

A case of allergic contact dermatitis caused by Olanedine solution – A diagnostic patch-testing method involving dried filter paper

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Abstract

Background: Olanedine solution is a new antiseptic, and several cases of allergic contact dermatitis caused by the agent were reported in 2018; however, these cases were diagnosed based on positive results in 2-day closed patch testing Olanedine solution “as is”.

Objectives: To present another case of Olanedine-induced allergic contact dermatitis and to analyze the optimal patch-testing method for this condition.

Methods: A 34-year-old Japanese female patient and 25 healthy control subjects were patch tested using wet filter paper, which had been treated with 15 μ L Olanedine solution, and dried filter paper, which had been treated with 15 μ L Olanedine solution and then dried.

Results: The patient and all of the control subjects exhibited false-positive reactions due to irritation in the 2-day closed patch tests with wet filter paper containing Olanedine solution “as is”. The tests with dried filter paper produced a positive reaction on day 7 in the patient, and negative reactions in all control subjects.

Conclusions: It is preferable to perform 2-day closed patch tests using filter paper with the test solution “as is” which had been dried before application in order to correctly diagnose antiseptic-induced allergic contact dermatitis.

Keywords: allergic contact dermatitis, CAS no. 799787-53-4, filter paper, Olanedine solution, olanexidine gluconate, patch test

1. Introduction

Olanedine solution (1.5%) (Otsuka Pharmaceutical Factory, Tokushima, Japan) is a new biguanide antiseptic, which is used to pre-operatively prepare skin. It first became commercially available in Japan in 2015. It has marked bactericidal effects against a wide range of bacteria, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and *Pseudomonas aeruginosa*¹⁾²⁾. The active ingredient of Olanedine solution is olanexidine gluconate (Fig. 1) (CAS no. 799787-53-4, $C_{17}H_{27}Cl_2N_5 \cdot C_6H_{12}O_7$, molecular weight: 568.49)¹⁾³⁾, which has a similar structural formula to chlorhexidine gluconate (CAS no. 18472-51-0, $C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$, molecular weight: 897.76). Several cases of allergic contact dermatitis caused by Olanedine solution were reported in 2018, in which the patients were diagnosed based on positive results being obtained in 2-day closed patch tests of Olanedine solution “as is”⁴⁾⁵⁾. However, we suspect that such 2-day patch testing is not suitable for diagnosing patients with Olanedine-induced allergic contact dermatitis because other antiseptics, such as 1% chlorhexidine gluconate and acetate⁶⁾ or 10% povidone-iodine⁷⁾⁸⁾, can induce strong irritant reactions during patch testing as well as during clinical use.

Therefore, a dried filter paper technique⁹⁾ and a dilution method¹⁰⁾ were proposed as methods for differentiating allergic contact dermatitis caused by 10% povidone-iodine from irritant contact dermatitis caused by 10% povidone-iodine. Here, we present another case of Olanedine-induced allergic contact dermatitis, together with a suggestion regarding the optimal patch-testing method for diagnosing this condition.

2. Case report

A 34-year-old Japanese female underwent a Caesarean section under epidural anesthesia because of fetal hypoxia, which resulted in the delivery of her second baby in the middle of November 2018. She was discharged from hospital without any problems after a week. At 10 days after the operation, she noticed itchy rashes on her gluteal region and around her navel, which spread widely by the next day. Thus, she visited our clinic at 12 postoperative days. The patient had no relevant family or medical history, including no history of atopic dermatitis or allergies.

A physical examination revealed sharply demarcated, irregularly shaped, flesh-colored infiltrative erythema on the patient's abdomen and lumbar and gluteal regions

(Figs. 2a and b). No erythema was present around the operation scar or the puncture site used to induce epidural anesthesia, to which adhesive tape had been attached. On both flanks, several bands of erythema were seen (Figs. 2c and d). No blood tests or skin biopsy was performed. We consulted the abovementioned hospital to find out which antiseptic had been used before the operation and found that Olanedine solution had been applied once to the patient's abdomen and lumbar area, before being wiped away within a minute.

3. Methods

3.1 Substances and preparation for patch testing

The test substances were Olanedine solution "as is", and its two additives, polyoxyethylene (20) polyoxypropylene (20) glycol 1% aq. (the manufacturer is a commercial secret; CAS no. 9003-11-6) and glucono- δ -lactone 0.025% aq. (the manufacturer is a commercial secret; CAS no. 90-80-2). In addition, chlorhexidine gluconate 0.1% aq. (Maruishi Pharmaceutical, Osaka, Japan), which is chemically

similar to olanexidine gluconate, was also tested. Provision of the crystallized

Olanedine powder had been refused.

Olanedine[®] solution “as is” (x1) was diluted 2-fold (x2), 5-fold (x5), 10-fold (x10), 20-fold (x20), and 100-fold (x100), respectively, with distilled water. Pieces of filter paper attached to 8-mm Finn Chambers (SmartPractice, Phoenix, Arizona) were treated with 15 μ L of one of the diluted solutions (wet filter paper). A sufficient share of these were then spread out on an aluminum plate and left to dry in air for 3 hours (dried filter paper).

3.2 Patch testing in healthy control subjects

Twenty-five healthy control subjects, including one of the authors (S.I.), who had never been exposed to Olanedine solution, underwent patch tests. All of the control subjects gave their informed consent prior to their inclusion in the study. Their ages ranged from 22 to 61 (mean $\pm$ standard deviation: 39.0 $\pm$ 9.8) years old, and the male to female ratio was 14 to 11.

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First, S.I. underwent closed patch tests involving different periods of time. She was patch-tested with 6 sets of wet filter paper, which had been treated with x1, x2, x5, and x10 Olanedine solution. She removed one set of wet filter paper after 1 h, 3 h, 6 h, 12 h, 24 h, and 48 h. Furthermore, she was patch-tested with one set of dried filter paper, which had been treated with x1, x2, x5, and x10 Olanedine solution and then dried in air, and she removed all of the pieces of filter paper after 48 h. In these preliminary studies, clearly demarcated infiltrative erythematous reactions or partly erythematous reactions appeared after the 24-h and 48-h closed patch tests involving x1, x2, or x5 Olanedine solution. On the other hand, the patch tests with dried filter paper did not produce any reactions. The authors decided on the optimal Olanedine solution concentration and exposure time for the tests of the control subjects based on these results.

Then, all of the control subjects underwent 12-h, 24-h, and 48-h closed patch tests with wet filter paper, which had been treated with x1, x2, x5, and x10 Olanedine solution, respectively, and 48-h closed patch tests with dried filter paper, which had been treated with x1, x2, x5, and x10 Olanedine solution, respectively, and then allowed

to dry. Twelve of the control subjects were further patch-tested with wet filter paper that had been treated with x20 Olanedine solution.

The closed patch tests were all performed with 8-mm Finn Chambers on Scanpor tape (Norgesplaster, Vennessla, Norway). The readings were obtained on day 3 (D3) and D7 and were categorized according to the following three grades: a well-demarcated infiltrative erythematous reaction, a partly erythematous reaction, and no reaction. This study was approved by the medical ethical committee at Ryugasaki Saiseikai Hospital (No. 201914).

3.3 Patch testing in the patient

Open patch tests were performed on the medial aspect of the patient's forearm as follows: 1) 50 μ L of x1 Olanedine solution was applied to a skin region with a diameter of 2 cm and wiped away a minute after its application (application and wiping); 2) 50 μ L of x1 Olanedine solution was applied to a skin region with a diameter of 2 cm (application only); and 3) 50 μ L of x1 Olanedine solution was applied to a skin region with a diameter of 2 cm, wiped away a minute after its application, and then the application site was covered with adhesive tape (application and taping). At the same

time, 48-h closed patch tests were also performed on the outer aspects of the patient's upper arms, using wet or dried filter paper that had been treated with x1, x10, or x100 Olanedine solution; its additives; or 0.1% chlorhexidine gluconate. The closed patch tests were all performed as above and read on D2, D3, D4, and D7, according to International Contact Dermatitis Research Group criteria.

4. Results

4.1 *Results obtained in the control subjects*

The patch test results are summarized in Online supplemental Table 1. The table shows the numbers of the control subjects who exhibited (a) well-demarcated infiltrative erythematous reactions, (b) partly erythematous reactions, and (c) no reaction on D3 or D7 during the patch testing. None of the control subjects exhibited any reaction to the dried filter paper that had been treated with x1, x2, x5, x10, or x20 solution on D3 or D7. In the tests with wet filter paper, all of the control subjects displayed well-demarcated, round, slightly elevated, and infiltrative erythematous reactions on D3 after x1 Olanedine solution was applied for 48 h. The strength of the

reactions depended on the exposure time and the concentration of the antiseptic agent.

In the patch tests with x20 Olanedine solution, most of the control subjects exhibited no reaction to the wet filter paper. The reactions slowly subsided, and the peak reaction, which involved erythema or itching, was seen on D3 or D4. The reactions completely disappeared within three weeks of the application of x1 Olanedine solution and within two weeks of the application of x10 solution for 48 hr. There were no signs of active sensitization, such as flare-up reactions, after the reactions disappeared. Fig. 3 shows pictures of the patch test results obtained in one of the control subjects on D3 and D7.

4.2 Results in the patient

The patch test results are summarized in Online supplemental Table 2. All open patch tests produced negative reactions. The closed patch tests involving wet filter paper seemed to produce positive reactions to x1 and x10 Olanedine solution on D2, D3, D4, and D7, with the peak reactions on D2 to D4. The reactions involved well-demarcated, round, and infiltrative erythematous lesions, which looked like those seen in the control subjects. Further tests of x1 Olanedine solution involving dried filter paper produced a

partial papular (doubtful) reaction on D4 and a poorly marginated, papular erythematous (positive) reaction on D7 (Fig. 4). The patch tests of the Olanedine solution additives and 0.1% chlorhexidine gluconate solution produced negative results.

We finally diagnosed the patient with allergic contact dermatitis caused by the main component of Olanedine solution, olanexidine gluconate. Her skin rash was treated with a high potency corticosteroid ointment twice daily and 120 mg/day oral fexofenadine, achieving resolution of the rash within a week.

5. Discussion

Olanedine solution (1.5%) (pH: approximately 5, specific gravity: approximately 1.0), with its main component olanexidine gluconate, was launched as a new antiseptic agent in 2015, but it is currently only commercially available in Japan. Several studies¹⁾²⁾¹¹⁾ have demonstrated that it exhibits fast-acting and long-lasting antimicrobial activity. The bactericidal activity of Olanedine solution persists for 12 hours after the solution is used for antiseptic rinsing, while other antiseptics, such as 0.5%

chlorhexidine gluconate and 10% povidone-iodine, hardly display any long-lasting effectiveness¹¹⁾. This was explained by the results of a previous study¹¹⁾, in which it was found that the amount of olanexidine gluconate present in the stratum corneum peaked at 4 h, but was still high at 12 h after the application of Olanedine solution. The amount of olanexidine gluconate present in the stratum corneum was ≥ 2.8 times greater than the amount of chlorhexidine gluconate present in the stratum corneum after the application of chlorhexidine gluconate to the skin.

We diagnosed our patient with allergic contact dermatitis caused by olanexidine gluconate. She might have become sensitized to olanexidine gluconate 10 days after the antiseptic was applied to her abdomen and lumbar region for the first and only time, even though it was wiped away within a minute. This quite unique contact allergy might occur because of the long persistence of Olanedine solution in the stratum corneum¹¹⁾. The fact that no dermatitis was seen at the sites at which adhesive tape was applied might have been because the stratum corneum was stripped away when the tape was removed. A study of the tape-stripping method involving a Yucatan micropig skin model revealed that the quantity of olanexidine gluconate in the stratum corneum was

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gradually reduced by tape stripping, and it had almost reached the lower limit of quantification after the tape stripping had been performed 15 times¹¹⁾. In the present case, the bands seen on both of the patient's flanks were considered to have been caused by the antiseptic agent running over the skin after its application.

How patch testing of antiseptics should be performed is a difficult problem, because 10% povidone-iodine solution, a strong antiseptic, can cause skin irritation, even when 1% povidone-iodine solution is applied to the skin for several hours⁸⁾. Lachapelle⁷⁾ reported that 14 out of 500 consecutive patients exhibited positive patch-test reactions to 1% povidone-iodine solution, and among the 14 patients, 2 were proved to be allergic, and the rest were irritated by the antiseptic agent, according to repeated open application tests with a 10% povidone-iodine solution. These results demonstrated that it is difficult to distinguish between allergic responses and irritation via standard patch testing. Kozuka⁹⁾ proposed a way of using dried 10% povidone-iodine solution in order to avoid irritant reactions. Nishioka et al¹⁰⁾ proposed that patch tests should be performed with 2% povidone-iodine solution in order to correctly diagnose allergic contact dermatitis caused by this agent. In addition, a case was reported in which the

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patient was diagnosed with allergic contact dermatitis caused by 10% povidone-iodine solution on the basis of a positive patch test reaction to dried 10% povidone-iodine solution as well as povidone-iodine 2% aq.¹²⁾.

In our study, all healthy control subjects demonstrated well-demarcated infiltrative erythematous reactions in 48-h closed patch tests involving wet filter paper that had been treated with x1 Olanedine solution, and half of them exhibited such reactions to x10 Olanedine solution. Furthermore, our patient also demonstrated similar reactions from D2 onwards, when 48-h patch tests with x1 or x10 Olanedine solution were performed. These results indicate that reactions produced using wet filter paper can be false-positive reactions caused by irritation.

Regarding the morphologies of irritant reactions to patch testing, very strong reactions result in sharply demarcated, promptly healing, “burn-like” lesions, whereas allergic responses involve a spreading eczematous reaction, which disappears more slowly¹³⁾. However, relatively weak irritant and allergic reactions cannot be distinguished based on their morphologies¹³⁾. Our patch test study, in which wet filter paper was used in healthy control subjects, revealed mild to moderate reactions,

involving well-demarcated, round, slightly elevated regions of infiltrating erythema without visible vesicles, bullae, or erosive lesions, which was quite different from that induced by 10% povidone-iodine solution, which produced a very intense reaction involving vesicles and bullae⁸). In our patient, the most intense erythema and itching appeared from D2 to D4, and it slowly subsided on D7. Based on the readings conducted from D2 to D7, the reaction process seen in our patient seemed to be almost the same as those observed in the control subjects; i.e., the reaction peaked on D3 to D4 and then decreased on D7. No obvious flare-up reactions; i.e., an initial irritant reaction followed by subsequent allergic reactions, occurred, and the patient's reactions did not take longer to subside than those of the control subjects. Different results might have been obtained if we had performed patch tests in our patient with x2 or x5 Olanedine solution using wet filter paper, or if we had read the results on D14 or D21. We could not do this because we first subjected the patient to patch tests of antiseptics in order to obtain a prompt diagnosis and then conducted patch tests in the control subjects in order to search for clues about the most appropriate patch-testing method. Thus, the patch tests performed with wet filter paper that had been treated with Olanedine solution

produced characteristics of both irritant and allergic reactions. We considered that this was because olanexidine gluconate can persist for long periods of time, perhaps even for several days, in the epidermal layers, including the stratum corneum, after Olanedine solution is applied once to human skin.

Furthermore, the patient exhibited a partial papular reaction on D4, which enlarged and became irregularly shaped and infiltrated on D7 to dried filter paper that had been treated with x1 Olanedine solution, while none of the healthy control subjects displayed any reactions to such tests. These findings confirmed that the patient had experienced an allergic reaction, so we diagnosed the patient with allergic contact dermatitis due to Olanedine solution on the basis of the patch test results. This could be also explained if olanexidine gluconate remains for several days in the epidermal layers, after the application of Olanedine solution. Performing patch tests with x2 and x5 Olanedine solution using dried filter paper would have provided more evidence for a diagnosis of allergic contact dermatitis in the present case. On the other hand, in previous cases of allergic contact dermatitis due to Olanedine solution ⁴⁾⁵⁾, the patients were diagnosed on the basis of positive results in 48-h closed patch tests with x1

Olanedine solution applied wet. These results might have been due to irritation because similar reactions also occurred in our healthy control subjects.

In a phase III clinical trial of Olanedine solution, the safety of the antiseptic was evaluated in 52 patients, who were scheduled to undergo endoscopic operations. Among these, 3 patients (5.8%) experienced side effects, including dermatitis, erythema, and itching in one case each, at the application site¹⁴). Details of the cases could not be supplied by the company that conducted the study. Several cases in which skin rashes developed at sites at which Olanedine solution was applied have been reported since Olanedine solution became commercially available. Nagai et al⁴) reported two cases, in whom eruptions appeared at 10 and 6 days after an operation, respectively. Matsukoka et al⁵) retrospectively compared the incidence of skin reactions to Olanedine solution with that of reactions to povidone iodine solution. As a result, they found that skin eruptions appeared more often in the group in which Olanedine solution was used (23/567 cases, 3.7%) than in the group in which povidone iodine solution was used (4/626 cases, 0.7%). The authors stated that in the Olanedine group skin eruptions appeared on the 3rd to 17th day after surgery (median: 7 days after surgery). Forty-eight-

h closed patch tests were only performed in 3 of the 23 cases in which Olanedine solution caused skin eruptions.

We consider that there might be other undiagnosed cases in which patients became sensitized to Olanedine solution after an operation. This is because most of the doctors that encounter such skin rashes are surgeons, orthopedists, or gynecologists, who use strong skin disinfectants before operations, and such doctors are not used to performing patch testing. The second reason is that the optimal patch-testing method for detecting such reactions had not been established yet. Clinicians should be aware that contact allergies can occur several days after Olanedine solution is used for the first and only time for preoperative skin cleaning. Such conditions should be diagnosed via 48-h closed patch testing, involving dried filter paper that has been treated with 15 μ L of the test solution “as is” and then dried, as soon as a patient presents with suggestive symptoms after surgery, in order to correctly diagnose allergic contact dermatitis caused by this antiseptic.

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Figure legends

Fig. 1 Structural formula of olanexidine gluconate

Fig. 2 Clinical findings obtained at the patient's first visit

Sharply demarcated, irregularly shaped, flesh-colored infiltrated erythema was seen on the patient's abdomen and lumbar and gluteal regions (a, b). No erythema was present around the operation scar or the puncture site used to induce epidural anesthesia, to which adhesive tape had been attached. On both flanks, several bands of erythema

were seen (c, d), which were caused by the antiseptic agent running over the skin after its application.

Fig. 3 Closed patch test results obtained with wet or dried filter paper in one of the healthy control subjects

The results obtained in 12-h, 24-h, and 48-h patch tests with wet filter paper and 48-h patch tests with dried filter paper are shown. The tests were conducted on D3 or D7 and involved x1, x2, x5, or x10 Olanedine solution. A well-demarcated infiltrated erythematous reaction was seen in the 48-h closed patch test with wet filter paper carried out on D3, which subsided by D7. The strength of the reactions depended on the exposure time and the concentration of the antiseptic agent. No reaction was observed in the 48-h patch tests with dried filter paper at any Olanedine concentration.

Fig. 4 Forty-eight-hour closed patch test results obtained with wet or dried filter paper in the patient

The results obtained with wet or dried filter paper that had been treated with x1, x10, or x100 Olanedine solution are shown. Patch tests using wet filter paper seemed to produce positive results for x1 and x10 Olanedine solution on D3, D4, and D7; however, the reactions resulted in well-demarcated infiltrative erythema. Patch tests performed using dried filter paper that had been treated with x1 Olanedine solution produced a doubtful reaction on D4 (*) and a positive reaction on D7 (**).

Dried: dried filter paper, Wet: wet filter paper

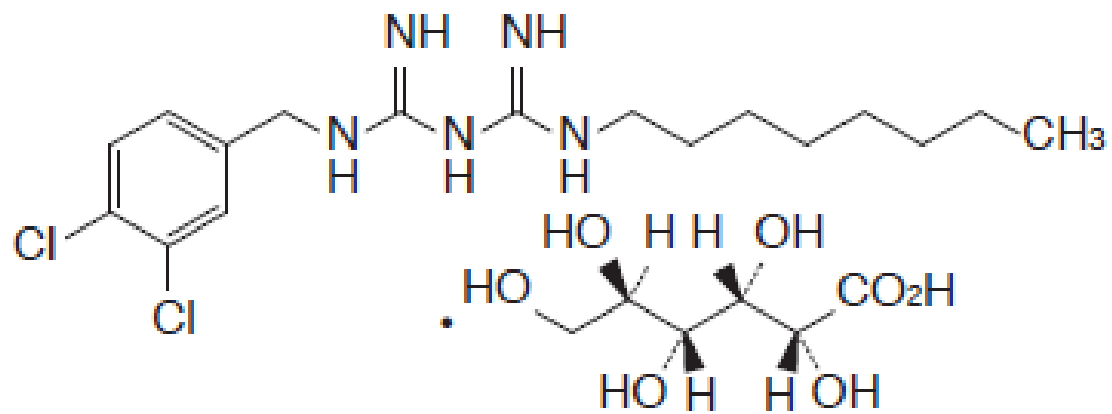
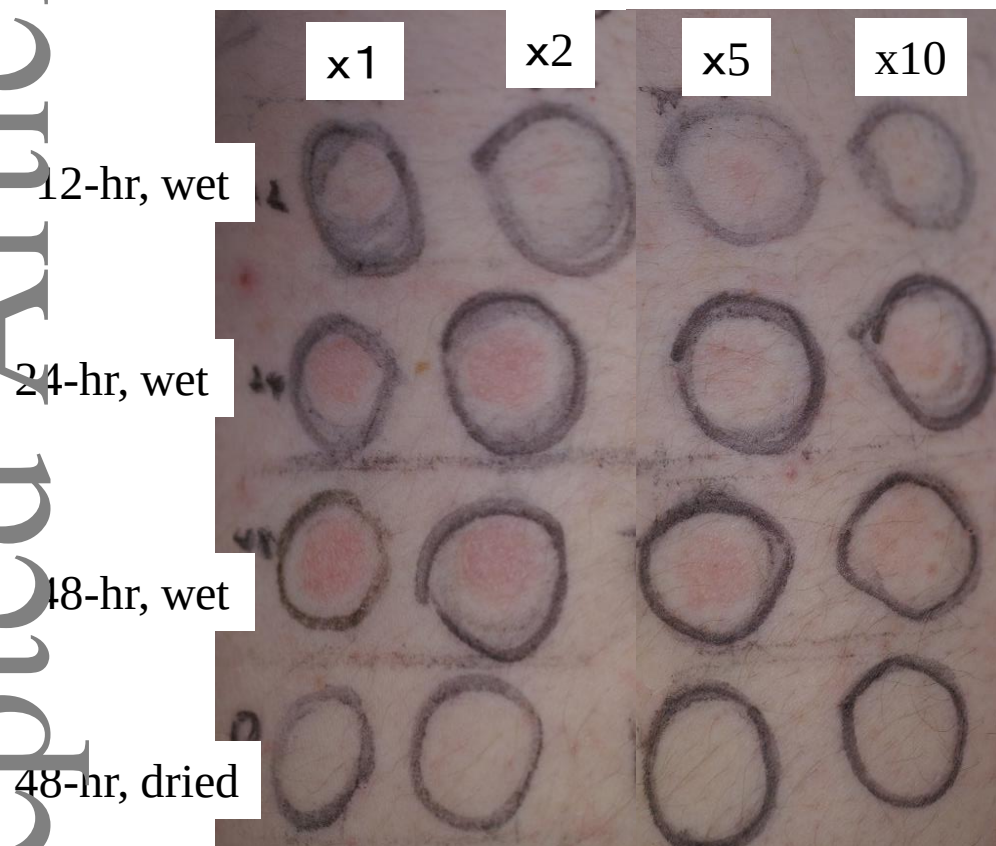


Fig. 1 Structural formula of olanexidine gluconate



Fig. 2 Clinical findings obtained at the patient's first visit

D3



D7

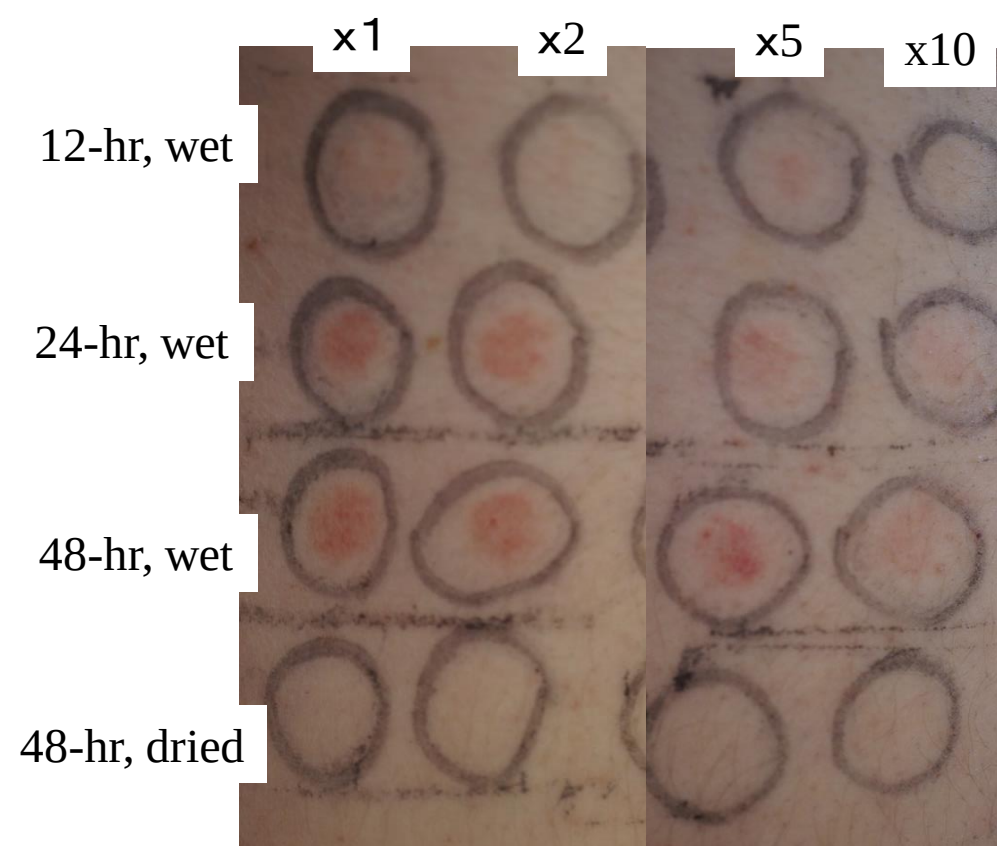


Fig. 3 Closed patch test results obtained with wet or dried filter paper in one of the healthy control subjects

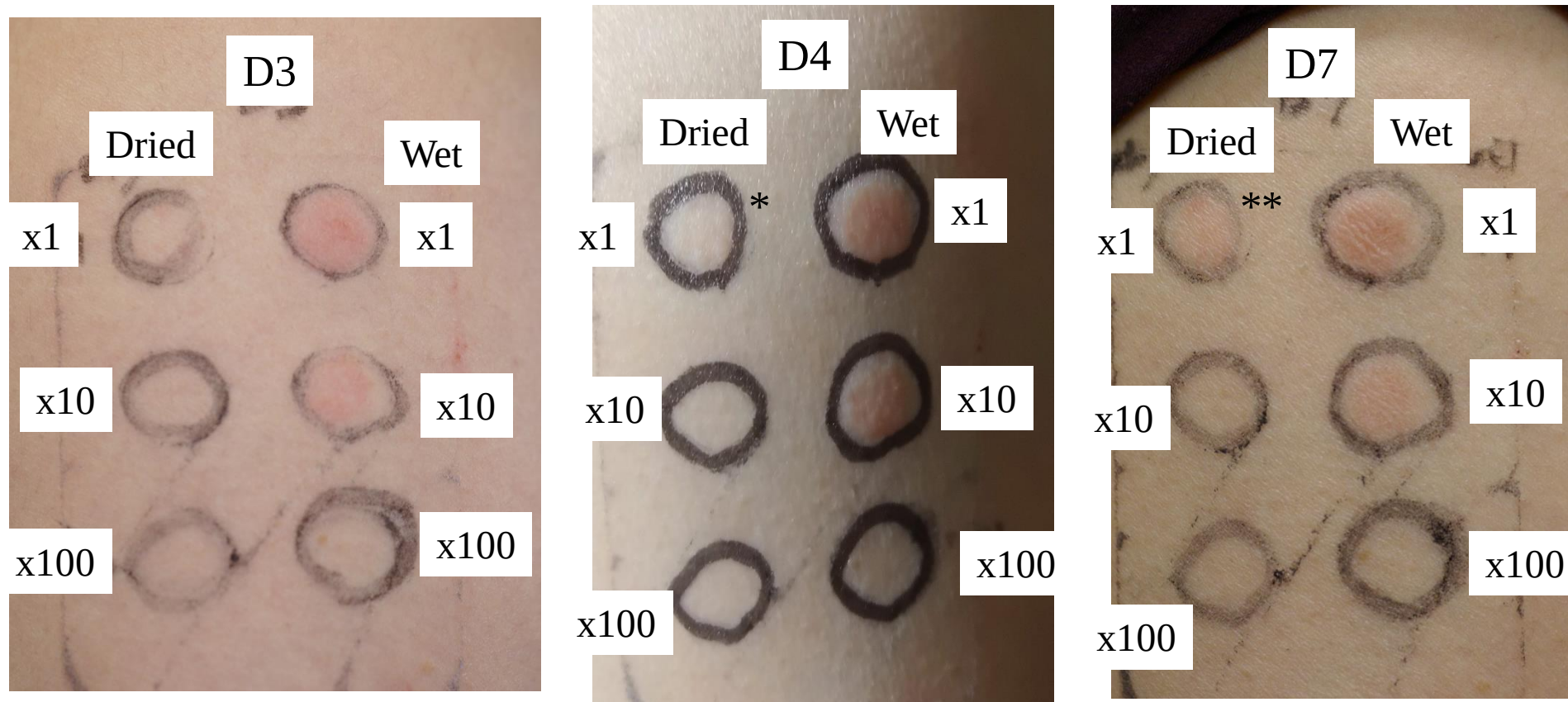


Fig. 4 Forty-eight-hour closed patch test results obtained with wet or dried filter paper in the patient

Table 1 Summary of the patch test results obtained in the 25 healthy control subjects on days 3 and 7

Material	Filter paper	Dilution	Vehicle	Exposure time	No. of controls	D3			No. of controls	D7				
						a	b	c		a	b	c		
Olanedine solution	Wet	x1	aq.	12 hr	25	9	3	13	24	4	4	16		
				24 hr	25	16	7	2	24	8	5	11		
				48 hr	25	25	0	0	24	15	4	5		
		x2	aq.	12 hr	22	7	6	9	21	3	5	13		
				24 hr	22	20	2	0	21	7	7	7		
				48 hr	22	22	0	0	21	11	6	4		
		x5	aq.	12 hr	25	3	6	16	24	4	2	18		
				24 hr	25	11	7	7	24	8	6	10		
				48 hr	25	19	3	3	24	9	8	7		
	x10	aq.	12 hr	25	2	4	19	24	0	3	21			
			24 hr	25	4	10	11	24	1	8	15			
			48 hr	25	13	5	7	24	4	9	11			
	x20	aq.	12 hr	12	0	0	12	12	0	0	12			
			24 hr	12	0	0	12	12	0	0	12			
			48 hr	12	2	0	10	12	1	2	9			
	Dried	x1	aq.	48 hr	25	0	0	25	24	0	0	24		
				x2	aq.	48 hr	22	0	0	22	21	0	0	21
				x5	aq.	48 hr	25	0	0	25	24	0	0	24
		x10	aq.	48 hr	25	0	0	25	24	0	0	24		
				x20	aq.	48 hr	12	0	0	12	12	0	0	12
				Wet: wet filter paper, Dried: dried filter paper										
a: well-demarcated infiltrative erythematous reaction,														
b: partly erythematous reaction, c: no reaction														

Table 2 Summary of the patch test results obtained in the patient					
Patch test	Materials patched	D2	D3	D4	D7
Open	OLG as is, application and wipe	-	-	-	-
	OLG as is, only application	-	-	-	-
	OLG as is, application and tape	-	-	-	-
Closed	OLG as is, dried filter paper	-	-	+?	+
	OLG x10, dried filter paper	-	-	-	-
	OLG x100, dried filter paper	-	-	-	-
Closed	OLG as is, wet filter paper	†	†	†	†
	OLG x10, wet filter paper	†	†	†	†
	OLG x100, wet filter paper	-	-	-	-
Closed	Additive 1	-	-	-	-
	Additive 2	-	-	-	-
	0.1% Chrolhexidine gluconate	-	-	-	-
OLG: Olanedine® solution					
Additive 1: 1% polyoxyethylene (20) polyoxypropylene (20) glycol					
Additive 2: 0.025% glucono-δ-lactone					
†: a well-demarcated infiltrative erythematous reaction					

((I guess the authors need to supply this in an editable format; the red colour needs to be removed, and the typo “Chrolhexidine” corrected to “Chlorhexidine”))