Skin Irritancy from Propylene Glycol

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Wahlberg JE, Nilsson G. Skin irritancy from propylene glycol. Acta Derm Venereol (Stockh) 1984: 64: 286–290.

Two sensitive methods for the assessment of skin irritancy reactions to propylene glycol (PG) have been used: laser Doppler flowmetry in man for erythema and skin fold thickness measurements in man, guinea pigs and rabbits for edema. Single (open and occlusive) and repeated (open) exposures were used. Trafuril® was used as positive control for the flowmetric studies. In man an increased blood flow was recorded only when PG was applied under occlusion. A statistically significant increase in skin fold thickness was observed from day 7 in the guinea pig, but not in man (daily exposures for 36 days). It is concluded that occlusion seems to be a crucial factor and that skin fold thickness measurements in guinea pigs and rabbits is a useful, complementary method for the detection and prediction of marginal irritants. *Key words: Laser Doppler flowmetry; Skin fold thickness measurements; Man; Guinea pigs; Rabbits; Occlusion; Open.* (Received September 26, 1983.)

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The irritant and sensitizing properties of propylene glycol (PG) have recently been reviewed by Cronin (1), Trancik & Maibach (2) and Adams (3). Using the cumulative irritation procedure described by Phillips et al. (4), Trancik & Maibach (2) concluded that PG is at least a minimal irritant in man. Frosch & Kligman (5), using the chamber scarification test, found that PG irritated scarified and normal skin at about the same concentration and classified it as a moderate irritant.

However, in the latter studies the test sites were assessed according to the original Draize scoring system (visual examination and palpation), which is subjective and said to vary considerably (6).

The aim of the present study was to apply two alternative and more objective methods for the assessment of the irritancy reactions to PG: laser Doppler flowmetry for erythema and skinfold thickness measurements for edema. Laser Doppler flowmetry was previously used for sodium lauryl sulfate (SLS) (7) and skin fold thickness measurements for SLS, nonanoic acid, organic solvents and other irritants (8–10).

MATERIALS AND METHODS

Test substances. 1,2-propyleneglycol (propandiol-1,2) (Art 7478, E. Merck, Darmstadt, W. Germany). Trafuril® (CIBA) was used as positive control in the flowmetric studies.

Laser Doppler flowmetry in man

The apparatus (Periflux®, Perimed, Stockholm, Sweden) and the measuring technique has been described in detail in our previous study (7) with SLS. PG was applied under three different conditions: single application with and without occlusion and repeated open applications.

Single, open exposure. 1.0 ml of PG (neat) was applied to the test sites on the ventral aspects of the thighs for 5 and 15 min respectively. Trafuril® was applied for 2 min. The remaining PG and Trafuril® were removed with cotton, the test sites dabbed dry and the measuring probe attached.

Repeated, open exposure. 1.0 ml of PG (neat) was applied once daily for 12 days to the same skin site on the ventral aspect of the right thigh. The blood flow was recorded on day 13.

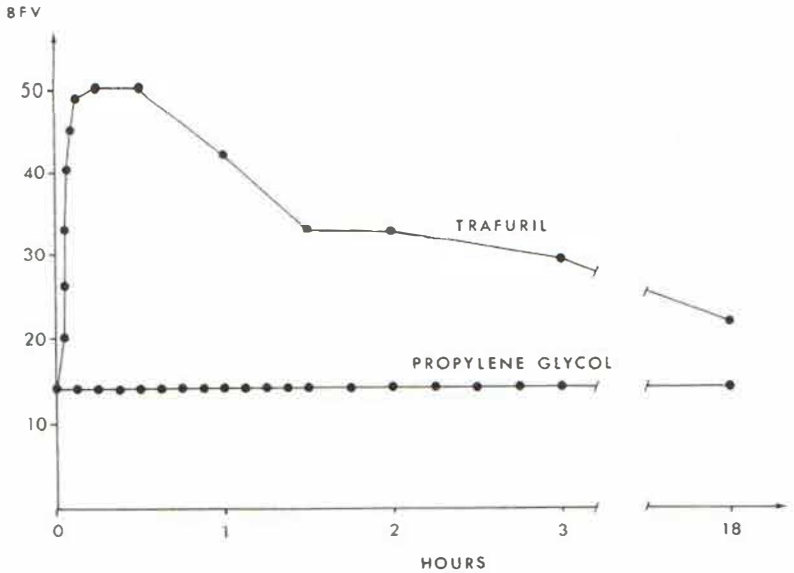

Fig. 1. Blood flow values after treatment with propylene glycol for 15 min and Trafuril® for 2 min. Ventral aspects of thighs in man.

Single exposure under occlusion. PG (neat) and distilled water were applied to the volar forearms for 24 h using large Finn Chambers (Epitest Ltd, Oy, Finland) with filter paper discs and Scanpore tape. The blood flow was recorded prior to the application, 2 h after removal and then 22 h later, i.e. 48 h after the application.

Skin fold thickness measurement

Clipping and the measuring technique, using a Harpenden skin fold caliper, has been described in detail in a previous study (9) with SLS and nonanoic acid.

Man. PG (neat) was applied once daily for 36 days to the same skin site on the volar forearm. Measurements were made on each of 4 days prior to the first application and then once daily during the whole experimental period. The site was left open and the treatment was repeated immediately after the skin fold measurement. Unexposed control sites were measured for comparison.

Guinea pigs, rabbits. Guinea pigs with initial weights above 600 g were used (10). PG (neat) was applied once daily for 10 days to sites on the flanks of guinea pigs and on the back of rabbits. The sites were left open. Measurements were made on each of 4 days prior to the first application and then once daily. Unexposed control sites were measured for comparison.

Visual scoring. All sites were examined for erythema, edema, scaling, etc.

Statistical evaluation. Analysis of variance.

RESULTS

Laser Doppler flowmetry in man

The output signal from the flowmeter is expressed in relative and dimension less blood flow values (BFV) (7).

Table I. *Laser Doppler flowmetry*

Mean blood flow values after 24 h exposure to propylene glycol (4 sites) and distilled water (4 sites) under occlusion. Human volar forearms

	Before	26 h	48 h
Propylene glycol	2.4	5.1	3.3
Distilled water	3.3	2.5	1.8
Controls	3.0	1.5	2.0

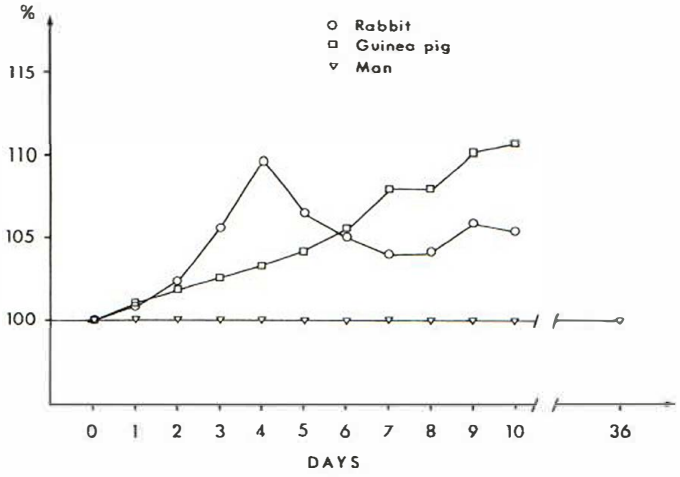

Fig. 2. Mean increase in skin fold thickness (%) after daily treatment with propylene glycol in guinea pigs, rabbits and man.

Single, open exposure. Treatment with PG for 5 or 15 min did not cause any increase in blood flow (Fig. 1) compared to the pretreatment period and the sites looked normal to the naked eye. On the other hand, treatment with Trafuril® for 2 min caused an immediate increase in blood flow and the peak value (about 50) was reached within 8 min. It then gradually decreased, but after 18 h there was still an increased blood flow compared to the pretreatment value. This corresponded to a weak erythema.

Repeated, open exposure. Daily treatments for 12 days of the same skin site on the thigh did not cause any increase in blood flow nor any macroscopical changes compared to the pretreatment period.

Single exposure under occlusion. For PG and increase in blood flow was recorded compared to the pretreatment period (Table I), with a peak value at the 26 h measurement. It corresponded to a weak erythema. For the distilled water and the control sites no increase in blood flow was recorded and they appeared normal to the naked eye.

Table II. *Increase (mean±SEM) in skin fold thickness (%) after daily treatment with propylene glycol*

	Guinea pig			Rabbit		
Day	PG $n=27$	Control $n=9$	p	PG $n=20$	Control $n=5$	p
0	100	100		100	100	
1	101.0±0.5	100.4±0.4	NS	100.7±0.6	100.0±0	NS
2	101.7±0.5	101.1±0.6	NS	102.4±0.8	100.0±0	NS
3	102.6±0.8	99.9±0.6	NS	105.6±1.0	101.4±2.4	NS
4	103.3±0.8	101.9±0.6	NS	109.7±1.9	103.8±1.6	NS
5	104.2±0.6	99.8±1.1	NS	106.5±1.5	102.6±1.6	NS
6	105.5±0.8	102.4±1.3	NS	105.0±1.0	100.0±0	NS
7	107.9±0.9	101.7±1.2	<0.01	104.1±1.0	101.0±1.0	NS
8	107.9±0.7	102.3±0.6	<0.001	104.2±1.0	103.6±2.3	NS
9	110.2±1.0	103.1±1.2	<0.001	105.9±1.0	102.2±1.4	NS
10	110.6±1.2	102.6±1.2	<0.001	105.4±0.7	101.2±1.2	NS

Skin fold thickness measurements

The obtained values (in mm) were converted to % s, where the mean of the pretreatment values was indicated as 100%.

Man. Daily treatments with PG for 36 days did not cause any increase in skin fold thickness (Fig. 2) and the test site looked normal to the naked eye.

Guinea pigs, rabbits. A slight increase in skin fold thickness for both species was observed (Table II, Fig. 2). In the guinea pig there was a gradual increase and from day 7 it was statistically significant compared to the control sites. In the rabbits a peak value on day 4 was observed.

In 4 of the 27 treated sites in the guinea pigs a weak erythema was noticed after 7 days (one site), 8 days (two sites) and 10 days (one site). In 15 of 20 treated sites in the rabbits an erythema was noticed already after the first application of PG. In spite of repeated treatments it did not intensify or spread and in 11 cases it faded.

DISCUSSION

As was pointed out in previous papers (7, 9) it is desirable to use more objective methods than visual scoring for the assessment of skin irritancy reactions. The methods used in the present study gave quantitative information on the degree of irritancy from PG—laser Doppler flowmetry recorded the erythema and skin fold thickness measurements the edema (i.e. the fluid accumulation) in the test sites.

The irritant properties of PG do not seem mainly to be expressed by an erythematous response. Single and repeated exposures in man without occlusion did not cause any increase in blood flow (Fig. 1). On the other hand, administration under occlusion caused a slight increase in blood flow (Table I), also detectable by the naked eye as a weak erythema. Occlusion is then a crucial factor and its use in predictive testing for irritancy may be questioned. It obviously increases the sensitivity of the predictive test methods, but on the other hand it has been criticized since administration under occlusion does not mimic actual exposure condition.

PG induced some fluid accumulation in guinea pig skin as revealed by the skin fold measurements (Table II, Fig. 2). The majority of the test sites in the rabbits demonstrated redness already after 24 h, but this did not increase in intensity and eventually faded in spite of continued treatment. The tradional visual scoring system then seems to be unreliable.

The peak value of skin fold thickness observed in the rabbits (Fig. 2) after a few days of treatment has also been seen for SLS, nonanoic acid and some organic solvents (9, 10).

By using guinea pigs weighing more than 600 g the disadvantage of an increase in skin fold thickness also at untreated (control) sites could be eliminated (10) and this finding was confirmed (Table II).

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