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REVIEW

Quaternary Ammonium Compounds and Contact Dermatitis: A Review and Considerations During the COVID-19 Pandemic

Chidubem AV Okeke[1], Ramona Khanna[2], Alison Ehrlich[3]

[1]Department of Dermatology, Howard University College of Medicine, Washington, DC, USA; [2]Georgetown University School of Medicine, Washington, DC, USA; [3]Foxhall Dermatology, Washington, DC, USA

Correspondence: Chidubem AV Okeke, Department of Dermatology, Howard University College of Medicine, 520 W Street NW, Room 3035/3036, Washington, DC, USA, Email chidubem.okeke@bison.howard.edu

Abstract: The recent global pandemic has resulted in increased use of quaternary ammonium compounds (QACs). Currently, QACs are active ingredients in 292 disinfectants recommended by the US EPA for use against SARS-CoV-2. Among QACs, benzalkonium chloride (BAK), cetrimonium bromide (CTAB), cetrimonium chloride (CTAC), didecyldimethylammonium chloride (DDAC), cetrimide, quaternium-15, cetylpyridinium chloride (CPC), and benzethonium chloride (BEC) were all identified as potential culprits of skin sensitivity. Given their widespread utilization, additional research is needed to better classify their dermal effects and identify other cross-reactors. In this review, we aimed to expand our knowledge about these QACs to further dissect its potential allergic and irritant dermal effects on healthcare workers during COVID-19.

Keywords: patch test, systemic contact dermatitis, hypersensitivity, allergic contact dermatitis, COVID-19, healthcare

Introduction

Quaternary ammonium compounds (QACs) are active ingredients in 292 disinfectants recommended by the US EPA for use against SARS-CoV-2.[1] QACs are amphiphilic cationic surfactants that reduce interfacial tension through self-assembly behavior.[2] Their ability to denature cell proteins and disrupt cell membranes make them effective against a spectrum of organisms and essential components in hospital, industry and cosmetic formulations (see Table 1).[3,4] However, growing evidence suggests that exposure to these compounds may result in contact dermatitis (see Table 2).[5–9] Herein, this article explores the most frequently used QACs in both personal products and cleaning supplies and their association with contact dermatitis.

Benzalkonium Chloride

Benzalkonium chloride (BAK) is marketed as a potent disinfectant and antiseptic[36] and reportedly an ingredient in approximately 20% of personal care products.[21] It has the potential to penetrate milled smooth rubber gloves in conditions of prolonged exposure.[37] The most common sources of BAK exposure are ophthalmic eye drops, topical antiseptics, and cosmetics and various dental composites.[10,38] Though frequently used, the literature suggests that there has been an increasing rate of allergenicity associated with BAK since 1998.[39] A comparative study confirmed that as compared to other bis-QACs, BAK had caused significant damage to human epidermis models, demonstrating increased stratum corneum permeability and increased inflammatory cytokine mRNA expression.[40] Several case reports and retrospective studies have highlighted associations between irritant contact dermatitis (ICD) or allergic contact dermatitis (ACD) and BAK-containing products as well.[5,21,39,41–43] Currently, healthcare workers are most likely to be exposed to BAK,[10] making dental personnel an occupational subgroup with a high risk of BAK contact sensitivity.[44] Patients commonly present with eczematous rashes, eruptions or dermatitis,[9,41,45–47] noting clinical improvement with discontinued use of BAK-containing products.[9,41,48,49]

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Table 1 No. of QAC-Containing Products in Online Databases

Compound	CPID Database*	EWG's Skin Deep Database*	CAMP Database*
Benzalkonium Chloride	52	270	7360
Quaternium-15	102	10	7296
Didecyldimethylammonium Chloride	206	202	–
Cetrimonium Bromide	5	47	–
Cetrimonium Chloride	314	1509	–
Cetrimide	–	–	–
Cetylpyridinium Chloride	38	119	–
Benzethonium Chloride	34	34	–

Notes: *This value excludes Medications (Rx + OTC), – Information not available.

Table 2 Summary of Contact Dermatitis Cases Caused by QACs

Compound	Product (s)	Final Diagnosis	Patch Test (±)	Location	Reference (s)
Benzalkonium Chloride (BAK)	Ophthalmic solutions, Topical antiseptics and anesthetic formulations, Personal care products, Plaster of Paris, disinfectant wipes and hand sanitizers, hand wash, and antibacterial laundry rinses containing 0.1% aq. BAK	ACD	+	Face, hands, legs	[10]
	Plaster of Paris bandage	ACD	+	Finger, forearm, wrist	[10–12]
	Non-adherent portion of antibacterial bandage	ACD	+	Shin	[13]
	Preservatives	ACD	+	Eyelid	[14]
	Dorzolamide (eyedrops) with containing 0.1% BAK	ACD	+	Eyelid	[15]
	Olapatidine (eyedrops) with containing 0.02% BAK	ACD	N/A	Eyelid	[16]
	Disinfectant containing 0.1% aq. BAK	ACD	+	Buttocks, upper part of the thighs	[17]
	Oilatum™ Plus (antiseptic bath emollient) containing 6.0% BAK	ICD	N/A	Scrotum, penis	[18]
	Eyedrops persevered with 0.07% aq. BAK	ACD	+	N/A	[19]
	Hand Sanitizer containing BAK and DDAC	ACD	+	Dorsal and palmar hands, arms, trunk	[20]
	Eczema Cream containing BAK	ACD	+	Trunk, legs	[21]
	Disinfectant wipes	ACD	+	Face	[21]

(*Continued*)

Table 2 (Continued).

Compound	Product (s)	Final Diagnosis	Patch Test (±)	Location	Reference (s)
Didecyldimethylammonium Chloride (DDAC)	0.1% pet. DDAC	ACD	+	Hand	[22]
	Bath disinfectant and surface disinfectant containing DDAC 0.1% pet.		+	Eyelids, neck, Hands	[23]
	Disinfectant containing 10% DDAC diluted 1:5 (2%) and 1:20 (0.5%) in pet.;	ICD	–	Face, neck, chest	[24]
	Gigasept®AF (detergent-disinfectant) containing 0.1% aq. DDAC	ACD	+	Hands, arms	[25]
	Shoe refresher spray containing 0.08% aq. DDAC	ACD	+	Feet, lower legs	[26]
Cetrimonium Bromide (CTAB)	Preservatives containing 0.5% pet. CTAB (ie facial cleansers, cosmetics, skin lighting creams, and hair conditioning agents)	PCD/ACD	+	Face, neck, scalp, upper back, fingers, earlobes, arm, forearm	[27]
Cetrimide	3% cetrimide antiseptic solution	ICD	+	Neck, groin, scrotum, flexor sites	[28]
	Antiseptic solution containing 0.1% cetrimide	ACD	+	Scrotum, Penile skin	[29]
	Kumkum, Hair dye, and Lipstick and Solution containing 0.5% cetrimide	ACD	+	Face, scalp, arms, forearms, trunk, feet	[30]
	Shampoo containing 12% cetrimide solution	ACD	+	Chest	[31]
	Gypsona® (Plaster of Paris) containing 0.5% cetrimide	ACD	+	Lower arm, forearm, hand	[32]
Cetylpyridinium Chloride (CPC)	Cetylpyridinium chloride 0.1%	ACD	+	N/A	[33]
	Protexis™ PI polyisoprene sterile surgical gloves with CPC inner coating	ACD	+	Hand	[34]
Benzethonium Chloride (BEC)	Topical Disinfectant MakironS® containing 0.1% aq. BEC	ACD	+	Sole, hand, lower legs, finger, head	[35]

Abbreviations: ACD, Allergic contact dermatitis; ICD, Irritant contact dermatitis; PCD, Pigmented cosmetic dermatitis.

Cetrimonium Bromide and Cetrimonium Chloride

Cetrimonium bromide (CTAB) is an effective bactericidal agent[50] with various purposes in cosmetic and personal care products. It is broadly utilized in formulations as an emulsifier, anti-static agent, and surfactant.[27,51,52] CTAB's ability to penetrate and neutralize electrical charge on the hair surface has made it a favorable ingredient in hair care products, especially in conditioners.[53] Experimental studies using human cell types have reported CTAB's ability to cause keratinocyte proliferation, sensitization and irritation.[54–56] Although relatively rare, cetrimonium bromide sensitivity upon skin contact has been reported to cause hyperpigmentation, eczema and skin swelling.[27,29,57]

Cetrimonium chloride (CTAC) is an ingredient found in over 300 products listed on the Environmental Working Group (EWG) and CPID databases.[58] It is a constituent of a variety of household, pet, auto, and personal care products.

In Europe, it can be found in haircare and cosmetic items at concentrations between 0.5 and 2.5% due to its potential irritancy.[59] There has been one case reported associating CTAC with contact dermatitis. The patient presented with pruritic dermatitis and had a strong positive patch tests to both benzalkonium chloride and cetrimonium chloride.[13]

Didecyldimethylammonium Chloride and Cetrimide

Didecyldimethylammonium chloride (DDAC) is a biocidal agent used in industrial and commercial products[60,61] and is listed as an ingredient in 142 brands on CPID.[58] There is a paucity of data evaluating DDAC toxicity; however, few studies have revealed potential irritancy and sensitivity associated with DDAC exposure. Following topical application on BALB/c mice, it was observed that DDAC significantly increased the activation of lymphocytes (T-cells, CD8 T-cells, B-cells, CD4 and dendritic cells).[62] Another study confirmed a mixed-type hypersensitivity response upon DDAC exposure.[61] Several case reports have highlighted DDAC-containing products as a source of contact dermatitis.[23–26,63] Mowitz & Ponten reported a case of a patient who developed oozing foot dermatitis after using a shoe refresher spray (containing 0.08% aq. DDAC).[26] Patch testing later confirmed ACD induced by DDAC exposure, and her symptoms healed upon discontinuation of the spray.

Cetrimide is an amalgam of tetradecyltrimethylammonium, dodecyltrimethylammonium, and hexadecyltrimethy lammonium.[64] Its disruption of cell membranes makes it highly cytotoxic and therefore a common ingredient in cosmetic products as an antimicrobial agent.[28,64] Though considered rare, several cases have reported ACD associated with the use of cetrimide-containing antiseptics and cosmetic products.[28–30,65–67] Documented clinical presentations include skin swelling, burning, vesicular rashes, necrosis and photosensitivity.[28–31,68,69]

Quaternium-15, Cetylpyridinium Chloride, Benzethonium Chloride

There is limited research on healthcare-related reactions, such as contact dermatitis, associated with quaternium-15, cetylpyridinium chloride, and benzethonium chloride (BEC). Quaternium-15 is utilized in a wide variety of products as both a preservative and as an antistatic agent. Due to concerns about its release of formaldehyde, the Cosmetic Ingredient Review Expert Panel confirmed that it should only be used in concentrations below 0.2%.[70] An isolated case report described evidence of hand dermatitis with a positive patch test to both quaternium-15 and formaldehyde in a nurse that used a quaternium-15-containing lotion.[71]

Cetylpyridinium chloride (CPC) is used for its high antimicrobial activity[72,73] commonly utilized in oral hygiene products. CPC is also used as a constituent in rubber gloves, antiseptic products, mouth rinses and throat sprays.[33,72,74] Several case studies have reported sensitivity after CPC use resulting in either allergic contact dermatitis or irritant contact dermatitis.[33,75,76] Some manifestations of CPC induced contact dermatitis include swelling, pruritic rashes and burning flares.

Benzethonium chloride (BEC) is a synthetic quaternary amine. Allergic sensitization and irritation have been documented in a small number of patients who had known exposure to BEC,[35] but an evident association between contact dermatitis and BEC has not been well established. Common presentations of suspected contact dermatitis in BEC positive patch test patients include skin ulceration, well-defined erythema and vesicular rashes.[35] Due to its limited irritancy data, products containing less than 0.5% BEC may be considered safer than products comprised higher BEC concentrations.[48,77]

Cross Reactivity Between QACs

Patch test reactions can reflect sensitivities between specific allergens. Cross reactors result from an immune response to compounds with similar chemical structures that might not otherwise be present.[78] Therefore, due to their structural similarity, QACs may exhibit cross-reactivity between one another.[49] According to the Camp database[79] and case reports,[13,21,48,49] benzalkonium chloride (BAK) cross reacts with 20 chemicals which include benzethonium chloride (BEC), cetrimide, cetrimonium bromide, cetrimonium chloride, and cetylpyridinium chloride, quaternium-15. A case report by Staniforth[32] documented a patient who developed swollen hands and blistering skin upon use of a BAK containing plaster cast. Upon further evaluation, investigators found that the patient was also sensitive to a cream containing cetrimide. The patient's patch tests were positive to both cetrimide and BAK, suggesting cross reactivity. Another patient, who had known exposure to BAK but no history of exposure to BEC, had positive patch tests to both compounds, suggesting possible cross reactivity.[48] An additional study described a patient with positive patch reactions

and potential cross reactivity to both cetrimide and cetrimonium bromide after use of a tape containing cetrimide.[29] Overall, the existence and patterns of cross-reactivity between QACs are not fully delineated as evidence is limited.

QACs Impact in Healthcare Settings During COVID-19

The recent global pandemic due to SARS-CoV-2 and subsequent COVID-19 infection has resulted in increased QAC awareness. Studies evaluating QACs' action against viral pathogens determined that QACs were effective disinfectants against SARS-CoV-2.[80–82]

To prevent virus transmission, the US Environmental Protection Agency (EPA) released List N, a catalogue of disinfectants effective against Sars-COV-2.[1] Notably, QACs were the most widely represented active ingredients in all List N, found in 44% of the 538 products. In regard to skin testing, specifically, the compounds: benzalkonium chloride, didecyldimethylammonium chloride, cetrimonium bromide, cetrimide, cetylpyridinium chloride, and benzethonium chloride have all elicited a positive patch test causing photosensitive contact dermatitis, allergic contact dermatitis, and irritant contact dermatitis (see Table 2). Out of such compounds, a disinfectant containing 10% of didecyldimethylammonium chloride diluted 1:5 and 1:20 was the only instance of a negative patch test. Skin findings included ulcerations, well-defined erythema and vesicular rashes to compounds inducing a positive patch test.[35]

Due to the presence of QACs in disinfectants and rubber gloves (latex and latex free), increased sanitary measures and personal protection equipment utilization during the pandemic has been thought to lead to increased irritation among healthcare workers. Currently, many surfactants, sterilization agents, antiseptics and preservatives used in household and healthcare environments contain QACs (see Table 3).[2,4,83] Routine surface cleaning and handwashing make healthcare workers highly susceptible to QAC's potential allergic and irritant dermal effects compared to non-healthcare workers.[39,84] Several cases of

Table 3 Selected Listing of Common Household Products Containing QACs

Compound	Household Product	% Concentration
Benzalkonium Chloride	Clorox® Disinfecting Wipes, Fresh Scent	0.145
	Lysol® Brand Disinfectant All Purpose Cleaner, Lemon Scent	0.08
	Purell® Hand Sanitizing Wipes, Clean Refreshing Scent	0.1–1
	Dial Complete® Liquid Antibacterial Hand Soap White Tea	0.13
	Dial Complete® 2 in 1 Moisturizing & Antibacterial Beauty Bar, Manuka Honey	0.115
	Up & Up® Citrus Scent Hand Wipes	0.115
Didecyldimethylammonium Chloride	Pursue™ Disinfectant Cleaner Concentrate	0.684
	Claire® Surface Sanitizing Wipes	0.01-0.1
	Glade® Fabric and Air Refresher, Clean Linen	0.01-0.1
	Lysol® Healthy Touch, No-Touch Liquid Hand Soap, Creamy Vanilla Bliss	0.01-0.1
	Swiffer® WetJet™ Antibacterial Cleaner	0.03
Cetrimonium Bromide	Quit Nits® Complete Lice Kit	<10
	Rejuvenol® Keratin After Treatment Conditioner	<0.1
Cetrimonium Chloride	Lysol® Healthy Touch, No-Touch Liquid Hand Soap, Vanilla Sugar & Spice	1.0–2.5
	Suavitel® Complete Fabric Conditioner Dryer Sheets, Field Flowers	0.1–1.0
Cetylpyridinium Chloride	Cepacol® Antibacterial Mouthwash Mint-(Canadian Market)	0–0.1
	Crest® Pro-Health Rinse, Refreshing Clean Mint-Old Product	0.07
Benzethonium Chloride	Dial® White Tea & Vitamin E Antibacterial Hand Soap with Moisturizer	0.1

contact dermatitis in response to the use of QAC-containing products have been reported in healthcare workers.[5,10,84–86] Many of these cases also demonstrated that avoidance of those products resulted in overall improvement of symptoms.[5,85]

Conclusion

In summary, quaternary ammonium compounds may cause irritancy and contact dermatitis, and should be used cautiously in patients with compromised skin barriers. Reported reactions include ulcerative skin lesions, hyperpigmentation, and erythema. Given their widespread utilization, additional research is needed to better classify their dermal effects and identify other cross-reactors. Healthcare workers' have significantly increased exposure to QACs, but, considering the frequency and importance of hygiene and sterilization in a pandemic setting, it will be difficult to decrease utilization.

Disclosure

The authors report no conflicts of interest in this work.

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