OBSERVATION

Antimicrobial Allergy From Polyvinyl Chloride Gloves

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Background: Contact allergy to plastic gloves is rare. Benzisothiazolinone is a biocide that is mainly used in industrial settings. We first suspected delayed-type contact allergy to benzisothiazolinone from polyvinyl chloride (PVC) gloves in 2004. We looked through our medical records from 1991 to 2005 to find similar cases.

Observations: We found a total of 8 patients who are allergic to benzisothiazolinone and who had had exacerbations of their hand dermatitis while using PVC gloves. Patch testing revealed that 3 of them had weak allergic or doubtful reactions to the glove materials. Six of them had used Evercare Soft, Medi-Point, or Derma Grip PVC gloves, which in chemical analysis were shown to contain 9 to 32 ppm of benzisothiazolinone. Seven of the patients worked in dentistry or health care and 1 in farming. All of them had had hand dermatitis for many years.

Conclusions: To our knowledge, there have been no previous reports of contact allergy to antimicrobial agents in plastic gloves. Benzisothiazolinone is widely used as a biocide in the manufacture of disposable PVC gloves. Small amounts of benzisothiazolinone in the gloves may sensitize those who already have hand dermatitis. We recommend that all patients with hand dermatitis while using PVC gloves should be patch tested with benzisothiazolinone.

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ALLERGIC CONTACT DERMATITIS from plastic gloves is rare compared with that from rubber gloves. Plastic gloves may be made from several types of polymers but most commonly are made from polyvinyl chloride (PVC). In past examinations of contact allergy to PVC gloves, the specific causative allergens have often remained unknown. Several cases of bisphenol A allergy[1,2] and single cases caused by an organic pigment[3] and adipic polyester[4] have been reported, but to our knowledge, there are no previous case reports of allergic contact dermatitis from any antimicrobial substance in PVC gloves. Gloves made of PVC also contain phthalates that are potential allergens.

Benzisothiazolinone (1,2-benzisothiazolin-3-one [BIT]; Chemical Abstracts Service No. 2634-33-5) is an antimicrobial agent that is used in industry as a preservative in water-based solutions such as paints, lacquers, cutting fluids, printing inks, cleaning agents, polishes, fabric softeners, pigments, surfactants, binders, plasticizers, construction materials, curing agents, impregnating agents, antiadhesive agents, pesticides, adhesives, and glues.[5,6] Occupational allergic contact dermatitis from handling the pure chemical or preservatives with a high concentration of BIT has been reported in industrial laboratory work[7-10] and in the manufacture of paints,[9,11,12] varnishes,[9,13] plastic emulsions,[7] paper,[14] rubber,[15] dyes,[16] air fresheners,[17] water softeners,[18] and carpets.[19] Other sources of sensitization include the use of metalworking fluids,[20-22] paints,[23,24] putties, wallpaper paste,[24,25] shoe glue,[26] a releasing oil in the pottery industry,[27] and gum arabic in lithographic printing.[28] Allergic patch test reactions to BIT have also been found in 6 woodwork teachers,[29] a plumber, and a silkscreen printer.[25] Most of the reports consist of only a few cases.

We first suspected that 1 of our patients (patient 1 in the **Table**) had been sensitized to BIT by using PVC gloves in August 2004. Then, 3 other patients (patients 2-4) were seen for BIT contact allergy and hand dermatitis while using PVC gloves. We analyzed the gloves for BIT and looked through our medical records from January 1991 to September 2005 to find similar cases.

METHODS

The Section of Dermatology at the Finnish Institute of Occupational Health (FIOH) is a special clinic for occupational skin diseases. We have just under 200 new patients each year, and they come from all parts of Finland.

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Table. Patients Allergic to BIT, Their Occupation, Patch Test Reactions, Exposure, and Diagnoses

Patient No.	Occupation	Patch Test Reactions			Exposure to BIT: Patch Test Reaction to the Glove Material*	Diagnosis
		BIT	CMI/MI	OIT		
Recent Cases of Patients Who Had Used PVC Gloves						
1	Assistant nurse	++	–	–	Evercare Soft PVC glove: +	OICD from detergents and disinfectants
2	Dentist	++	–	–	Medi-Point PVC glove: ?+ Derma Grip PVC glove: ?+ Top Dent PVC glove: –	Recurrent vesicular palmar dermatitis ACD from an formaldehyde-liberating antimicrobial in a liquid soap used at home
3	Dentist	+	+	–	Medi-Point PVC glove: –	Atopic dermatitis since childhood and atopic irritant hand dermatitis
4	Dental nurse	+	–	–	Evercare Soft PVC glove: ?+ Derma Grip PVC glove: + Derma Grip nitrile glove: –	OICD from wet work
Previous Cases From the Test Files of Patients Who Had Used PVC Gloves at Work						
5	Dentist	+	–	–	Derma Grip PVC glove: –	Hand dermatitis and contact urticaria from NRL gloves
6	Dental nurse	++	–	–	Derma Grip PVC glove: –	OACD from thiuram rubber chemicals OICD from wet work and occlusive gloves
7	Dentist	+++	–	–	NF (PVC gloves: IR)	OICD from wet work and occlusive gloves
8	Farming worker	+	–	–	NF (PVC gloves: –)	OICD from wet work
9	Dental nurse	++	–	–	NF (PVC gloves: NT)	Dermographism (no dermatitis)
Previous Cases of Patients Who Had Not Used PVC Gloves at Work						
10	Machine assembler	++	++	+	NF (rubber gloves)	OICD from oils and petroleum
11	Carpenter	+	?+	++	NF (leather gloves)	OICD from mineral wool and concrete dust
12	Electrician	+++	–	–	Had previously used water-based paints	OACD from epoxy and epoxy additives
13	Laboratory assistant	++	–	–	NF (rubber gloves)	OACD from methylnitroso-p-toluensulfonamide laboratory chemical
14	Process worker in the manufacture of foam inhibitors and other chemicals	++	–	–	BIT (15%-30%) in a biocide (Nipacide BIT 20)†	OACD from BIT in a biocide
15	Farmer	+	+++	–	NF	Status post-OACD from thiuram rubber chemicals OICD from dirty work
16	Laboratory worker in a paint factory	++	–	–	BIT (17%-23%) in a biocide (Proxel GLX)†	OACD from BIT in a biocide
17	Machinist	+++	–	–	0.1% BIT in an MWF‡	OACD from BIT in an MWF
18	Paint production worker	+	–	–	BIT (5%-15%) in a biocide (Metatin K 518)†	OACD from BIT in a biocide
19	Machine repairer	+++	+++	–	NF, but had used various MWFs (rubber gloves, leather/textile gloves)	OACD from a coco-fatty acid derivative in a liquid soap and diethanolamine in MWFs
20	Newsman	+	–	–	NF (textile grip gloves)	OICD from dirty work and mechanical irritation

Abbreviations: ACD, allergic contact dermatitis; BIT, benzisothiazolinone (1,2-benzisothiazolin-3-one); CMI/MI, 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one; IR, irritant reaction; MWF, metal-working fluid; NF, not found; NRL, natural rubber latex; NT, not tested; OACD, occupational allergic contact dermatitis; OICD, occupational irritant contact dermatitis; OIT, 2-*N*-octyl-4-isothiazolin-3-one; PVC, polyvinyl chloride; +, weak positive; ++, strong positive; +++, extreme positive; ?+, doubtful reaction; –, negative.

*Manufacturer information: Derma Grip (Oriola Oy, Espoo, Finland), Evercare Soft (Selefatrade AB, Spånga, Sweden), Famon (Famon Oy, Helsinki, Finland), Medi-Point (Insinööritoimisto Medi-Point Oy, Helsinki), Metatin K 518 (Acima Chemical Industries Ltd, Buchs, Switzerland), Nipacide (Clariant UK Ltd, Leeds, England), Roxel GLX (Avecia Inc, Wilmington, Del), Top Dent (Oriola Oy).

†Information in the material safety data sheet, label, or product description.

‡Chemical analysis was performed at the Finnish Institute of Occupational Health, Turku.

We have included BIT in our oil and lubricant series since 1991, and in 1992 it was also added to our antimicrobial series. It was first tested at a 0.05% concentration in alcohol and since 1994 at the same concentration in petrolatum (Chemotechnique Diagnostics, Malmö, Sweden). Also, BIT 0.1% in petrolatum (Trolab; Hermal, Reinbeck, Germany) was included in a dental patch series that was used in a study of dental nurses in 1999.[30]

We analyzed our skin test files for reactions to BIT. We checked the clinical records of the patients with an allergic re-

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action (+, weak positive; ++, strong positive; and +++, extreme positive) for other skin test reactions, symptoms, exposure, and diagnosis. The skin tests of the 3 most recent cases of allergic reaction to BIT (patients 2-4) were not yet in the skin test files, but we nevertheless analyzed their medical records in the same way. (These patients were not yet in the file when analysis took place because the test results of a patient are not put into the file until the examination is complete and the report sent to the insurance company.)

Glove material was tested in 1 test chamber (Finn Chamber; Epitest Oy, Tuusula, Finland) with a drop of acetone and in another with a drop of water. We tested the acetone extract of the glove material made in an ultrasonic cleaning bath in 3 cases (patients 1, 3, and 4), and in 1 case (patient 1) we also tested the water and ethanol extracts.[31]

The concentrations of BIT in the suspected gloves (patients 1, 2, and 4) were analyzed by high-performance liquid chromatography with a UV detector at 230 nm. Mass spectrometry confirmed the detection. Accurately weighed slices taken from the palm or the back of a glove (100 and 200 mg, respectively) were extracted with 5 mL of a mixture of water and methanol (3:1) overnight at room temperature. The liquid chromatography column was a reversed-phase C18 column (Symmetry Shield; Waters Corp, Milford, Mass) (3.5-µm particles, 150 × 2 mm). The mobile phase was methanol and water (32:68) with 2mM of ammonium acetate, and the flow rate was 0.2 mL/min^{-1}. The relative standard deviation of the repeatability of the analysis was about 25% for concentration levels corresponding to 20 to 200 ppm (wt/wt). The detection limit was about 2 ppm.

RESULTS

PATCH TEST REACTIONS TO BIT IN 2264 PATIENTS

From January 1991 to September 2005, BIT was tested on a total of 2264 patients, and 17 (0.75%) of them had an allergic reaction to it. We tested 163 patients with 0.05% BIT in alcohol (with 2 allergic reactions), 123 with 0.1% BIT in petrolatum (with no allergic reactions), 1963 with 0.05% BIT in petrolatum (with 15 allergic reactions), and 15 with both 0.1% and 0.05% BIT in petrolatum (with no allergic reactions). The reaction index[32] for the current test substance, 0.05% (petrolatum), in 1978 patients was –0.34.

PATIENTS WITH ALLERGIC REACTION TO BIT

From 1991 to 2005 we had a total of 20 patients who had an allergic patch test reaction to BIT. Their patch test reactions to BIT and PVC gloves, occupations, exposure to BIT, and diagnoses are presented in the Table. Four of these 20 patients (patients 3, 10, 15, and 19) reacted to the mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one (CMI/MI) and 2 (patients 10 and 11) to 2-*N*-octyl-4-isothiazolin-3-one (OIT).

BIT CONCENTRATIONS IN PVC GLOVES (PATIENTS 1, 2, AND 4)

According to the analysis, the Evercare Soft (Selefatrade AB, Spånga, Sweden) PVC glove samples of patients 1 and 4 contained 20 and 22 ppm of BIT, respectively. The Derma Grip (Oriola Oy, Espoo, Finland) PVC glove samples of patients 2 and 4 contained 9 and 22 ppm of BIT, respectively. The Medi-Point (Insinööritoimisto Medi-Point Oy, Helsinki) PVC glove of patient 2 contained 31 ppm of BIT. (The Medi-Point glove of patient 3 was not analyzed because it was the same brand.) We also analyzed other gloves the patients had used, the Top Dent (Oriola Oy Hammashoito, Espoo) PVC glove of patient 2 and the Derma Grip nitrile glove of patient 4, but they did not contain BIT (concentrations were below the detection limit of 2 ppm). Patch tests with the Evercare Soft glove moistened with water and acetone were negative for allergic reaction in 5 control patients.

COMMENT

On patch testing, BIT is an irritant, and the test concentration has been gradually lowered since the 1980s from 1% to the present concentration of 0.05%.[21,33] Although the possibility of false-positive reactions to BIT cannot be excluded in the present series of patients, it is also possible that some patients with irritant or doubtful reactions might truly have been sensitized to BIT. Among these patients was a dentist with a doubtful reaction to BIT who had used the BIT-containing Derma Grip gloves.

Despite the similarity in chemical structure, BIT is not considered to cross react with CMI/MI or OIT.[33-35] Concomitant reactions to these isothiazolinones were not common among our patients, which supports the idea of separate sensitization.

Occupational allergic contact dermatitis from BIT has been reported in a variety of industries using biocides with high BIT concentrations (>10%), and the relevance of the allergic reaction is usually clear in these cases. At the FIOH we have had 3 cases of occupational allergic contact dermatitis belonging to this category (patients 14, 16, and 18). In addition to these 3 cases, we have come across 1 case (patient 17) of occupational allergic contact dermatitis caused by BIT (1000 ppm) in a metalworking fluid; BIT is used in paints and putties at concentrations of 50 to 250 ppm.[23] Our series included 1 patient (patient 12) who had possibly been sensitized to BIT when using water-based paints and another (patient 19) who had been handling metal-working fluids.

Among our patients there were 9 patients who were allergic to BIT and who had used PVC gloves at work daily. One of them (patient 9) had apparently not had dermatitis but rather dermographism, which explains why her symptoms arose from the use of various different gloves. Thus, we have had a total of 8 patients (patients 1-8) with BIT allergy and hand dermatitis in connection with PVC glove use. Six of them had used gloves that in the chemical analysis were shown to contain small amounts of BIT.

The question is whether the low BIT concentrations of 9 to 32 ppm in the gloves can sensitize or elicit contact allergy. Chemically, BIT is related to the extremely strong allergen CMI/MI, but it has been a somewhat weaker sensitizer in the local lymph node assay[33,36] and in the human repeated insult patch test.[33] Although the BIT concentrations in the PVC gloves were lower than those in the paints and putties, they were at the same level

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or a little higher than ordinary concentrations of CMI/MI in cosmetic products (3-15 ppm).[37]

In the present series of patients, the PVC glove material (or an ultrasonic bath extract from it) caused allergic reactions on patch testing in only 2 patients. One patient had doubtful reactions to the glove, and in 3 patients the BIT-containing glove was negative for allergic reaction in the patch test. In the 2 positive cases, the connection between BIT allergy and the PVC gloves is probable. However, the other patients' negative patch test results do not exclude sensitization from the glove. Similarly, CMI/MI–containing cosmetic products, although positive on repeated open application test, are often negative for reaction on patch testing.[37] Also, BIT does not belong to the frequent sensitizers in dentistry[38] or health care.[39] We searched for other possible sources of BIT sensitization, but of all the products our patients had used, we found BIT only in the PVC gloves. In Finland, the use of BIT is forbidden as an antimicrobial agent in cosmetics,[40] but in daily life consumers may have skin contact with BIT in fabric softeners, cleaning agents, and polishes.[5]

A common feature of patients 1 to 8 was a long history of hand dermatitis (of at least 5 years' duration), and they had also been diagnosed with other types of hand dermatitis besides BIT contact allergy. Thus, sensitization to BIT in the gloves was probably not the primary event. The occlusive effect of the PVC gloves on their eczematous skin might have enhanced the percutaneous penetration of BIT so that they had become sensitized despite the low allergen concentration.

Most of our patients were able to continue their work after they changed to a different type of glove, usually to nitrile gloves. Only 1 patient (patient 6), a dental nurse with primary rubber glove allergy, had to change her job because the dermatitis reappeared with use of Derma Grip PVC gloves. At that time we were not aware that these PVC gloves contained BIT. This allergy may have quite serious consequences if it is not recognized.

Antimicrobial additive systems are increasingly used in plastic polymers, mainly in PVC plastics,[41] and particularly in the medical and food industries.[42] Products that are already on the market include domestic applications such as rubbish bins, kitchen utensils, tubing, air filters, containers, and mattresses. Medical antimicrobial products such as gloves, catheters, wound dressings, and bedding are also available.[42] Antimicrobial agents are used in plastics to reduce microbe populations both within the material and at the surface.[42] The organic antimicrobials used in plastics include 10′,10′-oxybisphenoxyarsine, OIT, dichloro-2-*N*-octyl-4-isothiazolin-3-one, tributyl tin, 2,4,4′-tricloro-2′-hydroxy diphenyl ether, zinc pyrithione, zinc omadine, *N*-butyl-1,2-benzisothiazolin-3-one, 3-iodo-2-propynyl butyl carbamate, and *N*-(tricholoromethylthio) phthalamide.[41,43] The plasticizer can act as the carrier for the biocide (eg, 10′,10′-oxybisphenoxyarsine or OIT).[42]

The number of patients treated for allergic reaction to BIT in PVC gloves at our small clinic is alarming, although our patient material is strongly selected. The true extent of the problem remains to be settled in other clinics with larger patient populations. It is interesting that all 8 of these patients (patients 1-8) were investigated in 2001 or later, although we have tested BIT in almost every patient since 1992. Inquiries to several representatives of PVC glove sales representatives in Finland have uniformly revealed that BIT is a component in a biocide compound that has been widely used for at least 15 years as a slimicide in the manufacturing process of disposable PVC gloves. The market for these products has considerably increased over recent years.

At the FIOH, BIT is included in the antimicrobial series, which is tested on most of our patients, irrespective of their occupation. In the commercial patch test series, BIT is included in Chemotechnique Diagnostics' "Oils and Cooling Fluids" series and in Trolab's "Cutting Oils" and "Industrial Biocides" series. It is possible that BIT is not commonly tested on dental and health care personnel. We recommend that all patients with hand dermatitis while using PVC gloves should be patch tested with BIT.

In summary, to our knowledge, there are no previous reports of antimicrobial skin contact allergy deriving from PVC gloves. We described herein 8 patients with BIT allergy and hand dermatitis in connection with PVC glove use. In findings from chemical analysis, 3 brands of disposable PVC gloves contained small amounts of BIT, and 6 of the patients had used at least 1 of these brands. All of the patients had a long history of hand dermatitis. Small amounts of BIT in the glove seem to be able to sensitize persons who already have hand dermatitis. We recommend that BIT should be tested on all patients with hand dermatitis who use PVC gloves.

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