Acta Derm Venereol (Stockh) 1998; 78: 60–62

Skin Symptoms in Patients with Atopic Dermatitis Using Enzyme-containing Detergents

A Placebo-controlled Study

PETER HUNDEVADT ANDERSEN[1], CARSTEN BINDSLEV-JENSEN[2], HOLGER MOSBECH[3], HUCH ZACHARIAE[1] and KLAUS EJNER ANDERSEN[2]

Departments of Dermatology, [1]Marselisborg Hospital, Århus, [2]Odense University Hospital, Odense and [3]Chest and Allergy Clinic, Frederiksberg Hospital, Fredriksberg, Denmark

Detergent enzymes may cause skin irritation and occasionally hypersensitivity reactions. The potential hazards of these enzymes have led some physicians to advise atopic dermatitis patients against the use of enzyme-enriched detergents. A three-phased randomised, double-blind, cross-over experiment was designed to question this recommendation. Each period was of 1 month's duration. In the first phase patients continued using their normal washing detergent. In phase II patients used trial detergent with or without added enzymes, and during phase III patients were given the opposite trial detergent. A total of 25 patients completed the study. The primary efficacy parameters were inter-period changes in corticosteroid usage and changes in SCORAD. Secondary efficacy parameters were altered subjective symptoms scored during the final 2 weeks of each interval. Analyses of all data revealed no statistical differences in any of the primary or secondary parameters comparing treatment and placebo periods. Our data therefore seem to exclude that atopic dermatitis may exacerbate during 1 month's exposure to enzyme-enriched detergents. Since no significant irritant capacity was detected in atopic dermatitis patients, it is unlikely that consumers with "normal skin" will experience any skin discomfort when enzyme-enriched detergents are used.

(Accepted August 12, 1997.)

Acta Derm Venereol (Stockh) 1998; 78: 60–62.

Klaus Ejner Andersen, MD, Ph.D., Department of Dermatology, Odense University Hospital, DK-5000 Odense C Denmark.

Enzymes are used as catalysts in several industrial processes and occasionally respiratory reactions or skin irritation are reported in workers handling these products. The potential hazards of such enzymes were originally identified when asthmatic symptoms occurred in workers handling powdered proteolytic enzymes used in laundry detergents at that time (1–4). Initial studies failed to confirm cutaneous sensitisation, but prolonged exposure revealed mild and non-allergic skin irritation in animal and human skin (1–6). Today the skin irritation capacity of proteolytic and lipolytic enzymes is documented and the ability to induce respiratory symptoms is well known, but the occurrence of true type 1 or type 4 allergies is low (7–15). The possibility of sensitisation and the irritant capacity of these compounds have made the public somewhat reluctant to use enzyme-containing detergents. Nevertheless, the addition of enzymes (proteases, lipases and amylases) to washing products enhances their efficacy at lower temperatures.

Although much debated, the use of enzyme-containing detergents in atopic patients has generally been discouraged (16). A sensitisation to these enzymes could exacerbate atopic dermatitis and possibly asthma in these patients, but presently no scientific evidence supports these restrictive recommendations. Therefore, we investigated the influence of enzyme-containing detergents versus placebo on disease activity in atopic dermatitis patients.

MATERIALS AND METHODS

Study design

The study design was randomised, double-blind and cross-over with three phases, each of 1 month's duration. Phase I: patients continued using their normal washing detergent with or without enzymes; Phase II: patients were to use trial detergent with or without added enzymes, and Phase III: patients were given the opposite trial detergent. Detergent enzymes consisted of protease (Savinase 4.0 T, 1%), lipase (Lipolase 100T, 0.4%) and amylase (Termamyl 60T, 0.4%), all supplied from Novo-Nordisk Ltd, Bagsværd, Denmark. A visually identical detergent without enzymes served as control. The enzyme concentrations used in the study reflect the highest quantities in commercial enzyme-enriched detergents. Before the study and after completing the trial patch testing was performed using the European standard series (True-test, Pharmacia & Upjohn, Stockholm, Sweden). Detergent enzymes were tested in aqueous solutions using Finn chambers: Savinase, Termamyl and Lipolase at 0.01%, 0.05% and 0.1% (w/v). Polyethylene glycol (PEG 4000) in water was applied in concentrations of 2%, 5% and 10% (w/v) in Finn chambers, since this vehicle served as enzyme coating in detergents. Before inclusion and at study termination blood samples were analysed for specific IgE against common inhalant allergens and the described enzymes.

Patients

The main inclusion criterion was mild to moderate atopic dermatitis involving clothing-covered body areas. Patients with severe eczema necessitating systemic therapy or local treatment with group IV corticosteroids within 1 month prior to the study were not included. During the 3 test months only Locoid® was used by the subjects. As concomitant medication only Mildison® was allowed for facial eczema. A total of 26 adult Caucasians entered the study during late autumn and early vinter and 25 completed according to the protocol. Mean age was 26 years (range: 17–59) and 21 were females. Of the atopic dermatitis patients completing the experiment asthma was present in 12 patients and 19 had hay fever. In 17 patients type 1 allergy was documented and 7 presented type 4 hypersensitivity.

Observations

At inclusion and before each trial period eczema severity was assessed by a trained dermatologist using the SCORAD index (17). Each patient was evaluated by the same investigator. By weighing the tubes at each visit the total usage of Locoid® was calculated. Patients kept a daily record of itching and eczema intensity, using an arbitrary scale from 0 (no symptoms) to 3 (severe symptoms). Furthermore, the number of antihistamine tablets and the number of Locoid® applications were registered.

 ISSN 0001-5555

Table I. *Data for all observation phases*

The numbers without parentheses give average ± standard deviation for all recorded observations. The data shown in parentheses are calculated as the individual change in percentage, setting the individual run-in value to 100%. No statistically significant differences were observed between periods.

	Run-in	Active	Placebo	Active – placebo	*p*
Investigator data					
SCORAD score	30 ± 18	29 (101%) ± 21 (59%)	29 (93%) ± 22 (29%)	0 (9%) ± 6 (13%)*	> 0.99 (0.52)
Locoid® (g/period)	43 ± 52	44 (155%) ± 49 (197%)	43 (117%) ± 52 (100%)	1 (42%) ± 15 (45%)**	0.96 (0.36)
Patient data					
Itch (average score/day)	1.4 ± 0.7	1.3 (98%) ± 0.8 (39%)	1.3 (111%) ± 0.7 (72%)	0 (−12%) ± 0.2 (18%)	0.82 (0.51)
Eczema (average score/day)	1.5 ± 0.7	1.4 (98%) ± 0.7 (26%)	1.4 (100%) ± 0.7 (37%)	0 (−3%) ± 0.2 (10%)	0.95 (0.73)
No. of Locoid® appl. (times/day)	1.1 ± 0.7	1.0 (159%) ± 0.6 (209%)	0.9 (128%) ± 0.6 (128%)	0.1 (39%) ± 0.2 (56%)	0.58 (0.49)

* Confidence interval for the mean difference: 95%: (−4 to 5) on 22 df.
** Confidence interval for the mean difference: 95%: (−4 to 4) on 22 df.

Efficacy parameters

Statistical comparisons were performed using phase 2 and 3, comparing enzyme-containing detergents versus placebo. The primary efficacy parameters were inter-period changes in corticosteroid usage and changes in SCORAD. Secondary efficacy parameters were altered subjective symptoms scored during the final 2 weeks of each interval. To compensate for the interdependence between the objective parameters SCORAD and corticosteroid usage or patient information, such as "number of Locoid® applications" and "eczema severity or pruritus", a combined parameter was defined. A decreased SCORAD could be induced by increased corticosteroid usage. In this additional analysis "improvement" was defined as improved in both parameters (decreased SCORAD and reduced Locoid® consumption) or improved in one observation and unchanged in the other. A decline in one value and improvement in the other were considered as "unchanged", whereas an increase in both measures was registered as "worsening". The calculations were performed at several levels of equivalence from ±0% to ±20% with 5% intervals.

Statistical analyses

The recorded parameters were investigated separately for differences between active and placebo only (phase 2 versus phase 3), using cross-over analysis of variance (SAS statistical package).

RESULTS

A total of 25 patients completed the study according to the protocol but in 4 patients minor protocol violations were found: in one patient the corticosteroid consumption could not be calculated for one observation period and in 3 patients diary data were incomplete. In 3 patients patch testing at study termination did not take place.

No statistical differences in any of the primary or secondary parameters were obtained between treatment and placebo periods. All results are given schematically in Table I. The mean value of Locoid® utilisation and the SCORAD was slightly higher in the active period for the whole group, but a paired analysis did not disclose any difference (Table I). When all data had been compiled and the patients had been classified into three groups – worsened, unchanged or improved – no significant differences between active and placebo periods were found.

No patients were considered true patch test-positive to the enzymes, but some irritant reactions were noticed at test sites exposed to the highest enzyme or polyethylene glycol (PEG 4000) concentrations. Before and after the experiment 2 patients were RAST-positive to detergent enzymes with low RAST class values of 1–2. Both patients had initially very high total IgE values and had also been sensitised to *Aspergillus* species with very high specific IgE titres. No sensitisation to new type 1 or type 4 allergens was seen during the trial and no change in patch test reactions to standard series was found

DISCUSSION

In the present experiment the use of enzyme-enriched detergents was without significant influence on disease activity in atopic dermatitis patients. However, our data do not exclude that atopics during long-time exposure may experience increased disease activity due to the possible irritant capacity of detergent enzymes. A study with extended treatment periods may elaborate this question. Due to the low number of patients and the short observation period the experiment does not exclude that atopics can be sensitised to detergent enzymes, but our observations do not support the view that the use of enzyme-containing detergents in atopic patients must be discouraged generally.

The patients who were RAST-positive to detergent enzymes with low RAST class values of 1–2 were not considered true allergic, since both had been sensitised to *Aspergillus* species with very high specific IgE titres. The enzymes investigated are all derived from this mould. However, if hypersensitivity is suspected it is advisable to perform both patch-testing with several dilutions of detergent enzymes and to measure specific IgE, but possible cross-reactivity must always be considered.

In the present experiment no significant influence on the severity of atopic dermatitis was found. Therefore, it is probably also unlikely that consumers with "normal skin" will experience any skin discomfort when enzyme-containing detergents are used.

REFERENCES

1. Griffith JF, Weaver JE, Whitehouse HS, Poole RL, Newmann EA, Nixon GA. Safety evaluation of enzyme detergents. Oral and cutaneous toxicity, irritancy and skin sensitization studies. Food Cosmet Toxicol 1969; 7(6): 581–593.
2. Pepys J, Longbottom JL, Hargreave FE, Faux J. Allergic reactions

of the lungs to enzymes of Bacillus subtilis. Lancet 1969; 1(607): 1181–1184.
3. Zachariae H, Thomsen K, Rasmussen OG. Occupational enzyme dermatitis. Results of patch testing with Alcalase. Acta Derm Venereol (Stockh) 1973; 53(2): 145–148.
4. Zachariae H, Hoech Thomsen J, Witmeur O, Wide L, Thomsen K, Rasmussen OG, et al. Detergent enzymes and occupational safety. Allergy 1973; 28(4): 250–259.
5. Gupta BN, Mathur AK, Srivastava AK, Singh S, Singh A, Chandra SV. Dermal exposure to detergents. Vet Hum Toxicol 1992; 34: 405–407.
6. Loomans ME, Hannon DP. An electron microscopic study of the effects of subtilisin and detergents on human stratum corneum. J Invest Dermatol 1970; 55(2): 101–114.
7. Flindt ML, Flindt M. Variables affecting the outcome of inhalation of enzyme dusts Allergy to alpha-amylase and papain [letter] [published erratum appears in BMJ 1995 Mar 4; 310(6979): 603]. Ann Occup Hyg 1995; 310(6973): 195–81.
8. Hannuksela A, Hannuksela M. Irritant effects of a detergent in wash and chamber tests. Contact Dermatitis 1995; 32(3): 163–166.
9. Suzuki Y, Nomura J, Koyama J, Horii I, Hori J, Takahashi M. The role of proteases in stratum corneum: involvement in stratum corneum desquamation Detection and characterization of endogenous protease associated with desquamation of stratum corneum. Arch Dermatol Res 1993; 285(6): 372–377.
10. Pepys J. Allergic asthma to Bacillus subtilis enzyme: a model for the effects of inhalable proteins. Am J Ind Med 1992; 21(4): 587–593.
11. Osmundsen PE. Contact dermatitis due to an optical whitener in washing powders. Br J Dermatol 1969; 81(11): 799–803.
12. Pepys J, Mitchell J, Hawkins R, Malo JL. A longitudinal study of possible allergy to enzyme detergents. Clin Allergy 1985; 15(2): 101–115.
13. O'Brien IM, Bull J, Creamer B, Sepulveda R, Harries M, Burge PS, et al. Asthma and extrinsic allergic alveolitis due to Merulius lacrymans. Clin Allergy 1978; 8(6): 535–542.
14. Andersen PH, Bucher AP, Saeed I, Lee PC, Davis JA, Maibach HI. Faecal enzymes: in vivo human skin irritation. Contact Dermatitis 1994; 30: 152–18.
15. Kanerva L, Tarvainen K. Allergic contact dermatitis and contact urticaria from cellulolytic enzymes. Am J Cont 1997; 1(4). 244–245.
16. Rothe MJ, Grant Kels JM. Atopic dermatitis: an update. J Am Acad Dermatol 1996; 35(1): 1–13.
17. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology 1993; 186(1): 23–31.