Terfenadine, given in sufficient dose to cause maximum H$_1$ receptor blockade, had no effect on the intensity of UVB or UVC erythema measured with a reflectance instrument at 4, 8, and 24 h after irradiation. Histamine, acting on the H$_1$ receptor, is not a significant mediator of UVB or UVC erythema. J Invest Dermatol 87:771–774, 1986

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ncreased amounts of histamine have been found in suction blister fluid [1,2] and dermal perfusate samples [3] obtained at various times after irradiation of human skin with 3–5 times the minimal erythema dose (MED) from a broadband UV radiation (UVR) source (medium pressure mercury arc lamp). The significance of histamine as a mediator of UVR-induced erythema in human skin is uncertain, however, as administration of the H$_1$ receptor antagonists mepyramine maleate and triprolidine had no effect on the MED, or the erythematous response to higher doses (assessed visually) [4,5]. The lack of observed response to these antihistamines could be due to inadequate H$_1$ receptor blockade or inability of the detection threshold estimate (MED) or visual grading system to detect small changes in erythema response.

Since these early experiments [4,5] were performed, H$_1$ receptor antagonists of greater potency have become available and a reflectance instrument [6] has been developed to quantify erythema and allow dose-response curves to be constructed for UVR of different wavelengths [7]. In the present study, the effect of terfenadine on the UVR log(dose) erythema-response curve for UVB and UVC radiation has been determined.

**MATERIALS AND METHODS**

**Subjects** Eight adult volunteers (4 male, 4 female; age range 24–37 years; sun-reactive skin type II–III) with clinically normal skin were studied. No subject was known to exhibit abnormal sensitivity to sunlight or was taking any medication known to provoke such a reaction.

**Photirradiation Apparatus and Radiation Dosimetry** Two optical radiation sources were used:

1. **UV-C**, a germicidal lamp (Philips type TUV 15W) for irradiation principally at 254 nm. The lamp was mounted inside an opaque plastic housing with a cylindrical collimator (15 mm internal diameter) positioned orthogonally to the midpoint of the long axis of the lamp.

2. **UV-B**, a 500-W medium-pressure mercury arc lamp in conjunction with Schott WG305 (3 mm thick) and UGS (1 mm thick) color glass filters. Radiation from the lamp was focused into a liquid-filled light guide (1 m in length) with an applicator attached to the distal end of the light guide to produce a uniform beam of radiation (10 mm diameter) on the skin surface. Spectral irradiance from both lamps (Fig 1) was measured in the plane of the skin surface using a double holographic grating spectroradiometer (Optronic Laboratories Inc., model 742) with a bandwidth set at 1.5 nm, calibrated by reference to a deuterium spectral irradiance standard (obtained from the National Physical Laboratory, U.K.). The integrated irradiance from 200–290 nm (UV-C waveband) from the germicidal lamp was 27.2 W/m$^2$; this is 96% of the UV output and is almost entirely due to the 254 nm characteristic line. The integrated irradiance (unweighted by any biologic action spectrum) from 290–320 nm (UV-B waveband) from the optically filtered mercury arc lamp was 79.4 W/m$^2$. Approximately 97% of the erythemally effective power from this source lies within the spectral interval 290–320 nm.

An actinic radiometer (International Light, model 730A), designed to respond only to UVB and UVC radiation and calibrated against the spectroradiometer, was used to monitor the irradiance from both lamps during the study. Measurements were made before and after irradiation of each subject.

**Subject Irradiation** Six closely apposed circular sites (20 mm diameter) were marked on either side of the midback of each subject. One group of sites was irradiated consecutively with UVC and the other with UVB radiation. On either side of the back one site was not irradiated and served as a control area. A geometric series of increasing exposures was used: the dose increment factor being 2 for UVC and 2$^{0.4}$ for UVB radiation. All subjects were exposed to 5 different doses from each lamp, ranging from 0.25–4.0 j/m$^2$ and 1.24–3.75 j/m$^2$ for UVC and UVB radiation, respectively. Within a period of 2 weeks [during which time none of the subjects’ backs was exposed to natural or artificial UV radiation (UVB)], dose-response studies were repeated to obtain 2 sets of measurements in each subject: while on no medication, and during treatment with terfenadine. On the second occasion, adjacent areas of skin to those used in the first measurements were marked and irradiated.

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Abbreviations:

UVB: ultraviolet B radiation (290–320 nm)

UV-C: ultraviolet C radiation (100–290 nm)

UVR: ultraviolet radiation
Measurement of Erythema Erythema was measured using a reflectance instrument which compares the amount of red and green light reflected from the skin and thus obtains an “erythema index” related to the blood content of the superficial dermis [6]. Before irradiation, 3 measurements of the erythema index were made at each of the sites, with the subject lying prone on a couch. In all subjects, the erythema measurements were repeated at 4, 8, and 24 h after irradiation. The increase in vasodilation due to the irradiation is expressed as the difference (ΔE) between the mean post- and mean preirradiation erythema index at each site. This value has been shown to be a more reliable indicator of vasodilatation than the postirradiation erythema index alone [8].

Administration of Terfenadine Terfenadine (120 mg twice daily) was taken orally for 2 days before irradiation and this dosage continued during the period of measurement of the erythema. Dose-response measurements were made in 4 subjects while on no medication and then repeated during treatment with terfenadine. In the remaining subjects the order of terfenadine administration was reversed.

Histamine Injection Immediately after each irradiation, 8 μg of histamine acid phosphate (dissolved in 0.1 ml of saline) was injected intradermally into the volar aspect of the forearm of each subject. Ten minutes after injection, the border of the histamine-induced weal was marked with a ball-point pen and an impression transferred onto paper using adhesive cellophane tape. The weal area was then measured using a computer-linked digitizing tablet.

RESULTS

Measurements of Erythema The increase in erythema index (ordinate) was plotted against the logarithm of the UVR dose (abscissa) for each waveband, time of observation and subject, and for irradiation both before and while being treated with terfenadine. An example of the responses obtained is shown in Fig 2. At doses in excess of the least dose of UVR to result in visible erythema, an approximate straight-line response was obtained. Linear regression was applied to the straight-line part of the curve, selecting the limits of fitting by eye. By this process, a slope was calculated for each response together with a “threshold dose” defined as that dose of UVR where the extrapolated linear regression line intersects the abscissa at ΔE = 0. As reported previously [7], the slope of response was greater for UVB radiation than for UVC radiation at all times of observation after irradiation.

Analysis of variance applied to regression [9] showed that in 34 of 48 cases (71%) there was no significant difference (p > 0.05) between the slopes of the dose-response curves for each waveband determined pre- and post-terfenadine in a given subject and time of observation. The pooled slopes of the dose-response curves obtained for all 8 subjects are summarized in Table I. A paired t-test indicated no significant change in the slopes of any of the responses (at a given waveband and time of observation) obtained before and while taking terfenadine.

Since analysis of variance indicated no strong reason for postulating a difference between the slopes of the regression lines in the various groups, analysis of covariance was used to examine the relative position of the parallel regression lines. In 36 of 48 cases (75%) the pre- and post-terfenadine regression lines were found not to coincide (p < 0.05). The logarithm of the threshold doses determined by regression are listed in Table II. As the distribution of doses required for a minimally perceptible erythema show a log-normal distribution [10], parametric statistical analysis (paired t-test) was applied to the logarithm of the threshold doses determined pre- and post-terfenadine for each waveband and time of observation. In each case, there was no significant difference between the 2 sets of measurements.

Histamine-Induced Weal Weal area was reduced in each subject after treatment with terfenadine (Fig 3). The mean pre- and post-terfenadine weal areas (corrected for the injection volume) were 1.82 and 0.18 cm², respectively (90% reduction). A paired t-test showed the change in weal area to be significant (p < 0.001).
The present study has shown that the potent H₁ receptor antagonist terfenadine has no effect on the slope of the dose-response curve for either UVB or UVC erythema measured 4, 8, or 24 h after irradiation despite almost complete ablation of histamine-induced weal. A small, but significant, change in the threshold dose was found in 71% and 79% of cases when the results on all subjects were considered together there was no significant systematic change in threshold dose at either wavelength after treatment with terfenadine. In all cases, the pre- and post-terfenadine measurements were made at adjacent sites on the back and within 2 weeks of each other; it is unlikely, therefore, that any change in threshold dose was due to site-to-site variation in erythemal response over the back [8] or alteration of the physical properties of the skin during this period. Other factors are presumably responsible, such as the uncertainty in measurement of irradiance (estimated at ± 5%), errors in the reflectance measurement of erythema (coefficient of variation of a single reading on the skin is 3% [8]), and altered environmental or physiologic conditions. The differences in threshold dose between pre- and post-terfenadine measurements were greater for UVC than for UVB radiation; this is due to the much shallower slope of the UVC dose-response curve compared with UVB [7], resulting in a larger uncertainty in UVC threshold dose.

In all subjects, significant inhibition of histamine-induced weal was seen after treatment with terfenadine. The dose of terfenadine and the treatment period of 48 h were chosen to ensure that maximum H₁ receptor blockade was achieved both at the time of irradiation and during the development of erythema. The degree of histamine weal inhibition (99%) was similar to the maximum reported for terfenadine using a variety of dosage regimens [11,12] and was considerably greater than that obtainable with conventional H₁ receptor antagonists [13,14].

This study has shown that histamine (acting on the H₁ receptor) is not a significant mediator of UVB or UVC erythema at 4, 8,

### Table I. Summary of Pooled Slopes (Mean ± 1 SE) of Dose-Response Curves Obtained Before (Pre) and While Taking (Post) Terfenadine

<table>
<thead>
<tr>
<th>Time after Irradiation (h)</th>
<th>UVC</th>
<th>UVB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>4</td>
<td>0.077 ± 0.003</td>
<td>0.068 ± 0.003</td>
</tr>
<tr>
<td>8</td>
<td>0.069 ± 0.003</td>
<td>0.056 ± 0.003</td>
</tr>
<tr>
<td>24</td>
<td>0.083 ± 0.002</td>
<td>0.080 ± 0.003</td>
</tr>
</tbody>
</table>

### Table II. Logarithm of Threshold Dose (Im⁻²) Before (Pre) and While Taking (Post) Terfenadine

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>4 h</th>
<th>8 h</th>
<th>24 h</th>
<th>4 h</th>
<th>8 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.L.</td>
<td>F</td>
<td>1.55</td>
<td>1.56</td>
<td>1.62</td>
<td>3.14</td>
<td>2.99</td>
<td>3.15</td>
</tr>
<tr>
<td>J.S.</td>
<td>M</td>
<td>1.92</td>
<td>1.58</td>
<td>1.31</td>
<td>3.11</td>
<td>3.20</td>
<td>3.00</td>
</tr>
<tr>
<td>M.D.</td>
<td>F</td>
<td>1.69</td>
<td>0.84</td>
<td>0.88</td>
<td>3.00</td>
<td>3.02</td>
<td>2.72</td>
</tr>
<tr>
<td>F.H.</td>
<td>M</td>
<td>1.52</td>
<td>1.58</td>
<td>1.11</td>
<td>3.03</td>
<td>3.18</td>
<td>2.98</td>
</tr>
<tr>
<td>C.F.</td>
<td>F</td>
<td>1.74</td>
<td>1.86</td>
<td>1.34</td>
<td>3.16</td>
<td>3.13</td>
<td>2.96</td>
</tr>
<tr>
<td>P.F.</td>
<td>M</td>
<td>0.48</td>
<td>0.49</td>
<td>0.60</td>
<td>3.18</td>
<td>3.08</td>
<td>3.01</td>
</tr>
<tr>
<td>B.D.</td>
<td>M</td>
<td>1.37</td>
<td>0.85</td>
<td>0.74</td>
<td>3.19</td>
<td>3.03</td>
<td>3.01</td>
</tr>
<tr>
<td>J.J.</td>
<td>M</td>
<td>1.83</td>
<td>1.31</td>
<td>1.31</td>
<td>3.11</td>
<td>3.10</td>
<td>2.96</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>1.51</td>
<td>0.88</td>
<td>1.31</td>
<td>3.06</td>
<td>3.02</td>
<td>2.97</td>
</tr>
<tr>
<td>± 1 SD</td>
<td></td>
<td>±0.42</td>
<td>±0.63</td>
<td>±0.40</td>
<td>±0.06</td>
<td>±0.07</td>
<td>±0.07</td>
</tr>
</tbody>
</table>

**Discussion**

Figure 3. Pre- and post-terfenadine histamine-induced weal areas in each subject. The mean (± 1 SD) weal areas are also shown.

or 24 h after irradiation and, although it is not known whether other cutaneous histamine receptors [15] are involved, it seems likely that the increased histamine concentration found in suction blister fluid [1,2] and dermal perfusate samples [3] from areas of UVB-exposed skin plays no part in the erythema. It remains to be established whether histamine is a mediator of other components of the inflammatory response to UVR, or whether this
release of histamine is merely a response of tissue that is already inflamed to external trauma such as suction or dermal perfusion.

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REFERENCES