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Concomitant contact-allergic reactions to iodopropynyl butylcarbamate and iodine

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Abstract

Background: Iodopropynyl butylcarbamate (IPBC) is a broad-spectrum preservative for use in several product types, including cosmetics in which its concentrations have been limited by EU legislation because of concerns related to its iodine content and release, and risk of subsequent overdose.

Objectives: To report about concomitant patch-test reactions observed with iodine and IPBC in patients sensitized to iodine-containing antiseptics.

Patients: Between 2012 and 2018, 7 patients, six from Belgium and one from France, two suffering from acute dermatitis during surgical interventions, four from dermatitis due to wound treatment, and one from occupational dermatitis, were shown to be sensitized to iodine and/or povidone-iodine (PVP-I) which were considered relevant for their dermatitis. All patients were coincidentally also patch-tested with IPBC.

Results: All patients presented positive patch-test reactions to several other allergens, including IPBC. No relevance could be detected for IPBC.

Conclusions: We suspect that, notwithstanding the absence of firm evidence of IPBC being dehalogenated to produce free iodine in animals or in humans, the patch-test reactions to IPBC in iodine-allergic subjects were possibly caused by free iodine released from this

preservative agent, thus underlining the EU restrictions regarding the use of this preservative in cosmetics.

1. Introduction

Iodopropynyl butylcarbamate (IPBC) (CAS no. 55406-53-6) is a broad-spectrum preservative with bactericide, fungicide, and acaricide properties, originally used in the 1970s as a paint and wood preservative, and later in household detergents and a variety of industrial products. Since 1996 it has been also approved for use in cosmetics, in which use concentrations have been limited by EU legislation because of concerns related to its iodine content and release, and risk of subsequent iodine overdose (1). The maximum authorized concentrations are 0.02% and 0.01% in rinse-off and leave-on cosmetic products, respectively, with an even lower limit of 0.0075% in deodorants and antiperspirants. Furthermore, IPBC has been approved by the FDA as an antifungal in items used in the packaging, transporting, and/or holding of food (2).

IPBC is a small, water-soluble molecule that readily penetrates the skin, displays marginal irritant properties and is considered to have a low sensitizing potential. However, several case reports of allergic contact dermatitis have been published, mainly related to use in industrial and cosmetic products, and even from an alcoholic rub for hospital use (3). In recent years, an increasing prevalence of contact-allergic reactions has been observed, mainly in the US, and which has been ascribed to its use in cosmetics. Indeed, the North American Contact Dermatitis Group (NACDG) reported increasing sensitization rates to IPBC, from 0.3-0.5% between 1998 and 2006 to 4.2% in 2011–2012 (4). Likewise, the sensitization rates to IPBC have increased in Europe, although to a lesser extent, from 0.2-0.3% in the 1990s to 1.2% in 2009–2012 (5). This difference in sensitization rates between Europe and the US can be

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attributed to differences in cosmetic regulations, but also to the use of different patch-test concentrations (6): While the recommended test concentration of IPBC in Europe is 0.2% pet. since 2005, it is 0.5% pet. in the US since 2007, and the higher positivity rates potentially reflect partly also false-positive reactions. According to a Danish study, the frequency of 0.55% positive reactions in routinely patch-tested subjects during the period 2000-2011 was mainly related to occupational exposure, and these authors observed in their patients an over-representation of concomitant contact allergy to thiuram components, known to have a chemical structure similar to IPBC. This association could not be explained by co-exposure at, for example, the workplace (7). We hereby describe and discuss 7 cases of concomitant patch-test reactions to IPBC and iodine, which, as far as we know, has not been previously reported.

2. Case reports

2.1 Case 1

A 40-year-old woman consulted the UZA department twice, in 2009 and 2013, respectively, because of a recurrent episode of acute dermatitis, first located on one of her legs following a surgical intervention for varicose veins, and subsequently on the gluteal area and thighs following a laparoscopic procedure. The sharply demarcated, inflammatory, and oedematous plaques are shown in **Figure 1**. The patient's medical history was otherwise unremarkable except for intolerance to perfumed products. In 2009, she had presented with positive patch-test reactions to methyldibromo glutaronitrile and 2-bromo-2-nitropropane-1,3-diol (bronopol); in 2013, patch tests were performed with a baseline, cosmetic and pharmaceutical

series (all from Chemotechnique Diagnostics, Vellinge, Sweden), as well as all topical products used. Patch tests were applied on the upper back using Allergeaze patch test chambers (Smartpractice, Calgary, Canada), fixed with Fixomull stretch (BSN Medical, Hamburg, Germany), and read after day (D) 2 and D4. The tests revealed a doubtful reaction to linalool hydroperoxides, but clear positive reactions to povidone-iodine (PVP-I) 5% aq., iodine (0.25% alc.), and chloramine 0.5% aq. on D4 (**Table 1**) (**Figure 2**). These antiseptics had been most likely responsible for the two postoperative episodes of allergic contact dermatitis, probably initially preceded by an irritant skin reaction as evidenced by the sharp demarcation, oedema, and, as recalled by the patient, besides itching, also partly painful lesions. However, also IPBC 0.2% pet., as present in the cosmetic series, showed a positive reaction on D4 (**Figure 3**), for which no relevance could be found. The previous positive patch-test results to the preservative agents could not be reproduced, only a doubtful positive reaction was obtained to cinnamyl alcohol (fragrance mix I being negative), possibly relevant for the patient's adverse skin reactions to fragranced products (**Table 1**).

2.2 Case 2

A 69-year-old female consulted the UZA department twice, first in 2011, because of a skin reaction located on the breasts following surgery and radiotherapy, and again in 2014, because of persistent eyelid dermatitis. Patch tests were performed in 2011, as in Case 1, showing on D4 positive reactions (**Table 1**) to iodine (0.25% alc.), considered to be the cause of the postoperative cutaneous skin reaction, but also to *Myroxylon pereirae*, formaldehyde and releasers, i.e. quaternium-15, imidazolidinyl and diazolidinyl urea, and

toluenesulfonamide formaldehyde resin, as well as to cetylstearyl alcohol, cocamidopropyl betaine, lauryl and decyl glucoside, and fusidic acid. She also reacted positively to several pharmaceutical products, including Isobetadine dermicum 10% solution (Meda Pharma, Brussels, Belgium) tested semi-open “as is”, and to several cosmetics she was applying at that time and which contained one or more of the allergens identified. In 2014, patch tests were again performed, in a similar way, with the same series and products used at that time, with all previous positive reactions being confirmed, as well as additional positive reactions to PVP-I and IPBC. No relevance could be established for IPBC (**Table 1**). Furthermore, she also reacted to a preparation from the pharmacist which contained cetostearyl alcohol.

2.3 Case 3

A 57-year-old female patient consulted UZ Leuven in 2012 because of a generalized itching dermatitis that had occurred after long-lasting treatment of a posttraumatic ulcer on the left lower leg, for which she was using several topical products, among which Furacine ointment (Sanico, Turnhout, Belgium) and Isobetadine dermicum 10% solution. Furthermore, she recalled having had an allergic reaction to leather shoes in the past. Patch tests were performed with the European baseline series, a pharmaceutical series, a shoe series (Chemotechnique Diagnostics), and all topical products used by the patient, using IQ Ultra[®] patch test chambers (Chemotechnique Diagnostics), additionally fixed with Mefix (Mölnlycke Health Care, Göteborg, Sweden). The patch-test readings were performed on D2 and D4. Positive reactions (**Table 1**) were observed to Isobetadine dermicum (+ on D2, ++ on D4), iodine (mixed allergic and irritant reaction), and polyethylene glycol 400 (100%), the

latter a component of Furacine ointment that most likely initiated the dermatitis, followed by sensitization to Isobetadine dermicum. IPBC also reacted positively for which no relevance could be detected. The positive reactions to chromium and cobalt, and perhaps also to *Myroxylon pereirae*, the latter in view of a potential relationship with phenol-formaldehyde resins in glues, could account for her previous intolerance to leather shoes.

2.4 Case 4

A 52-year-old, non-atopic truck driver consulted the UZA department in 2014 because of a dermatitis on the hands, and the lateral sides of the chest and back. Patch tests, performed as in Cases 1 and 2, and supplemented with a rubber series, showed positive reactions (**Table 1**) on D4 to thiuram derivatives and carbamates that were considered relevant for the rubber glove dermatitis on his hands, and to the preservatives methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and methyldibromo glutaronitrile, for which no relevance could be determined since the patient had not brought in his personal products. He also reacted to chloramine, iodine, and PVP-I, the latter being present in Isobetadine dermicum 10% solution, which he had applied in the past to treat a superficial skin tear and which, at that time, had caused an eczematous skin reaction. A weak positive reaction was also observed to IPBC for which no relevance could be found.

2.5 Case 5

A 64-year-old female consulted the Hospices Civils de Lyon in 2018 because of a bullous erysipelas as a complication of a burn wound caused by a hot water bottle applied onto her

right ankle. She had applied several topical pharmaceutical products, including an antibiotic ointment, a greasy wound dressing, and ultimately Betadine dermique (Napp Pharmaceuticals, Cambridge, UK), which had induced dermatitis. Patch tests, performed in a similar way as in the above cases, with the European baseline series and ingredients of the products used, showed positive reactions (**Table 1**) on D3 to nickel (related to previous intolerance of jewelry) and to Betadine dermique (“as is”; +++), which was considered relevant (**Figure 4**). She also reacted to IPBC, *Myroxylon pereirae* and fragrance mix I, for which no relevance could be determined.

2.6 Case 6

A 25-year-old midwife, who suffered from eyelid and hand dermatitis, was referred to UZ Leuven in 2017 for patch testing in the context of a possible occupational disease. During her work in the hospital she was exposed to Alcolgel and Dax alcohol-free gel (both Dialex Biomedica, Bilzen, Belgium), Isobetadine dermicum 10% solution (Meda Pharma), Sterilium (Hartmann, Heidenheim, Germany), Aquasonic ultrasone gel (Parker Laboratories, Fairfield, Connecticut), Clinell Universal Wipes (Gama Health Care, Watford, UK) and Kimberly Clark Kleenex luxe foam (Kimberly-Clark, Surrey, UK). At home she used several hand creams and topical corticosteroids. She had a known intolerance to jewellery, and a possible intolerance to nitrile gloves. Patch tests performed in 2015 had shown positive reactions to MI and limonene hydroxyperoxides, but not to nickel, which had, however, tested positive a few years earlier. In 2017 patch tests were again performed, as described in Case 3, with the European baseline series, a cosmetic and rubber series, available components of her own

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topical products, and pieces of her gloves and wet wipes. Positive patch tests (**Table 1**) were again observed to: MI and MCI/MI, found in the foam cleanser and a dishwashing detergent, to 2-bromo-2-nitropropane-1,3-diol, a component in a hand soap, and to polyhexamethylene biguanide (PHMB), an antimicrobial agent present in the cleansing wipes used at work and also in an eyelid cleanser. Cyclohexyl thiophthalimide reacted positively and could possibly explain her intolerance to nitrile gloves, and the use of vinyl gloves was advised. Moreover, she also reacted to PVP-I (which she used in the hospital) tested with the Iso-betadine gel preparation and iodine, as well as to IPBC, the latter without any relevance.

2.7 Case 7

A 63-year-old, non-atopic glass worker consulted the UZA department because of a widespread skin eruption which had started as an intermittent dermatitis on the feet, with secondary spreading towards the calves, and, later, to the hands and the scalp. More recently, the skin problems had generalized for which he had to be treated with oral corticosteroids until 10 days before patch testing. Patient's history revealed that, during the past few months, he had regularly applied Daktarin spray (Janssen Pharmaceutica, Beerse, Belgium) and Isobetadine 7,5% soap and 10% dermicum solution (Meda Pharma) because of a relapsing tinea pedis. Once, the presumed fungal infection became complicated with foot dermatitis for which several other topical medications were prescribed, including topical corticosteroids, Flammazine cream (Alliance Pharmaceuticals, Chippenham, UK), as well as two compounded creams. Furthermore, according to his past medical history he had previously presented with dermatitis from leather shoes, a metal buckle belt, and rubber gloves. Patch

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tests were performed, as in Case 1, with the baseline series, as well as a cosmetic, metal, corticoid, (extended) shoe and textile series, and with Flammazine cream. The results in terms of multiple positive patch-test reactions are shown in **Table 1**. Clinical relevance can be explained as follows: palladium chloride, disodium tetrachloropalladate, and copper pentahydrate, all possibly cross-reacting with nickel: metal belt buckle; chromate and cobalt: leather shoes; Disperse Blue 85 and 106: dyes possibly present in (leather) shoes; several biocides, i.e. formaldehyde, MI, benzisothiazolinone (BIT), and methyldibromoglutaronitrile: all potential biocides in leather; MI and decyl glucoside: components of a hair conditioner and shampoo, respectively, explaining his scalp dermatitis; lauryl glucoside and sodium metabisulfite (both in a shower gel) potentially important in eliciting and maintaining generalized dermatitis; propylene glycol: an ingredient of Flammazine cream, and butylene glycol, possibly cross-reacting with the former, but also present in a hair conditioner; miconazole: in Daktarin spray; several fragrances, i.e., limonene and linalool hydroperoxides, and *Myroxylon pereirae*, the latter containing benzoic acid to which he also reacted, and being a preservative ingredient in Daktarin spray; sorbic acid and potassium sorbate: components of the two compounded preparations, having accounted for further worsening of his dermatitis; dithiodimorpholine and diphenylguanidine: rubber gloves; finally, he reacted to PVP-I as well as to iodine, although irritancy was difficult to exclude for the latter. Isobetadine dermicum had been applied to a wound on his back, after which he had developed dermatitis, which disappeared after having stopped it; however, he had continued using the soap from the same brand to treat his foot dermatitis. Interestingly, IPBC again tested positive, without any relevance. Other patch test reactions for which no relevance

could be found included: gold sodium thiosulfate, cocamide DEA, cetrimide, and benzoyl peroxide, except that concomitant reactions between the latter and benzoic acid might occur.

3. Discussion and Conclusion

We here present 7 chance cases of patients sensitized to iodine and/or PVP-I, considered responsible for an acute dermatitis during surgical interventions in two of them, for perilesional dermatitis from the treatment of a wound in four other cases, and for one case of occupational dermatitis. All seven patients presented with positive patch-test reactions to several other allergens tested, including IPBC, the latter without any relevance.

We suspect that, notwithstanding the absence of firm evidence that IPBC can be effectively dehalogenated to produce free iodine in animals or in humans (1), the positive patch tests to IPBC in iodine-allergic subjects were potentially caused by free iodine released from this preservative agent. If so, this observation might underline the EU restrictions regarding the use of this preservative in cosmetics, which were imposed based on concerns of possible systemic absorption of iodine. IPBC use concentrations have consequently been limited, and it cannot be used in oral and lip products, body lotions and creams, nor in products for children under 3 years of age, except in bath products, shower gels and shampoos. This was also the reason why the Scientific Committee on Cosmetic and Non-Food Products (SCCNFP), in 2004, proposed that leave-on cosmetics, containing more than 0.02 % of IPBC should be labelled with 'contains iodine' (8).

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Evidently, positive patch-test results with iodine and PVP-I need to be interpreted carefully, as both molecules may have irritant properties, especially under occlusion. Hence, irritant reactions might be misinterpreted as allergic ones (9), however, mixed irritant and allergic patch-test and clinical lesions may also occur (10). Likewise, IPBC is also a potential irritant. Thus, alternatively, concomitant reactions might still be explained by irritant patch test reactions to all three molecules, with iodine and PVP-I accounting for clinically relevant contact-irritant, but not contact-allergic, skin reactions. However, contrary to iodine and PVP-I, irritant reactions occur less likely with IPBC 0.2 % pet., certainly as compared to the 0.5% preparation (6). In a population of 1733 patients tested to IPBC 0.2% pet. in the KU Leuven department, between 1990 and 2016, only 8 (0.46%) presented with a positive reaction to this preservative agent, which can still be considered an uncommon sensitizer, while no irritant reactions were observed. Moreover, in the cases presented here, except for Case 3 and Case 7 for which contact-irritation to iodine was indeed difficult to exclude, only patch-test reactions that had a clear allergic morphology were considered.

If immunologic cross-reactivity between iodine and IPBC does occur, this might argue for iodine being a contact-allergen, and not just an irritant, since the occurrence of immunologically mediated cross-reactivity is limited to contact-allergy as opposed to contact-irritation. However, there is very little knowledge relating to the breakdown or release of iodine from IPBC and to what extent this occurs in products. In some of our case reports a weaker patch test reaction was noted with IPBC (0.2%) vs iodine (0.25%) which suggest that, if these observations are due to presence of free iodine in IPBC or release of IBPC when in contact with skin, then the breakdown is partial, which warrants further investigation. The occurrence of simultaneous reactions to iodine and IPBC has, as far as we are aware, not been reported yet, and this observation may deserve to be investigated in a larger number of

subjects for confirmation. Finally, as in the aforementioned Danish study (7), we also observed one concomitant reaction to thiurams, known rubber allergens, which in this case (nr 4) was considered relevant for rubber gloves' dermatitis on the patient's hands.

Table 1 : Patch-test reactions in Cases 1-7.

Cases	1	2	3	4	5	6	7
	Patch test readings:						
Allergens:	on day 4:				on day 3:	on day 4:	
Iodopropynyl butylcarbamate (IPBC) 0.2% pet.	+	+	+	+	+	+	+
Iodine 0.25% alc	++	+++	+/irr	++	NT	+	+/irr
Polyvidone-iodine (PVP-I) 5% aq.	+	+	+++*	+++	+++*	+++*	+
Potassium dichromate	-	irr	+	-	-	-	++
Thiuram mix	-	-	-	+++	-	-	-
Cobalt chloride	-	-	+	-	-	-	++
Formaldehyde	-	++	-	-	-	-	+
<i>Myroxylon pereirae</i> (balsam of Peru)	-	+	+	-	+	-	++
Methyldibromo glutaronitrile	-	-	-	+	+	-	++
Fragrance mix I	-	-	-	-	+	-	-
Quaternium-15	-	+	-	-	-	-	-
Nickel sulfate	-	-	-	-	++	-	+
MCI 0.015%	NT	NT	NT	+	NT	-	NT
MI 0,2%	-	-	-	++	-	++	+
MI 0,05%	-	-	-	-	NT	+	NT
MCI/MI 0.02 %	-	-	-	++	-	++	-
Limonene hydroperoxides 0.3% pet.	-	-	-	-	-	-	+
Linalool hydroperoxides 1% pet.	+	-	-	-	-	-	+
Imidazolidinyl urea	-	++	-	-	-	-	-
Sodium metabisulfite	-	-	NT	-	NT	-	-
2-bromo-2-nitropropane-1,3-diol (bronopol)	-	-	NT	-	-	+	-
Diazolidinyl urea	-	++	NT	-	-	-	-
Lauryl glucoside 3% pet.	-	+	NT	-	-	-	+
Decyl glucoside 5% pet.	-	+	NT	-	-	-	+
Propylene glycol 20% and 30%	-	-	-	-	-	-	+
Cetostearyl alcohol	-	+	-	-	-	-	-

Cetrimide 0,05%	-	-	-	-	-	-	+?
Benzoic acid	-	-	-	-	-	-	+
Cocamidopropyl betaine 1% aq.	-	+	-	-	-	-	-
Chlorhexidine digluconate 0.5% aq.	-	irr	-	-	-	-	-
Fusidic acid	-	+	-	-	NT	-	-
Benzisothiazolinone 0,1% pet.	-	-	-	-	-	-	+
Carba mix	NT	NT	-	++	-	-	-
Disperse Blue 85 and 106	-	-	-	NT	-	-	+
Chloramine	++	-	-	+		-	NT
Cinnamyl alcohol	+?	-	NT	-	NT	NT	NT
Toluenesulfonamide formaldehyde resin	-	+	-	-	-	-	-
Polyethyleneglycol (PEG)	NT	NT	+	NT	NT	-	NT
Tetramethylthiuram disulfide	NT	NT	NT	++	NT	-	NT
Tetramethylthiuram monosulfide	NT	NT	NT	+	NT	-	NT
Tetraethylthiuram disulfide	NT	NT	NT	+++	NT	NT	NT
Dipentamethylenethiuram disulfide	NT	NT	NT	++	NT	NT	NT
Zinc diethyldithiocarbamate	NT	NT	NT	++	NT	-	NT
Zinc dimethyldithiocarbamate	NT	NT	NT	++	NT	-	NT
Compounded cream ("as is")	-	+	NT	-	NT	NT	NT
Furacine ointment ("as is")	NT	NT	++	NT	NT	NT	NT
Cyclohexyl thiophthalimide	NT	NT	NT	NT	NT	+	NT
Polyhexamethylene biguanide	NT	NT	NT	NT	NT	++	NT
Palladium chloride	NT	NT	-	NT	NT	NT	++
Tetrachloropalladate	NT	NT	-	NT	NT	NT	++
Copper pentahydrate	NT	NT	NT	NT	NT	NT	++
Gold sodium thiosulfate	NT	NT	NT	NT	NT	NT	++
Sorbic acid	-	-	-	-	NT	-	+
Potassium sorbate	NT	NT	-	NT	NT	NT	+
Dithiodimorpholine	NT	NT	-	NT	NT	NT	+
Diphenylguanidine 1%	NT	NT	-	NT	NT	NT	++
Diphenylguanidine 0,3%	NT	NT	-	NT	NT	NT	+?
Cocamide DEA	NT	NT	-	NT	-	-	++
Benzoyl peroxide	NT	NT	-	NT	NT	NT	+?
Miconazole	NT	NT	-	NT	NT	NT	+

NT: not tested

irr: mixed irritant and allergic reaction

MCI: methylchloroisothiazolinone

MI: methylisothiazolinone

*tested with the commercial preparation (Iso)Betadine solution

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**tested also with Iso-betadine gel (does not produce irritant reactions)

Figure legends

Fig.1: sharply demarcated, inflammatory and oedematous plaques on the gluteal area (Case 1)

Fig.2: Positive patch-test reactions to chloramine ++ and iodine + , and to iodopropynyl butylcarbamate (IPBC) + on day 4 (D4) in the same patient (Case 1)

Fig. 3: Positive patch-test reactions to iodine +++ and iodopropynyl butylcarbamate (IPBC) + on day 4 (D4) (Case 2)

Fig. 4: Positive patch-test reaction to Betadine dermique 10% solution ++, tested “as is”, on day 3 (D3) (Case 5)

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Figures and figure legends

Figure 1: sharply demarcated, inflammatory and edematous plaques on the gluteal area (Case 1)

Figure 2: Positive patch-test reactions to chloramine ++ and iodine ++ , and to iodopropynyl butylcarbamate (IPBC) + on day 4 (D4) in the same patient (Case 1)

Figure 3: Positive patch-test reactions to iodine +++ and iodopropynyl butylcarbamate (IPBC) + on day 4 (D4) (Case 2)

Figure 4 : Positive patch-test reaction to « Betadine[®] dermique » 10% solution ++, tested « as is » on day 3 (D3) (Case 5)