Review Article

Aluminium in dermatology – Inside story of an innocuous metal

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Abstract

Aluminium, the third most abundant element in the earth's crust, was long considered virtually innocuous to humans but has gained importance in the recent past. Aluminium is ubiquitous in the environment, with various sources of exposure like cosmetics, the food industry, occupational industries, the medical field, transport and electronics. Aluminium finds its utility in various aspects of dermatology as an effective haemostatic agent, anti-perspirant and astringent. Aluminium has a pivotal role to play in wound healing, calciphylaxis, photodynamic therapy and vaccine immunotherapy with diagnostic importance in Finn chamber patch testing and confocal microscopy. The metal also finds significance in cosmetic procedures like microdermabrasion and as an Nd:YAG laser component. It is important to explore the allergic properties of aluminium, as in contact dermatitis and vaccine granulomas. The controversial role of aluminium in breast cancer and breast cysts also needs to be evaluated by further studies.

Keywords: Allergen, alum, alumina, aluminium

Introduction

Aluminium is the third most abundant element in the earth's crust, the unique properties of this lightweight metal (symbol: Al; atomic number: 13; weight: 26.98; density: 2.7 g/cm^3) and its alloys make it a versatile and economical metal with various uses.[1] Despite its ubiquity, aluminium was long considered virtually innocuous to humans but has gained importance in the recent past. This review discusses the role of aluminium in various dermatological conditions and its use in diagnostic and therapeutic modalities.

(I) Therapeutic applications of aluminium

1) Anti-perspirant

Aluminium salts are effective antiperspirants used in the treatment of axillary and palmoplantar hyperhidrosis of all grades of severity. This aluminium-containing agent can be either prescription based or available over the counter (OTC) whose differences are elucidated in Table 1. The mechanism of action of aluminium chloride hexahydrate (ACH) as an anti-perspirant is elucidated in Figure 1.[2] ACH is the most frequently used agent, starting at a lower concentration (10%) for palmar and axillary hyperhidrosis and at a higher concentration (20%) for plantar hyperhidrosis [Figure 2].[3] A prolonged administration of this agent is often needed to prevent recanalisation of injured eccrine duct epithelium, thereby providing a sustained hypohidrotic effect.[4–6] A randomised half-side trial for assessing the efficacy of aluminium chloride for plantar hyperhidrosis found that clinical score decreased by 38.9% at two weeks from baseline with an additional 7.9% reduction at 6 weeks.[7] According to a systematic review, the efficacy of aluminium chloride in axillary hyperhidrosis showed striking difference in Hyperhidrosis Disease Severity Scale (HDSS) response rates in two trials (33% and 72%).[8]

How to cite this article: Murthy AB, Palaniappan V, Karthikeyan K. Aluminium in dermatology – Inside story of an innocuous metal. Indian J Dermatol Venereol Leprol. doi: 10.25259/IJDVL_188_2023

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Received: February, 2023 **Accepted:** July, 2023 **EPub Ahead of Print:** February, 2024

DOI: 10.25259/IJDVL_188_2023

Table 1: Difference between over-the-counter (OTC) and prescription-based antiperspirants

S.No	Features	OTC antiperspirant	Prescription based antiperspirant
1	Composition	Aluminium zirconium trichlorohydrate glycine complexes aluminium chloride hexahydrate (lower concentration upto 12.5%)	20% aluminium chloride in ethyl alcohol, 12% aluminium chloride in carbonate water, 6.25% aluminium tetrachloride
2	Irritation	Less irritation due to 80% less production of hydrochloric acid (HCl)	More irritation
3	Plug formation	Superficial plug formation in eccrine ducts	Deeper plug formation
4	Frequency of application	Daily application is needed	Every 1–2 days
5	Absorption in hairy regions	Unaffected	Decreased as the highly charged particles bind to anionic groups on hair surface

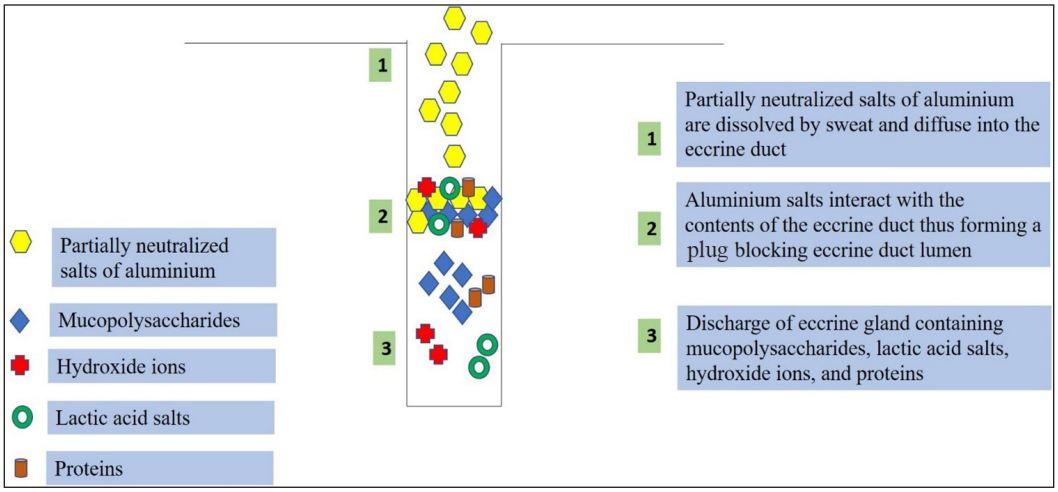

Figure 1: Mechanism of antiperspirant action of aluminium-based compounds.

Aluminium chloride ($AlCl_3$) can also be added to iontophoresis to amplify the anhidrotic effect due to better penetration of aluminium salts into sweat glands.[9] The addition of 2% salicylic acid gel to 15% ACH has better efficacy and tolerability due to the keratolytic, antiperspirant and astringent properties of salicylic acid.[10]

Apart from hyperhidrosis, ACH can also be used for bromhidrosis, transient aquagenic keratoderma, trichomycosis axillaris, epidermolysis bullosa simplex, gustatory hyperhidrosis and local hyperhidrosis associated with eccrine naevi.[11] The adverse effects of using aluminium-based antiperspirants include pain, pruritus, hyperpigmentation, irritation, fissuring, scaling and pustules. Factors like high chloride content, low pH and anhydrous alcohol vehicles contribute significantly to the irritant effects of aluminium.[12] In mouse models, the use of $AlCl_3$ as an antiperspirant has resulted in axillary granular parakeratosis. It was proposed to be due to aluminium-induced apoptosis resulting in keratinisation arrest at the granular layer of the epidermis.[13]

2) Topical haemostatic agent

Aluminium chloride ($AlCl_3$) (20–40%) in isopropyl alcohol, ether or glycerol works as an effective chemical haemostatic agent, especially in minor dermatological procedures

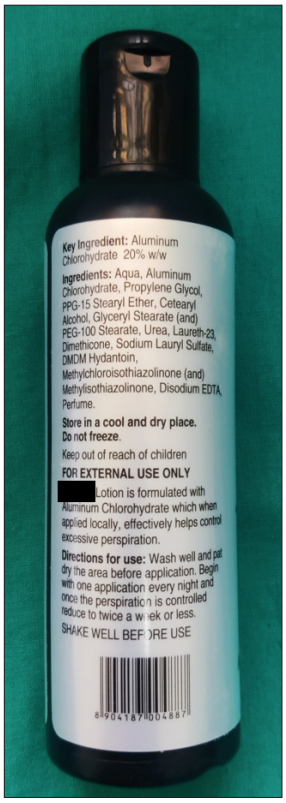

Figure 2: Prescription-based antiperspirant (20% aluminium chlorohydrate).

including skin biopsy. Low cost, easy utility and storage at room temperature attract its usage as a haemostatic agent.[14,15] The application of $AlCl_3$ with a cotton-tipped applicator in a twisting motion perpendicular to the skin surface helps establish sufficient haemostasis.[14] The advantages of $AlCl_3$ over Monsel solution and electrocautery for haemostasis include less pigmentation and less tissue charring, respectively. The mineral zeolite (microporous crystalline aluminosilicate) and clay minerals such as kaolin and smectite (a combination of octahedral aluminate sheets and tetrahedral silicate in a ratio of 1:1 and 2:1, respectively) have also been used as haemostatic agents.[16–19] The mechanisms of action of aluminium chloride, zeolite and clay minerals as topical haemostatic agents are depicted in Table 2.[19,20]

3) As an astringent

Aluminium acetate (Burow's solution) is prepared by combining aluminium sulphate, acetic acid, tartaric acid and calcium carbonate. It is an effective astringent and antiseptic used for exudative lesions like eczemas, pompholyx and tinea pedis, especially if vesiculation or maceration is present and for chronic exudative ear infections.[21] Aluminium, with a high degree of protein-precipitating properties, alters the ability of proteins to swell and hold water, and draws water out of the cell, leading to the drying up of exudative lesions.[22,23] $AlCl_3$, due to its astringent action, has proved efficacious even in post-surgical hypergranulation tissue by its ability to contract and retract the tissues.[24]

4) Bentonite in contact dermatitis and eczema

Bentonite (colloidal hydrated aluminium silicate) is an insoluble, odourless, white, yellow, pink or grey powder forming a homogenous, viscous gel or colloidal suspension mixed with 10 parts of water. It is incompatible with mineral acids and salts, thus displaying thixotropy.[25] It is reported to be effective in hand eczema and diaper dermatitis by causing reduced percutaneous allergen absorption and skin barrier function improvement.[26,27]

Table 2: Mechanisms of action of aluminium based compounds as topical haemostatic agents

Aluminium chloride	Zeolite	Clay mineral
$AlCl_3$	Exothermic reaction	1:1 (Kaolin) / 2:1 (Smectite) (based on the ratio of octahedral to tetrahedral sheets)
Hydrolysed to hydrochloric acid (HCl)	Absorbs liquid and causes aggregation of	Thermal stability Large surface area Small size Ion exchange capability
Vasoconstriction	• Platelets • Clotting factors • Red blood corpuscles	Intrinsic coagulation pathway activation
Activation of the extrinsic pathway of coagulation and arrest of bleeding		

$AlCl_3$: Aluminium chloride

5) Wound healing

Anodic aluminium oxide (AAO) is found to enhance wound healing by acting as a membrane for the firm attachment of cells aiding in the migration and proliferation of epithelial cells.[28]

6) As sanitizer for controlling transmission of COVID-19 (SARS-CoV-2)

Bentonite clays carrying a net negative charge and positive charge on edges with high cation exchange capacity act as an excellent adsorbent for SARS-CoV-2 preventing COVID-19 transmission.[29]

7) Role of aluminium in calciphylaxis and treatment of calcinosis cutis

A close relationship is observed between calcium phosphorus products in plasma and the tendency for ectopic calcification. Administration of aluminium hydroxide (2.8 g/100 mL- 15 to 20 mL four times a day) leads to the formation of insoluble aluminium phosphate, decreasing intestinal absorption of phosphorus and thereby reducing the calcium phosphorus product in plasma.[30,31] Aluminium hydroxide (1.8–2.4 g/day) has been used to treat idiopathic calcinosis cutis, calcinosis universalis, calcinosis associated with juvenile dermatomyositis, systemic sclerosis and systemic lupus erythematosus.[32] There are no accepted standard treatment protocols or algorithms for the use of aluminium hydroxide in calcinosis cutis, since the recommendations are based on individual case reports with a low quality of evidence.[32]

Weenig et al., in a retrospective study, noted a fourfold increase in the risk of developing calcific uremic arteriolopathy (CUA) with elevated serum aluminium levels (>25 ng/mL).[33] A case-control study conducted at the Mayo Clinic identified serum aluminium concentration as a significant factor for calciphylaxis in patients with end-stage renal disease.[34] The speculative causes of aluminium overload in calciphylaxis could be attributed to poor urinary excretion of aluminium, low serum transferrin levels resulting in competition for transferrin binding sites between iron and aluminium, and mobilisation of aluminium from bone stores due to high bone turnover in secondary hyperparathyroidism.[35–37]

8) Role in photodynamic therapy for cutaneous malignancies

Aluminium-chloride-phthalocyanine (AlClPc), a second-generation photosensitising agent, is used for photodynamic therapy with the advantages of high photodynamic efficiency and low cutaneous photosensitivity.[38,39] Aluminium (III) phthalocyanine chloride tetra sulphonate (AlPcS4Cl) is another aluminium-based photosensitizer used.[40]

9) Aluminium adsorbed allergen preparation for honey bee venom allergy

Venom immunotherapy (VIT), a type of allergen-specific immunotherapy or systemic allergen immunotherapy is a highly effective treatment for protecting honey bee venom (HBV) allergic patients from anaphylaxis. In this, aluminium hydroxide (75%) as an adjuvant is mixed with the honey bee venom extract, and the mixture is administered subcutaneously, which protects patients from developing systemic allergic symptoms if re-stung.[41] The injections are given in gradually increasing quantities of the allergen until immunological tolerance is achieved.[42] Comparative trials show that aluminium hydroxide adsorbed extracts are better tolerated than non-purified extracts, particularly in severe reactions.[43]

10) Nd YAG and Er Yag laser

Crystals of aluminium garnet and yttrium are doped with neodymium to produce Nd: YAG laser that is used for pigment removal and vascular lesions like telangiectasia, spider veins and hemangioma. Aluminium is a desirable laser host material due to its stability, hardness and optically isotropic nature.[44]

11) Aluminium oxide crystals for microdermabrasion

Aluminium oxide crystal microdermabrasion (AOCM) was initially developed in 1985 in Italy.[45] Aluminium oxide is the most commonly used abrasive in microdermabrasion because of its coarse, uneven surface and chemically inert nature [Figure 3]. AOCM has been found to enhance lipid barrier function through decreased transepidermal water loss (TEWL) and increased hydration in the stratum corneum. The bactericidal property of AOCM has the advantage of treating acne, as acne is associated with bacterial proliferation.[46] It has a lower propensity to cause bleeding and allergic contact dermatitis. The hazards associated with AOCM are pain, redness of the eyes, photophobia, epiphora, adherence of crystals to the cornea, and flares of herpes simplex infections.[45]

12) Topical antibiotic

French green clay, rich in iron-smectite, has been used for Buruli ulcers caused by Mycobacterium ulcerans due to its antibacterial properties. It is usually applied in a paste form to the ulcers, left for a week and reapplied again, resulting in wound debridement and regeneration of healthy tissue.[17] It was found that the pH and oxidation state buffered by the surfaces of clay minerals control the solution chemistry and redox related events occurring at the bacterial cell wall.[17]

13) Bentonite as a component of calamine lotion

During the preparation of calamine lotion, bentonite (Al_2O_3. $4SiO_2$. xH_2O) is added to the powders prior to the addition of water. The main function of bentonite in shake lotions like calamine is to act as a stabiliser/suspending agent.[47]

Figure 3: Aluminium oxide crystals used in microdermabrasion.

14) Aluminium in sunscreens

Aluminium is found to be a component of sunscreens, wherein they help in preventing the agglomeration of titanium dioxide particles. However, due to its pro-oxidant effect, it exaggerates the oxidative damage induced by the chronic use of sunscreens.[48]

15) Aluminium in friction blisters

A double-blind placebo-controlled trial found that the topical application of 20% ACH applied three times on three different days reduced friction blisters in those involved in hiking.[49] The mechanism proposed was reduced sweating by ACH decreases the friction between the skin and the contact surface, thereby reducing the incidence of friction blisters.[49]

The uses of aluminium in dermatology are summarised in Table 3.

16) Aluminium as an allergen

Contact with aluminium in the environment is inevitable due to the widespread use of aluminium metal as mentioned in Table 4. Aluminium was first identified as an allergen by Hall in 1944 among aircraft workers.[50] The "allergen of the year" award for 2022 has been awarded to aluminium by the American Contact Dermatitis Society (ACDS).[1] In a systematic review, the prevalence of aluminium contact allergy was found to be 5.6% and 0.4% in children and adults, respectively.[51] ACD to aluminium can present as eczematous dermatitis (localised in hands, legs, axilla or widespread systemic contact dermatitis).[1] A report of contact urticaria secondary to aluminium-containing coins has been reported.[52] The aluminium salts reported to have

Table 3: Uses of aluminium in dermatology

S.No	Uses	Form of aluminium
1	Haemostatic agent	Aluminium chloride
		Zeolite (microporous crystalline aluminosilicate)
		Clay mineral (Kaolin and smectite group) – octahedral aluminate sheets and tetrahedral silicate
2	Antiperspirant	Aluminium chloride hexahydrate
		Aluminium zirconium trichlorohydrate gly
		Aluminium chloride in ethyl alcohol or carbonate water
		Aluminum tetrachloride
		Aluminium sesquichlorohydrate foam
		Aluminium lactate
3	Astringent (Burow's solution)	Aluminium acetate
4	Contact dermatitis	Bentonite (colloidal hydrated aluminium silicate)
5	Wound healing	Anodic aluminium oxide
6	As sanitizer for controlling COVID-19 transmission	Bentonite
7	Calciphylaxis and calcinosis cutis	Aluminium hydroxide
8	Photodynamic therapy for cutaneous malignancies	Aluminum-chloride-phthalocyanine Aluminium (III) phthalocyanine chloride tetrasulphonate
9	Venom immuno-therapy for honey bee venom allergy	Aluminium hydroxide
10	Tattoo, pigment and hair removal	Nd YAG and Er YAG laser
11	Microdermabrasion	Aluminium oxide
12	Topical antibiotic	French green clay (Iron smectite)
13	Stabiliser for shake lotions like calamine lotion	Bentonite
14	Friction blisters	Aluminium chloride hexahydrate
15	Finn chamber (patch testing)	Aluminium chloride hexahydrate
		Aluminum hydroxide
		Aluminum sulphate
		Aluminum lactate
		Aluminum acetate
		Aluminum acetotartrate
16	Contrast agent in confocal microscopy	Aluminium chloride

Er:YAG: erbium-doped: yttrium aluminum and garnet, Nd:YAG: neodymium-doped: yttrium aluminum garnet

Table 4: Source of Aluminium exposure

S.No	Source of aluminium exposure
1	Food industry Processed foods As aluminium foils for food packaging Drinking water As a food additive to prevent caking Colourant
2	Cosmetics (as abrasive, anticaking agent, absorbent, buffering agent, corrosion inhibitor, pH adjuster, bulking and opacifying agent) Antiperspirants Sunscreens Tooth paste
3	Occupations Mining Welding Scraping metal cycling Construction Sewage treatment Leather tanning Crude oil refining Cracking of petroleum Printing ink Pottery Cement and paints
4	Medical Antacids Haemodialysis Measuring radiation exposure Vaccines
5	Transport
6	Electronics
7	Fireproofing
8	Glass and ceramics
9	Fumigants and pesticides

allergic potential include aluminium chloride hexahydrate, aluminium lactate, alum, aluminium hydroxide, aluminium phosphate and aluminium acetotartrate.[53]

17) Granulomatous conditions

a) Aluminium granuloma

Aluminium salts are used in various vaccines as adsorbents to enhance a specific and long-lasting immune response to antigens [Table 5]. The rationale behind using aluminium as an adjuvant points out theories like "depot theory" (slow elimination of aluminium precipitated antigens) and "antigen targeting theory" (particulate nature of adjuvants favouring phagocytosis and subsequent activation).[54] Aluminium salts (aluminium hydroxide, aluminium phosphate and alum) are one of the few adjuvants formulated for the SARS-CoV-2 COVID vaccines. Alum binds with the receptor binding domain (RBD) of S-protein to induce the production of neutralising antibodies, thus offering protection against SARS-CoV-2.[55] Aluminium adjuvants mediate inflammation through two pathways, namely NLRP3 inflammasome and NLRP3 independent pathways leading to immune responses and cytokine production.[56] The subcutaneous administration of aluminium-containing vaccines is known to produce granuloma by either of the two mechanisms; i) delayed hypersensitivity reaction, and ii) non-allergic reaction to such as direct toxicity. It is estimated that around 1% of all vaccinated children develop vaccine granuloma which appears from 2 weeks and 13 months after injection and persists for an average of 4.6 years.[51,57]

Table 5: Vaccines containing aluminium salts as adsorbents

S.No	Vaccines containing aluminium as adjuvants
1	Diphtheria–Tetanus–acellular Pertussis vaccine (DTaP)
2	Diphtheria–Tetanus–Pertussis vaccine (DTP)
3	Haemophilus influenzae type b vaccine (Hib)
4	Meningococcal group C conjugate vaccines
5	Hepatitis A and B vaccines
6	Human papillomavirus vaccine
7	Malaria vaccines
8	Human hookworm vaccine
9	Anthrax vaccine
10	Rabies vaccine
11	Leishmaniasis vaccine
12	HIV vaccines
13	SARS-CoV-2 COVID vaccine

Clinically, it may present as asymptomatic or pruritic erythematous subcutaneous nodules. Associated hypertrichosis and hyperpigmentation may be observed. The aluminium-containing Td vaccine has resulted in recurrent interconnected sterile abscesses.[58] The exacerbating factors for vaccine granuloma in children include infections, consumption of tin-foiled or canned food and the use of aluminium-containing sunscreens.[57] The aluminium granulomas can result in poor quality of life among children.[59] The various histopathological features observed in aluminium granuloma include necrobiotic granuloma with surrounding histiocytes, panniculitis, pseudolymphoma and granuloma annulare like patterns.[60]

b) Tattoo granuloma

Localised aluminium-induced delayed hypersensitivity granulomatous reactions in tattoos have been observed, proposed to be due to delayed type hypersensitivity.[61] Granulomatous reactions are observed in 26.3% of the patients getting tattooed.[61,62] Similar reactions following blepharopigmentation with aluminium-silicate have been reported.[63]

c) Foreign body granuloma

Aluminium is one of the inciting agents for foreign body granulomatous reactions in cutaneous sarcoidosis as evidenced by the electron probe microanalysis revealing aluminium peaks in the foreign bodies.[64]

18) Podoconiosis

Aluminium from the soil that penetrates the skin gets engulfed by the macrophages, resulting in inflammation and fibrosis of the vessel's lumen thereby blocking lymphatic drainage and resulting in podoconiosis.[65,66] A study conducted in the Great Rift Valley in Kenya found that aluminium at a concentration of 10303.82 mg/kg in the soil was significantly associated with the log of expected counts of podoconiosis cases.[67]

19) Uraemic pruritus

In patients undergoing haemodialysis, exposure to aluminium occurs with the water used for dialysate solution and aluminium-containing phosphate binders. Higher aluminium levels in serum are more associated with uraemic pruritus.[68] A ten-fold increase in serum aluminium was associated with a 5.6 fold increase in the risk of developing uraemic pruritus.[69] Serum aluminium levels ≥2 µg/dL were significantly associated with a greater risk of uraemic pruritus.[69]

20) Malignancies

The use of aluminium-containing antiperspirants in the axilla has been implicated in breast cysts and malignancies.[70,71] Aluminium by producing DNA alterations, epigenetic effects and interfering with the function of oestrogen receptors can predispose to breast malignancies in the upper outer quadrant.[70] The side effects of aluminium in Dermatology are summarised in Table 6.

(II) Diagnostic applications

1) Finn chamber

Finn chamber made of aluminium is the most preferred test chamber system in patch testing [Figure 4].[72] The amount of aluminium released from an empty Finn chamber corresponds to a skin dose of 0.03% to 0.5% ACH applied in a plastic chamber.[1] Aluminium salts, including ACH, aluminium hydroxide, aluminium sulphate, aluminium lactate, aluminium acetate and aluminium acetotartrate, have been used for patch testing instead of elemental aluminium, with petrolatum as the predominant vehicle.[53] Studies suggest that patch testing with 10% ACH is better than 2% ACH to detect aluminium allergy, although 2% ACH is sufficient for patch testing in children younger than 7 to 8 years.[73] In a study

Table 6: Side effects of aluminium in dermatology

S.No	Disease
1	Allergic contact dermatitis (eczematous dermatitis)
2	Irritant contact dermatitis
3	Contact urticaria
4	Sterile abscesses
5	Pruritic subcutaneous nodules (vaccine granulomas)
6	Podoconiosis (Mossy foot)
7	Granuloma - Vaccine granuloma - Tattoo granuloma - Foreign body granuloma
8	Axillary granular parakeratosis
9	Nephrogenic pruritus
10	Hyperpigmentation
11	Hypertrichosis
10	Systemic diseases - Breast cancer - Breast cyst - Alzheimer's disease

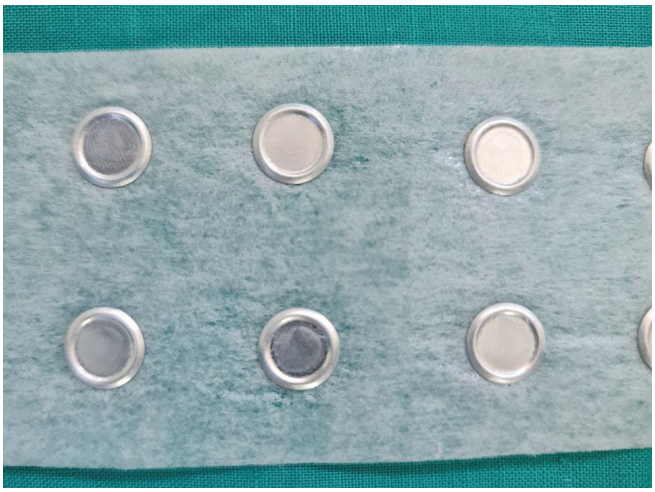

Figure 4: Finn chamber (containing aluminium salts as the predominant vehicle) used in patch testing.

analysing positive patch test results for elemental/metallic aluminium (empty Finn chamber) and 2% ACH in petrolatum in 366 children with vaccine-induced persistent itching nodules, it was found that 31% of children showed positive patch test to 2% ACH with a negative patch test to elemental aluminium.[74] Hence, patch testing with elemental/metallic aluminium (empty Finn chamber) is not recommended since it is less sensitive than 2% ACH in petrolatum to diagnose aluminium hypersensitisation.[1]

2) As a contrast agent for confocal microscopy

$AlCl_3$ is used as a contrast-enhancing agent in reflectance confocal microscopy (RCM). Tannous et al., utilised 20% $AlCl_3$ as a contrast-enhancing agent in RCM for performing Mohs micrographic surgery for basal cell carcinoma. The $AlCl_3$-stained tumour cells exhibited intensely bright nuclei with excellent contrast.[75] In a study by Flores et al., it was found that in keratinocyte carcinomas, when $AlCl_3$ was applied topically post-surgically to wounds, it provided a consistently enhanced contrast of tumour morphology at a cellular level.[76]

Conclusion

The role of aluminium and its salts has gained importance over the past few years in various fields of medicine. Aluminium is a vintage metal that has potential applications in various diagnostic and therapeutic armamentariums in dermatology. The emergence of aluminium as an allergen and its use in cosmetic products require special concern for both producers and consumers.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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