Improving povidone-iodine and iodine preparations for patch testing

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Abstract
Background: Allergy evaluation by patch testing with povidone-iodine (PVP-I) or iodine remains challenging, because current patch test preparations frequently lead to false-positive or irritant skin reactions.

Objectives: To investigate different preparations for iodine patch tests and to assess their clinical relevance with repeated open application tests (ROATs).

Methods: We monocentrically analyzed 95 patients with suspected allergy to disinfectants in retrospect who underwent parallel iodine patch testing with four preparations: PVP-I 2% aq., 5% aq., 10% aq., and iodine 0.5% pet.

Results: In 27 of 95 patients (28.4%), we found positive reactions to one of the four test preparations. After ROATs in 22 of these 27 positively tested individuals, only one patient was diagnosed with iodine allergy. In contrast, 31 of 95 patients (32.6%) showed irritant or questionable patch test reactions on day 2 (D2) and/or D3 and/or D7 to one or more test preparations. Testing with PVP-I 2% aq. resulted in the lowest number of doubtful skin reactions while detecting the single allergic patient.

Conclusion: PVP-I 2% aq. was found to be the optimal patch test preparation. In general, iodine allergy appears to be substantially overestimated, and positive patch test responses to iodine should prompt an urgent ROAT for confirmation before diagnosing iodine allergy.

KEYWORDS
antiseptics, contact hypersensitivity, iodine, povidone-iodine

INTRODUCTION

Iodine compounds have been used as antiseptics at least since the 18th century.1 The inhibitory effects of iodine on bacteria, viruses, and fungi led to large-scale applications of iodine in virtually all medical fields. Free iodine is not easily dissolved in water; further disadvantages include its skin-irritating properties, unstable chemical preparations, and high reactivity in oxidation processes. These negative properties of iodine may be overcome by supplementation with polyvinylpyrrolidone (commonly called povidone [PVP]), a free-iodine binding iodophor. The combination of the water-soluble polymer PVP with iodine results in a stable solution.2 Thus PVP-iodine (PVP-I) is used almost exclusively, instead of iodine alone, owing to its low irritancy and toxicity.3 German PVP-I products usually contain 10% releasable iodine in the form of PVP-I. For the diagnosis of iodine contact allergy, patch tests must be performed. However, the well-known irritant properties of iodine3,4 may complicate evaluation of patch test results, particularly with this compound.5,6

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In an earlier study, 500 patients were patch tested with different preparations of 1% PVP-I diluted in ethanol, glycerol, or water, and 14 of these individuals exhibited positive patch test reactions to PVP-I 1%. However, in additional repeated open application tests (ROATs), only two reactions were found to be relevant. In another study from 2005, various iodine preparations were investigated in patch tests in 24 healthy volunteers without suspicion of iodine allergy. Here, the tests were performed with iodine in petrolatum (0.5%, 1%, 5%, and 10%), iodine in 70% isopropyl alcohol (0.5%, 0.75%, and 1%), and PVP-I in water (1%, 5%, 7.5%, and 10%). With regard to the petrolatum-based test preparations, iodine 0.5% pet. was mostly nonirritating. Iodine 1% pet. revealed some skin irritation, whereas 5% and 10% iodine in pet. showed strong irritating properties. Patch tests with the water-based test preparations with PVP-I 1% and 5% were completely negative. Among all volunteers, only one individual demonstrated a skin reaction to PVP-I 7.5% aq. and 10% aq. without suspected allergy.

In a previous study, we investigated 79 patients with suspected contact dermatitis caused by antiseptics. Patch tests were performed with PVP-I 0.1%, 1%, and 10% aq., and with iodine 0.5% pet. The relevance of positive tests was assessed with ROATs. Testing with PVP-I 0.1% aq. and 1% aq. proved to be unsuitable, because no positive reactions were identified at these low test concentrations. Strong positive reactions to PVP-I 0.75%, and 1% aq. and positive reactions to iodine 0.5% pet. correlated well in this former study. However, testing with PVP-I 10% aq. also revealed some false-positive reactions. This test concentration is well known to frequently result in irritant skin reactions, which are sometimes difficult to distinguish from weak-positive reactions. Less-experienced allergologists frequently diagnose iodine allergy in patients showing these results. Owing to the high number of irritant and therefore potentially false-positive reactions, patch testing with iodine preparations remains highly unsatisfactory. In our previous study, we concluded that patch testing with PVP-I 2% aq., 5% aq., and iodine 0.5% pet. appears to be more promising than PVP-I 10% aq., which is currently included in the German patch test series for disinfectants. From this starting point, we continued our search for the best possible test concentration and the optimal vehicle. In addition, we investigated whether late readings on day (D) 7 might add any value to the results of patch tests with iodine preparations.

PVP-I (Caelo) was prepared at test concentrations of 2%, 5%, and 10% in water. All patients except one were tested with these different vehicles and concentrations of iodine and PVP-I in parallel. Patch tests were performed with 48 hour exposure through the use of Finn Chambers (8 mm inner diameter) on Scanpor tape (Smart-Practice, Greven, Germany) and read at D2, D3, and D7, according to the current guidelines of the German Contact Dermatitis Research Group. This retrospective study was reviewed and approved by the local ethics committee at the University Medical Center Göttingen.

### 2.2 | Consumption data

Data regarding the annual consumption of antiseptics were kindly provided by Insight Health (Waldems-Esch, Germany). Data were extracted from pharmacy prescriptions in the years from 2010 to 2019 and are reported as the defined daily dose (DDD), a medico-economic value used to analyze a prescribed amount of a pharmaceutical, representing the average amount of an adult’s daily consumption. Because iodine is not used for mucosal applications in Germany, antiseptics used in lubricants for catheter systems and exclusively mucosal applications were excluded from the evaluation.

### 3 | RESULTS

#### 3.1 | High frequency of positive skin reactions to iodine test preparations

A total of 95 patients with suspected contact allergy were included in this study. The majority were female (70.5%) and between 20 and 59 years of age at the time of testing (81.1%), and most patients were patch tested for suspected allergic contact dermatitis to disinfectants/antiseptics. Seven patients presented with suspected iodine allergy after they had contact dermatitis following surgery. One patient underwent allergy tests because of anaphylaxis during a medical procedure. Sixty-three of the 95 patients were patch tested because of occupational dermatitis. Forty-nine worked in health care professions at the time of the allergy tests, for example, as nurses, physiotherapists, or physicians. Most patients presented with hand dermatitis (56/95), and about one third were diagnosed with atopic dermatitis (29/95).

Regarding the test preparations, all patients except one were tested simultaneously with iodine 0.5% pet. and PVP-I 2% aq., 5% aq., and 10% aq., and the reactions were read on D2 and D3. One third (31/95) demonstrated an irritant or doubtful reaction on D2 and/or D3 and/or D7 to one or more test preparations (Table 1). Furthermore, 27 of 95 patients (28%) had a positive reaction to one of the test preparations at any time. Of these 27 positively tested patients, 22 received an additional ROAT with PVP-I 10% ointment (Braunol Creme, B. Braun Melsungen, Melsungen, Germany) twice daily for 7 days on the inner side of the upper left arm. The ROAT resulted in an irritant reaction in 2 of the 22 patients and in a true allergic reaction in only one patient (Figure 1). The latter convincingly described a history of allergic contact...
dermatitis after surgical therapy of a pilonidal sinus. The wound cavity was originally tamponaded with iodine gauze, and the patient subsequently developed severe contact dermatitis spreading to the trunk. Of the remaining five patients tested positive who did not receive a ROAT, three individuals were lost to follow-up. The last two patients of the five positively tested patient without ROAT received iodine-based disinfectants without complications during surgery later, thus eliminating the need for a ROAT.

### 3.2 PVP-I 2% aq. revealed the lowest rate of irritant and false-positive reactions

Analysis of the D3 results of the different iodine test preparations showed that PVP-I 2% aq. resulted in the lowest number of doubtful or irritant reactions, and four patients had only a weak positive reaction (Table 1). PVP-I 5% aq. and 10% aq. led to a comparable number of positive test reactions, with an almost identical number of doubtful and irritant reactions. Iodine 0.5% pet. resulted in positive test reactions in only seven patients, but had the highest number of doubtful and irritant reactions (24/95). A strong reaction was observed in the single patient with contact allergy to iodine, as mentioned earlier, who demonstrated extreme positive reactions to PVP-I 5% aq. (+++) and 10% aq. (+++), as well as to iodine 0.5% pet. on D3 (+++). PVP-I 2% aq. yielded a weak positive reaction (+) at the time (Figure 1).

We expected the test preparations PVP-I 2% aq. and iodine 0.5% pet. to be best suited in terms of sensitivity and specificity, on the basis of our previous work. Comparison of these two test preparations is depicted in Table 2. Only two patients revealed positive skin reactions to both test preparations, and only the patient with contact allergy to iodine had an extreme positive (+++) reaction to iodine 0.5% pet. as well as a (+) positive reaction to PVP-I 2% aq. In a second analysis using the most widely used test preparation, PVP-I 10% aq., we compared the patch test results with this patch test preparation with those with PVP-I 2% aq. (Table 2). Fifteen patients showed positive skin reactions to the commonly used test preparation of PVP-I 10% aq., thus underscoring the high share of false-positive iodine patch tests. The number of doubtful and positive reactions was markedly high for the test concentrations PVP-I 5% aq., PVP-I 10% aq., and iodine 0.5% pet. However, notably, even weak positive reactions with PVP-I 2% aq. must be assessed for their clinical relevance.

To assess the possible value of a late reading, 91 of 95 patients were also read on D7. The detailed results are displayed for the test preparations PVP-I 10% aq. D3 vs D7, and PVP-I 2% aq. D3 vs D7 (Table 3). The late reading did not provide added value. In addition, no increasing reactions were observed from D3 to D7, a finding that would have been relevant in the evaluation of weak or borderline positive skin reactions on D3.

### 3.3 Annual consumption data of skin disinfectants reveals a strong increase in octenidine use from 2010 to 2019

To correct for an indirect effect on iodine allergy due to a possible change in the use of antiseptics, we analyzed the annual sales of skin...
disinfectants in German pharmacies from 2010 to 2019 (Figure 2). Of note, skin disinfectants may also be purchased in German drugstores. Thus the data presented here underestimate the number of sold products in total. However, we aimed primarily to investigate relevant changes in sales of iodine-containing antiseptics, and we were unable to obtain total sales numbers from the industry. Thus these pharmacy sales over 10 years are still a valid indicator of general changes in the use of antiseptics. The sales of iodine-containing skin products slowly decreased over these 10 years, and the average sales volume was approximately 170 million DDD in 2019. In contrast, a strong increase

**TABLE 2**  Concomitant reactivity of PVP-I 2% aq. and iodine 0.5% pet. on day 3 (D3) (panel A), and concomitant reactivity of PVP-I 2% aq. and PVP-I 10% aq. on the same day (panel B)

| Day 3 | PVP-I 2% aq. |  |  |  |  | IR | Total |
|-------|--------------|---|---|---|---|----|-------|
|        | Neg. | ?+ | + | ++ | +++ | IR | Total |
| (A)    |      |    |  |  |  |    |       |
| Iodine 0.5% pet. | Neg. | 64 | 0 | 0 | 0 | 0 | 64 |
|         | ?+  | 12 | 0 | 2 | 0 | 0 | 14 |
|         | +   | 4  | 1 | 0 | 1 | 0 | 6  |
|         | ++  | 0  | 0 | 0 | 0 | 0 | 0  |
|         | +++ | 0  | 0 | 1 | 0 | 0 | 1  |
|         | IR  | 8  | 1 | 0 | 0 | 0 | 10 |
|         | Total | 88 | 2 | 3 | 1 | 0 | 95 |

| (B)    |      |    |  |  |  |    |       |
| PVP-I 10% aq. | Neg. | 55 | 2 | 0 | 1 | 0 | 58 |
|         | ?+  | 8  | 0 | 0 | 0 | 0 | 8  |
|         | +   | 11 | 0 | 0 | 0 | 0 | 11 |
|         | ++  | 2  | 0 | 1 | 0 | 0 | 3  |
|         | +++ | 0  | 0 | 1 | 0 | 0 | 1  |
|         | IR  | 12 | 0 | 0 | 0 | 0 | 13 |
|         | Total | 88 | 2 | 2 | 1 | 0 | 94 |

Abbreviations: IR, irritant; Neg., negative.

**TABLE 3**  Comparison of the skin reactions of PVP-I 10% aq. on day 3 (D3) vs D7 (panel A), and of PVP-I 2% aq. on D3 vs D7 (panel B) in 91 of the 95 patients

| Day 3 vs Day 7 | Day 7 PVP-I 10% aq. Day 7 |  |  |  |  | IR | Total |
|----------------|---------------------------|---|---|---|---|----|-------|
| Day 3 PVP-I 10% aq. | Neg. | 55 | 0 | 0 | 0 | 0 | 55 |
|                  | ?+  | 6  | 2 | 0 | 0 | 0 | 8  |
|                  | +   | 2  | 4 | 2 | 0 | 0 | 11 |
|                  | ++  | 0  | 0 | 2 | 0 | 0 | 3  |
|                  | +++ | 0  | 0 | 0 | 1 | 0 | 1  |
|                  | IR  | 5  | 1 | 0 | 0 | 0 | 6  |
|                  | Total | 68 | 7 | 4 | 0 | 1 | 90 |

| (B)    |      |    |  |  |  |    |       |
| Day 3 PVP-I 2% aq. | Neg. | 84 | 0 | 0 | 0 | 0 | 84 |
|         | ?+  | 1  | 0 | 0 | 0 | 0 | 2  |
|         | +   | 1  | 0 | 1 | 0 | 0 | 3  |
|         | ++  | 0  | 0 | 1 | 0 | 0 | 1  |
|         | +++ | 0  | 0 | 0 | 0 | 0 | 0  |
|         | IR  | 0  | 0 | 0 | 0 | 0 | 1  |
|         | Total | 86 | 0 | 2 | 0 | 3 | 91 |

Abbreviations: IR, irritant; Neg., negative.
was observed in the sales of octenidine-containing preparations. We calculated an increase from approximately 307 million DDD in 2010 to 407 million DDD in 2019 (+33%). Chlorhexidine-containing products play only a minor role in skin disinfection and wound treatment. However, compared with other antiseptics, chlorhexidine clearly leads the market share for mouthwash solutions and products for catheter systems, for example, lubricant gels in urinary catheterization (data not shown).

4 | DISCUSSION

The German Contact Dermatitis Research Group currently recommends patch testing with PVP-I 10% aq. for diagnosing iodine contact allergy. In our study, PVP-I 10% aq. continued to produce a high proportion of false-positive, doubtful, and irritant skin reactions, in line with findings from earlier studies on PVP-I 10% in different vehicles such as water or petrolatum.1,10 Of our 15 positively tested individuals with this test preparation, only one patient was diagnosed with a convincing iodine allergy, as confirmed by a ROAT. In line with our previous work, only extreme positive skin reactions (+++) in patch testing with PVP-I 10% aq. were associated with clinical relevance in terms of allergic contact dermatitis caused by PVP-I.5 However, in contrast to findings from our earlier study, a fairly high number of doubtful and irritant skin reactions was also found in patch tests with iodine 0.5% pet. (~25% of patients).

Regarding the aqueous test preparations, PVP-I 5% aq. continued to result in multiple ambiguous results. According to our current results, PVP-I 2% aq. appears to be a reasonable test concentration, because the number of doubtful and irritant reactions was markedly lower than that with PVP-I 10% aq., PVP-I 5% aq., and iodine 0.5% pet. This finding is consistent with results from a small case series from 2000, in which 10 patients with suspected allergy to PVP-I were tested.11 In this earlier study, patients were considered allergic if a patch test with PVP-I 2% aq. revealed positive reactions. However, PVP-I 2% aq. produces predominantly weak reactions. Even the single patient in our cohort diagnosed with iodine allergy demonstrated a weak positive reaction in the D3 reading only for PVP-I 2% aq., whereas stronger reactions to the other test concentrations were observed. Nevertheless, even with PVP-I 2% aq., false-positive reactions occur, and therefore the results must be verified by a subsequent ROAT. In summary, our previous work10 and this current study revealed PVP-I 2% aq. to be the optimal patch test preparation. We further addressed the benefit of late readings in iodine patch testing because the current literature has described up to 15% more positive reactions, in general, for readings at D7.8 In this respect, some allergens are well known for delayed positive reactions, for example, neomycin. In brief, there was no relevant additional information at D7 beyond the results from D3; that is, we would not have missed any relevant test result without D7 readings.

Another important issue of suspected iodine allergy concerns its specific use during surgery. In a more recent study, iodine-associated contact dermatitis was observed after surgical interventions, which lasted for more than 2 hours.12 These forms of induced contact dermatitis were located primarily in occluded areas during prolonged surgical procedures and were ultimately assessed as irritant contact dermatitis. Some patients appeared to develop irritant contact dermatitis to PVP-I. We speculate that individual vulnerabilities or predisposition might have been responsible for this observation. Of interest, exposure-time-dependent erythema during patch tests with PVP-I 10% aq. has been examined earlier.6 After 8 hours of occluded patch testing in eight healthy volunteers, all individuals revealed positive reactions. These data support the assumption that occlusion may facilitate irritant dermatitis. Therefore, if PVP-I solutions are used for surgical interventions, physicians should ensure that the skin is dry after PVP-I application, and that no pools of PVP-I solutions remain in anatomic areas with pits (eg, the navel).13

Because recent analyses revealed that skin disinfection with chlorhexidine solutions compared with iodine significantly reduces the risk of surgical site infections,14,15 we hypothesized that the frequency of iodine use might have declined in recent years. We therefore investigated real-life data on the sales of PVP-I as well as octenidine- and chlorhexidine-containing disinfectants, dispensed from German pharmacies over the past 10 years (2010-2019). However, iodine consumption has been largely stable over the years, whereas sales of octenidine have strongly increased. A major advantage of octenidine is its effectiveness against methicillin-resistant Staphylococcus aureus, thus potentially explaining its increased use.16 Chlorhexidine-containing products are mainly preparations for oral use.

In summary, in contrast to the number of suspected cases, the literature and our own experience suggest a low frequency of actual iodine allergy. We conclude that PVP-I 2% aq. is the best possible test preparation for patch tests that can currently be achieved. Evaluating this test preparation in adequately powered studies is strongly recommended.

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AUTHOR CONTRIBUTIONS

Susann Forkel: Conceptualization; data curation; formal analysis; investigation; writing—original draft. Caroline Beutner: Data curation; formal analysis; investigation; validation; writing—review and editing.

Katharina Amschler: Conceptualization; data curation; formal analysis; investigation; methodology; writing—review and editing. Silke Schröder: Data curation; formal analysis; investigation; methodology; writing—review and editing.

Michael Schön: Formal analysis; methodology; resources; validation; writing—review and editing. Johannes Geier: Conceptualization; formal analysis; methodology; software; supervision; validation; writing—review and editing. Timo Buhl: Conceptualization; data curation; project administration; resources; supervision; writing—original draft; writing—review and editing. Susann Forkel, Johannes Geier and Timo Buhl designed the study; Susann Forkel, Caroline Beutner, Katharina Amschler, and Silke Sabina Schröder collected data; Johannes Geier extracted and compiled the data; all authors discussed the data; Susann Forkel and Timo Buhl drafted the manuscript; and all authors jointly discussed, reviewed, and amended the manuscript.

CONSENT FOR PUBLICATION

All authors reviewed the final manuscript version and consented to its submission.

CONFLICT OF INTEREST

None of the authors have a conflict of interest in relation to this work. The authors have no ethical conflicts to disclose.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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