

Phototoxicity of methoxsalen in various vehicles

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Methoxsalen (8-methoxypsoralen) was used as the phototoxic substance in the study of the properties of various vehicles in photoepicutaneous testing. Macrogols as such were relatively poor bases, and positive reactions were seen only occasionally at a concentration of 0.05 % methoxsalen.

Increasing amounts of water in macrogols brought forth more numerous and stronger reactions. The phototoxicity also increased when ethanol was added. The reactions were, however, weaker than to those with aqueous bases.

Wool fat and glycerol as vehicles usually reacted in the same way as polyethylene glycols when water was added. An explanation of the mechanism of the changes in the properties of vehicles due to the addition of water/ethanol requires further investigation.

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Before a photosensitivity reaction can take place, the photoactive compound has to be carried into the skin; in photoepicutaneous testing the vehicle plays an important role in this event. The vehicle must have neither irritating nor sensitizing properties. Moreover, it should be suitable for testing various kinds of photosensitizing substances.

Thus far, there has been no vehicle which completely fulfills the above-mentioned criteria for photoepicutaneous testing. In previous papers marked differences in test results with different standard vehicles have been shown (Suhonen 1976).

The aim of this investigation was to study the influence of various compositions of different vehicles on the results of photoepicutaneous testing, using methoxsalen as the phototoxic compound.

Material and Methods

The test subjects were dermatologic patients. Persons with known photosensitivity and those on potentially photosensitizing medication were excluded.

Methoxsalen (8-methoxypsoralen, 8-MOP) was used as the phototoxic agent at 0.05 % and 0.25 %.

The vehicles used in the tests were polyethylene glycols (PEG) 400, 3000 and Ung. Macrogoli DF – a mixture of PEG 400 (60 %) and 3000 (40 %) –, wool fat and glycerol. Water was added to the vehicles in concentrations of 20, 40, 60 and 80 %, with the exception of wool fat, where 60 % was the maximal amount of water added. PEG 3000 is a solid material, and therefore could not be used without the addition of

water. In the same way, abs. ethanol in a concentration of 20, 40, 60 and 80 % and a mixture of ethanol and water (40 % and 40 % as final concentrations, respectively) were added to Ung. Macrogoli DF.

The materials were applied using the chamber method (Pirilä 1975). The amount of test substance was 20 μ l in each chamber. The application of the test substance in liquid vehicles was made using a filter paper disc in each chamber. In order to study the possible influence of the paper disc on the test results, identical tests were made both with and without the filter paper using wool fat-water mixtures as the vehicles.

The occlusion time in all tests was 2 hours. Before irradiation, one half of each

test site was covered with black adhesive tape. The covered half served as a dark control. The irradiation was performed with a unit consisting of six Philips TL 20W/08 black light tubes emitting in a range of 320–380 nm with a maximum of 365 nm (Suhonen et al. 1976). The irradiation time was 5 min at a distance of 5 cm. The test sites were covered after irradiation with lightproof carbon paper fixed on the skin with porous adhesive tape (Scanpor®, Norgesplaster A/S, Oslo).

The test reactions were evaluated after 24, 48 and 72 h and graded on a 0–4 scale, where 0 means no reaction and 4 a uniform bulla. The results were also evaluated on the basis of the percentage of positive phototoxic reactions.

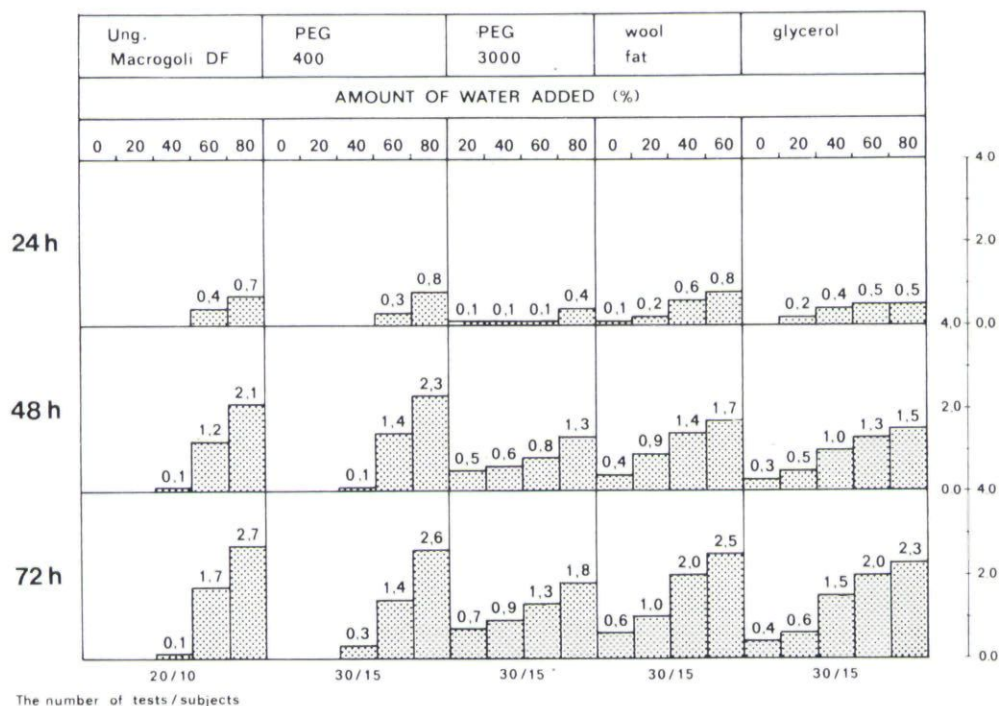


Fig. 1. Mean reaction indices of reactions elicited by 0.05 % methoxsalen in vehicles with increasing amounts of water. The occlusion time was 2 hours.

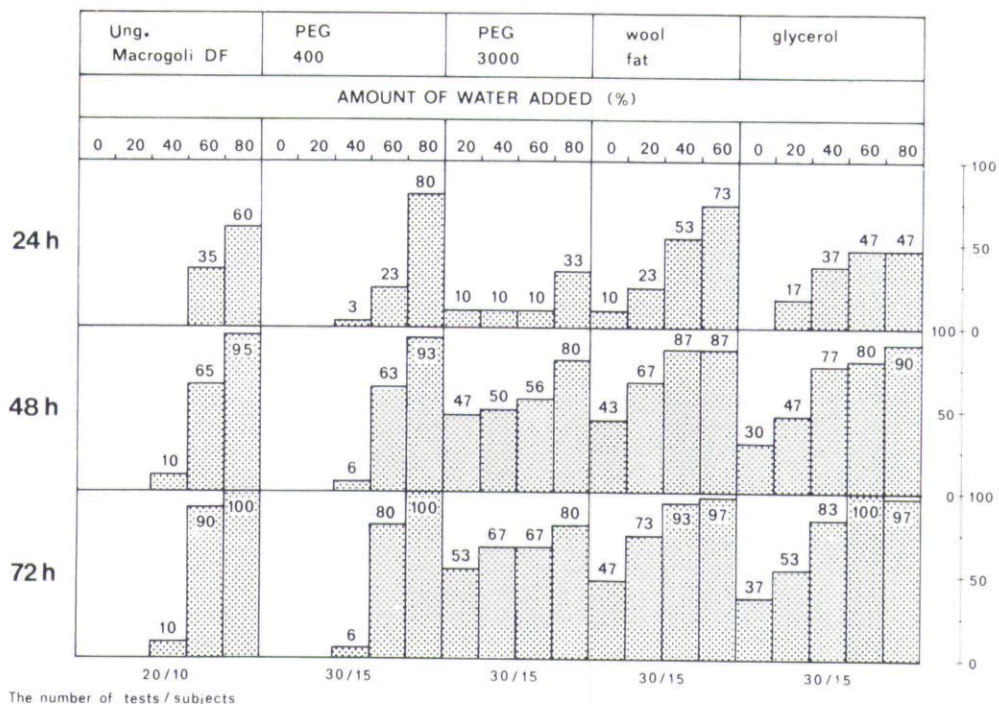


Fig. 2. The rate of positive reactions elicited by 0.05 % methoxsalen in different vehicles with increasing amounts of water. The occlusion time was 2 hours.

Results

Methoxsalen did not evoke phototoxic reactions in a concentration of 0.05 % in Ung. Macrogoli DF and PEG 400. Adding water elicited constant and strong phototoxic reactions; their strength increased as more water was added (Figs. 1 & 2). Methoxsalen in PEG 3000 with 20 % water produced marked phototoxic reactions. On the other hand, PEG 400, a liquid, needed more than 40 % water to achieve the same effect in methoxsalen tests. The test results using PEG 3000 with larger amounts of water as the vehicle were poorer than with other vehicles. Methoxsalen 0.25 % in Ung. Macrogoli DF gave weaker reactions than methoxsalen 0.05 % in a mixture of Ung. Macrogoli DF and 80 % water. The mean

reaction indices at 72 h were 1.1 and 2.8 and the number of positive reactions 70 % and 98 %, respectively.

The addition of ethanol to Ung. Macrogoli DF improved the test results much less than the addition of water (Fig. 3). The mixture of Ung. Macrogoli DF, ethanol (40 %), water (40 %) and methoxsalen (0.05 %) produced the highest reaction indices and the highest percentage of positive reactions of all the vehicles used, the mean reaction index being 3.0 at 72 h. All 30 tests on 10 subjects were positive.

Although methoxsalen 0.05 % gave satisfactory phototoxic responses in glycerol and wool fat as such, with these vehicles the responses were also markedly increased when water was added (Figs. 1 & 2). The results of comparative tests with and with-

out filter paper using wool fat-water mixtures as vehicles did not differ significantly.

No reactions in dark control areas were seen. The borderline between the test and the control areas was sharp.

Discussion

Methoxsalen is a compound that invariably produces a phototoxic skin reaction during optimal conditions. It should be liberated into the skin rapidly enough and irradiated with a proper UVA source because it is metabolized easily (Pathak et al. 1974). An occlusion time of 2 hours is optimal for methoxsalen and common black light tubes are suitable for irradiation (Suhonen et al. 1976).

There are pronounced differences among various vehicles in the ability to liberate methoxsalen into the skin (Kaidbey & Kligman 1974, Suhonen 1976). Radiolabelled methoxsalen has also been used to study the influence of the vehicle on the resorption of the active drug (Kammerau et al. 1976).

The factors that may influence the test results are:

1. the concentration of the test substance
2. the solubility of the active substances in the vehicle
3. the interaction between different ingredients of the vehicle and the active principle
4. the interactions between the vehicle and the skin
5. the viscosity of the vehicle.

In this work, it was mainly the influence of the water content of some vehicles on photoepicutaneous test reactions that was studied *in vivo*.

Macrogol as such is considered to be a poor vehicle for methoxsalen (Kaidbey & Kligman 1974, Suhonen 1976). The addition of water changed its properties markedly. The phototoxic reactions became stronger

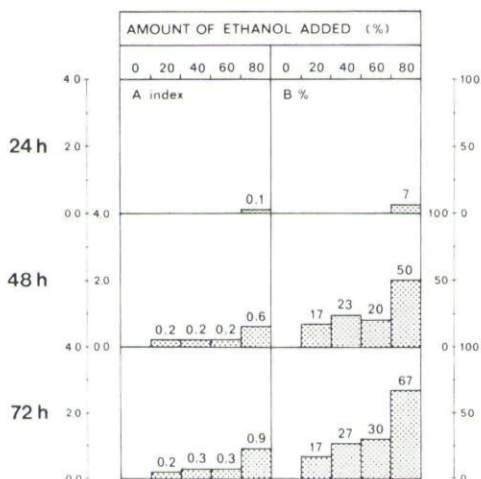


Fig. 3. (A) Mean reaction indices and (B) the rate (%) of positive reactions elicited by 0.05 % methoxsalen in Ung. Macrogoli DF with increasing amounts of ethanol. The occlusion time was 2 hours.

with increasing water concentrations (Fig. 1) and correspondingly, 0.05 % 8-MOP in water-Ung. Macrogoli DF mixture (80/20) elicited stronger reactions than 0.25 % methoxsalen in Ung. Macrogoli DF without water.

Changes in the viscosity of the vehicle may be one factor influencing the phototoxic response. However, with equal amounts of ethanol instead of water the reactions were significantly weaker (Figs. 3 & 4), in spite of the approximately equal viscosity of these mixtures. The results with PEG 400 compared with those obtained with PEG 3000 also speak against the hypothesis that the low viscosity is the major reason for the increase in the phototoxic reactions.

Obviously the addition of water to the vehicles studied promoted the liberation of methoxsalen from the base. In pure water, methoxsalen is not readily dissolved. Its solubility is better in PEG-ethanol mixtures and pure PEG (Stecher 1969). It is pos-

sible that the solubility properties of the components in the final mixture play an important role in the liberation of the active substance into the skin. The fact that methoxsalen in Ung. Macrogoli DF with 40 % water and 40 % ethanol gave stronger reactions than in Ung. Macrogoli DF with water (80 %) alone, speaks in favour of this concept.

Investigation of the physicochemical events involved should be instituted.

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