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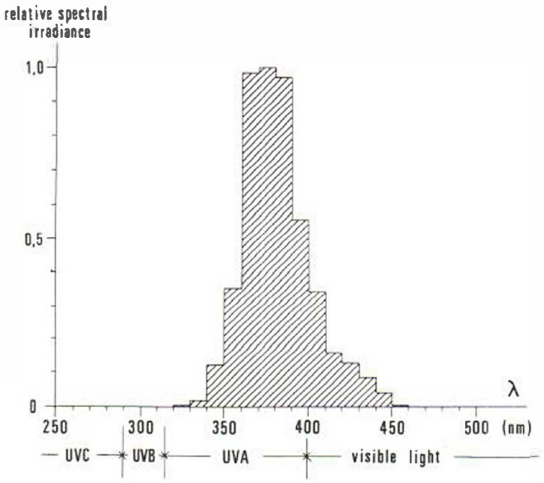

Fig. 1. Spectral distribution of the test lamp.

Phototoxic Reactions from Some Common Drugs Provoked by a High-intensity UVA Lamp

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Abstract. Human volunteers were tested for phototoxic reactions with high UVA doses after intake of four different drugs. Four out of ten became more sensitive to UVA light after intake of nalidixic acid, two out of ten for hydrochlorothiazide, one out of ten for doxycycline but no one of the ten taking promethazine reacted with a higher sensitivity to UVA radiation. One test person reacted unexpectedly with a polymorphous light eruption for 48 J/cm² UVA even without drug intake. The safety of giving high UVA doses for cosmetic purposes in connection with drug intake is discussed.

Key words: Hydrochlorothiazide; Doxycycline; Nalidixic acid; Promethazine; UVA-radiation phototoxicity

Textbooks on dermatology often contain long lists of drugs that can cause phototoxic reactions. These lists are compilations from case reports in the literature and give us practically no information on how often one can expect such reactions to occur. Magnus (3) has however tried to relate the frequency of reported phototoxic and photoallergic reactions to the overall prescribing of the drugs. The mere distinction between phototoxic and photoallergic reactions is rather difficult (4). Systematic studies have not been made in the human but have been made on microorganisms and laboratory animals (1, 2).

As ultraviolet therapy is becoming very common for skin diseases and cosmetic purposes, it is necessary to gather better information on the risk of adverse reactions arising from the use of common drugs in connection with UV light exposure.

High-intensity UVA sources to be used for cosmetic purposes have been developed. These light sources are practically free of UVB irradiation and are therefore very suitable for experiments on phototoxic reactions in the human.

We have tested some commonly used drugs that are reported in the literature as being photosensitizing. After drug ingestion the skin was exposed to UVA light. The short-term use of the drug before exposure to light and the fact that each individual was tested for only one drug minimizes the risk of involving immunological reactions. On this basis we feel that it is relevant to characterize the reactions as phototoxic if they have a morphology which does not indicate a delayed-type immunological reaction.

MATERIALS AND METHODS

The four drugs tested were hydrochlorothiazide (Esidrex-K forte, Ciba, in a dose of 50 mg o.d. for 3 days), doxycycline (Idocycline, Ferrosan, first day 100 mg b.i.d. and the following 2 days 1 tablet of 100 mg), nalidixic acid (Negram, Winthrop, 1 g q.i.d. in 3 days) and promethazine (Lergigan, Recip, 25 mg 4 hours prior to light exposure).

Forty human healthy volunteers (17 males, 23 females) took part in the study. They were medicial students and

Table I. *Number of phototoxic reactions to the four drugs tested*

Hydrochlorothiazide	2/10
Doxycycline	1/10
Nalidixic acid	4/10
Promethazine	0/10

staff of the hospital. The mean age was 31 (range 17–65) years.

As light source, a high intensity sun lamp UVA-SUN 2000 (Mutzhas, Munich, Germany) was used. This is a metal halide high-pressure discharge lamp (5). Fig. 1 shows the relative spectral intensity distribution of the lamp. According to measurements made at the Swedish National Institute of Radiation Protection this lamp delivers about 660 W/m² at a distance of 20 cm. Our measurement at 25 cm distance gave 400 W/m² at the time of the present investigation. Practically no detectable amount of UVB radiation is delivered by the lamp.

The test persons were first tested on the volar side of one forearm for 5, 7.5, 11, 15, 21 and 30 min or 12, 18, 26, 36, 50 and 72 Joules/m² respectively on about 4 cm² areas.

The reactions after 24 and 72 hours were recorded and graded as follows: 0, no reaction; +, slight erythema; ++, strong erythema; +++, erythema and oedema; ++++, blistering.

After 1 week or more a group of 10 subjects took drug no. 1, another 10 subjects drug no. 2 and so on. For the first three drugs the test was made on the third day. For the fourth drug, promethazine, just one tablet of 25 mg was given 4 hours prior to testing. Exposures to the same doses of UVA-light were given as in the previous test without drugs but to the other forearm.

A positive phototoxic reaction was registered when minimal erythema dose after drug intake (MPD) was two steps lower than before, or for the persons not reacting to 72 Joules when the MPD was 48 Joules or lower.

RESULTS

Reactions to UVA-radiation before drug intake

Most of the test-persons got an immediate pigment darkening which was most pronounced in the test area illuminated with 72 Joules. In 30 of the 40 individuals tested, no recognizable erythema was found for the doses given when examined 24 and 72 hours after exposure. In 7 subjects the minimal erythema dose was 72 Joules, in two others, 48 Joules and one person reacted to only 12 Joules. The latter person was a red-haired, fair-skinned individual. He reacted with an edema to 72 Joules after 24 hours. The edema has disappeared by 72 hours.

Reactions to UVA after drug intake

In the hydrochlorothiazide group 2 persons had a positive phototoxic reaction. For the doxycycline group only 1 person had a positive reaction. In the nalidixic acid group, 4 persons reacted, 2 of them with edematous reactions. In the promethazine group no patient reacted with a phototoxic reaction. See Tables I and II.

Table II. *Type and UVA doses for the phototoxic reactions observed after 24 hours (see Material and Methods)*

	Time (min)					
	5	7.5	11	15	21	30
Hydrochlorothiazide (2/10)						
Without drug	0	0	0	0	0	+
With drug	0	0	0	+	++	+++
Without drug	0	0	0	0	0	0
With drug	0	0	0	+	+	+
Doxycycline (1/10)						
Without drug	0	0	0	0	+	++
With drug	0	0	+	+	++	++
Nalidixic acid (4/10)						
Without drug	0	0	0	0	0	0
With drug	0	0	0	++	+++	+++
Without drug	0	0	0	0	0	0
With drug	0	0	++	++	+++	+++
Without drug	0	0	0	0	0	0
With drug	0	0	0	+	+	+
Without drug	0	0	0	0	0	0
With drug	0	0	0	+	+	+

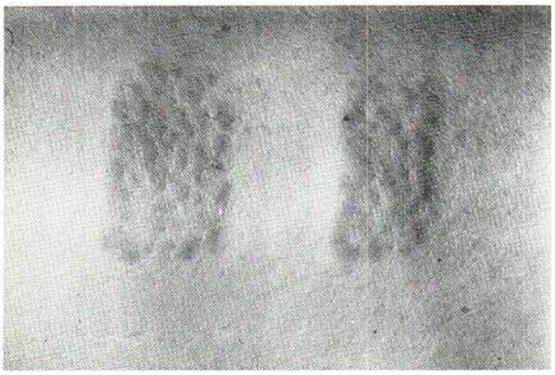

Fig. 2. Polymorphos light eruption provoked by the test in a woman who can tolerate Swedish summer sun well.

Most of the subjects with an increased sensitivity to UVA-light after drug intake noticed a burning and stinging sensation shortly after exposure. The erythematous reaction had not disappeared at 72 hours in any of the cases.

One person who had a slight erythematous reaction to 32 Joules/cm^2 having taken hydrochlorothiazide noticed weeks later a papular response that began in the tests where 48 and 72 Joules had been given on the arm irradiated before drug intake. A few days later the same reaction appeared on the irradiated arm after drug intake with the same doses. The papules were very strictly confined to the test area, with sharp margins and were itching (Fig. 2). After having asked her a second time about any unusual reaction to sun-bathing she admitted that she got some papular reactions to sun-bathing in the Mediterranean area many years ago. The papules provoked by our test disappeared after the use of steroid-cream but a few month later they reappeared on the same area without any exposure to ultraviolet light. This localized eruption was classified as polymorphous light eruption.

DISCUSSION

The UVA source used gives an intensity in this spectral region about 10 times that of midday summar sunlight. The time it would have taken to elicit the reactions observed with natural sunlight would be of the order of a couple of hours. In that time the UVB part of the solar spectrum had given rise to a stronger reaction. Therefore one may question the practical value of the present findings for out-door exposure.

We do not know the exact action spectrum for the phototoxic reactions of the drugs used. The shorter wavelength included in sunlight might very well be very effective compared with the spectral distribution of the lamp used, with regard to provoking the phototoxic reactions.

The drugs used are, according to our experience, very weak sensitizers compared with 8-methoxypsoralen. No interference of these drugs with PUVA treatment seems likely, therefore. This is in accordance with our practical experience with patients undergoing PUVA treatment using some of the drugs tested in this experiment.

Another question is the safety of this type of UVA lamp in suntanning apparatuses used in so-called solaria. It is evident that in a general population treated with these types of drugs there would be some unpleasant reactions to doses that are used in solaria. What might be more serious is that in this group of 40 persons, selected to be able to withstand sunlight, one red-haired man got a rather intense reaction and one woman got a polymorphous light eruption. Relatively safe UVA doses would in this respect be about 20–30 Joules. The Swedish National Institute of Radiation Protection has forbidden the general use of suntan lamps with an intensity exceeding 200 W/m^2, which would correspond to 36 Joules for a half-hour exposure (6).

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