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Irritation and Staining by Dithranol (Anthralin) and Related Compounds III. Cumulative Irritancy and Staining during Repeated Chamber Testing

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Received August 10, 1982

Abstract. Irritation and staining, the side effects of dithranol and related compounds have previously been studied after a single chamber-exposure. To mimic the therapeutic situation, the chamber application was repeated for 3 weeks on the uninvolved back skin of 17 psoriasis patients. In equimolar concentrations corresponding to 0.05% dithranol, dithranol caused markedly more erythema and staining than 10-propionyl dithranol and 10-butyryl dithranol, whereas 10-butyryl dithranol irritated and stained less than 10-propionyl dithranol. To reach the irritation and staining level of dithranol, a 4-fold higher concentration of 10-butyryl dithranol was required. During the first week the irritation culminated, declining later despite repeated applications, possibly because of exhaustion of anthrone-induced inflammatory mediators.

Key words: Psoriasis; Dithranol; Anthralin; 10-propionyl dithranol; 10-butyryl dithranol; Irritation; Staining; Repeated chamber testing

In previous papers (4, 5, 6, 7), skin irritation and staining caused by a single exposure of dithranol

and some related anthrones was studied by applying the chamber-testing technique of Pirilä (8). In uninvolved skin of psoriasis patients the Irritant Dosis 50 (ID₅₀) as mmol/kg of petrolatum for dithranol, 10-acetyl dithranol, 10-propionyl dithranol and 10-butyryl dithranol were 0.2, 0.5, 1.5 and 4.5, respectively (6, 7). A single exposure of irritating and staining anthrones does not mimic the therapeutic situation as well as repeated applications, and therefore the cumulative irritancy and staining of uninvolved skin of psoriasis patients was studied.

MATERIALS AND METHODS

17 hospitalized psoriasis patients volunteered for this study. In addition to dithranol, 10-propionyl dithranol and 10-butyryl dithranol were applied on the uninvolved back skin using 12 mm Finn chambers (8). The application was repeated every second day on exactly the same sites. In 9 patients the concentration used was 2 mmol/kg of white petrolatum for all three anthrones, and in 8 patients the concentration of dithranol was 2 mmol/kg, and those for 10-propionyl dithranol and 10-butyryl dithranol were 4 and 8 mmol/kg, respectively. In all patients the vehicle, white petrolatum, was estimated at every application. The reading scales were the same as before (4).

RESULTS

Fig. 1 shows the average alternate day alterations in erythema and staining in the group of 9 patients tested by the 2 mmol/kg concentration of dithranol (D), 10-propionyl dithranol (PD) and 10-butyryl dithranol (BD). There was no evidence of irritation or staining at the control sites tested with the vehicle white petrolatum. In the equimolar concentration of 2 mmol/kg D caused markedly more erythema and staining than PD and BD, and BD irritated and stained less than PD. During the first week of repeated testing the irritation reached the highest intensity: 2.7 for D, 1.3 for PD and 1.0 for BD. Later, despite repeated applications, the irritation declined, the average erythema value of the 20th day being 0.8, 0.6 and 0.3 for D, PD and BD, respectively. For D the staining was most intense during the second week (average value 2.5) and later decreased a little because of peeling. For PD and BD the staining value of 1.1 was reached during the third week.

Fig. 2 illustrates the average alternate day alterations in erythema and staining in the group of 8 patients tested with 2 mmol/kg of D, 4 mmol/kg

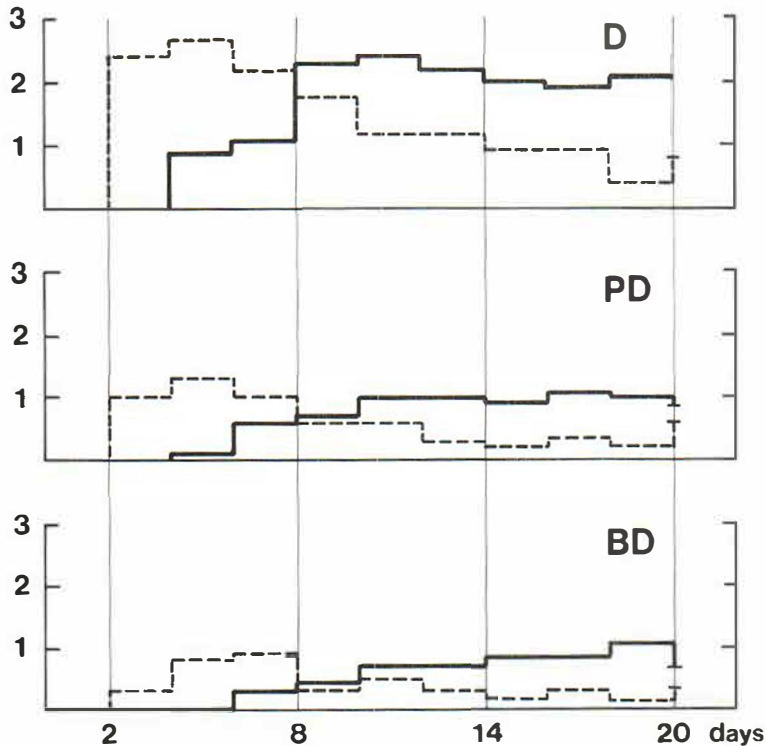


Fig. 1. Irritation (---) and staining (—) caused by 2 mmol/kg concentration of dithranol (D), 10-propionyl dithranol (PD) and 10-butyryl dithranol (BD) on the uninvolved skin of 9 psoriasis patients on alternate day application. Reading scales:

0 = no erythema
 1 = faint erythema
 2 = moderate erythema
 3 = intense erythema

0 = no staining
 1 = brownish hue
 2 = reddish brown
 3 = dark brown

of PD and 8 mmol/kg of BD. In both patient groups the irritation and staining caused by 2 mmol/kg of D followed a similar course, whereas 4 mmol/kg of PD and 8 mmol/kg of BD caused more irritation and staining than when used in the 2 mmol/kg concentration.

DISCUSSION

Staining of clothing and linen and irritation and staining of the skin, especially of the uninvolved skin around the psoriatic lesions, limits the ambulatory use of dithranol. Even after a single application, dithranol causes an exposure-time and dose dependent delayed erythema and staining (4). The determination of the minimal erythema dose gives a useful hint of the greatly varying individual tolerance. For this purpose and for the determination of ED_{50} of dithranol and related compounds the chamber-testing technique of Pirilä (8) has been used (6, 7), and it is suited even for repeated appli-

cation at exactly the same sites which mimics the therapeutic situation better than a single application.

Similar repeated-application tests have been applied to the study of potential irritancy and allergenicity of topical medicaments and cosmetic products, which would be repeatedly placed in contact with the skin (1, 2, 3). Marzulli & Maibach (3) have studied dithranol irritancy by multiple application tests. They used a 16-day cumulative irritation test in rabbits and a 21-day test in man. Dithranol in two concentrations (0.01 and 0.1% in petrolatum) was daily applied at the same site of the back under a non-woven pad fixed with acrylic tape. The lower concentration produced well-defined erythema in rabbits and slight erythema in man, and the higher concentration vesiculation in rabbits and well-defined erythema in man. Our test concentration of dithranol (2 mmol/kg) corresponds to 0.05% w/w and the 3-week of alternate day testing resulted in

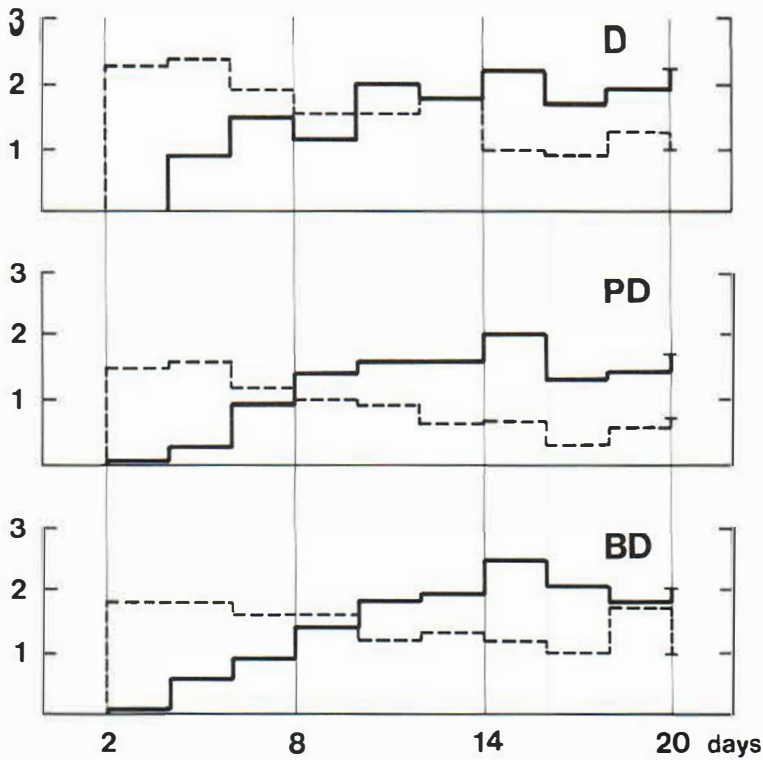


Fig. 2. Irritation (---) and staining (—) caused by 2 mmol/kg dithranol (D), 4 mmol/kg 10-propionyl dithranol (PD) and 8 mmol/kg 10-butyryl dithranol (BD) on the unin-

involved skin of 8 psoriasis patients on alternate day application. Reading scales as in Fig. 1.

stronger irritation than 0.1% in the subjects of Marzulli & Maibach. Probably the aluminium chambers provided better occlusion than the acrylic tape.

When repeated chamber testing was compared with single chamber exposure (5) the 0.05% concentration of dithranol caused more intense irritation and staining by multiple application than by single exposure. The single 24-hour exposure resulted in moderate erythema, whereas the alternate day exposure resulted within one week in intense erythema. For the 10-acyl analogues of dithranol too, repeated application caused stronger irritation and staining than a single 24-hour exposure (5), but when they were used in comparable concentrations the erythema and the staining were distinctly less marked than with dithranol. To reach the irritation and staining level of dithranol, a four-fold higher concentration of 10-butyryl dithranol was required. When irritation and staining after single exposure of dithranol and 10-butyryl dithranol were compared, the difference was more

pronounced, e.g. the ID_{50} of 10-butyryl dithranol was 20 times as high as that of dithranol (6, 7).

For all three anthrones, the intensity of erythema began to wane at the end of the first week, continuing throughout the 3 weeks of repeated testing. This tachyphylaxis-like phenomenon may be the result of exhaustion of anthrone-induced inflammatory mediators such as hydroperoxy fatty acids and prostaglandins (4, 6).

During the 3 weeks of repeated testing, none of the 17 psoriasis patients developed any signs of allergy to these three anthrones.

The antipsoriatic effects of equimolar concentrations of dithranol and 10-butyryl dithranol were almost equal in these 17 patients, and will be published later.

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Solar Simulators: Modifications for Testing with Visible Light

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Received August 11, 1982

Abstract. The Berger Solar Simulator is designed to test light-sensitive patients for their sensitivity to ultraviolet light. The present modification was performed to make testing with UV and visible light possible. The modification consists in replacing the dichroic mirror with a beam splitter (BSP 580) and the filters with a WG 340 allowing 340-565 nm to pass. Subdivision of that spectrum is performed by inserting a Wratten 12 (500-565 nm) or a Wratten 2B (400-565 nm). Infrared is excluded by a KG3 filter.

Key words: Solar simulator; filter modifications; Light-sensitive patients; Tests with UV-light; Tests with visible light

Solar simulators are widely used in testing light-sensitive patients for their sensitivity to ultraviolet (UV) light. Some UV-sensitive patients are sensitive to visible light too and a few patients will only react to visible light (3).

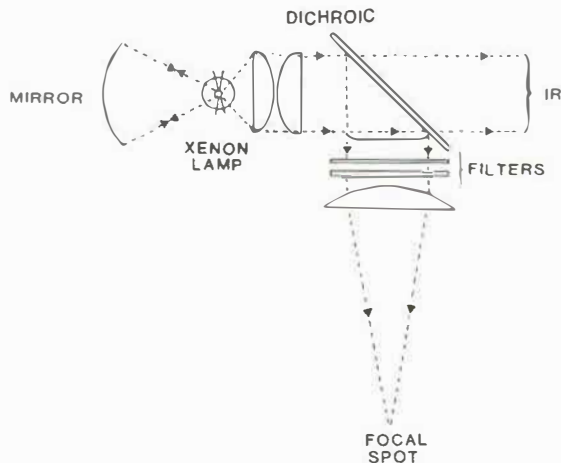


Fig. 1. Light path in the Berger Solar Simulator.

In the following we describe a modification of the filters used in a Berger solar simulator (1) whereby the emission spectrum is widened to include visible light.

METHODS

The light path in the solar simulator is seen in Fig. 1 (1). The light source in a solar simulator is a xenon arc lamp. In our solar simulator the UV is reflected from an angled dichroic mirror and the reflected light is cut off by a Corning blue filter (3 mm) and by a WG 320 filter (1.5 mm) to give an UV-spectrum comparable to sunlight. Only UV-A is transmitted when a WG 340 is inserted into the light path. The reflection curve for the dichroic mirror and the transmission curves for the filters are shown in Fig. 2, together with the resulting light output at different wavelengths.

Modifications (Fig. 3). When the dichroic mirror was replaced by a beam splitter (BSP 580), some UV and visible light up to about 565 nm (50% transmission) was reflected. The reflection below 350 nm was minimal and difficult to measure, and is not given in Fig. 3. We consider that the UV-B is better excluded in order not to disturb the evaluation of the reaction to longer wavelengths. This was obtained by placing a WG 340 filter in the light path. Not all infrared (IR) passed the mirror, but some was reflected. The reflected IR could be absorbed by means of a KG 3 (3 mm thick) filter (Fig. 3).

A subdivision within the visible spectrum was chosen by inserting a Wratten 12 (Kodak) into the light path, giving 500-565 nm only, or a Wratten 2B giving 400-565 nm (Fig. 3) only.

RESULTS AND DISCUSSION

Irradiation with the modified solar simulator of subjects with different skin types gave a weak bluish skin colour within 4-10 min of irradiation