

Establishing aluminium contact allergy

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Summary

Background. Traditionally, contact allergy to aluminium has been established by patch testing with aluminium chloride hexahydrate in petrolatum at 2.0% and an empty Finn Chamber®.

Objectives. The aim of this study was to investigate different aluminium test preparations regarding an optimal compound and an optimal test concentration.

Methods. Six different aluminium compounds and an empty Finn Chamber® were used to patch test 21 patients with aluminium contact allergy. Aluminium chloride hexahydrate in saline was used for intracutaneous injection of 19 patients.

Results. One test preparation, aluminium lactate 2.4%, was found to show significantly more positive patch test reactions than aluminium chloride hexahydrate 2.0% ($p = 0.03$). Aluminium chloride hexahydrate at 10.0% pet. gave the highest number of positive reactions to aluminium [14/21 (67%)]. No positive reactions were noted to an empty Finn Chamber®, and 3 of 19 (16%) patients reacted positively to the intradermal test.

Conclusions. The results of this study indicate that patch testing with aluminium chloride hexahydrate 2.0%, with an empty Finn Chamber® and the intradermal test with the salt and doses used are insufficient methods to detect contact allergy to aluminium. Aluminium chloride hexahydrate at 10.0% gave the highest number of positive reactions to aluminium.

Key words: aluminium; aluminium chloride hexahydrate; delayed hypersensitivity; intradermal test; patch testing.

Allergic contact dermatitis is a common environmental and occupational skin disease. It is defined as an inflammatory process of the skin caused by contact with exogenous substances, generally having a low molecular weight. Since Jadassohn introduced his 'application method' in 1895, which is regarded as the beginning of modern patch testing, this has become the most important tool in establishing contact allergy (1, 2). The allergic

patch test reaction (elicitation) is a dose-dependent reaction; that is, the amount of allergen applied per skin area unit is decisive for the outcome. Today, the test procedure is well standardized with regard to concentration and vehicle for many test substances. This is also true for the application technique and the duration of occlusion, as well as the reading criteria. However, there are many test preparations and test concentrations that are not based on systematic investigations to find the optimal test conditions but have been chosen arbitrarily (3).

Aluminium is the most abundant metal in the Earth's crust, and aluminium compounds are widely used, for example in antiperspirants, in medical preparations, in toothpaste, and in dental cements. Aluminium, both in its elemental and in its salt form, has been considered to

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be a weak allergen, and contact allergy to aluminium is considered to be rare, considering the extent of exposure (4).

Traditionally, contact allergy to aluminium has been established by patch testing with aluminium chloride hexahydrate in petrolatum at 2.0% and an empty test chamber (Finn Chamber®, Ø = 8 mm; Epitest Ltd Oy, Tuusula, Finland) made of elemental aluminium. However, recently, aluminium chloride hexahydrate 10% pet. was suggested as the preparation of choice for the diagnosis of contact allergy to aluminium (3, 5, 6).

The aim of the present study was to investigate different aluminium test preparations in order to find an optimal compound and an optimal test concentration. We report results from patch testing with different aluminium compounds and results from intradermal testing with an aluminium compound at two different concentrations.

Materials and Methods

Ethics

The Ethics Committee at Lund University Medical Faculty approved the study. Written informed consent was obtained from each patient.

Subjects

Twenty-one patients, 7 males and 14 females (mean age 48 years, range 23–81 years), all with contact allergy to aluminium, were enrolled (Table 1). An exception was made for 1 patient, number 16, who had doubtful reactions but, instead, had clinical manifestations strongly indicating aluminium allergy. At the department of Occupational and Environmental Dermatology, Skane University Hospital, Malmö, various aluminium compounds at different concentrations have been used to find an optimal test preparation since 2005. Patients 1–16 (Table 1) were patch tested for suspected allergic contact dermatitis. The remaining 5 patients, number 17–21, were patch tested because of suspected contact allergy to aluminium at the Department of Dermatology and Venereology, Skane University Hospital, Lund. The previous results of patch testing with aluminium and information collected from the patients' medical records are given in Table 1.

The study was performed in the autumn of 2009 at Skane University Hospital, Malmö, with 14 patients (numbers 1–14), and in the spring of 2010 at Skane University Hospital, Lund, with 7 patients hypersensitive to aluminium (numbers 15–21). The same personnel performed the study on both test occasions.

Controls

Twenty patients referred for suspected allergic contact dermatitis to the Department of Occupational and Environmental Dermatology, Skane University Hospital, Malmö served as controls. They were patch tested with alum at 39.0%, aluminium lactate at 24.0%, aluminium phosphate at 10.0%, aluminium hydroxide at 6.5%, all in pet., and with aluminium acetotartrate at 25.0% in water.

Chemicals

Aluminium chloride hexahydrate 99%, alum (aluminium potassium sulfate dodecahydrate $\geq 98\%$), aluminium lactate (aluminium L-lactate 97%) and aluminium hydroxide (reagent grade) were obtained from Sigma Aldrich (Steinheim, Germany), and aluminium phosphate 97% was obtained from Alfa Aesar GmbH (Karlsruhe, Germany). Aluminium acetotartrate 50% in water was obtained from Apoteket Produktion och Laboratorier (Göteborg, Sweden).

The test solutions for intradermal testing consisted of aluminium chloride hexahydrate at 1.0 $\mu\text{mol/ml}$ (0.24 mg/ml) and at 10.0 $\mu\text{mol/ml}$ (2.4 mg/ml) in saline (aluminium chloride hexahydrate 0.24 mg and 2.4 mg, respectively, sodium chloride 9 mg, and aqua for injection to 1 ml). They were obtained from Apoteket APL (Umeå, Sweden).

Patch testing

In the laboratory of the Department of Occupational and Environmental Dermatology at Skane University Hospital, Malmö, Sweden, five different aluminium compounds in concentrations equimolar to a dilution series of aluminium chloride hexahydrate in pet. were prepared (Table 2). All 21 patients were patch tested with aluminium chloride hexahydrate, aluminium hydroxide, aluminium phosphate, aluminium lactate, and alum, all in pet. Pet. was chosen as the vehicle because of the insolubility of some of the aluminium compounds in water. Seven of 21 patients were tested additionally with aluminium acetotartrate in water.

All patients were also patch tested with aluminium chloride hexahydrate at 10.0% wt/wt in pet. as well as with an empty Finn Chamber®, which is made of elemental aluminium (Ø = 8 mm; Epitest Ltd). No other aluminium compound in a concentration equimolar to aluminium chloride hexahydrate at 10.0% was tested. IQ Chambers®, which are made of additive-free polyethylene plastic and applied on a non-woven adhesive tape (Chemotechnique Diagnostics, Vellinge, Sweden), were

Table 1. Information collected from the medical records for 21 patients diagnosed with aluminium allergy

Patient	Sex, F/M	Age (years)	Atopy ^a	Deodorant sensitivity	Reason for patch testing	Year ^b	Patch testing with aluminium, % pet.			
							20.0 ^c	15.0 ^c	10.0 ^c	2.0 ^c
1	M	25	No	Unknown	Hand and foot eczema	2008	+	NT	NT	–
2	F	28	Yes	Yes	Head and neck eczema	2005	–	+	+	–
3	M	45	No	Yes	Head and neck eczema	2005	++	+	+	–
4	M	49	No	No	Hand eczema	2008	++	NT	NT	+
5	F	30	No	Unknown	Eczema	2007	++	++	NT	+
6	F	24	Yes	Yes	Hand eczema	2008	++	NT	NT	–
7	F	71	No	No	Head and neck eczema	2006	+	–	NT	NT
8	F	23	No	Yes	Hand and foot eczema	2009	+	NT	NT	–
9	F	65	No	Unknown	Lichen sclerosis et atrophicus	2007	NT	NT	NT	+
10	F	61	Yes	No	Hand eczema	2005	+	+	NT	NT
11	M	45	No	Yes	Hand eczema	2006	++	+	NT	NT
12	M	47	No	Yes	Hand eczema and other eczema	2006	++	–	NT	NT
13	F	56	Yes	Yes	Hand eczema	2008	++	–	NT	NT
14	F	56	Yes	Yes	Eyelid dermatitis	2008	++	–	NT	NT
15	M	55	No	Unknown	Hand eczema	2005	+	–	–	–
16	F	40	Yes	Unknown	No current rash. Local reaction after ASIT	2010	(+)	NT	(+)	–
17	F	51	Yes	Unknown	No current rash. Recurrent facial and oral dermatitis	1995	NT	NT	NT	+
18	F	65	No	Unknown	Eyelid dermatitis. Positive reactions to Finn Chambers® used in baseline series	1994	NT	NT	NT	++
19	F	25	Yes	Yes	Local reaction after ASIT, vaccination, and use of deodorant	2010	NT	NT	NT	++
20	F	50	Yes	Yes	No current rash. Local reaction after ASIT and use of deodorant	1998	NT	NT	NT	+++
21	M	54	Yes	Unknown	No current rash. Recurrent flares of eczema after tooth repair	1994	NT	NT	NT	+++

ASIT, allergen-specific immunotherapy; F, female; M, male; NT, not tested.

Patients 1–14 were tested in autumn of 2009 at Skane University Hospital, Malmö. Patients 15–21 were tested in spring of 2010 at Skane University Hospital, Lund. The strongest recorded reaction on D3 or D7 is given.

The concentrations of 20.0%, 15.0%, 10.0% and 5.0% were added to the baseline series in Malmö in 2005.

^aAtopy: childhood eczema and/or rhinoconjunctivitis and/or allergic asthma.

^bYear aluminium contact allergy established.

^cAluminium chloride hexahydrate in pet.

used to fasten the allergens on the upper back of the patients. The patch tests with the dilution series were placed as rows of decreasing concentration, substance by substance, with an empty Finn Chamber® at the end, as listed in Table 3.

For the test preparations in pet., an amount of ~30 mg was applied. For the test preparation in aqueous solution, 25 µl of the liquid test preparation was pipetted onto the IQ Chamber®.

The use of micropipettes enables exact dosing, and thus application to the same dose/skin area (7). After

48 hr, the patients removed the patches, and the reactions were read on D3 and D7.

Intradermal testing

Nineteen patients were tested intradermally: 14 of 19 with 0.10 ml of aluminium chloride hexahydrate in saline at a concentration of 1.0 µmol/ml (0.24 mg/ml), and 5 of 19 with 0.10 ml of aluminium chloride hexahydrate in saline at 10.0 µmol/ml (2.4 mg/ml). The injection site was the volar aspect of the forearm, and a wheal of diameter

Table 2. Equimolar dilution series of the aluminium compounds used for patch testing

Aluminium chloride hexahydrate ($\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, MW 241) Pet. (% wt/wt)	Aluminium hydroxide [$\text{Al}(\text{OH})_3$, MW 78] Pet. (% wt/wt)	Aluminium phosphate (AlPO_4 , MW 122) Pet. (% wt/wt)	Aluminium lactate [$\text{Al}(\text{C}_3\text{H}_5\text{O}_3)_3$, MW 294] Pet. (% wt/wt)	Alum [$\text{AlK}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$, MW 474] Pet. (% wt/wt)	Aluminium acetotartrate ($\text{C}_6\text{H}_7\text{AlO}_8$, MW 234) Water (% wt/vol)
20.0	6.5	10.0	24.0	39.0	25.0
10.0					
6.3	2.1	3.2	7.7	12.0	8.8
2.0	0.65	1.0	2.4	3.9	2.9
0.63	0.21	0.32	0.77	1.2	0.91
0.20	0.065	0.10	0.24	0.39	0.29

MW, molecular weight; Pet., petrolatum; wt, weight; vol, volume.

≥ 4 mm was raised, corresponding to 0.1 ml of fluid. The skin reaction was read on D3 (8).

Test reading criteria

Patch tests were scored according to International Contact Dermatitis Research Group guidelines (9). Additionally, strong + and ++ reactions were graded +(+) and ++(+), respectively (10). The reactions were noted as doubtful (+) when the morphological feature of the reaction was consistent with an allergic reaction but where the minimal criteria for an allergic reaction were not present on the whole test area. For the intradermal test, a red and raised dermal infiltration of diameter ≥ 4 mm after 72 hr was considered to be a positive result (8).

Statistical analysis

The two-sided McNemar test was used to compare the number of positive reactions to aluminium chloride hexahydrate 2.0% and to aluminium lactate 2.4%. For comparison of the positive patch test results between the two independent groups, study group versus control group, regarding one aluminium compound at the highest concentration, Fisher's exact test was used. Differences were considered significant at $p < 0.05$.

Results

Patch testing

A summary of all patch test reactions and of the reactions to intradermal testing is shown in Table 3. Among the patients, 15 of 21 (71%) reacted positively to at least one dilution of aluminium chloride hexahydrate. The responses were strongest on D3, but 1 patient reacted positively only on D7 to aluminium chloride hexahydrate. Twelve of 21 (57%) patients reacted positively to the highest concentration of 20.0%, and 4 of 21 patients

(19%) reacted to aluminium chloride hexahydrate at 2.0%. Fourteen of 21 (67%) patients were found to have a contact allergy to aluminium chloride hexahydrate at 10.0% (Fig. 1). One of them reacted positively only to this test preparation.

Testing with aluminium lactate showed positive reactions in 13 of 21 patients (62%). It was the dilution at 7.7% that verified all of these positive reactions. Higher and lower concentrations of aluminium lactate gave fewer positive reactions. However, 10 of 21 patients (48%) reacted positively to the dilution at 2.4% (Fig. 1). Thus, significantly more patients reacted to aluminium lactate at 2.4% than to aluminium chloride hexahydrate at 2.0% ($p = 0.03$).

Alum, aluminium hydroxide and aluminium phosphate each gave positive reactions in 2 of 21 patients, and aluminium acetotartrate gave positive reactions in 3 of 7 patients. None of 21 patients reacted positively to an empty Finn Chamber®.

In all, none of the six aluminium compounds alone verified all patients as having contact allergy to aluminium. Aluminium chloride hexahydrate, aluminium lactate and aluminium acetotartrate together gave positive reactions in 19 of 21 patients (91%). Two of 21 patients did not react to any of the six aluminium compounds.

Intradermal testing

Among the 21 patients previously diagnosed with aluminium allergy, 19 were tested intracutaneously: 1 of 14 reacted positively to the lower concentration of aluminium chloride (1.0 mol/ml), and 2 of 5 reacted positively to the higher concentration (10 mol/ml) (Table 3). These 3 patients also reacted positively in patch testing.

Controls

When 20 consecutive patients were patch tested with five different aluminium compounds at the highest

Table 3. The results of patch testing^a and intradermal testing^b

Substance Vehicle	Concentration (%)	Patient numbers																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Aluminium chloride hexahydrate Pet. (% wt/wt)	20.0	++	-	+	++(+)	++	(+)	(+)	+	++	++	-	-	-	+ ^c	++	(+)	-	(+)	++	++	++
	10.0	+ ^c	-	+	++(+)	++	(+) ^c	-	+	++	++	+	+	-	++ ^c	++	(+)	-	-	++	++	+
	6.3	+	-	(+)	(+)	-	+ ^c	-	+	+	(+)	(+)	-	-	+ ^c	+	(+)	-	-	+	+	++
	2.0	(+)	-	+	(+)	-	(+) ^c	-	(+)	-	-	-	-	-	-	(+)	-	-	(+)	+	+	++
	0.63	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	++
Aluminium lactate Pet. (% wt/wt)	0.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	24.0	++	-	+	++	-	+	+	+	-	(+)	(+)	-	(+)	++	++	+	+	++	++	+	++
	7.7	++	-	+	++	-	+	+	+	-	(+)	(+)	-	(+)	++	++	+	+	++	++	+	++
	2.4	+	-	+	+	(+)	+	-	+	-	-	-	-	-	++	+	(+)	-	+	+	+	+
	0.77	(+)	-	-	(+)	(+)	-	-	-	-	-	-	-	-	(+)	-	(+)	-	(+)	-	(+)	+
Alum Pet. (% wt/wt)	0.24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(+)	-	-	-	(+)	-
	39.0	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	(+)	-	-	-	(+)	-
	12.0	(+)	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(+)	-	++
	3.9	(+)	-	-	(+)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(+)	-	++
	1.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(+)	-
Aluminium hydroxide Pet. (% wt/wt)	0.39	(+)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NT
	6.5	-	-	-	-	-	-	-	-	-	-	-	+	-	+ ^c	-	-	-	-	-	-	NT
	2.1	-	-	-	(+)	-	-	-	-	-	-	-	(+)	-	++ ^c	-	-	-	-	-	-	NT
	0.65	-	-	-	(+)	-	-	-	-	-	-	-	(+)	-	+ ^c	-	-	-	-	-	-	NT
	0.21	-	-	-	(+)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NT
Aluminium phosphate Pet. (% wt/wt)	0.065	-	-	-	(+)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NT
	10.0	-	-	(+)	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	3.2	-	-	(+)	+	-	-	-	-	-	-	-	-	-	-	-	(+)	-	-	-	-	-
	1.0	-	-	-	+	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
	0.32	-	-	-	(+)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Aluminium acetotartrate Water (% wt/vol)	0.1	-	-	-	(+)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NT
	25.0	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
	8.8	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
	2.9	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
	0.91	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Finn Chamber® Aluminium chloride hexahydrate ^d	0.29	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
	-	-	-	-	-	-	-	-	-	-	-	(+)	-	-	-	-	(+)	-	-	+	+	-
	1 µmol/ml	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NT
	10 µmol/ml	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
	-	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	Pos.

NT, not tested; Pos, positive reaction.

^aThe strongest recorded reaction on D3 or D7 is given.^bPatch testing was performed with different aluminium compounds at concentrations equimolar to a dilution series of aluminium chloride hexahydrate and an empty Finn Chamber®.^cIntradermal testing was performed with aluminium chloride hexahydrate in saline.^dThe strongest reaction was recorded on D7. All other recorded reactions were strongest on D3.^eUsed with intradermal testing.

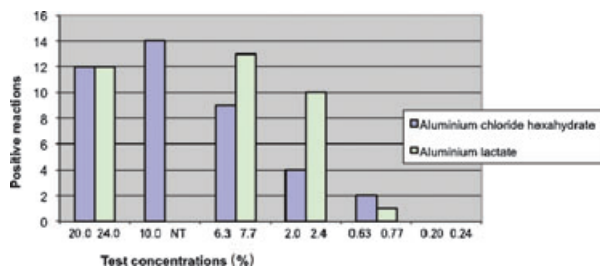


Fig. 1. The bars represent the number of positive reactions to aluminium chloride hexahydrate and to aluminium lactate at different equimolar concentrations. NT, not tested.

concentration, we noted 1 patient with a positive reaction to aluminium acetotartrate at 25.0% pet. On comparison of the patients with regard to how many positive reactions they had to aluminium lactate at 24.0%, there was a statistically significant difference between the group with previously known aluminium allergy and the controls (12/21 study subjects versus 0/20 controls; $p = 0.0001$). There was no statistically significant difference either for alum 39.0% (2/21 study subjects versus 0/20 controls; $p > 0.3$), for aluminium hydroxide (2/21 study subjects versus 0/20 controls; $p > 0.3$), for aluminium phosphate (2/21 study subjects versus 0/20 controls; $p > 0.3$), or for aluminium acetotartrate 25.0% (3/7 study subjects versus 1/20 controls; $p > 0.3$).

Aluminium chloride hexahydrate at 20.0% pet. was not patch tested in the controls, because it has been included in the baseline series at our department in Malmö since 2005.

Discussion

There are different aluminium compounds that have been used in patch testing to demonstrate contact allergy to aluminium (5). Hemmer et al. (11) routinely patch tested 1922 patients with aluminium chloride hexahydrate 2% in water added to the baseline series for 18 months. Patients reacting positively were additionally tested with a series of aluminium acetate, aluminium phosphate and potassium aluminium sulfate equimolar to a dilution series of aluminium chloride 2% in water. They were also tested with aluminium hydroxide 0.5% pet. and an empty Finn Chamber®. Four of the 1922 patients showed positive reactions to aluminium chloride hexahydrate 2% in water, but they showed no reactions when retested with the aluminium series and the empty Finn Chamber®. Hemmer concluded 'that positive reactions to aluminium compounds are not reliably reproducible' (11).

A higher test concentration of aluminium hydroxide at 10.0% pet and of aluminium chloride hexahydrate at

10.0% pet have been used previously in patch testing to show contact allergy to aluminium (12–14). Recently, aluminium chloride hexahydrate at 10.0% pet was recommended (3, 5, 6) for the detection of aluminium allergy.

In the present study, the highest test concentration for patch testing with aluminium chloride hexahydrate was 20.0% pet. This seems to be a very high concentration as compared with other allergens in the baseline series for routine patch testing. However, the amount of aluminium in this preparation is only 2.24% (0.45 mg/applied patch test dose). In comparison, with nickel sulfate (NiSO_4) at 5.0% pet. for patch testing, the amount in the test preparation is 1.9% (0.38 mg/applied patch test dose) nickel. On the other hand, this high concentration of aluminium chloride hexahydrate is not remarkable if we consider reports in the literature about the treatment of axillary hyperhidrosis with antiperspirants containing aluminium chloride hexahydrate in concentrations in ethanol of up to 25–35% (15, 16).

Interestingly, the highest number of positive reactions was not noted to aluminium chloride hexahydrate at 20.0%, but to the lower concentration of 10.0%, a result that is similar to the findings of previous surveys (3, 6). Another aluminium salt, aluminium lactate, which, to the best of our knowledge, has never been used in patch testing before but which is also used as an ingredient in antiperspirants and toothpaste, showed a similar pattern of elicitation as aluminium chloride hexahydrate. More patients reacted positively to the test concentration at 7.7% than to the test concentration at 24.0% (Fig. 1).

In 2007, Friedmann wrote (17) 'In the same way as for the induction of sensitization, the dose per unit area is a crucial determinant of response to elicitation challenge.' He described strongly sensitized individuals who were tested with series of dinitrochlorobenzene doses, and showed dose-related responses. The aluminium allergen seems not to work in this way. We do not know why, but a possible explanation may be the astringent effect of aluminium salts. It is possible that the test concentration of aluminium chloride hexahydrate at 20.0% and the equimolar concentration of aluminium lactate at 24.0% lead to impaired penetration through the epidermis as compared with the lower corresponding test concentrations.

However, the most surprising result in our study is that significantly more patients reacted to aluminium lactate at 2.4% than to the equimolar concentration of aluminium chloride hexahydrate at 2.0% ($p = 0.031$). We can only speculate about the reason for this result. Aluminium lactate is more lipophilic than aluminium

chloride hexahydrate, and might be able to penetrate the human skin more easily than aluminium chloride hexahydrate. Aluminium lactate at 12.4% pet., the concentration that is equimolar to aluminium chloride hexahydrate at 10.0% pet., was not used in patch testing in the present study, but has now been added to the baseline series at our department in Malmö.

There is another interesting observation concerning patch testing with aluminium chloride hexahydrate 2.0% pet., which, as mentioned above, together with an empty Finn Chamber[®], is traditionally used to demonstrate aluminium allergy. Eight of 21 patients had previously been diagnosed with contact allergy to aluminium because of a positive reaction to aluminium chloride hexahydrate 2.0% pet. (Table 1). Three of 8 patients (38%) now reacted positively to this concentration. This means that, in 5 of 8 patients (63%), the aluminium allergy could not be verified with the same test concentration as used before. These findings may support Hemmer's conclusion that positive reactions to aluminium compounds are difficult to reproduce. A similar result was presented in a follow-up study (18) at the congress of the European Society of Contact Dermatitis in Strasbourg 2010. Seventy-five per cent of the children did not show any reactions to aluminium chloride hexahydrate at 2.0%, to which they had earlier reacted positively. But 3 of our 5 patients who earlier reacted positively to aluminium chloride hexahydrate at 2.0% now reacted positively to higher concentrations of aluminium chloride hexahydrate. Finally, when other aluminium compounds were included in patch testing, the aluminium allergy in these 8 patients was reproducible. This phenomenon may indicate that aluminium reactivity decreases over time. Another explanation might be individual variation in aluminium reactivity, which has been shown for nickel contact allergy (10).

Only a few patients showed positive reactions when patch tested with aluminium hydroxide and aluminium phosphate. These aluminium compounds are most frequently used as adjuvants in allergen vaccines and other vaccines (6, 19). In the literature, patch testing

with these salts was performed in a few cases, with only one positive reaction to aluminium hydroxide at 10.0% (11–13). Both salts are insoluble in water (20), which might be the reason for the quite low number of positive reactions.

Aluminium acetotartrate is an ingredient in common topical medications for the treatment of, for example, wounds and leg ulcers. It has previously been used in patch testing, and in all 3 cases, positive reactions to this salt were described (14, 21). We noted positive aluminium acetotartrate reactions in 3 of 7 (43%) patients. One of these 3 patients reacted only to this aluminium compound.

As mentioned above, none of the six aluminium compounds could verify contact allergy to aluminium in all patients. Aluminium chloride hexahydrate, aluminium lactate and aluminium acetotartrate together confirmed aluminium allergy in 91% of the patients.

What about patch testing with an empty Finn Chamber[®] as a recommended method to show aluminium allergy? In this study, none of the patients reacted positively to an empty Finn Chamber[®]. We know that Finn Chambers[®] are sometimes coated with a plastic film, which could explain the negative reactions. In our study, however, we used non-coated chambers.

In the literature, there are reports of patients reacting positively to an aluminium salt and, at the same time, reacting positively or negatively to an empty Finn Chamber[®] made of elemental aluminium (3, 6, 11–13, 21–26). There are only three other studies/case reports on simultaneous testing with aluminium chloride hexahydrate at 2.0% and 10.0% and with an empty Finn Chamber[®] (Table 4).

Including the results of the present study, 11 patients reacted positively to aluminium chloride hexahydrate at 2.0% and 30 reacted to 10.0%. In the whole population, there was only 1 person with a positive reaction to aluminium chloride hexahydrate at 2.0% who also reacted positively to an empty Finn Chamber[®] (6). These results may support our hypothesis that only individuals

Table 4. Studies/case reports on patch testing with aluminium chloride hexahydrate ($\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$) 2.0% and 10.0%, and an empty Finn Chamber[®]

Studies/case reports	$\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ 2.0% pet.	$\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ 10.0% pet.	Empty Finn Chamber [®]	Numbers of positive patients/study population
Present study	4/21	14/21	0/21	14/21
Bruze et al. (3)	0/1	1/1	0/1	1/1
Netterlid et al. (6)	2/61	8/61	1/61 ^a	8/61
Netterlid et al. (27)	5/205	7/205	0/205	8/205
Total numbers of positive reactions	11	30	1	

^aThis patient reacted positively to $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ 2.0% pet. but negatively to $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ 10.0% pet.

with a strong contact allergy to aluminium react positively to aluminium tested in its elemental form.

Previous investigators have regarded the intradermal test as a valuable complementary method to patch testing in diagnosing contact allergy to metals (8, 28, 29) and also as a more sensitive method (30, 31). The solubility of the test agent, which is crucial for the penetration of the epidermis, plays a minor role in this method. The tested compound is injected directly into the dermis. There are only a few reports on intradermal tests being performed at the same time as patch testing with aluminium compounds (13, 22, 24, 32). Intracutaneous testing in the present study was performed with aluminium chloride hexahydrate 1.0 µmol/ml in saline. This concentration was used in intradermal testing with other metal salts (8, 28). We noted only 1 of 14 patients with a positive reaction. Therefore, the concentration of aluminium chloride hexahydrate was increased to 10 µmol/ml for testing of the other 5 patients. The higher concentration gave positive reactions in 2 of 5 patients (Table 3). These 3 individuals also reacted positively to aluminium chloride hexahydrate at 2.0% and/or to the equimolar concentration of aluminium lactate at 2.4% in patch testing. Thus, in only 3 individuals (16%) with a strong aluminium contact allergy, could the allergy be verified by

the intradermal test. In our study, the intradermal test appeared to be less sensitive than patch testing in detecting aluminium allergy.

The following conclusions can be drawn from this study:

- (i) Patch testing with aluminium chloride hexahydrate at 2.0% pet and an empty Finn Chamber®, and the intradermal test with the salt and doses used, are insufficient methods to demonstrate contact allergy to aluminium.
- (ii) None of the aluminium compounds alone could verify the previously diagnosed aluminium allergy in all 21 patients.
- (iii) Aluminium lactate at 2.4% pet gave significantly more positive reactions in patch testing than the equimolar concentration of aluminium chloride hexahydrate at 2.0%.
- (iiii) Aluminium chloride hexahydrate at 10.0% pet gave the highest number of positive aluminium reactions.

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References

- Fischer T, Maibach H I. Improved, but not perfect, patch testing. *Am J Contact Dermat* 1990; **1**: 73–90.
- Bruze M, Conde-Salazar L, Goossens A, Kanerva L, White I R. Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. *Contact Dermatitis* 1999; **41**: 241–250.
- Bruze M, Lundh K, Gruvberger B, Hindsén M. Aluminium chloride hexahydrate at 2% is insufficient to trace contact allergy to aluminium. *Contact Dermatitis* 2008; **59**: 183–184.
- Lidén C, Bruze M, Menné T. Metals. In: *Contact Dermatitis*, 4th edition, Menné T, Lepoittevin J-P, Frosch P J (eds): New York, Springer, 2006: pp. 537–568.
- de Groot A. *Patch Testing, Test Concentrations and Vehicles for 4350 Chemicals*, 3rd edition: Wapserveen, Acdegroot Publishing, 2010.
- Netterlid E, Hindsén M, Bjork J, Ekqvist S, Guner N, Henricson K A, Bruze M. There is an association between contact allergy to aluminium and persistent subcutaneous nodules in children undergoing hyposensitization therapy. *Contact Dermatitis* 2009; **60**: 41–49.
- Frick-Engfeldt M, Gruvberger B, Isaksson M, Hauksson I, Pontén A, Bruze M. Comparison of three different techniques for application of water solutions to Finn Chambers. *Contact Dermatitis* 2010; **63**: 284–288.
- Möller H. Intradermal testing in doubtful cases of contact allergy to metals. *Contact Dermatitis* 1989; **20**: 120–123.
- Wilkinson D S, Fregert S, Magnusson B et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970; **50**: 287–292.
- Hindsén M, Bruze M, Christensen O B. Individual variation in nickel patch test reactivity. *Am J Contact Dermat* 1999; **10**: 62–67.
- Hemmer W, Wantke F, Focke M, Gotz M, Jarisch R. Evaluation of cutaneous hypersensitivity to aluminum by routine patch testing with AlCl₃(3). *Contact Dermatitis* 1996; **34**: 217–218.
- Böhler-Sommeregger K, Lindemayr H. Contact sensitivity to aluminium. *Contact Dermatitis* 1986; **15**: 278–281.
- Lopez S, Pelaez A, Navarro L A, Montesinos E, Morales C, Carda C. Aluminium allergy in patients hyposensitized with aluminium-precipitated antigen extracts. *Contact Dermatitis* 1994; **31**: 37–40.
- Cosnes A, Flechet M L, Revuz J. Inflammatory nodular reactions after hepatitis B vaccination due to aluminium sensitization. *Contact Dermatitis* 1990; **23**: 65–67.
- Glent-Madsen L, Dahl J C. Axillary hyperhidrosis. Local treatment with aluminium-chloride hexahydrate 25% in absolute ethanol with and without supplementary treatment with triethanolamine. *Acta Derm Venereol* 1988; **68**: 87–89.
- Solish N, Bertucci V, Dansereau A, Hong H C, Lynde C, Lupin M, Smith K C, Storwick G. A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian Hyperhidrosis Advisory Committee. *Dermatol Surg* 2007; **33**: 908–923.
- Friedmann P S. The relationships between exposure dose and response in induction and elicitation of contact hypersensitivity in humans. *Br J Dermatol* 2007; **157**: 1093–1102.

- 18 Gente Lidholm A, Bergfors E, Trollfors B, Inerot A. Loss of patch-test reaction to aluminium years after vaccination with aluminium adjuvants in a population of 76,000 children. *Contact Dermatitis* 2010; **63**: 39–57.
- 19 Netterlid E, Bruze M, Hindsen M, Isaksson M, Olin P. Persistent itching nodules after the fourth dose of diphtheria-tetanus toxoid vaccines without evidence of delayed hypersensitivity to aluminium. *Vaccine* 2004; **22**: 3698–3706.
- 20 Budavari S, O'Neil M, Smith A, Heckelman P, Kinneary J. *The Merck Index*, 12th edition: Merck Research Laboratories, Whitehouse Station, New Jersey, 1996: pp. 61–63.
- 21 Meding B, Augustsson A, Hansson C. Patch test reactions to aluminium. *Contact Dermatitis* 1984; **10**: 107.
- 22 Clemmensen O, Knudsen H E. Contact sensitivity to aluminium in a patient hyposensitized with aluminium precipitated grass pollen. *Contact Dermatitis* 1980; **6**: 305–308.
- 23 Veien N K, Hattel T, Justesen O, Norholm A. Aluminium allergy. *Contact Dermatitis* 1986; **15**: 295–297.
- 24 Tosti A, Vincenzi C, Peluso A M. Accidental diagnosis of aluminium sensitivity with Finn Chambers. *Contact Dermatitis* 1990; **23**: 48–49.
- 25 Brodbaker E, Pratt M. Contact sensitivity to aluminum. *J Cutan Med Surg* 2009; **13**: 226–229.
- 26 Garg S, Loghdey S, Gawkrödger D J. Allergic contact dermatitis from aluminium in deodorants. *Contact Dermatitis* 2010; **62**: 57–58.
- 27 Netterlid E, Hindsén M, Siemund I, Björk, Werner S, Güner N, Jacobsson H, Bruze M. Does allergen-specific immunotherapy induce contact allergy to aluminium? *Acta Dermatol Venereol* 2012 (accepted for publication).
- 28 Christensen O B, Wall L M. Open, closed and intradermal testing in nickel allergy. *Contact Dermatitis* 1987; **16**: 21–26.
- 29 Bruze M, Björkner B, Möller H. Skin testing with gold sodium thiomalate and gold sodium thiosulfate. *Contact Dermatitis* 1995; **32**: 5–8.
- 30 Epstein S. Contact dermatitis due to nickel and chromate. Observations on dermal delayed (tuberculin-type) sensitivity. *Arch Dermatol* 1956; **73**: 236–255.
- 31 Marcussen P V. Comparison of intradermal test and patch test using nickel sulfate and formaldehyde. *J Invest Dermatol* 1962; **40**: 263–266.
- 32 Fischer T, Rystedt I. A case of contact sensitivity to aluminium. *Contact Dermatitis* 1982; **8**: 343.