

The results of ingredient patch testing in contact dermatitis elicited by povidone-iodine preparations

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10 cases of contact dermatitis which began during the application of povidone-iodine preparations were examined with patch tests using 2 kinds of povidone-iodine preparations and their ingredients, i.e., povidone-iodine, polyoxyethylene nonylphenyl ether and glycerin, and also the components of povidone-iodine, i.e., iodine and polyvinylpyrrolidone. All 10 cases reacted positively to the povidone-iodine preparations and povidone-iodine, 3 out of the 10 to polyoxyethylene nonylphenyl ether, 1 out of the 9 tested to iodine, while no positive response was found to glycerin or polyvinylpyrrolidone. It was difficult to distinguish between allergic responses from irritation, as responses to patches of povidone-iodine and its preparations usually include irritation at high frequencies. Based on comparison of results with a control group, however, those showing + or stronger reactions to 2% povidone-iodine at days 3 to 5 were considered to be allergic. Thus, 4 out of the 10 cases were considered as sensitization to povidone-iodine. Another 3 cases were found to be polyoxyethylene nonylphenyl ether sensitized, and another 1 iodine sensitized, while the patch test reactions of the other 2 were considered to have been elicited by irritation.

Key words: povidone-iodine; polyoxyethylene nonylphenyl ether; contact dermatitis; allergy, irritation, patch testing technique; false-positive reactions; medicaments. © Munksgaard, 2000.

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Povidone-iodine preparations (Isodine[®] solution, Negmin[®] solution and others) are antibacterial agents and antiseptics. As active ingredient, they contain 10% povidone-iodine with additives of concentrated glycerin and polyoxyethylene nonylphenyl ether (Fig. 1). Their active agent, povidone-iodine, is a clathrate compound of iodine and polyvinylpyrrolidone (Fig. 2).

Such preparations are frequently used in clinical practice due to their effective bactericidal action. It is not rare, however, to observe cases of contact dermatitis suspected of having been caused by them. Only a few detailed examinations have been available as to their mechanism of onset, namely, whether they are allergic or irritant, whether they are associated with iodine allergy or not, whether causative ingredients are the active agent or not, and whether some of the reactions are induced by the additives or not.

We performed ingredient patch testing for con-

tact dermatitis elicited by povidone-iodine preparations. The following are our findings concerning the above issues.

Patients and Methods

The subjects were 10 patients, with onset of contact dermatitis during the application of povidone-iodine preparations, who proved positive to patch tests with the preparations. Their ages ranged 39 to 80 years, with 8 men and 2 women. The underlying indications for the preparations were skin ulcer in 7 cases, and surgical wound, atopic dermatitis and occupational exposure in 1 case each. 7 cases were involved on the lower leg or foot, while the remaining 3 were involved at other sites. The duration of exposure before onset was 7 days to 16 years. 6 cases were found to be positive to patch test substances other than povidone-iodine preparations (Table 1).

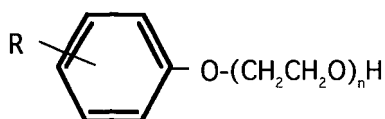


Fig. 1. Chemical formula of polyoxyethylene nonylphenyl ether.

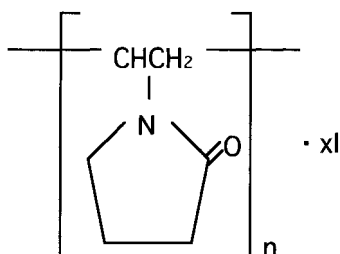


Fig. 2. Chemical formula of povidone-iodine.

Patch testing was conducted with samples of 2 povidone-iodine preparations and their ingredients, i.e., povidone-iodine, polyoxyethylene nonylphenyl ether and glycerin, and also the components of povidone-iodine, i.e., iodine and polyvinylpyrrolidone. Using Finn Chambers on Scanpor tape, 2-day closed patch testing was performed on the backs of the patients. The reactions were scored at 30 min after removal and 3 or 5 days (D) after application, according to the ICDRG recommendations.

Results

Among the patient group, a positive reaction, i.e., + or stronger, was observed at D 3 to 5 in all 10 cases to 10% povidone-iodine, all 9 cases tested to 5% and 5 of the 9 cases tested to 2%. As for polyoxyethylene nonylphenyl ether, equivalent results were seen in 3 of the 10 cases to 1% dilutions, 2 of the 9 cases tested to 0.5% and 1 of the 9 cases tested to 0.05%, 0.1% and 0.3% dilutions, respectively. All 10 cases proved positive to the povidone-iodine preparation (as is), but their reactions

turned out to be somewhat irregular; of the 9 patients who underwent patch tests with the 2 preparations, 8 were positive to both while 1 subject was positive only to 1 of the preparations. 1 among the 9 patients tested had a positive reaction to 0.2% iodine. No + or stronger reactions were observed to 10% glycerin and to 1% to 10% polyvinylpyrrolidone (Table 2).

In the control group, readings at D 3 revealed + reactions in 3 of the 10 cases to 5% and 10% povidone-iodine, and also to the preparations (as is), while no reactions exceeding + were found at a concentration of less than 2%. On the other hand, no + or stronger reactions were found to polyoxyethylene nonylphenyl ether, glycerin, iodine or polyvinylpyrrolidone (Table 3).

With regard to case no. 10, a repeated open application test (ROAT) was performed on the left forearm for 7 days within an area of 2 cm in order to differentiate an irritant reaction. No reproduction of dermatitis, however, could be observed.

Discussion

Since the control group in the present patch testing demonstrated positive reactions to povidone-iodine preparations and 5% and 10% povidone-iodine, the positive reactions to preparations (as is) were interpreted to include irritant reactions at high frequencies. The results of povidone-iodine patch tests also seemed to show that the minimal concentration for allergic reactions was approximately that for irritant ones. Patch-test results cannot easily be distinguished between allergic and irritant reactions, but it was decided, on the basis of comparison of the groups of controls and patients, that those cases showing + or stronger reactions to 2% povidone-iodine at D 3 to 5, were allergic. Thus, case nos. 1 to 4 were accepted as sensitized. In previous reports (1–7) of allergic contact dermatitis induced by povidone-iodine preparations, patch tests were performed with povidone-iodine preparations (as is) or 7.5% to 10% dilutions. In light

Table 1. Clinical data of patients

Patient no.	Age (years)	Sex	Clinical condition requiring antiseptic preparation	Area of dermatitis	Duration of exposure	Other patch-test-positive materials
1	64	M	diabetic ulcer	right sole	6 years	l-menthol
2	65	M	traumatic ulcer	right leg	20 days	acrinol
3	39	M	atopic dermatitis	feet	7 days	nil
4	66	F	traumatic ulcer	right ankle	8 days	nil
5	80	F	leg ulcer with varix	right leg	4 years	nil
6	65	M	decubitus	left buttock	7 years	nil
7	44	M	occupational exposure (surgeon)	hands	16 years	Hibiscrub®, rubber glove, thiuram mix
8	66	M	surgical wound	abdomen	1 month	neomycin
9	62	M	leg ulcer with varix	left leg	6 years	Chlomy P® ointment
10	39	M	traumatic ulcer	left leg	10 days	neomycin, gentamicin

Table 2. Patch test results in patients

[illegible]

Table 3. Patch test results in controls ($n=10$)

Materials	Conc. (%)	Veh	D2					D3				
			—	?+	+	++	IR	—	?+	+	++	IR
povidone-iodine	1.0	aq.	10	0	0	0	0	10	0	0	0	0
	2.0	aq.	9	0	1	0	0	9	1	0	0	0
	5.0	aq.	6	2	2	0	0	5	1	3	0	1
	10.0	aq.	5	3	2	0	0	4	2	3	0	1
polyoxyethylene nonylphenyl ether	0.05	aq.	10	0	0	0	0	10	0	0	0	0
	0.1	aq.	10	0	0	0	0	10	0	0	0	0
	0.3	aq.	10	0	0	0	0	10	0	0	0	0
	0.5	aq.	10	0	0	0	0	10	0	0	0	0
	1.0	aq.	10	0	0	0	0	10	0	0	0	0
glycerin	10.0	aq.	10	0	0	0	0	10	0	0	0	0
Isodine [®] solution	as is		5	1	4	0	0	4	2	3	0	1
Negmin [®] solution	as is		5	1	4	0	0	4	2	3	0	1
iodine	0.2	gl.	10	0	0	0	0	10	0	0	0	0
polyvinylpyrrolidone	1.0	aq.	10	0	0	0	0	10	0	0	0	0
	2.0	aq.	10	0	0	0	0	10	0	0	0	0
	5.0	aq.	10	0	0	0	0	10	0	0	0	0
	10.0	aq.	10	0	0	0	0	10	0	0	0	0
control (aq.)	as is		9	1	0	0	0	10	0	0	0	0

of the present examinations, these cases might possibly have included irritant reactions. Tsunoda et al. (8) reported that their survey of 22 contact dermatitis cases indicated positive reactions to 2% to 2.5% povidone-iodine solutions to be most significant for identifying allergic reactions. The results of our examination were generally identical to those of their research.

5 out of the 10 cases in the patient group showed + or stronger reactions to 2% povidone-iodine at D 3 to 5. Because 4 of these (case nos 1 to 4) were negative to iodine and polyvinylpyrrolidone, they were considered to have been sensitized to povidone-iodine, but not to iodine. The remaining 1 case (case no. 8), positive to iodine and negative to polyvinylpyrrolidone, was interpreted as sensitization to iodine. In previous reports of allergic contact dermatitis from povidone-iodine preparations, povidone-iodine was found to act as an allergen. These reports included cases reacting positively to povidone-iodine and negatively to iodine (1–3), as well as cases reacting positively to both substances (4, 5). It was suggested that positive cases to povidone-iodine occur somewhat rarely on the basis of iodine sensitization.

On the other hand, our study demonstrated cases where positive patch test reactions were apparently caused by irritation, case no. 9 was negative to 1 of the preparations and also to 2% povidone-iodine, while case no. 10 was negative to the latter on both patch testing and a ROAT. These 2 cases were found to be positive to other substances, which were concluded to be allergic. We presumed,

therefore, that their dermatitis was allergic and elicited by these allergens, rather than associated with the preparations. Another possibility is that allergic contact dermatitis induced by other preparations was followed by irritant contact dermatitis caused by povidone-iodine preparations. There have been some reports of irritant contact dermatitis from povidone-iodine (9, 10). The affected sites in these reports are limited to the backs of children after operations. Povidone-iodine liquid may have been retained against the back during the operation. Among povidone-iodine preparations, liquid ones are known to produce skin irritation by releasing $[I_3^-]$ continuously into the solution in order to maintain the equilibrium of electrolytic dissociation. In contrast, gel preparations do not usually release much $[I_3^-]$, because povidone-iodine is conjugated in polymers and other bases. Thus, skin irritation is only rarely observed with gel products. It is advised, therefore, that both liquid and gel preparations be applied simultaneously as a method to distinguish between allergic and irritant reactions on patch testing.

The present study observed 3 cases (case nos. 5–7) where positive reactions were found to 1% polyoxyethylene nonylphenyl ether. This fact confirmed that sensitization occurred to a chemical used as an additive, i.e., polyoxyethylene nonylphenyl ether, as well as to the active agent, i.e., povidone-iodine. The additive, a nonionic surfactant, is compounded into povidone-iodine preparations to promote permeability. The one chosen for our study was with $n=10$, n being the number

of ethylene oxide chains and an average of plural mixtures (Fig. 1). Cases of sensitization have been reported with those of $n=6, 8.3, 9, 10$ and 12 (11–17). Dooms-Goossens et al. reported 12 cases of allergic contact dermatitis induced by this preparation and added that cross-sensitization was observed with chemicals of variable, ns (14). Furthermore, Tsunoda et al. (7) reported examples of sensitization by the same substance included in povidone-iodine preparations, in which patch testing with 0.2% mixture proved positive. In our study, all 3 cases of sensitization were seen with the 1% solution, while there were no such cases in the control group. Accordingly, we presumed that a 1% solution would be appropriate for patch testing with polyoxyethylene nonylphenyl ether. Dooms-Goosen et al. (14), on the other hand, recommended dilutions of 0.5% to 2% in white petrolatum, though they now also use a 2% aqueous solution (Goossens, personal communication). Recently, polyoxyethylene nonylphenyl ether was pointed out as a possible endocrine disruptor. It is desirable, therefore, to avoid using it as an additive and to delete it from marketed products.

As shown above, it is necessary to determine carefully whether the preparations are truly involved in cases where contact dermatitis is suspected as being associated with povidone-iodine preparations, on the basis of history of application, clinical signs and patch test results.

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