

INVESTIGATIVE REPORT

Efficacy of a New Class of Perfluoropolyethers in the Prevention of Irritant Contact Dermatitis

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Perfluoropolyethers (Fomblin® HC products) are chemical non-reactive polymers with special physico-chemical properties that recently showed promise as protective preparations in the prevention of irritant contact dermatitis. We evaluated the efficacy of a new class of perfluoropolyethers (perfluoropolyether phosphate, Fomblin® HC/P2) in the prevention of experimentally induced cumulative irritant contact dermatitis if applied prior to irritation. A panel of 20 healthy volunteers was tested with a repetitive irritation test using 4 standard irritants (sodium lauryl sulphate of highest purity, sodium hydroxide, lactic acid and toluene) in a randomized double-blind study. Application sites were assessed clinically and by the use of bioengineering techniques (transepidermal water loss and chromametry). Three gel preparations each containing 5% perfluoropolyether phosphate showed significant efficacy against irritation due to sodium lauryl sulphate and sodium hydroxide, while one test preparation containing 2% showed inferior benefit, indicating a dose-related effect. Preparations containing perfluoropolyether phosphates can be recommended for workplaces with water-soluble irritants. Further studies under real workplace conditions are indicated. Key words: bioengineering; irritant contact dermatitis; occupational dermatology; protective preparations; repetitive irritation test.

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Irritant contact dermatitis (ICD) is one of the most relevant problems in occupational medicine. Detergents, solvents, acids, alkaline solutions, cutting oils or even plain water may lead to damage of the epidermal barrier function and cause ICD. Protective creams play an important part in the prevention of occupational contact dermatitis. Skin protection in the workplace consists of pre-exposure protective creams, mild skin cleansers and post-exposure skin care. While protective creams are designed to prevent skin damage due to irritant contact, skin cleaning should remove aggressive substances from the surface, and post-exposure skin care is intended to enhance barrier regeneration (1).

Perfluoropolyethers, with average molecular weights ranging from 650 (Fomblin® HC/01) to 6250 (Fomblin® HC/R), are innovative compounds obtained by the polymerization of hexafluoroprene with oxygen activated by UV radiation with proven safety (2, 3). Owing to their particular physico-chemical properties (odourless and colourless, water and oil repellent, film-forming and not occlusive, chemically and

thermally resistant, biologically inert liquid polymers with a high content of fluorine atoms and an ethereal chemical structure) (4), these polymers offer several advantages and can be used in skin care products and cosmetics. Preliminary investigations on protective ointments containing perfluoropolyethers (Fomblin® HC/R) have shown statistically significant clinical improvement in the initial conditions of ICD and when compared to inert creams (5–7).

In a recent study, we evaluated the efficacy of oil-in-water emulsions containing perfluoropolyethers in varying concentrations in the prevention of experimentally induced cumulative irritation. Using a repetitive irritation test (8), it was shown that both the emulsion base and all perfluoropolyether-containing preparations significantly suppressed irritation induced by sodium lauryl sulphate (SLS) and sodium hydroxide (NaOH). Additionally, the highest concentration of the perfluoropolyether-containing preparations, a 4% emulsion, significantly inhibited irritation induced by lactic acid and toluene (9).

In the present study, we therefore evaluated the efficacy of a different class of perfluoropolyethers, which are obtained by polymerization of tetrafluoropropene. Unlike the perfluoropolyethers we studied previously, these perfluoropolyether phosphates (Fomblin® HC/P2 1000 and 2000) are water-soluble substances, which makes it possible to incorporate them in homogenous aqueous systems, including gels. We therefore investigated perfluoropolyether phosphate-containing gel preparations in a human cumulative irritancy model using non-invasive biophysical techniques. Following a modification of the repetitive irritation test (8) we quantified the irritant cutaneous reactions by visual scoring, transepidermal water loss (TEWL) and chromametry. The results obtained were compared to untreated control sites.

MATERIAL AND METHODS

Study design

The study was conducted in a randomized double-blind design under standardized laboratory conditions.

Study population

Twenty healthy Caucasian volunteers (13 women and 7 men) without any skin disease, aged between 18 and 33 years (mean 24.6), participated in the study after informed consent in accordance with the Helsinki declarations. The study had passed review by the Ethics Commission of the Friedrich-Schiller-University of Jena.

The volunteers were allowed to shower, as usual, but they had to avoid application of detergents, moisturizers or emollients on their backs during the 12 days of investigation. They were asked to avoid sunbeds and solar radiation, too.

Induction of irritation

The application area was the paravertebral skin of the mid-back. The test areas were marked with a pencil according to the number of test preparations (5 plus 1 control being exclusively irritated) and irritants, resulting in 6 vertical rows, each consisting of 4 fields, with a space of 3 cm between. The test areas were randomized.

Test fields were pretreated with 0.05 ml of test preparations applied onto a skin area 2 cm in diameter with a gloved finger. The test preparations were allowed to dry for 30 min while the volunteers avoided strenuous movement.

After 30 min of pretreatment, 0.05 ml of the irritants (SLS of highest purity dissolved in water 5%; NaOH dissolved in water 0.5%; lactic acid dissolved 20% in water; and toluene undiluted) were applied using large Finn chambers and filter paper discs (12 mm diameter, filling volume 0.05 ml, Epitest Ltd., Hyrlä, Finland). After 30 min of exposure the chambers were removed and the test areas were dried carefully with a paper tissue without rubbing.

Using this scheme of application, each test site was repeatedly treated each day from Monday to Friday in the first week and in the second week from Monday to Thursday (in each case at the same time of day ± 1 h).

Test preparations

The following five perfluoropolyether phosphate containing gels (trade name: Fomblin® HC/P2, INCI name: Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate, CAS number: 200013-65-6) were tested in a randomized double-blind study design: **B**: gel base 1 (Xanthan Gum) (base preparation/placebo); **C**: gel base 1 (Xanthan Gum) containing 2% HC/P2 1000 (molecular weight 1000); **D**: gel base 1 (Xanthan Gum) containing 5% HC/P2 1000 (molecular weight 1000); **E**: gel base 2 (Carbomer) containing 5% HC/P2 1000 (molecular weight 1000); and **F**: gel base 1 (Xanthan Gum) containing 5% HC/P2 2000 (molecular weight 2000). One vertical row of test fields served as control fields which were exclusively treated with the irritants (**A**).

Clinical assessment and skin measurements

Prior to determination of clinical changes and all measurements, volunteers had to rest for at least 15 min in the air-conditioned laboratory under standardized conditions. Room temperature was 20–22°C, and humidity was 36–40%. The study was performed in November and December 1999. All visual scorings and bioengineering measurements were performed by the same investigator (S.S.-W.).

Clinical changes were determined each day before the application of the test substances using an erythema score 0 (none) to 5 (very severe with epidermal changes) modified from Willis et al. (10). TEWL as an indicator of the barrier function was measured using the Tewameter® (Courage & Khazaka, Cologne, Germany) at days 0/1, 5 and 12 prior to application of the test substances. The measurements ($\text{g}/\text{m}^2\text{h}$) were conducted in accordance with the guidelines of the Standardization Group of the European Society of Contact Dermatitis (11). Measurements of skin colour were performed using the Chroma-Meter CR-200® (Minolta, Osaka, Japan) following the recommendations of Elsner (12). Only values of the red-green dimension (a^* value) were considered, since these allow quantification of the degree of erythema.

For TEWL, each value for the final calculations represented the average of two measurements ($\text{g}/\text{m}^2\text{h}$), and in chromametry (a^*) that of three measurements.

If the erythema score developed to a value of 5 (break-off point), the exposure was discontinued. For these test areas, the maximal scores and values for TEWL and chromametry obtained on the day of discontinuance were used for the final calculations.

Statistical analysis

Statistical analysis was performed using the statistical software program SPSS 8.0 for Windows. Differences between pretreated sites and control sites were checked for significance using the Wilcoxon test for the non-parametric visual score, and Student's *t*-test for paired comparison of TEWL and Chroma-Meter values as follows: * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. Since multiple comparisons of pairs had to

be conducted, the levels of significance were adjusted according to Bonferroni in order to avoid overestimation of significance.

RESULTS

All test preparations were well-tolerated by the volunteers, and there was no evidence of any increase of irritant reaction caused by the test products themselves. There were no adverse effects and no drop-outs. All four irritants induced a significant irritant reaction from day 1 to the end of the first week, and to a smaller extent from the end of week 1 to the end of week 2, as indicated by the values of visual score, TEWL and chromametry of the control sites.

Sodium lauryl sulphate 5%. The highest efficacy for suppressing irritation was observed for test preparation E compared to the control site, which had been exclusively treated with the irritant: E significantly suppressed erythema (chromametry) and TEWL at day 5 and also showed benefit regarding the visual score at day 5, but without reaching significance. Furthermore, there was a significant suppression of TEWL for preparation D at day 5 and day 12, and for preparation F at day 5 in comparison to the control site. No significant protective effect was observed for preparation C.

Sodium hydroxide 0.5%. Preparations E and F showed a benefit against NaOH irritation indicated by significant suppression of erythema (visual score and chromametry) and TEWL in the first week. In the second week, products E and F still showed a tendency for suppressing TEWL, but without reaching significance.

Lactid acid 20%. Against lactic acid, only preparation E showed a significant suppression of irritation demonstrated by the TEWL in the first week. However, for test preparation C a significantly lower ($p \leq 0.05$) visual score was observed compared to the control site.

Toluene 100%. Although there was a tendency for preparations C, D and E to suppress the visual score at day 5, no significant protective effect for any product could be observed in any measurements against toluene; this was confirmed by the measurements of TEWL and chromametry.

DISCUSSION

In our study, we followed the model of a repetitive irritation test originally proposed by Frosch & Kurte (8) and previously modified (13) for the clinical investigation of protective creams. The different measurements of erythema, the visual score and chromametry, on the one hand, and the TEWL, on the other, characterize distinct aspects of irritation and complete one another.

All four irritants induced a significant irritant reaction from day 1 to the end of the first week, and to a smaller extent from the end of week 1 to the end of week 2, as indicated by the values of visual score, TEWL and chromametry of the control sites. The smaller increase of values from the end of week 1 to week 2 can be explained by the fact that the visual break-off point was already reached between day 5 and day 12 in several test fields, although we lowered the concentration of the irritants in comparison to the recommended doses of Frosch & Kurte (8). This was especially the case with NaOH 0.5% and SLS 5%. For these test areas, the maximal scores and values obtained at the day of discontinuance were used

for the final calculations. As a consequence, significant differences of efficacy between the test preparations could be mainly observed at day 5, confirming previous remarks concerning methodological aspects of the repetitive irritation test (14).

The present results indicate a benefit of some preparations tested against cumulative irritation by water-soluble irritants. Since no significant benefit of the base alone (preparation B, placebo) could be observed against any irritant in this study, the efficacy of the perfluoropolyether-phosphate containing test preparations has to be attributed to the perfluoropolyether phosphates themselves as "active ingredients" of the test preparations. This finding is in contrast to the results of a previous study with perfluoropolyether-containing oil-in-water emulsions as both the emulsion base and all perfluoropolyether-containing preparations significantly suppressed irritation by SLS and NaOH (9).

In the current study, test preparations E and F, in particular, showed significant protective efficacy against water-soluble irritants such as SLS and NaOH. Furthermore, preparation D demonstrated significant benefit against SLS, too. All of these test preparations contained 5% perfluoropolyether-phosphate, while test preparation C, which only contained 2% of the active ingredient, was of inferior efficacy. Thus, a dose-related effect of the perfluoropolyether phosphate could be demonstrated. Test product F differed from preparations D and E with respect to the molecular weight of the active compound that was 2000 in preparation F and 1000 in compositions D and E.

Preparations D and E differed only with regard to their base: In contrast to the remaining four test products that contained Xanthan Gum as jellying agent, composition E contained Carbomer. Clinically, this resulted in a higher viscosity and elasticity of the latter product on the skin surface. In contrast, the others seemed to be more watery and tended to break and peel off after drying, although the volunteers avoided movement. The circumstance that preparation E formed a more elastic film on the skin might be responsible for the superior efficacy that was observed in the prevention of irritation compared to the other products C, D and F.

In accordance with one of our previous studies (9), we did not find any significant protective efficacy of any test preparation against the organic solvent toluene. There seemed to be only a weak tendency for preparations C, D and E to reduce the clinical score at day 5 and day 12. However, the irritant reaction induced by toluene was comparatively weak. Since it is well known that there is a considerable interindividual variability of irritancy induced by toluene, it may be argued that our test population was fairly tolerant against toluene induced irritation. Furthermore, cumulative application of toluene may induce a hardening effect (15). This could explain the observed decreases of TEWL and Chroma-Meter values in the second week of our study.

Although this was not the objective of our study, it should be mentioned that in concurrence with the results of acute and chronic toxicity testings of perfluoropolyethers (2, 3) and especially with testings on both acute and chronic irritancy of

Fomblin® HC/P2 (unpublished data) there was no evidence of irritancy by the test preparations themselves.

In conclusion, it could be demonstrated that gel preparations containing perfluoropolyether phosphate have a dose-related significant efficacy in the prevention of experimentally induced ICD. These compounds can therefore be recommended for use in individuals working in places where they are exposed to water-soluble irritants such as by SLS, NaOH and lactic acid. Clinical studies under real workplace situations with these promising protective compounds seem warranted.

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