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Efficacy of Protective Creams in a Modified Repeated Irritation Test

Methodological Aspects

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The effect of 3 protective creams and petrolatum was tested in a repetitive irritation test. On 15 healthy volunteers, the irritants (sodium lauryl sulfate 10%, sodium hydroxide 0.5%, lactic acid 15%, and toluene undiluted) were applied on the paravertebral skin of the mid-back after 30 min pretreatment with the products tested. The volunteers were treated for 9 days. The irritant cutaneous reactions were quantified by erythema score, transepidermal water loss, and chromametry. The results showed a specific profile of efficacy against the 4 irritants used. For all creams a significant protective effect was obtained against irritation by sodium lauryl sulfate, sodium hydroxide and lactic acid in different degrees. Less efficacy was observed against toluene. Even an amplification of inflammation by pretreatment with 1 product could be demonstrated. The results indicate that a 1-week period of cumulative irritation might be enough to evaluate the efficacy of protective creams against most irritants.
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Irritant contact dermatitis (ICD) is a major occupational disease resulting in damage to the individual and in high costs to the community. Therefore, protective creams (PC) are targeted as one of the classical means of skin protection against noxious chemicals from the environment (1). They play an important role in the prevention of occupational ICD since for some workplaces gloves carry the risk of accidents, and the substitution of noxious products by less aggressive substances is sometimes not possible for technical or economic reasons.

In addition to worker information about the proper use of PCs and training of workers at risk (2, 3), testing their efficacy is of utmost importance since the benefit of PCs has been debated controversially. They are considered to alter the penetration of substances into the skin by interaction between PC and the substance or interaction between PC and the stratum corneum, or they may reduce harmfulness by chemical alteration of the substance (4). To investigate the efficacy of PCs as pre-exposure skin protectors a number of tests have been developed. Apart from *in vitro* techniques (5, 6) several *in vivo* tests on animals or human skin have been used which are presented in recent reviews (7, 8). *In vivo* methods in humans are based on assessment of the reduction in the induced irritant and inflammatory changes in the skin when a protective cream is used before application of an irritant (4). Recently, Zhai & Maibach presented an *in vivo* method using cyanoacrylate strips of protected skin samples to measure the effectiveness of PCs against 2 dye indicator solutions: methylene blue in water and red O in ethanol, representative of model hydrophilic and lipophilic compounds (9).

In the present study, we evaluated the efficacy of 3 different preparations designed as PCs. Following a modification of the repetitive irritation test (RIT) (10) the PC products and petrolatum were compared simultaneously to a non-pretreated control site. Furthermore, we collected data to discuss the optimal concentration of the irritants and the days of irritation.

PATIENTS AND METHODS

Subjects

Fifteen healthy Caucasian volunteers (9 women, 6 men), aged 23–36 years (28.3 ± 4.2 [mean ± standard deviation]) without any skin diseases, were included in the study after signing a written informed consent form. The study had passed review by the ethics committee of the University Hospital Zurich. Subjects were allowed to bath as usual, but they avoided the direct application of detergents, moisturizers or emollients on their backs during the 12 days of investigation.

Protective creams (La Roche-Posay Pharmaceutical Laboratory, France)

Cream A recommended as a specific cream for irritated and dry hands. Composition: aqua, glycerin, octyl dodecanol, stearic acid, PEG-100 stearate, cetostearyl alcohol, steareth-10, mineral oil, dimethicone, allantoin, PVP/eicosene copolymer, xanthan gum, cetyl alcohol, phenoxyethanol, methylparaben, ethylparaben, butylparaben, propylparaben, triclosan, fragrance.

Cream B recommended as a specific cream for irritated and dry hands. Composition: aqua, glycerin, caprylic/capric triglycerides, cetyl dimethicone copolyol, isocetyl stearate, C12-15 alkyl benzoate, stearic acid (and) hydrolyzed almond protein (and) sodium chloride, aluminum starch octenylsuccinate, capryloyl glycine, zinc gluconate, dimethiconol + cyclomethicone, cyclomethicone (and) dimethiconol (and) quaternium-18 hectorite (and) alcohol, cyclomethicone, polyglyceryl-4 isostearate, perfluoropolymethylisopropyl ether.

Cream C recommended as a water-repelling barrier cream. Composition: W/O emulsion containing polydimethylsiloxane and dimethyltrimethylmethylpolysiloxane.

White petrolatum (delivered by the Pharmacy of the Zurich University Hospital) used as standard for internal validation.

Procedure

Using a modified RIT, application area was the paravertebral skin of the mid-back, and the test fields (5 vertical rows with 4 chambers each) were randomized. Test fields were treated with 0.05 ml of PC or petrolatum rubbed onto a skin area 2 cm in diameter with a gloved finger, though up to 20% of the cream remains on the glove. One row of chambers served as untreated control. After 30 min pretreatment, the irritants [sodium lauryl sulfate (SLS, dissolved in water 10%, Sigma, St. Louis, MO), sodium hydroxide (NaOH, dissolved in water 0.5%, E. Merck, Darmstadt, Germany), lactic acid (LA, dissolved in

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water 15%, Fluka Chemie AG, Buchs, Switzerland), and toluene (TOL, undiluted, minimum 99.5%, E. Merck, Darmstadt, Germany)] were applied with large Finn Chambers (12 mm diameter, filling volume 0.05 ml; Epitest Ltd., Hyrlä, Finland). The chambers were removed after 30 min of exposure and the skin rubbed dry with a paper tissue. Using this scheme of application the volunteers were treated from Monday to Friday in the first week and after the weekend from Monday to Thursday (in each case at the same time of day ± 1 h).

Clinical examination and skin measurements

All visual scorings (VS) and bioengineering measurements were performed by the same observer. The clinical changes were determined daily using the following erythema score: 0 (none) to 5 (very severe with epidermal defects) modified from Willis et al. (11). Transepidermal water loss (TEWL) was performed using the Tewameter (Courage & Khazaka, Cologne, Germany). Measurements (g/m^2 h) were done before application of the test substances at the beginning, at the end of week 1, and at the end of week 2 according to the guidelines described by the Standardization Group of the European Society of Contact Dermatitis (12). Measurements of skin colour were taken with the Chroma-Meter CR-200 (Minolta, Osaka, Japan) following the recommendations of Elsner (13). The colour coordinates were expressed in the L*a*b* 3-dimensional colorimetric system. The a* is the component of separation between red (positive value) and green (negative value).

If the erythema score developed to a severe degree (5), the exposure was discontinued. For these test areas, the maximal scores were used and the measured values for TEWL and chromameter obtained on the day of discontinuance were used for the final calculations.

Statistics

All data were analysed with a statistical package (SPSS for the Macintosh, SPSS, Chicago, ILL, USA) on an Apple Macintosh computer. Differences of medians between treatment and untreated control sites were checked for significance using the Wilcoxon U-test for the non-parametric erythema score, and Student's *t*-test for paired comparison of TEWL and chromameter values.

RESULTS

The results of the daily visual erythema score are shown in Fig. 1a–d. Data of the TEWL and chromametry are given in Table Ia–c.

Protection against sodium lauryl sulfate

The results of SLS irritation show a significant suppression of erythema in both weeks for all PCs and petrolatum compared with the untreated sites (Fig. 1a). The test parameters for TEWL and chromametry confirm this observation and also indicate a significant suppression of irritation (data not shown). In all measurements, cream B is the most effective one.

Protection against NaOH

Fig. 1b shows the results for NaOH regarding the visual score. The highest efficacy was observed for cream A and cream C suppressing erythema, TEWL and inflammation in both weeks (Table Ia). Petrolatum showed a better protection against NaOH than cream B as seen in the visual score (day 5), TEWL (day 12), and chromametry (both weeks). All volunteers reached the maximal erythema score at untreated sites at the end of the second week (score 5).

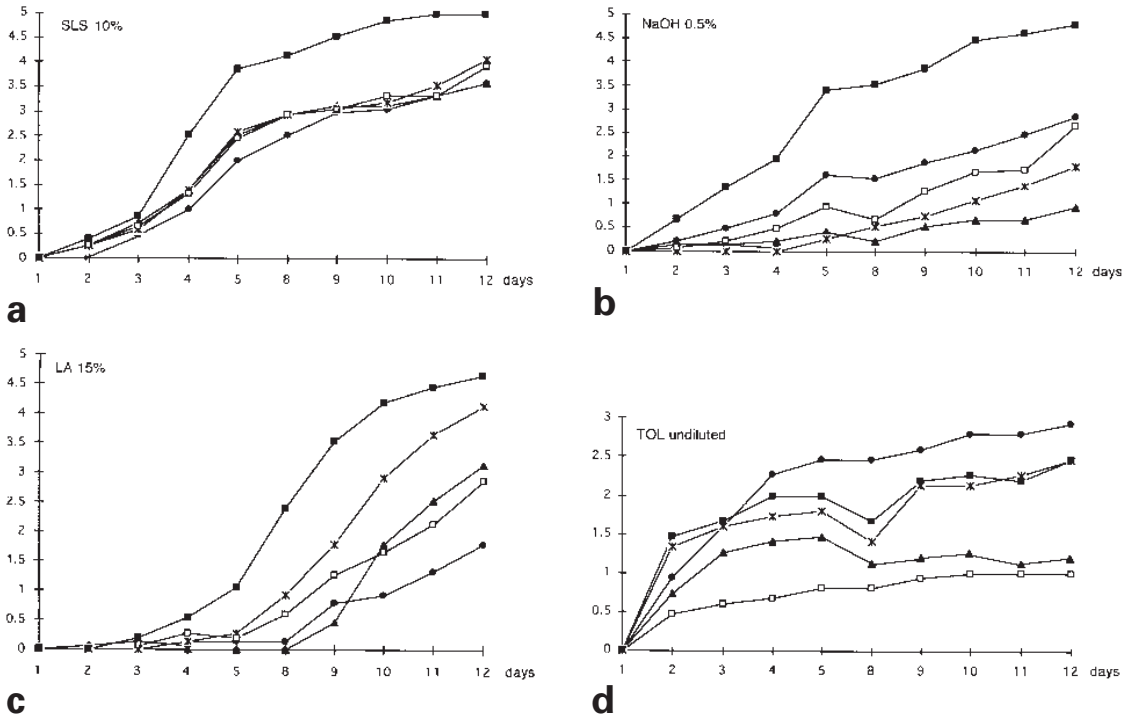

Fig. 1. The effect of PCs on the irritation induced by the 4 irritants after 2 weeks measured by the daily visual score (0–5). Results are given as means. (Cream A ▲, cream B ●, cream C *, cream D □, control ■).

Table I. *The mean values and standard errors of the mean (SEM) of the transepidermal water loss (TWEL) and chromametry after 5 days and 12 days repeated patch test with NaOH 0.5%, lactic acid 15% and toluene. Significances of differences between pretreated and control sites are marked in the table as follows: *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ns = not significant. (**) indicates a significant increase of erythema and inflammation, respectively*

Day		NaOH 0.5%						Lactic acid 15%						Toluene					
		TEWL			Chromametry			TEWL			Chromametry			TEWL			Chromametry		
		1	5	12	1	5	12	1	5	12	1	5	12	1	5	12	1	5	12
Control	mean	4.69	26.84	32.30	5.81	12.38	14.43	4.80	14.91	35.17	6.24	8.18	13.97	4.57	7.38	7.07	6.09	9.69	10.44
	SEM	0.41	3.61	3.69	0.39	0.99	0.99	0.48	3.56	4.70	0.38	0.86	0.92	0.56	0.81	1.29	0.45	1.19	1.23
Cream A	mean	4.43	7.61	10.41	6.17	6.61	8.04	4.58	5.73	23.64	6.35	6.36	10.79	4.15	5.94	5.59	6.17	8.16	7.77
	SEM	0.44	0.82	1.73	0.36	0.42	0.71	0.41	0.45	4.43	0.43	0.41	1.17	0.32	0.61	0.64	0.43	0.91	0.90
	signif.	ns	***	***	ns	***	***	ns	*	ns	ns	*	*	ns	ns	ns	ns	*	*
Cream B	mean	4.41	11.69	21.15	6.31	9.71	11.67	4.40	6.13	14.12	6.22	6.39	9.06	4.41	7.28	7.54	6.17	11.67	11.62
	SEM	0.39	1.34	3.86	0.41	0.86	1.26	0.36	0.41	3.55	0.46	0.39	1.06	0.35	0.69	0.72	0.43	1.06	1.21
	signif.	ns	***	ns	ns	*	**	ns	*	**	ns	ns	**	ns	ns	ns	ns	(**)	ns
Cream C	mean	4.47	8.37	13.79	6.10	6.82	8.78	4.71	7.15	32.31	6.03	6.60	12.96	4.78	6.15	8.57	6.32	9.41	9.80
	SEM	0.32	0.91	2.88	0.45	0.63	0.94	0.37	1.05	3.62	0.43	0.55	0.81	0.36	0.73	0.99	0.44	1.14	1.18
	signif.	ns	***	**	ns	***	***	ns	*	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Petrolatum	mean	4.51	9.99	18.68	5.85	8.05	10.44	4.46	5.91	18.87	5.96	5.89	9.13	4.46	5.92	5.81	6.04	7.56	7.68
	SEM	0.28	1.62	3.61	0.40	0.74	1.23	0.37	0.54	3.78	0.43	0.34	0.87	0.34	0.58	0.65	0.45	0.93	0.95
	signif.	ns	***	**	ns	***	***	ns	*	*	ns	*	***	ns	ns	ns	ns	ns	*

Protection against LA

While cream A showed a protective effect up to day 5, cream B was more effective over the 12-day period. Cream C had only some effect by day 5. Cream B and petrolatum were the most effective creams after the 2-week period in all measurements (Fig. 1c, Table I).

Protection against TOL

Cream A showed a significant protective effect in VS (Fig. 1d) and chromametry after 12 days. Cream C had no protective effect in all measurements and cream B even showed a significant amplification of the irritant reaction to toluene (Table I, (**)). Petrolatum suppressed erythema and inflammation due to TOL while we observed no significant suppression of the barrier disruption measured by the TEWL.

DISCUSSION

In spite of promising *in vitro* and *in vivo* data, the actual benefit of PCs is still regarded with skepticism since they may also have detrimental effects (8). Current PCs are still not perfect. Much effort is necessary to develop preparations that will give more protection and fewer side effects. Another reason of little acceptance might be the lack of suitable standardized techniques for the evaluation of their protective effect. Results of animal experiments may not be valid for humans, particularly when dealing with irritants, in view of their complex action mechanisms and the high interindividual variability in susceptibility of human skin (9). Regarding the various models for investigating the efficacy of PCs, the validation of a sensitive, standardized and widely accepted model proved by interlaboratory standardization or controlled clinical studies at the workplace seems to be necessary. Clearly, studies both under experimental conditions and in the workplace are needed before a rational recommendation can be made whether a product is safe and effective for skin protection at the workplace.

In our study, we followed the *in vivo* model of the RIT in humans for clinical investigation of PC efficacy. The different measurements visual score, TEWL, and chromametry that we used characterize distinct aspects of irritation and complete one another. Since in a previous study (14) the application of 1% NaOH and 30% LA recommended for the RIT had resulted in a high percentage of cases where most volunteers reached the maximal erythema score at untreated and sometimes in treated sites, in this study we lowered the dose of the irritants NaOH (0.5%) and LA (15%), with a result that confirmed our decision. For NaOH, even with a concentration of 0.5% all volunteers reached the maximal erythema score after 2 weeks. Fifteen per cent LA provided only mild erythema, increase of the TEWL, and inflammation after 5 days of cummulative irritation. However, over the 2-week period we still observed strong reactions that were significantly suppressed by some of the products tested.

Regarding the daily measurement of the VS (Fig. 1), we observed an increase in values for all irritants in between the first days of cumulative application. Since we did not perform an application at the weekend, the values by day 8 showed a

moderate increase or even a decrease of irritation due to a regeneration of barrier function. This was especially true for the application of TOL. The results indicate that there is no need for a 2-week period of cumulative irritation to obtain valid data about the efficacy of PCs against SLS 10%, NaOH 0.5% and TOL. Using LA 15%, 12 days of application seem to be adequate for valuing the benefit of a PC. While on the one hand, increasing the concentration of LA would provide early data about the benefit, on the other this procedure would result in a high number of severe reactions and early interruptions unacceptable to the volunteers. It should be debated whether LA is a useful substance for irritancy testings. Our experiences show that the skin lesions due to LA are spotty erosions that usually develop within 2 days. The day by which the barrier disruption is visible depends on the individual sensitivity of the volunteers. In general, PCs suppress or inhibit the barrier damage by irritants. PCs due to LA seem to delay the day of total barrier damage only but this will result in severe degree (5) defined as epidermal disruptions due to our VS. There is no hardening effect that can be seen with SLS, NaOH, or TOL. Concerning these substances a slow increase of irritation could be demonstrated. The question of standardized test substances still seems to be open.

In the present study, the tested products demonstrated a specific profile of efficacy against the chemical substances used in the RIT. We found efficacy of all 3 PCs against irritation by a detergent (SLS), NaOH and LA in different degrees. Less efficacy was observed against an organic solvent (TOL), but petrolatum could be recommended for use at workplaces with contact to TOL. However, for TOL an amplification of inflammation by pretreatment with cream B could be demonstrated. Our results underline the importance of careful selection of the PCs tested for specific workplaces. Petrolatum that can be recommended as a standard reference substance against which PCs may be compared (15) was very effective against SLS, NaOH and LA irritation, and provided moderate protection against TOL. However, the cosmetical acceptance of petrolatum and the risk of losing hold of a tool after applying petrolatum reduce its use at the workplace. In future testings it might be useful to compare the efficacy of PCs to the efficacy of petrolatum to irritants against which the PCs are designed to protect. Thus, a factor of protection might be envisaged to give practical data for the workplace situation.

REFERENCES

1. Lachapelle JM. Principles of prevention and protection in contact dermatitis (with special reference to occupational dermatology). In: Rycroft RJG, Menné T, Frosch PJ, eds. Textbook of contact dermatitis, 2nd edn, Berlin: Springer, 1995: 695–702.
2. Wigger-Alberti W, Maraffio B, Wernli M, Elsner P. Self-application of a protective cream: pitfalls of occupational skin protection. Arch Dermatol 1997; 133: 861–864.
3. Wigger-Alberti W, Maraffio B, Wernli M, Elsner P. Training workers at risk for occupational contact dermatitis in the application of protective creams: efficacy of a fluorescence technique. Dermatology 1997; 195: 129–133.
4. Fine Olivarius F, Hansen AB, Karlsmark T, Wulf HC. Water protective effect of barrier creams and moisturizing creams: a new in vivo test method. Contact Dermatitis 1996; 35: 219–225.
5. Tronnier H. Methodische Ansätze zur Prüfung von Hautschutzmitteln. Dermatosen 1993; 41: 100–107.
6. Treffel P, Gabard B, Juch R. Evaluation of barrier creams: an in vitro technique on human skin. Acta Derm Venereol (Stockh) 1994; 74: 7–11.
7. Lachapelle JM. Efficacy of protective creams and/or gels. In: Elsner P, Lachapelle JM, Wahlberg JE, Maibach HI, eds. Prevention of contact dermatitis. Curr Probl Dermatol Basel: Karger, 1996: 182–192.
8. Wigger-Alberti W, Elsner P. Do barrier creams and gloves prevent or provoke contact dermatitis? Am J Contact Dermatitis 1998 (in press).
9. Zhai H, Maibach HI. Effect of barrier creams: human skin in vivo. Contact Dermatitis 1996; 35: 92–96.
10. Frosch PJ, Kurte A. Efficacy of skin barrier creams (IV). The repetitive irritation test (RIT) with a set of 4 standard irritants. Contact Dermatitis 1994; 31: 161–168.
11. Willis C, Stephens J, Wilkinson J. Experimentally-induced irritant contact dermatitis. Contact Dermatitis 1988; 18: 20–24.
12. Pinnagoda J, Tupker RA, Agner T, Serup J. Guidelines for transepidermal water loss (TEWL) measurement. A report from the Standardization Group of the European Society of Contact Dermatitis. Contact Dermatitis 1990; 22: 164–178.
13. Elsner P. Chromametrie. Hardware, measuring principles and standardization of measurements. In: Berardesca E, Elsner P, Maibach HI, eds. Handbook of skin bioengineering. Cutaneous blood flow and erythema. Boca Raton: CRC Press, 1994.
14. Schlüter-Wigger W, Elsner P. Efficacy of 4 commercially available protective creams in the repetitive irritation test (RIT). Contact Dermatitis 1996; 34: 278–283.
15. Wigger-Alberti W, Elsner P. Petrolatum prevents irritation in a human cumulative exposure model in vivo. Dermatology 1997; 194: 247–250.