

Allergic contact dermatitis from iodine preparations: a conundrum

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Iodine preparations are widely used antiseptics, yet limited information exists on their irritant potential and threshold for diagnostic patch testing. We examine this issue by using iodine in different preparations and concentrations. A total of 24 fair-skinned, healthy volunteers without a history of iodine allergy, ranging in age from 18 to 65 years (mean age 49.5 ± 10.7 SD), were recruited. Concentrations of 0.5%, 1%, 5% and 10% iodine in petrolatum (pet.), 0.5%, 0.75% and 1% iodine in 70% isopropyl alcohol (IPA) and 1%, 5%, 7.5% and 10% of povidone-iodine (PVP-I) were applied for 2 days to the intrascapular area on the back or to the volar forearm between cubital fossa and wrist using Finn Chambers[®] on Scanpor. Test sites were read 2 days (D2) and 4 days (D4) after patch application. Skin reactions were graded according to the following scheme: 0 = no reaction, + = questionable erythema, 1 = definite erythema, 2 = erythema and induration and 3 = vesiculation. Mild-to-moderate reactions (+ to 2) were observed in 75% of the subjects patched with 5% iodine in pet. at 2–4 days after application. Almost all subjects reacted to 10% iodine at D2 and D4, with 65% exhibiting erythema and induration or vesiculation. A large number (33%) of the subjects developed some reactions to the low concentration (0.5%) of iodine in 70% IPA at D2. Vesicles were seen in 54% of the subjects patched with 1% iodine in 70% IPA at D4. Only 1 subject reacted to 7.5% and 10% PVP-I. Iodine can be irritant to normal skin in pet. and in 70% IPA. Pet. possibly enhances skin contact with iodine, thus increasing its irritant capacity. Alcohol removes sebum from the skin surface, and it might increase iodine penetration into the skin, causing a higher degree of irritation. PVP-I is relatively non-irritant, because its iodine is complexed in an iodophor. For diagnostic patch testing, we recommend using iodine at less than 1% in pet. and at less than 0.5% in 70% IPA. For PVP-I, 10% appears non-irritant. With the variation in patch-test irritant response, interpretation of the patch-test response in the light of clinical history is mandatory.

Key words: iodine; povidone-iodine; irritancy; isopropyl alcohol; patch test; petrolatum. © Blackwell Munksgaard, 2005.

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For centuries, iodine compounds have been used as antiseptics and disinfectants (1). Iodine preparations are available in aqueous solution, tincture of alcohol, aerosol, ointment, antiseptic gauze pad, foam and swab sticks (2). Solubility of iodine is 1 g in about 3000 ml of water and 13 ml of alcohol (3). In aqueous solution, iodine is present as 7 different species: elemental iodine (I_2), hypoiodic acid (HOI), iodine cation (H_2OI^+), triiodine ion (I_3^-), iodide ion (I^-), hypoiodite ion (OI^-) and iodate ion (IO_3^-). Elemental iodine, hypoiodic acid and iodine cation have potent germicidal activity; triiodide and hypoiodite ions are weak oxidants exhibiting mild antibacterial activity and an iodide ion has no antimicrobial

activity. Iodate ion has antimicrobial activity only at a pH less than 4 and therefore does not contribute to the germicidal activity of iodine (4). Povidone-iodine (PVP-I) solution is most commonly used worldwide because of its potent germicidal activity with relatively low irritancy and toxicity. However, cutaneous irritation has been reported (5–7). Iodine itself and iodine hydroalcoholic solution are well-known local irritants which can cause iodine burns. To the best of our knowledge, most studies concerning the irritancy of iodine were done either on patients with known iodine-induced contact dermatitis or on normal subjects with PVP-I solution or iodine in ethanol only (6–13). This study examines the irritant

potential and threshold of iodine in 3 different preparations, namely petrolatum (pet.), 70% isopropyl alcohol (IPA) and PVP-I with different concentrations in normal healthy subjects without iodine allergy, in the hope of refining our knowledge of appropriate non-irritant diagnostic patch-test concentrations.

Materials and Methods

24 fair-skinned subjects (6 men, 18 women; aged 18–65, mean 47), in good health and with no history of allergies or significant skin disease, were recruited to participate in this study. The study was approved by the UCSF Committee on Human Research and informed consent was obtained from all subjects. Iodine (99.99% purity) was purchased from Fisher Scientific (Pittsburgh, PA, USA). PVP-I solution 10% (PVP-I), IPA 70% and pet. USP were supplied by hospital pharmacy. All calculations and compoundings were performed and verified by 2 registered pharmacists. Finn Chambers[®] (Epitest, Helsinki, Finland) on Scanpor (Norgeplaster, Oslo, Norway) were utilized.

Using closed patch tests with Finn Chambers[®], concentrations of 0.5%, 1%, 5% and 10% iodine in pet., 0.5%, 0.75% and 1% iodine in 70% IPA and 1%, 5%, 7.5% and 10% of PVP-I were applied to the intrascapular area on the back or to the volar forearm between cubital fossa and wrist as per participants' wish. Purified water was used as a control. The chambers were removed at 2 days (D2). Test sites were read after chamber removal and at 4 days (D4). Skin reactions were graded according to the following scheme: 0 = no reaction, + = questionable erythema, 1 = definite erythema, 2 = erythema and induration and 3 = vesiculation.

Results

Iodine in pet

Most subjects did not react to 0.5% iodine in pet. 1 subject showed questionable erythema at D2, which had disappeared by D4. 2 subjects reacted to 1% iodine in pet. at D2. By D4, additional 3 subjects showed mild reactions. With 5% iodine in pet., only 4 subjects did not react. When increased to 10% iodine in pet., all 24 subjects reacted. Most developed erythema at D2 and induration or vesicles by D4 (Tables 1 and 2).

Iodine in 70% IPA

When adding iodine to 70% IPA, a 0.5% concentration elicited questionable erythema in 8

subjects at D2, with stronger reactions seen in 3 subjects. With the 0.75% concentration, more than half of the subjects had questionable erythema to definite erythema at D2. 4 subjects had vesicles by D4.

PVP-I and purified water

1 subject developed reactions to 7.5% and 10% PVP-I at D4. None had any skin reactions to purified water.

Discussion

Iodine 0.5% in pet. was almost non-irritant. Only 1 of 24 subjects exhibited a questionable skin reaction, which had resolved by D4. Its irritant threshold appears to reside near 1% concentration, as evidenced by 21% of the subjects having mild skin reactions at D4. Iodine 5% and 10% in pet. are definitely irritant. Almost all subjects had some reactions, with over 37% of the participants demonstrating vesicles. Pet. may increase the irritant potential of iodine by increasing its contact with the skin surface. 5 subjects did not react to all concentrations tested of iodine in 70% IPA, while others demonstrated significant reactions to the 1% concentration at D4. Both alcohol and iodine are acute irritants. The combination of alcohol with iodine may have additive irritant effects. Alcohol removes sebum from the skin surface, which might enhance the penetration of iodine causing more irritation. PVP-I solution at equal or less than 10% concentration proved to be the least irritant among the preparations tested. Only 1 subject had a reaction at D4. PVP acts as an effective iodophor which complexes with iodine in aqueous solution. A 10% PVP-I solution contains 10% bound iodine and 1% available iodine, making it less toxic and irritant, without reducing its antiseptic properties (11). Overall, iodine must be patch tested with caution. Considerable individual variation was noted. A larger population would presumably demonstrate even greater variation. In this clinical situation, a careful review of the various steps in the operational definition of allergic contact dermatitis seems appropriate when correlating patch-test response with clinical background. We note that only in the study by Marks (1) Mochida et al. (11) and Ancona et al. (12) were subjects patch tested with what now appear to be non-irritant preparations. We suspect that much of these reports represent irritation rather than allergy.

Table 1. Allergic contact dermatitis to iodine preparations: a conundrum

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Gender	F	M	F	F	M	M	F	F	M	F	F	F	M	F	M	F	F	F	F	F	F	F	F	F
Race	W	W	H	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W
Age	52	46	40	54	38	47	49	58	60	43	53	51	32	45	51	51	65	45	18	49	53	65	65	57
I exposed	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Site	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	A	B	B
I (pet.)	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5% D2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5% D4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1% D2	+	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1% D4	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5% D2	1	0	0	1	2	1	1	1	+	1	1	+	1	1	+	+	0	1	+	1	0	1	0	+
5% D4	1	0	0	+	2	0	2	2	1	1	1	1	0	1	1	+	0	1	2	3	+	2	0	1
10% D2	3	+	1	1	2	1	1	1	1	1	2	3	1	1	1	1	+	1	1	1	1	1	1	1
10% D4	3	1	1	2	3	3	2	2	2	2	3	3	0	1	2	+	+	1	3	1	3	2	1	2
I 70% IPA																								
0.5% D2	0	+	0	0	0	+	+	0	+	+	0	0	0	0	0	0	+	0	+	0	0	0	+	0
0.5% D4	0	+	0	0	0	0	1	0	0	0	0	0	0	0	0	2	+	0	0	0	0	0	+	3
0.75% D2	1	+	0	0	0	+	1	0	1	1	0	0	0	0	0	+	1	0	1	1	1	0	1	+
0.75% D4	1	1	0	0	0	+	0	0	0	1	0	+	3	0	0	3	1	0	0	3	1	0	1	3
1% D2	1	+	0	0	0	+	0	0	+	1	0	0	0	+	0	1	1	0	1	1	1	0	1	1
1% D4	3	3	0	3	0	3	0	3	0	2	0	3	0	3	0	3	1	0	3	3	3	3	1	3
PVP-I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1% D2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1% D4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5% D2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5% D4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7.5% D2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7.5% D4	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10% D2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10% D4	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
H ₂ O	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

F = female; M = male; W = white; H = hispanic; B = back; A = arm; I = iodine; pet. = petrolatum; IPA = isopropyl alcohol; PVP-I = povidone-iodine.

Test site was the back in 23 of 24 individuals and 23 of 24 were Caucasians. 6 were males. Subjects that were negative to all concentrations are not shown. Subject 6 was the only individual known to have repeated iodine exposure. Negative (not shown) were I (pet.) 0.5% on day 4; PVP-I 1% and 5% on day 2 and 10% on day 2 and 10% on day 2 and H₂O (control) on day 2 and day 4. Skin reactions were graded according to the following scheme: 0 = no reaction; + = questionable erythema; 1 = definite erythema; 2 = erythema and induration and 3 = vesiculation.

Table 2. Patch-test reactions to iodine preparations

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Age	52	46	40	54	38	47	49	58	60	43	53	51	32	45	51	51	65	45	18	49	53	65	65	57
I pet.																								
0.5% D2	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1% D2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0
1% D4	+	0	0	0	0	0	0	1	0	0	0	0	0	0	+	0	0	+	0	+	0	0	0	0
5% D2	1	0	0	1	2	1	1	1	+	1	1	+	1	1	+	+	0	1	+	1	0	1	0	+
5% D4	1	0	0	+	2	0	2	2	1	1	1	1	0	1	1	+	0	1	2	3	+	2	0	1
10% D2	3	+	1	1	2	1	1	1	1	1	2	3	1	1	1	1	+	1	1	1	1	1	1	1
10% D4	3	1	1	2	3	3	2	2	2	2	3	3	0	1	2	+	+	1	3	1	3	2	1	2
I 70% IPA																								
0.5% D2	0	+	0	0	0	+	+	0	+	+	0	0	0	0	0	0	+	0	+	0	0	0	+	0
0.5% D4	0	+	0	0	0	0	1	0	0	+	0	0	0	0	0	2	+	0	0	0	0	0	+	3
0.75% D2	1	+	0	0	0	+	1	0	1	0	0	0	0	0	0	+	1	0	1	1	1	0	1	+
0.75% D4	1	1	0	0	0	+	0	0	0	1	0	+	3	0	0	3	1	0	0	3	1	0	1	3
1% D2	1	+	0	0	0	+	0	0	+	1	0	0	0	+	0	1	1	0	1	1	1	0	1	1
1% D4	3	3	0	3	0	3	0	3	0	2	0	3	0	3	0	3	1	0	3	3	3	3	1	3
PVP-I																								
7.5% D4	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10% D4	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

I = iodine; pet. = petrolatum; IPA = isopropyl alcohol; PVP-I = povidone-iodine.

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