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Photoaugmentation in Drug Phototoxicity

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The phototoxic reaction to chlorpromazine and other drugs is provoked by long-wave ultraviolet light (UVA). It was shown by the *in vivo* mouse tail technique that the reaction is enhanced by medium-wave ultraviolet light (UVB), thus demonstrating the importance of photoaugmentation in this process.

Solar dermatitis is mainly caused by medium-wave ultraviolet radiation (UVB) but recent data indicate that the cutaneous response is the result of an action by different wavelengths of ultraviolet and visible light [1]. With regard to drug phototoxicity it is generally acknowledged that the reaction is elicited by long-wave ultraviolet light (UVA). It is, however, possible that radiation apart from UVA may influence a phototoxic dermatitis even if the action maximum of the photosensitizer is clearly in the UVA. The present study was undertaken to elucidate the cutaneous effect of combined UVA/UVB exposures with and without a photosensitizer. The quantitative mouse tail technique [2] was found most convenient for both types of experiments.

MATERIALS AND METHODS

Animals

Female albino mice (AB Anticimex, Sollentuna, Sweden) weighing around 30 gm were used. The mouse tail technique has been described earlier [3].

Phototoxic Drugs

Chlorpromazine chloride (CPZ) (Hibernal, AB Leo, Helsingborg, Sweden); chlordiazepoxide (CDO) (Librium, F. Hoffmann-La Roche & Co. AG, Basel, Switzerland); and 8-methoxypsoralen (8-MOP) provided by Draco AB, Lund, Sweden. CPZ and CDO were dissolved in water, and 8-MOP was suspended in a cellulose solution (sodium carboxymethylcellulose 7.5 gm, benzyl alcohol 9 ml, sodium chloride 5.7 gm, Tween 80 0.4 ml and distilled water ad 1 000 ml). The drugs were injected intraperitoneally immediately before irradiation.

Irradiation Procedure

During exposure to ultraviolet light the animals were fixed in horizontal plastic tubes allowing only the tails to be exposed. The distance between the light source and the tails was 12 cm. The radiation intensity was measured with an Optometer UDT-40X from United Detector Technology.

Irradiation with Long-wave Ultraviolet Light (UVA)

The animals were irradiated with 2 blacklight fluorescent tubes (Philips TLA 40W/08) the emission of which had a peak at 360 nm. As 1.6% of the total output consisted of radiation shorter than 320 nm a 3 mm window-glass filter was inserted. Hereby, the average intensity was 3.2 mw/cm^2 sec. A standard exposure of 5 hr equivalent to 58 J was given in all experiments.

Irradiation with Medium-wave Ultraviolet Light (UVB)

The animals were irradiated with 2 fluorescent tubes (Westinghouse Sun Lamp 40 w) emitting continuously from about 280 nm to 380 nm with a peak at 313 nm. The average intensity was 6.0 mw/cm^2 sec. The animals were irradiated for 10, 20 or 40 min (equivalent to 3.5–14 J) immediately before or after the UVA exposure.

Experimental Design

In all experiments 5 groups of 10 animals were treated according to the Table. As controls served group I consisting of animals exposed to UVA only; in previous [3] and fresh pilot experiments this treatment induced no inflammatory reaction whatsoever.

Evaluation and Statistics

The animals were sacrificed 24 hr after starting the exposure when given CPZ or CDO but at 48 hr when given 8-MOP. A piece of the tail was excised, weighed, dried at 110°C and weighed again. Results are presented as percent wet weight increase over controls. For the statistical evaluation the mean values from groups of 10 animals were treated with the Student's *t*-test.

RESULTS

Exposure to UVA and UVB without Photosensitizer

In 12 experiments the inflammatory response to combined UVA + UVB exposures was compared to that of UVB only. The UVA exposure was chosen so as not to induce any reaction at all and the UVB stimulation was weak throughout, doses of 3.5–7 J being used. The inflammatory response to the combination was stronger than to UVB alone in 8 experiments, the same in one experiment, and weaker than to UVB in 3 experiments (Fig 1). When the experiments were grouped according to order of UVA/UVB exposure (Fig 1) combined exposures induced stronger reactions than UVB alone in all experiments but one when UVA was given before UVB. With the reverse order the results were not uniform. However, in none of the 12 experiments was there a statistically significant difference between the reactions from combined UVA/UVB exposures and from UVB alone.

Addition of UVB to a Phototoxic Reaction

In order to study if there was a photoaddition or photoaugmentation when UVB was added to the phototoxic reaction (UVA + drug) the wet weight increase from group I to III was compared to that from group IV to V. This was studied in 10 experiments the results of which are presented in Fig 2. The UVA exposure was kept constant but the UVB dose, the UVA/UVB order, as well as the amount and type of photosensitizer varied. In 6 of the ten experiments the addition of UVB to the phototoxic reaction resulted in a significantly stronger inflammatory response than the addition of UVB to UVA only. In the other 4 experiments, 2 with the lowest UVB dose, one with the highest CPZ dose, and the one with 8-MOP, no such difference was observed. The results were not influenced by the UVA/UVB order.

DISCUSSION

In 1969, van der Leun and Stoop [4] showed that 250 and 300 nm erythema in man were reduced by subsequent exposure to long-wave and visible radiation, *i.e.* a photorecovery. If on the

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Abbreviations:
CDO: chlordiazepoxide
CPZ: chlorpromazine chloride
8-MOP: 8-methoxypsoralen

The different treatment of the 5 experimental groups[a]

Step No.	Group	I	II	III	IV	V
1	Drug	−	−	−	+	+
2	UVA	+	−	+	+	+
3	UVB	−	+	+	−	+

[a] In some of the experiments the order between step 2 and 3 was reversed.

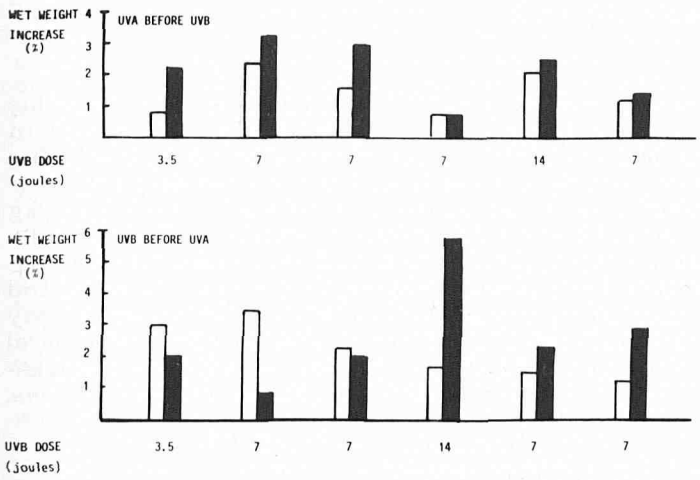

FIG 1. The 12 paired experiments where the effect of UVB alone (*open columns*) was compared with that of UVA + UVB (*black columns*). In the upper 6 experiments UVA was given first, in the lower UVB was given first. The height of the columns shows the wet weight increase over base line values.

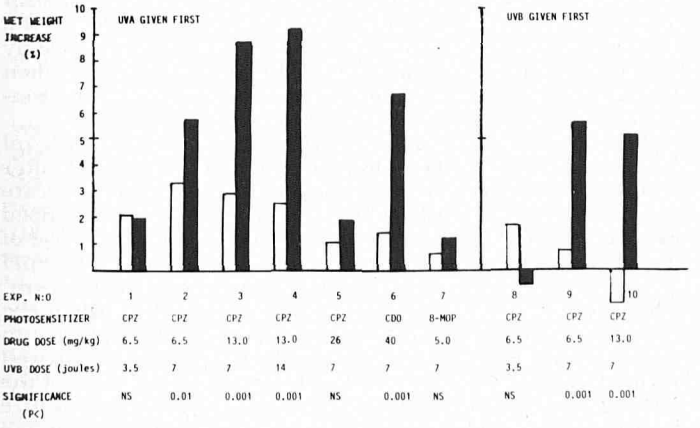

FIG 2. Results of UVB addition to UVA (group I vs. III according to the Table, *open columns*) compared to UVB addition to a phototoxic reaction (group IV vs. V, *black columns*). *CPZ* = chlorpromazine; *CDO* = chlordiazepoxide; *8-MOP* = 8-methoxypsoralen.

other hand UVA was given first there was an addition with the 250 nm radiation and a "reinforced addition" with 300 nm (UVB). The reinforcing effect of preexposure to UVA was also observed by Willis, Kligman, and Epstein [5] and by Kaidbey and Kligman [6] who therefore considered it a photoaugmentation. The principle of augmentation was denied by Parrish et al [7] and Ying, Parrish, and Pathak [8] who could explain the co-effect of UVA and UVB by simple addition of energies. Again, the recent experiments of Spiegel et al [9] speak in favor of a photoaugmentation. The augmentative effects were not influenced by the order in which UVA and UVB were given [6,9].

In the present experiments in which mouse tail edema (not erythema) was registered a noninflammatory dose of UVA did not influence the cutaneous response to a small dose of UVB. When UVA was given before UVB a tendency to photoaugmentation was observed in most experiments (Fig 1) but this was in no case statistically significant. Thus, our experimental design—which might not be optimal—could not confirm the phenomenon of reinforced addition or augmentation in the interplay between UVA and UVB.

In the second part of the present work the influence of UVB on drug phototoxicity was studied. We were able to show that an exposure of UVB increased the phototoxic reaction more than could be explained by simple addition, *i.e.*, a photoaugmentation was demonstrated (Fig 2). Most experiments were performed with chlorpromazine as a photosensitizer but the principle held true for another, chlordiazepoxide, and probably also for 8-methyoxypsoralen. Photoaugmentation occurred independent of the UVA/UVB order. It was not seen in 2 experiments with a very low UVB dose which evidently was insufficient to induce photoaugmentation.

It should be pointed out that UVB alone cannot activate chlorpromazine in the skin. Thus, when mice are injected with chlorpromazine in doses up to 20 mg/kg and later exposed to UVB 15 J there is no inflammatory reaction (Ljunggren & Möller, unpublished results). Also, the specificity of the phenomenon demonstrated may be questioned. Consequently, the possible influence of other inflammatory stimuli will be tested in future studies.

The present results with systemic drug phototoxicity are in accordance with those of Kaidbey and Kligman [6]. These authors, although working with qualitative erythema reading, were able to demonstrate augmentation in epicutaneous phototoxicity to coal tar and 8-methoxypsoralen.

It has long been known that in principle, photosensitizing drugs are not activated by UVB. The present results suggest, however, that UVB enhances phototoxic reactions caused by systemic drugs, not only by addition but by augmentation.

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