

Tolerance of Oat-Based Topical Products in Cereal-Sensitized Adults with Atopic Dermatitis

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Key Words

Atopic dermatitis · Tolerance, local and systemic · Oats

Abstract

Background: Few data suggest oat-based cosmetics may cause allergic reactions in atopic subjects, especially when sensitized to cereals. **Objectives:** To evaluate the risk of immediate and delayed allergic reactions to repeated and maximized applications (RMA) of oat-containing cosmetics and oat extracts and their tolerance in cereal-sensitized atopic adults. **Methods:** Open-label pilot study in 12 cereal-sensitized atopic adults over 45 days. Open tests and RMA were performed with Rhealba[®] oat-containing cosmetics at day 0 (D0) and D10, and from D10 to D31. Patch and prick tests were performed at D7 and D42 with wheat and Rhealba oat extracts and the study cream. **Results:** The RMA of oat-based cosmetics in cereal-sensitized atopic adults did not induce any immediate or delayed allergic reaction and was well tolerated. No immediate or delayed positive skin test to oat extracts was observed. **Conclusion:** Sensitization to cereals does not increase the risk of allergic reactions to oat-containing cosmetics.

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Introduction

Atopic dermatitis is a highly pruritic skin disease affecting 1–3% of adults [1]. It is mainly due to the development of an inflammatory immune response into the skin, along with abnormalities in cutaneous permeability barrier function characterized by a significant increase in basal transepidermal water loss [2] and dysfunctions in the stratum corneum lipid metabolism [3]. This higher epidermal barrier permeability favors the penetration of environmental irritants and allergens that trigger cutaneous inflammatory mechanisms [4]. By limiting water loss and restoring the lipid composition of the stratum corneum, emollients improve the barrier function and xerosis, leading to a reduction in pruritus and the risk of infection [5]. Therefore, they are recommended by the international guidelines in the prevention and maintenance treatment of atopic dermatitis [6]. Some of them, which contain active Rhealba[®] oat extracts with anti-inflammatory and anti-oxidant properties [7], may reduce steroid consumption when used as adjuvant to topical corticosteroid treatment in atopic dermatitis [8]. Used for more than 4 decades in atopic dermatitis treatment, the local and systemic tolerance to oat-based emollients has always been excellent. However, their safety was recently challenged by several reports of allergic contact dermatitis and contact urticaria to oats in atopic adults and children [9–13]. Since sensitization to oats, and more generally to cereals, is high in atop-

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ic patients [13], these observations raised the concern that oat cosmetics may be endowed with allergenic properties.

Therefore, to evaluate the tolerance of commercially available oat cosmetics in patients with atopic dermatitis, we set up an open clinical study in which selected cereal-sensitized adult atopic patients used Rhealba oat-based cosmetics in a maximized way for 3 consecutive weeks. Prick and patch tests were performed with different Rhealba oat extracts before and after the 3-week application of the tested products.

Patients and Methods

This monocentric prospective open-label pilot study was conducted in the Clinical Research immunology Unit of Lyon-Sud Hospital (Pierre-Bénite, France). This study was approved by the Human Ethics Committee of Lyon, France. As it was a pilot study, and in the absence of previous published studies on the subject, a number of 12 subjects was estimated to be sufficient to evaluate the risk of allergic reactions related to the application of oat-containing products in atopic adults sensitized to cereals.

Inclusion Criteria

Adults older than 18 years, after informed consent, with stable atopic dermatitis (according to the criteria of the atopic dermatitis working party [14]) for more than 3 months and with a known sensitization to cereals [15] were eligible for enrolment. In all patients, atopic dermatitis was quiescent and no flare of skin inflammation was observed in the last 3 months. Sensitization to cereals was defined by the positivity of either skin prick tests to wheat/oat extracts or presence of serum wheat/oat-specific IgE. No patient had personal history of allergy to cereals characterized by immediate or delayed hypersensitivity reactions. In the same way, no patient experienced gastro-intestinal symptoms after cereal intake.

The patients were instructed not to take antihistaminics, codeine-based and steroidal anti-inflammatory drugs, neuroleptics, hypnotics and antidepressants during the whole study.

Exclusion Criteria

Subjects having orally taken antihistaminic or codeine anti-tussive drugs within the 2 weeks prior to inclusion were excluded from the study, as well as pregnant or breastfeeding women, subjects with active atopic dermatitis, or those suffering from a progressive chronic pathology or with dermatological lesions incompatible with the study or able to interfere with atopic dermatitis evaluation.

Treatments

The tested products were a dermatological cleansing bar (A-DERMA®, Laboratoires Pierre Fabre Dermo-cosmétique) and a moisturizing skin cream (Exomega cream A-DERMA®, Laboratoires Pierre Fabre Dermo-cosmétique), both containing colloidal Rhealba oat extracts (12 and 3%, respectively) that have previously demonstrated beneficial effects on inflammation [7]. The moisturizing cream also contained: water, evening primrose oil, volatile silicone, glycerin, PEG, paraffin oil, benzoic acid, EDTA 3Na, myreth-3 myristate, chlorphenesin and 2-phenoxyethanol;

the cleansing bar contained: a superfatting agent and a complex of fatty alcohol hemisulfosuccinate and isethionate.

The placebo cream contained all the components of the study cream (vehicle), except oat extracts.

Allergic Investigations

Allergy tests (patch and prick tests) were performed with 5 Rhealba oat extracts (colloidal 5%, phenolic 5%, acetic 5%, enzyme-hydrolysed phenolic 5% and acetic 5% extracts) and 3 wheat extracts (2 wheat flours 20%, from Allerbio and Stallergenes Laboratories, and gluten 10%, from Allerbio Laboratory).

Patch Tests

Two sets of 15 patches (Finn chamber 11 mm) were applied on the back of the subjects: 3 negative controls (patch only, petrolatum, saline solution); 1 irritation control (sodium lauryl sulfate, SLS, 0.5%); 5 patches containing oat extracts, 1 with the enzyme used in the hydrolyzed oat extracts, 1 with the study cream, 1 with the study cream vehicle (cream without oat extract) and 3 with wheat allergens from desensitization solutions diluted in petrolatum (20% wheat flours, 10% gluten). Patch tests were performed and interpreted according to the International Contact Dermatitis Research Group guidelines [16]. One of the 2 patch sets was removed and read 30 min after application for assessment of immediate hypersensitivity reactions; the other one remained in place for 48 h, then was removed and read 30 min (48 h, D9) and 24 h later (72 h, D10) for testing of delayed hypersensitivity reactions.

Open Application Tests

The 8 oat and wheat extracts and the study cream were applied on 1 volar forearm and left in place for 15 min.

Skin Prick Tests

Fourteen skin prick tests were performed, according to the guidelines of the European Academy of Allergology and Clinical Immunology [17], on the anterior face of the left forearm: 1 negative control (phenol glycerosaline solution), 2 positive controls (histamine and codeine phosphate; 5 prick tests with oat extracts, 1 with the enzyme used in the hydrolyzed oat extracts, 1 with the study cream, 1 with the vehicle of the study cream (cream without oat extract) and 3 with wheat extracts. Results were read 30 min after the test. Skin prick tests were considered as positive if the diameter of the papule and the rash around the papule was equal to or greater than the half of the positive control reaction diameter.

IgE Dosage

Total IgE and oat- and wheat-specific IgE antibodies were determined with Phadia reagents on an Immunocap250 in the laboratory of Immunology of Hôpital Lyon Sud (Pierre-Bénite, France).

Study Design

The study was performed over a 45-day period divided in 3 phases, as shown in figure 1: a preliminary 10-day examination phase during which the subjects had to apply their usual cereal-free emollient once a day (D0–D9); a 21-day phase of repeated and maximized applications (RMA) of the studied oat-containing products (D10–D31); an assessment phase during which the sub-

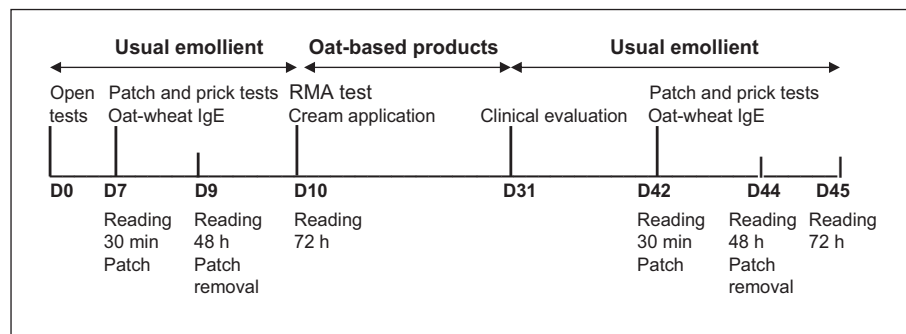


Fig. 1. Study design. RMA = Repeated and maximized application.

jects had to reapply their own emollient (D31–D45). At the visit of inclusion (D0), the investigator applied for the first time the studied cream on the elbow fold of the subject (open test) in order to monitor the potential onset of an allergic reaction. If a patient developed urticaria after this application, he was withdrawn from the study, and his IgE response specific to wheat and oat fractions was assessed.

At the second visit (D7), the patients underwent preliminary allergy tests (patch tests, skin prick tests and open application tests), and a blood sample was taken for IgE dosage. Patches were applied at D7 and read immediately and at D9 and D10.

At the beginning of the intervention phase (D10), the first application of the studied products was carried out. A nursing aid applied the study cream on one half of the patient's body and the placebo on the other side. The side of placebo and study cream application was randomly assigned according to a computerized randomization list. The investigator recorded the potential general and local reactions to the products after each application. Four hours after application of the creams, the subjects had a shower with the study dermatological bar and remained under observation for 30 min. If no reaction was observed, they received 2 study dermatological bars and 9 tubes of study cream and were instructed to have a shower once a day with the study bar and to apply the study cream on all the body twice a day, in the morning after the shower and in the evening, during 21 days. In case of clinical manifestation and/or intolerance reaction, they had to record its nature and to contact the investigator. At the end of the intervention phase (D31), the patients were examined and were informed they had to reuse their own emollient. At D42, patients were subjected to the same allergy tests they underwent at D7, and patch test readings were performed at D42, D44 and D45.

Evaluation Criteria

Primary Criterion of Evaluation

The risk of hypersensitivity to oat-containing studied cream was evaluated by monitoring local and systemic immediate and delayed hypersensitivity reactions throughout the study, i.e. D0, D10 and from D10 to D31.

Secondary Criteria

To evaluate immediate and delayed hypersensitivity to Rhealba oat extracts, allergy tests were performed before (D7) and 10 days after the intervention period (D42): patch tests containing Rhealba oat extracts read immediately at 30 min (D7 and D42) and 48 and 72 h after application (D9, D10, D44 and D45), prick

Table 1. Cereal sensitization data of patients at inclusion

Patient	Wheat		Oat	
	prick test	IgE	prick test	IgE
1	–	1		1
2		1	+	–
3	–	1		4 (pollen)
4	+	1		
5	–	4		4
6	+	2		2
7	–	2		2
8	?	2		2
9	–	2		
10		1	+	1
11	+	4		
12		2		2

Results of prick tests and/or dosages of IgE specific to wheat and/or oat performed in the 3 months preceding the inclusion.

– = Negative prick test; + = positive prick test; IgE class 0: <0.35; class 1: 0.35–0.69; class 2: 0.70–3.49; class 3: 3.50–17.49; class 4: 17.50–49; class 5: 50–99; class 6: >100 IU/l; ? = questionable.

tests with Rhealba oat fractions and open application tests on healthy skin. Furthermore, the IgE immune response specific to oat and wheat was assessed in blood samples collected at D7 and D42.

Tolerance

Global and local tolerance was evaluated at each postbaseline visit in all the subjects treated with the emollient using a 4-point scale: 0 (excellent tolerance: no sign of intolerance), 1 (good tolerance: subjective transient signs of intolerance), 2 (medium tolerance: objective signs with possible subjective signs) and 3 (bad tolerance: presence of subjective signs and at least 2 objective signs of intolerance). The investigator registered all adverse events reported by the patient.

Table 2. Total and specific serum IgE concentrations in the study population, 3 months before inclusion and at D7 and D42

No.	Total IgE UI/l			Wheat-specific IgE UI/l			Oat-specific IgE UI/l		
	3 months before D0	D7	D42	3 months before D0	D7	D42	3 months before D0	D7	D42
1	394 (6)	455 (6)	393 (6)	0.37 (1)	0.27 (0)	0.22 (0)	0.55 (1)	0.7 (2)	0.36 (1)
2	434 (6)	426 (6)	286 (6)	0.52 (1)	0.55 (1)	0.44 (1)	<0.35 (0)	0.4 (1)	0.32 (0)
3	n.p.	124 (6)	136 (6)	0.53 (1)	0.37 (1)	0.36 (1)	n.p.	0.29 (0)	0.27 (0)
4	128 (6)	108 (6)	99 (5)	0.37 (1)	0.22 (0)	0.24 (0)	n.p.	<0.10 (0)	<0.10 (0)
5	12,768 (6)	12,278 (6)	11,318 (6)	30.6 (4)	31.2 (4)	31.9 (4)	28.3 (4)	22.7 (4)	32.4 (4)
6	3,327 (6)	2,440 (6)	2,029 (6)	1.5 (2)	1.09 (2)	0.91 (2)	1.22 (2)	1.14 (2)	0.9 (2)
7	1,547 (6)	1,694 (6)	1,502 (6)	2.05 (2)	1.83 (2)	1.59 (2)	2.57 (2)	2.16 (2)	6.29 (3)
8	2,989 (6)	6,456 (6)	7,105 (6)	0.99 (2)	1.5 (2)	1.44 (2)	1.85 (2)	2.69 (2)	4.77 (3)
9	5,580 (6)	2,272 (6)	2,497 (6)	2.91 (2)	1 (2)	0.85 (2)	n.p.	1.28 (2)	1.28 (2)
10	467 (6)	382 (6)	418 (6)	0.52 (1)	0.42 (1)	0.4 (1)	0.35 (1)	0.39 (1)	0.16 (0)
11	33,320 (6)	37,365 (6)	31,336 (6)	39 (4)	31.4 (4)	33.5 (4)	n.p.	25.2 (4)	>100 (6)
12	403 (6)	464 (6)	449 (6)	1.05 (2)	1.15 (2)	1.4 (2)	0.79 (2)	0.41 (1)	0.48 (1)

Classes are shown in parentheses. Class 0: <0.35; class 1: 0.35–0.69; class 2: 0.70–3.49; class 3: 3.50–17.49; class 4: 17.50–49; class 5: 50–99; class 6: >100 IU/l. n.p. = Not performed.

Results

Demographics and Cereal Sensitization Data

At D0, 12 subjects (8 females, 4 males) with a mean age of 30.74 ± 8.41 years (range: 20–46), with stable atopic dermatitis were included in the study. All the patients were sensitized to wheat and 8 of them to oats as assessed by positive IgE and/or prick tests. Results of prick tests and dosages of wheat- and oat-specific IgE performed in the 3 months preceding the inclusion in the study are shown in table 1. The great majority of included patients had elevated total serum IgE concentrations, with values >100 IU/l (table 2). No patient was prematurely withdrawn from the study.

Primary Outcome

None of the 12 patients developed an immediate or delayed hypersensitivity reaction related to the application of products containing colloidal Rhealba oat extracts (cream or cleansing bar) throughout the study, whether at D0 at the first cream application, or D10 during the cream application on the patients' hemicorpus, or again through the RMA test, when the 2 study products were used daily at home for 21 consecutive days.

Secondary Outcomes

The results of allergy tests performed before and after the RMA test, i.e. during the initial and final testing ses-

sions (respectively D7–D10 and D42–D45), are summarized in table 3.

Patch Tests

No immediate (30 min) or delayed (48 and 72 h) positive allergic reaction to the tested components was observed in any patient, neither in the initial nor final sessions. An immediate irritation reaction was only observed for the cream and/or its vehicle in the first session of allergy tests (D7) in 2 patients (No. 1 and 12), and in the second session (D42) in 4 patients (No. 1, 3, 7 and 12), but it had disappeared at the 48- and 72-hour readings (table 3). These local and transient reactions observed at D7 were mild and were not of an allergic nature, since they disappeared in few days despite the continuation of the study.

Delayed irritation reactions were only observed with SLS, the irritation control, and the phenolic extract in 3 patients and with the acetonic extract in 1 patient in the first session, but they did not occur again in these patients in the second session (D42–D45; table 3). In the final testing session, 1 patient showed a delayed irritation reaction at 72 h (D45) to all the tested products, except gluten, vehicle and the study cream. Five patients also experienced a delayed irritation reaction to some Rhealba oat extracts (colloidal, phenolic, acetonic, hydrolyzed or not), but in no case was a delayed irritation reaction triggered by the study cream or its vehicle (table 3).

Table 3. Results of the 2 testing sessions performed before and 10 days after the daily application of study products

No.	Initial session (D7–D10)				Final session (D42–D45)			
	patches			pricks	patches			pricks
	30 min	48 h	72 h	30 min	30 min	48 h	72 h	30 min
1	vehicle ?+		SLS ?+	histamine+	cream ?+ vehicle ?+		acetic ext ?+ phenolic Hydr ext ?+	histamine+
2				histamine+		SLS?+	patch only ?+ petrolatum ?+ SLS ?+ all extracts ?+ enzyme ?+ wheat (2 brands) ?+	histamine+
3		SLS ?+	SLS ?+ phenolic ext ?+	histamine+ codeine+	cream ?+ vehicle ?+			histamine+
4				histamine+				histamine+ codeine+
5				histamine+ codeine+				histamine+
6				histamine+			phenolic ext ?+	histamine+
7			phenolic ext ?+ acetic ext ?+	histamine+ wheat +	vehicle ?+			histamine+ codeine+ wheat+ (2)
8				histamine+			acetic hydr ext ?+	histamine+ codeine+
9		phenolic ext ?+	phenolic ext ?+	histamine+ codeine+				histamine+ codeine+
10				histamine+ codeine+				histamine+ codeine+
11				histamine+ codeine+ wheat +		SLS?+		histamine+ codeine+ wheat +
12	cream ?+ vehicle ?+		SLS ?+	histamine+ codeine+	cream ?+ vehicle ?+		SLS?+ phenolic ext ?+ colloidal ext ?+ acetic hydr ext ?+	histamine+ codeine+

?+ = Irritation reaction; + = allergy reaction; (2) = reaction to the 2 brands.

Prick Tests

All patients responded to the prick tests with the 2 positive controls, histamine and/or codeine. By contrast, all prick tests performed with the study cream or its components (vehicle and the 5 Rhealba oat extracts) were negative, whether in the first or the second testing session. Furthermore, among the 12 patients sensitized to wheat,

only 2 showed positive prick tests with wheat. Patient No. 4, who displayed a positive response to wheat in prick tests performed during the 3-month period preceding his inclusion in the study, showed a negative prick test for wheat in both testing sessions. Conversely, patient No. 7 who previously had a negative prick test with wheat, responded positively in the 2 testing sessions.

Dosage of Serum IgE

Concerning total IgE, concentrations were elevated in all patients at D7 (class 6 >100 IU/l) and did not change appreciably throughout the study (table 2). Wheat IgE concentrations did not change class throughout the study and only varied slightly within the same class. Similarly, oat IgE concentrations were stable, except in 3 patients in whom they increased from 4 to 6 (for 1 subject) and 2 to 3 (for 2 subjects).

Tolerance

A good and excellent tolerance was recorded at D10 in 3 (25%) and 5 (41.7%) patients, without any difference between the left and right sides of the body. For 3 subjects, dry skin was experienced after the shower with the cleansing bar. After the 3-week RMA test, tolerance was excellent for 6 (50%) patients and good for 4 (30%) patients who experienced transient sensations of burning, arising during the application of the cream and disappearing 1 h later.

Discussion

This pilot study showed that the daily and maximized application of 2 colloidal Rhealba oat-based cosmetics (emollient and soap-free cleansing bar) for 3 weeks in cereal-sensitized atopic adults did not trigger any hypersensitivity reaction and was very well tolerated. The treatment did not aggravate the atopic dermatitis skin inflammation, since neither eczema flare nor worsening of pruritus was observed in the great majority of patients during the whole study duration. Conversely, the majority of patients were improved by the end of the study. Our results in adults are in agreement with those of Pigatto et al. [18] in children, who reported an excellent tolerance of topical oat colloidal grain suspensions in 65 normal and atopic children in a double-blind randomized patch study.

The only manifestations observed among certain patients were immediate irritation reactions to the vehicle or the cream and delayed irritation reactions to different oat extracts on patch and prick test areas, but not to the cream. In this respect, a positive reaction to SLS was often observed in patients along with irritant patch test reactions. Our results are consistent with previous studies showing that atopic skin is more prone to skin irritation than normal skin. Indeed, patch tests induced slightly more doubtful and irritation reactions in atopic than in nonatopic patients [19]. Furthermore, although atopic pa-

tients were at least as likely to have allergic contact dermatitis as nonatopics, they developed more irritant reactions, which correlated with a greater number of contact dermatitis responses [20]. That atopic patients are more susceptible to skin irritation is consistent with the observation that cosmetics, including those containing oat extracts, may occasionally induce a worsening of the skin inflammation especially in patients with active atopic dermatitis [11, 13].

Among the 8 patients sensitized to oats, none showed a positive reaction to prick tests with Rhealba oat extracts, though 2 had positive prick tests to commercially available oat allergenic extracts less than 3 months before entering in the study. Likewise, though all patients were sensitized to wheat, only 2 patients had positive prick tests. Furthermore, no manifestation of hypersensitivity to Rhealba oat extracts or oat-based cosmetic products was observed in wheat-sensitized patients, suggesting that oat does not induce any cross-reaction with wheat IgE, although antigenic homologies were demonstrated between wheat and oat globulins [21]. Collectively, our data show that the oat proteins contained in the tested cosmetics (colloidal Rhealba oat extract) do not cross-react with oat and cereal allergens towards which the patients are sensitized. These observations were expected, since allergens found in oat prick tests come from the oat pollen, whereas oat extracts contained in cosmetics are derived from the oat flour.

Concerning serum total and specific IgE levels, they only showed slight variations during the study, except for 2 patients for whom serum oat IgE levels were increased at the end of the study compared to the time of inclusion. However, no correlation was observed between high IgE levels and clinical sensitivity signs or the results of allergy tests, as it has also been shown by Varjonen et al. [22] who evaluated skin prick test and radioallergosorbent test responses to cereals in children with atopic dermatitis.

Although our study shows that Rhealba oat cosmetics are not allergenic in oat-sensitized patients, it is still possible that other oat-containing emollients made through different processes or containing oat pollen contaminants may trigger an allergenic response. Indeed, depending of their mode of preparation, the protein content of oat extracts may vary and their allergenic potential could be modified and induce differences of sensitization, even in patients tolerant to unmodified proteins. This effect has already been observed for wheat protein derivatives that are widely used in cosmetic formulations for their emulsifying and stabilizing properties [23, 24]. Several isolated cases of allergic contact dermatitis [25,

26] and contact urticaria [27, 28] due to hydrolyzed wheat cosmetics have been reported, alone or in association with a food allergy, and some studies pointed out the role of hydrolysis in the allergenicity of wheat proteins [29].

As it was a pilot study, we selected a small number of patients because the probability to be both atopic and wheat-sensitized in adulthood is rather low. Our patients were sensitized but not allergic to cereals, since they did not experienced features of immediate or delayed hypersensitivity and did not show any cereal-induced gastrointestinal symptoms. Therefore, these preliminary results need to be confirmed in allergic patients. Further-

more, as the repeated and maximized application of Rhealba oat-based cosmetic products was demonstrated as safe in atopic adults in our study, it is worth performing a similar study in children, more so since oat-based emollients are often used in this population.

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