Pure synthetic metalloporphyrins have been developed for experimental and clinical use as inhibitors of heme oxygenase, the rate limiting enzyme in the catabolism of heme to bilirubin. Tin (Sn)-protoporphin is one such compound, which potently suppresses bilirubin production and thus jaundice in animals and man. We have previously reported that this metalloporphyrin in conjunction with UVA might be useful as a treatment for psoriasis. To assess the photodynamic properties of Sn-protoporphyrin, 31 subjects were investigated with regard to photosensitivity. In all subjects, phototesting using UVB, UVA, and visible light as well as photopatch testing was performed. Our investigations revealed that 16 of the 31 individuals treated with Sn-protoporphyrin developed a mild photosensitivity, mainly erythema of the hands and face, and in some cases a mild conjunctivitis. The duration of this sensitivity, which in no cases caused discomfort, was dose-dependent and ranged from several weeks to 1-3 months. After administration of Sn-protoporphyrin, lower thresholds were found for both UVA and visible light, but the sensitivity for UVB was normal and photopatch tests were negative. In summary, the photosensitivity observed during Sn-protoporphyrin administration was of limited duration and magnitude and did not occur in all subjects. Thus, the combination of photoactive synthetic metalloporphyrins and artificial light might prove to be useful as a regimen for the treatment of skin disease. Key words: Photosensitivity; Synthetic metalloporphyrins; Heme oxygenase inhibitor.

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Pure synthetic metalloporphyrins have been developed for experimental and clinical use as inhibitors of heme oxygenase, the rate limiting enzyme in the catabolism of heme to bilirubin (1-6). Tin (Sn)-protoporphyrin is one such compound, which potently suppresses jaundice in animals and man. In the small doses used clinically, Sn-protoporphyrin has proved to be innocuous (3, 4, 7).

There have been to-date no published reports on clinical effects relating to photosensitivity produced by Sn-protoporphyrin in man. We have previously reported that this metalloporphyrin in conjunction with UVA might be useful as a treatment for psoriasis (8, 9). In this study we investigated in detail the clinical photosensitization phenomenon in man and report results of phototesting in individuals treated with Sn-protoporphyrin. Although Sn-protoporphyrin has been superseded by the heme analogue Sn-mesoporphyrin for clinical studies in newborn jaundice, because of its more desirable photophysical and other properties, the photosensitization which can be elicited by Sn-protoporphyrin make it of special dermatological interest.

MATERIALS AND METHODS

Subjects

Altogether 31 subjects, 21 men and 10 women, 9 of whom were normal volunteers, e.g. medical students and medical staff, were investigated. Of the 22 patients participating in the study, 11 had chronic liver disease, and 11 were psoriatics described in detail earlier (7-9). Before participation in the study, the patients underwent a full clinical examination and extensive biochemical tests as described before (7). The tests were repeated at the end of the study and no differences compared with baseline levels were observed. The study was approved by the ethical committee of Huddinge University Hospital, the Karolinska Institute, and the clinical trial department of the Swedish Drug Agency (Socialstyrelsens likemedelsavdelning), and all subjects participating gave informed consent. Throughout the study no restrictions of normal life pattern was given. However, the participants were advised to avoid excessive sunbathing and/or artificial UV-light. Patients no. 7-16 received suberythematoic UVA-treatment as part of a clinical trial for treatment of psoriasis (8). Individuals with known photosensitivity were not entered into the study, and the participating subjects were graded into skin types I-V on the basis of their recall of their reactivity to natural sunlight (10).

Experimental procedure

Fasting blood samples for measurements of various biochemical indices, including bilirubin and hematological values, were taken each morning for 3 days before entry to the study, and for 10 days after the administration of the metalloporphyrin. Sn-protoporphyrin was infused intravenously and a second identical infusion was given 8 h later as described before (7). The total dose given was 2 μmol/kg in 16 subjects and 1 μmol/kg body weight in 15 subjects. The duration, onset and body localization of the artificially induced light-sensitivity were assessed both by history and by clinical examination. The examinations were carried out by the same investigator (LE) on all occasions. The investigator was aware of the treatment of the subjects; thus this was not a blind study. Representative skin areas were documented by photography.

UVA-testing

In 25 subjects UVA threshold values were measured with a Waldmann UVA 800 unit (Waldmann, Schwenning, Germany) before administration of Sn-protoporphyrin (1 μmol/kg body weight) and for 2-4 days after the infusion. Six of the subjects given 2 μmol/kg body weight had no predetermined UVA threshold value, and in those the UVA-testing was done 4-6 weeks after the injections (nos. 1-6 in Table 1). Each subject's back was illuminated through a green cloth in which had been cut standardized open squares (5 × 5 cm). 5, 10, 15, and 25 J/cm² of UVA were given to each square. The test areas were evaluated 24 h after the irradiation. A positive minimum erythematous dose was defined as the lowest dose of UVA to produce an erythematous reaction in shape of a square (at least three corners had to be visible to be regarded as a positive reaction). The output of the lamps was measured weekly with a Waldmann meter type S85 100.
Table 1. Clinical photosensitivity and results of phototesting in subjects receiving a high dose of Sn-protoporphyrin (2 μmol/kg), n = 16

<table>
<thead>
<tr>
<th>Subjects no.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>Skin type (ref. 10)</th>
<th>Month of injection</th>
<th>Localization of photosensitivity</th>
<th>Dose of UVA (J/cm²) producing MED11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conjointiva</td>
<td>Face</td>
</tr>
<tr>
<td>1.</td>
<td>M</td>
<td>33</td>
<td>Control</td>
<td>II</td>
<td>May</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2.</td>
<td>M</td>
<td>33</td>
<td>Control</td>
<td>II</td>
<td>Apr</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>3.</td>
<td>M</td>
<td>55</td>
<td>Hemochromatosis</td>
<td>II</td>
<td>Apr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4.</td>
<td>F</td>
<td>67</td>
<td>Hemochromatosis</td>
<td>III</td>
<td>Apr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5.</td>
<td>M</td>
<td>25</td>
<td>Control</td>
<td>II</td>
<td>May</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>6.</td>
<td>F</td>
<td>23</td>
<td>Control</td>
<td>III</td>
<td>Apr</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>7.</td>
<td>M</td>
<td>54</td>
<td>Psoriasis</td>
<td>III</td>
<td>Apr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8.</td>
<td>M</td>
<td>63</td>
<td>Psoriasis</td>
<td>III</td>
<td>Apr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9.</td>
<td>F</td>
<td>60</td>
<td>Psoriasis</td>
<td>III</td>
<td>Feb</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11.</td>
<td>M</td>
<td>48</td>
<td>Psoriasis</td>
<td>III</td>
<td>Apr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12.</td>
<td>M</td>
<td>62</td>
<td>Psoriasis</td>
<td>III</td>
<td>Apr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13.</td>
<td>M</td>
<td>58</td>
<td>Psoriasis</td>
<td>I</td>
<td>Dec</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14.</td>
<td>M</td>
<td>54</td>
<td>Psoriasis</td>
<td>III</td>
<td>Apr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15.</td>
<td>M</td>
<td>42</td>
<td>Psoriasis</td>
<td>III</td>
<td>Mar</td>
<td>-</td>
<td>X</td>
</tr>
</tbody>
</table>

¹MED: minimal erythemal dose; ²nd: not done.

UVB-testing
In 8 subjects, UVB threshold values were measured in a similar manner as for UVA threshold, but here a XBO 150W high pressure xenon lamp (Zeiss, Oberkochen, Germany) and a WG 255 Schott filter (Schott, Mainz, Germany) were used.

Visible light testing
Testing for sensitivity to visible light was performed as described above for UVA. Here a lamp in an operating theatre (Angenicus 42570 type AX14 300 × 24 W, France) was used at a distance of 1 m and the open squares of the green cloth were 10 × 10 cm. The test areas were evaluated 24 h after the irradiation.

Table II. Clinical photosensitivity and results of phototesting in subjects receiving a low dose of Sn-protoporphyrin (1 μmol/kg), n = 15

<table>
<thead>
<tr>
<th>Subjects no.</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>Skin type (ref. 10)</th>
<th>Month of injection</th>
<th>Localization of photosensitivity</th>
<th>Dose of UVA (J/cm²) producing MED11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conjointiva</td>
<td>Face</td>
</tr>
<tr>
<td>17.</td>
<td>F</td>
<td>70</td>
<td>Primary biliary cirrhosis</td>
<td>III</td>
<td>May</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>18.</td>
<td>M</td>
<td>24</td>
<td>Hemochromatosis</td>
<td>III</td>
<td>Dec</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19.</td>
<td>M</td>
<td>27</td>
<td>Primary biliary cirrhosis</td>
<td>III</td>
<td>Dec</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20.</td>
<td>M</td>
<td>41</td>
<td>Control</td>
<td>III</td>
<td>Apr</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>21.</td>
<td>M</td>
<td>42</td>
<td>Primary biliary cirrhosis</td>
<td>II</td>
<td>Apr</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>22.</td>
<td>F</td>
<td>55</td>
<td>Primary biliary cirrhosis</td>
<td>I</td>
<td>Apr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>23.</td>
<td>F</td>
<td>49</td>
<td>Psoriasis</td>
<td>IV</td>
<td>Apr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>24.</td>
<td>M</td>
<td>32</td>
<td>Control</td>
<td>II</td>
<td>Oct</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>25.</td>
<td>F</td>
<td>65</td>
<td>Alcoholic cirrhosis, hyperpliolon</td>
<td>III</td>
<td>Nov</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>26.</td>
<td>M</td>
<td>27</td>
<td>Control</td>
<td>II</td>
<td>Oct</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>27.</td>
<td>M</td>
<td>42</td>
<td>Primary biliary cirrhosis</td>
<td>III</td>
<td>Nov</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>28.</td>
<td>F</td>
<td>51</td>
<td>Primary biliary cirrhosis</td>
<td>III</td>
<td>Jan</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>29.</td>
<td>M</td>
<td>38</td>
<td>Hemochromatosis</td>
<td>III</td>
<td>Nov</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>30.</td>
<td>M</td>
<td>38</td>
<td>Control</td>
<td>II</td>
<td>Dec</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>31.</td>
<td>F</td>
<td>71</td>
<td>Primary biliary cirrhosis</td>
<td>III</td>
<td>Oct</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

¹MED: minimal erythemal dose.
UV-sensitivity and UVB-sensitivity

In all persons except 2 the UV-thresholds were below 25 J/cm² after the injections with mean UV-threshold of 10 J/cm² (5–25 J/cm²) (Fig. 1; Tables I–II). All except 2 of the 15 individuals not developing a light sensitivity still had markedly lowered UV-thresholds. All persons tested had normal threshold values for UVB after the injections.

Sensitivity to visible light

The investigation of sensitivity to visible light was made in 2 subjects (patients no. 14 and 16). One reacted with a brisk erythema and edema 24 h after a 45 min exposure to the operating theatre lamp, and the other after a 30 min exposure (Fig. 1). In normal, not sensitized individuals such a lamp is used for up to 6–8 h during surgery without causing any skin reactions.

Photopatch-testing

Five individuals were tested and no immediate or late positive reactions were recorded.

DISCUSSION

Our investigations have revealed that 16 out of 31 individuals treated with Sn-protoporphyrin developed a moderate photosensitivity, including a slight conjunctivitis. The duration of this sensitivity was dose-dependent, ranging from 1 to 3 months, with onset after the injections. Lowered thresholds for both UVA and visible light were observed. The 14 of the 15 subjects who did not develop clinical photosensitivity also had a lower threshold for UVA sensitivity following the injections. Eight of the 16 individuals without an apparent light sensitivity were treated during the winter, with small amounts of natural sunlight. One would expect a higher number of subjects with clinical photosensitivity if the drug was given during April to September.

The action spectrum of Sn-protoporphyrin is in the long-wave range of UVA and/or in the visible light region of the solar spectrum, which is consistent with the previously described absorption spectrum of the compound, showing a peak at 406 nm (11, 12). Our findings of erythema and edema following the illumination of the sensitized patients with an ordinary operating lamp are consistent with previous reports on patients treated with porphyrins (13, 14) or patients with erythropaetic protoporphyrina (15) developing photosensitivity after general surgery.

Photopatch tests were negative in all 5 individuals tested, despite the fact that concentrations up to 10-fold above the therapeutic serum concentration were applied in the test. This argues against a phototoxic mechanism, although this presently cannot be completely ruled out. Phototoxicity in general should be confirmed in in vitro and animal models.

It should be emphasized that the described photosensitivity induced by Sn-protoporphyrin in the patients treated is mild, dose-dependent, and reversible. The substance can be given in single small doses intramuscularly or intravenously. It is not enzymatically metabolized to bile pigments in vivo and it has
no other known side-effects in the doses used clinically. The drug has been safely used in the treatment of hyperbilirubine-
mia of newborns (16), as well as in patients with liver diseases (17). The results of this study are consistent with the notion that photodynamic effects are obtained in the combined treat-
ment with synthetic porphyrins and UV-light. These effects could be beneficial in the treatment of skin disease, and partly equivalent to PUVA-treatment. We have with some success treated psoriasis patients with Sn-protoporphyrin and UVA (8, 9). When compared to the standard regime of PUVA in these patients (18), Sn-protoporphyrin treatment offers certain ad-
vantages including the fact that no patient treated with Sn-
protoporphyrin has suffered from nausea which is common in
PUVA-treatment. Another potential advantage of the use of
synthetic metalloporphyrins instead of psoralens for the treat-
ment of skin disease could be that the target site for cell killing
most likely is the cell membranes rather than DNA (19–21).
Therefore, little or no mutagenesis would be expected from
this mode of phototherapy. Recently, an increased incidence of
genital invasive squamous cell carcinoma has been reported
among male patients exposed to high levels of PUVA (22).
In a large-scale, epidemiological study we have confirmed previ-
ous reports of a dose-dependent increase in the incidence of
squamous cell cancer in patients treated with PUVA; signifi-
cant increases of some internal cancers have also been ob-
erved (23).

Dihematoporphyrin ether, also known as Photofrin-II, is
currently used in the treatment of a variety of epithelial ne-
oplasms, in a modality known as photodynamic therapy. A
major drawback of these porphyrins for photodynamic ther-
apy is their ability to evoke prolonged and intense cutaneous
photosensitization (for review, see 13). This photosensitization
is similar to that of patients with erythropoietic protopor-
phyria (24). By the use of Sn-protoporphyrin in the doses of
the present study this drawback may be circumvented.
Newly synthesized derivatives of tin-protoporphyrins, i.e. Sn-
mesoporphyrin and Sn-diododeuteroporphyrin, have recently
been shown to have reduced photoactive properties in vitro
compared to Sn-protoporphyrin (28), and may thus offer other
advantages in clinical use. Other routes to administer the
synthetic porphyrins, such as the development of topical he-
matoporphyrin derivatives (29) or targeting of heme oxyge-
nase inhibitors to the spleen (30), may minimize the potential
problem of phototoxicity. Recently, the porphyrin precursor
5-aminolevulinic acid (ALA) has successfully been applied
to superficial skin cancers followed by photoactivating
light, selectively destroying tumors (28, 29).

In conclusion, the photosensitivity observed during Sn-
protoporphyrin administration was of limited duration and magni-
titude and did not occur in all subjects. Thus, the combination
of photoactive synthetic metalloporphyrins and artificial light
might prove to be useful as a regimen for the treatment of skin
disease.

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tentially inhibits microsomal heme oxygenase activity in normal
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