead>
<tr>
<th>PUVA Group</th>
<th>Starting Dose</th>
<th>Increments</th>
<th>Maximum Dose, J/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>American style</td>
<td>0.75 (MPD)</td>
<td>0.5-1.0 J/cm²</td>
<td>22</td>
</tr>
<tr>
<td>American style plus lactic acid</td>
<td>0.75 (MPD)</td>
<td>0.5-1.0 J/cm²</td>
<td>22</td>
</tr>
<tr>
<td>Turbo-PUVA</td>
<td>0.75 (MPD × PF)</td>
<td>(DRS-derived PF) × prior dose</td>
<td>32</td>
</tr>
<tr>
<td>Turbo-PUVA plus lactic acid</td>
<td>0.75 (MPD × PF)</td>
<td>(DRS-derived PF) × prior dose</td>
<td>32</td>
</tr>
<tr>
<td>European style</td>
<td>0.75 (MPD)</td>
<td>Standard MPD assessment</td>
<td>22</td>
</tr>
<tr>
<td>European style plus DHA</td>
<td>0.75 (MPD)</td>
<td>Standard MPD assessment</td>
<td>22</td>
</tr>
</tbody>
</table>

* PUVA indicates psoralen–UV-A; Turbo-PUVA, topical UV-resisting barrier to optimize PUVA; MPD, minimal phototoxic dose; PF, protection factor; DRS, diffuse reflectance spectroscopy; and DHA, dihydroxyacetone.

\[\text{Table 2. Number of Subjects With Clearing}^{*}\]

<table>
<thead>
<tr>
<th>PUVA Group</th>
<th>Treatment No.</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>American style</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>American style plus lactic acid</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Turbo-PUVA</td>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turbo-PUVA plus lactic acid</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European style†</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>European style plus DHA†</td>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* PUVA indicates psoralen–UV-A; Turbo-PUVA, topical UV-resisting barrier to optimize PUVA; DHA, dihydroxyacetone; and ellipses, not applicable.
† Combinations of lactic acid and European-style PUVA treatment were not studied.
The tabulation below shows the mean cumulative incident UV-A dose by group.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (Range) Dose, J/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>American style</td>
<td>342 (129-632)</td>
</tr>
<tr>
<td>American style plus lactic acid</td>
<td>362 (243-522)</td>
</tr>
<tr>
<td>Turbo-PUVA</td>
<td>402 (334-518)</td>
</tr>
<tr>
<td>Turbo-PUVA plus lactic acid</td>
<td>546 (443-650)</td>
</tr>
<tr>
<td>European style</td>
<td>420 (266-425)</td>
</tr>
<tr>
<td>European style plus DHA</td>
<td>545 (273-586)</td>
</tr>
</tbody>
</table>

The cumulative dose in the Turbo-PUVA groups was comparable to those in the European-style groups, but higher than those in the American-style groups.

There was no difference in baseline PASI scores between the groups. Lactic acid had no apparent effect in this study and both American-style groups and both Turbo-PUVA groups were combined to examine the use of DHA. By as early as 18 treatments, the use of DHA (Turbo-PUVA groups, with 7 of 8 subjects showing clearing) vs its nonuse (American-style groups, with none of the 8 showing clearing) reached statistical significance ($P = .001$, Fischer exact test). No other significant differences were noted. The sample size in this pilot study was too small to detect any significant differences between American-style and European-style groups.

**COMMENT**

Turbo-PUVA is a new therapeutic modality developed for this study. The use of DHA during PUVA allowed larger-than-usual doses to be given, accelerating clearance of psoriasis such that all 8 subjects receiving Turbo-PUVA (with and without lactic acid) were in remission by treatment 24. Indeed, 7 of 8 had clearing by treatment 18 and 5 of the 8 had clearing by treatment 12. Comparing results of this study with those of studies of historical PUVA controls who showed clearance in no less than 20 to 25 treatments, Turbo-PUVA results in quicker clearance. Use of DHA adds protection of the uninvolved skin early in the treatment course, before PUVA pigmentation begins to set in. Uneven or inconsistent DHA application might remove that protection, resulting in burns. Only 2 moderate burns occurred in the Turbo-PUVA groups of this study, both at the first treatment after DHA was discontinued. Patients receiving Turbo-PUVA must be given clear instructions on the systematic, uniform application of DHA.

The DHA and European-style groups received a higher mean cumulative dose of UV-A over the course of this study than did the American-style groups. Despite fairly equivalent cumulative doses, the DHA groups had faster clearing than the European-type PUVA group and the American-type PUVA group, which did not result in clearance in most of the subjects. Of course, the actual amount of UV-A received by the skin of the subjects receiving Turbo-PUVA may not be well reflected by these numbers due to the protection afforded by the DHA. There is an increased risk of squamous cell carcinoma and malignant melanoma in patients after receiving PUVA therapy, which may be diminished by protecting uninvolved skin during Turbo-PUVA. Thus, Turbo-PUVA therapy has the potential for both faster and safer treatment of psoriasis.

Most DHA users liked the immediate “tan” achieved. Many spontaneously reported feeling better about themselves and their psoriasis as early as a few hours after the first DHA application, even though clinical improvement by PASI scores took 6 weeks. This study used 15% DHA, which resulted in a darker “tan” than most over-the-counter sunless tanning products, which contain about 3% to 5% DHA. Although admittedly multiple applications of any DHA formulations produce additive skin darkening, caution must be exercised in generalizing our results to any modified protocols involving other preparations.

Because its increments are based on phototesting, European-style PUVA has been consistently praised for its more rapid rate of clearing; however, it is time-consuming to perform weekly MPD tests to determine dose increments. The DRS technique used to determine the protection factor in this study could potentially be useful for setting dosimetry during non-DHA PUVA therapy as well. In this study, lactic acid did not make any appreciable difference in the rate of clearing. We expected to find a benefit from lactic acid, but did not.

In summary, DHA or presumably any other sunscreen that binds to stratum corneum can be used to preferentially protect uninvolved skin, allowing higher UV treatment doses and accelerated clearing of psoriasis.
Turbo-PUVA with DHA or Turbo–UV-B phototherapy with a skin-binding UV-B sunscreen may potentially improve both efficacy and safety. This pilot study should be followed by larger clinical trials.

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