

Generalized reactions during skin testing with clindamycin in drug hypersensitivity: a report of 3 cases and review of the literature

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doi:10.1111/cod.12956

Summary

Background. The diagnostic approach to drug hypersensitivity includes a detailed medical history, clinical examination, and skin testing and/or oral challenge with a culprit or alternative drug, depending on the type of reaction and the suspected drugs. Although skin testing is considered to be rather safe, cutaneous and systemic, including fatal, reactions have been described.

Objectives. To report 3 cases with generalized delayed reactions after skin testing with clindamycin, and to review the existing literature.

Methods. Thorough clinical examination, blood tests and prick, intradermal and patch tests were performed in 3 patients.

Results. All patients experienced generalized maculopapular exanthema after intradermal and patch testing with clindamycin and amoxicillin in the first patient, and clindamycin alone in the second and third patients. None of the patients showed immediate reactions to skin tests, while positive intradermal reactions after 24 h to amoxicillin and clindamycin were observed in the first patient, and positive intradermal reactions after 24 h to clindamycin were observed in the second and third patients.

Conclusions. Skin testing with clindamycin in the diagnosis of drug hypersensitivity carries some risk of adverse reactions. A stepwise and individual diagnostic work-up, considering potential risk factors, and testing in a specialized centre with emergency equipment available is highly recommended.

Key words: drug hypersensitivity; generalized reactions; skin testing.

Drug hypersensitivity reactions are interactions between a pharmacological agent and the human immune system, and can manifest as a heterogeneous clinical spectrum depending on the underlying pathophysiological and

immunological mechanisms (1). When drug hypersensitivity reactions are mediated by specific immunological mechanisms, they are referred to as drug allergy (2). Among adverse reactions to drugs, allergic reactions to β -lactams are the most common (3, 4).

Depending on the time interval between drug exposure and onset of the reaction, as well as the underlying immunological mechanisms, allergic hypersensitivity reactions are classified as immediate and non-immediate (1). Immediate reactions usually occur within 30–60 min after the last intake. They clinically manifest with urticaria and/or angioedema, rhinitis, bronchospasm, and anaphylactic shock (1, 5, 6).

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Conflicts of interest: None declared.

Accepted for publication 2 December 2017

Non-immediate reactions occur later than 1 h after the last drug intake, usually last for several days, and are regarded as being T cell-mediated (1). They commonly manifest with delayed maculopapular exanthema, but also with more severe reactions, such as generalized bullous fixed drug eruption (GBFDE), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN) (1, 7, 8).

The diagnosis of drug hypersensitivity includes a step-wise approach. First, a detailed medical history is taken, including the time interval between the both first and last intake of the suspected drug, the onset of symptoms and the description of the symptoms, the course of the symptoms, and treatment (9–11). In addition, information regarding previous drug intake, concomitant diseases and medication or any other potential risk factors has to be obtained. The allergologic work-up begins with an *in vitro* test, in particular the quantification of total IgE and specific IgE antibodies, if available (9–11). High levels of basal serum tryptase represent a marker for the risk of anaphylaxis. Skin testing includes three basic methods, namely prick, intradermal and patch tests, which have to be selected individually in each case. Prick testing is performed prior to intradermal testing, as this carries a very low risk of adverse reactions (9, 10, 12). The intradermal test carries a slightly higher risk of serious adverse reactions, is the most sensitive skin test, and must be performed with commercial products in injectable form (9). Non-immediate hypersensitivity drug reactions are often T cell-mediated, and can thus be shown by delayed positive readings (48 h; 72 h) of a patch test and/or intradermal test (9). Patch testing has a lower diagnostic value in the diagnosis of non-immediate hypersensitivity drug reactions than intradermal testing (13–15). Skin tests have a high positive predictive value, but a low negative predictive value, i.e., a positive test result normally confirms the diagnosis, whereas a negative skin test result alone does not rule out a drug allergy. If there are negative skin test results and if no contraindications exist, the clinician should consider proceeding to oral challenge tests with the culprit or an alternative drug after careful and individual evaluation of the risks and the benefits for each patient (16, 17).

Although skin testing, when properly performed, is considered to be rather safe, cutaneous or systemic reactions following the above-mentioned tests have been reported. These are usually mild, but can, in some cases, become serious or even life-threatening. For the clinician, it is important to take this into account and to provide emergency treatment in such a case. In this article, we

report 3 cases with delayed generalized reactions after skin testing for drug hypersensitivity. All patients developed generalized maculopapular exanthema and severe pruritus 24 h after allergy skin tests; the first case was related to clindamycin and amoxicillin, and the second and third cases were related to clindamycin. In addition, we reviewed the existing literature concerning cutaneous and generalized reactions caused by drug skin testing.

Materials and Methods

Case 1

A 72-year-old woman was admitted to our department for allergy testing with β -lactam antibiotics and clindamycin 6 months after the clinical index reaction. She had experienced gastric discomfort followed by generalized maculopapular exanthema and severe pruritus accompanied by dyspnoea, anxiety and tachycardia 24 h after starting parenteral treatment with amoxicillin because of a sore throat 10 years previously. Amoxicillin was discontinued the same day. The patient received no therapy, and the rash lasted for 4 weeks. She has avoided amoxicillin since then. Six months before consultation, she received parenteral treatment with clindamycin as endocarditis prophylaxis in the context of dental treatment. During the dental treatment, she was also given local anaesthesia with ultracaine (articaine plus epinephrine; unknown amount). One day later she again developed gastric discomfort followed by generalized maculopapular exanthema, pruritus, dyspnoea, anxiety, and tachycardia, similarly to the previous reaction 10 years previously. She was given 50 mg of methylprednisolone, but the symptoms again lasted for 4 weeks. Skin biopsy and laboratory examinations were not performed. Since then, no antibiotics or local anaesthesia have been used. The clinical history suggested non-immediate hypersensitivity to amoxicillin, clindamycin, or articaine. No antihistamines or corticosteroids were taken in the last weeks before consultation, and no risk factors were present.

Case 2

A 46-year-old woman was admitted for allergy testing with penicillin and clindamycin 7 months after the clinical index reaction to clindamycin. Her history showed that, 3 days before she developed skin symptoms, she had received two tablets of clindamycin following dental treatment. After 24 h she developed maculopapular exanthema beginning from the upper trunk that, within a few hours, became generalized, in addition to mild facial oedema, severe pruritus, and fatigue. No respiratory

or circulatory complaints were reported. The differential blood count and liver enzymes were normal. The patient was given 20 drops of dimetindene, and the symptoms diminished within a few hours. Clindamycin was discontinued on the same day, and the patient has avoided clindamycin since then. She did not remember the details of her previous clinical reaction to penicillin (rash), which occurred > 20 years previously. Concomitant diseases of the patient were rosacea, ulcerative colitis, Bechterew's disease, and fibromyalgia. The medical history of the patient showed no atopic predisposition or concomitant medication.

Case 3

A 55-year-old man was admitted to our department for allergy testing with clindamycin 3 months after the clinical index reaction. He had received clindamycin in preparation for dental sinus surgery. Two hours after taking the first tablet he developed generalized erythema and facial swelling; 2 h later, he experienced nausea and repeated vomiting with a short syncopal episode. Eighteen months before this episode he had received clindamycin and primaquin for the treatment of *Pneumocystis carinii* pneumonia. After 3 weeks of treatment he developed a generalized rash, and both clindamycin and primaquin were discontinued. Owing to the patients' poor medical condition at the time of the hypersensitivity reaction, he could not recall the duration of the rash or the treatment that he may have received for it. The clinical history was suggestive of a hypersensitivity reaction to clindamycin. At the time of diagnosis of *P. carinii* pneumonia, a diagnosis of human immunodeficiency virus infection was made. The patient had no atopic predisposition, and was currently well on treatment with elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate.

We performed blood tests in the first 2 patients for total serum IgE and IgE specific for amoxicillin, ampicillin, penicilloyl G, and penicilloyl V. In the first patient, basal serum tryptase and IgE specific for latex were also determined. In the third patient, total serum IgE and basal serum tryptase were determined. We continued with a drug skin test according to the guidelines (9, 12, 18). In detail, we started with a prick test on the forearm of the patients with clindamycin (150 mg/ml), penicillin-G-Na (100 and 10.000 IE/ml), amoxicillin (2 and 20 mg/ml), and ampicillin (2 and 20 mg/ml). In the first patient, we additionally tested articaine 2%, methyl-4-hydroxybenzoate 10 mg/ml, and sodium metabisulfite 10 mg/ml, according to her medical history. The third patient was tested only with clindamycin. The first reading was performed after 20 min, and further

Table 1. The cumulative applied dose of clindamycin in each patient that resulted in a systemic reaction

Case	Skin test dose of clindamycin (µg)	Total body weight (kg)
1	8250	98
2	8250	Unknown
3	500	Unknown

readings were performed after 24, 48 and 72 h. The allergologic work-up continued with intradermal tests with clindamycin (15 mg/ml), penicillin-G-Na (100 and 10.000 IE/ml), amoxicillin (2 and 20 mg/ml) and ampicillin (2 and 20 mg/ml) in cases 1 and 2, and additionally articaine 2% (predilution 1:20) in case 1. Because of the clinical history of nausea, vomiting and circulatory dysregulation in case 3, anaphylaxis could not be ruled out. As recommended for patients with a history of severe drug reactions, sequential intradermal tests, in this case with clindamycin 0.15, 1.5 and 15 mg/ml, were carried out (9, 10, 12, 18). The intradermal tests were again read after 20 min and 24, 48 and 72 h. Subsequently, we performed patch tests on the patients' backs with clindamycin (150 mg/ml), and, in cases 1 and 2, penicillin-G-Na (5000 IE/ml, pet.; 100.000 IE/ml, pet.; 200.000 IE/ml, NaCl), amoxicillin (200 mg/ml, NaCl), and ampicillin (50 mg/ml, pet. and 200 mg/ml, NaCl), which were supposed to be read after 48 and 72 h. The applied cumulative dose of clindamycin is shown in Table 1.

Results

Case 1

The basal serum tryptase level was normal, at 6.66 µg/l (Phadia Immuno-CAP, Upsala, Sweden), the total serum IgE level was 31.0 kU/l (Phadia Immuno-CAP), and the levels of IgE specific for amoxicillin, ampicillin, penicilloyl G, penicilloyl V and latex were < 0.02 kUA/l. In view of the absence of any immediate reactions to the above-mentioned agents in prick and intradermal tests, a patch test with clindamycin, penicillin-G-Na, amoxicillin and ampicillin was performed. Approximately 24 h later, the patient presented to our clinic with generalized maculopapular exanthema predominantly located on the trunk, accompanied by severe pruritus. The reading of the prick test after 24 h showed a doubtful positive reaction to clindamycin in terms of mild erythema of 2 mm, and no wheal or infiltration. Moreover, the intradermal test showed positive reactions to amoxicillin 20 mg/ml and clindamycin 15 mg/ml (Fig. 1a,b). No reactions were observed for the other concentrations of these antibiotics,

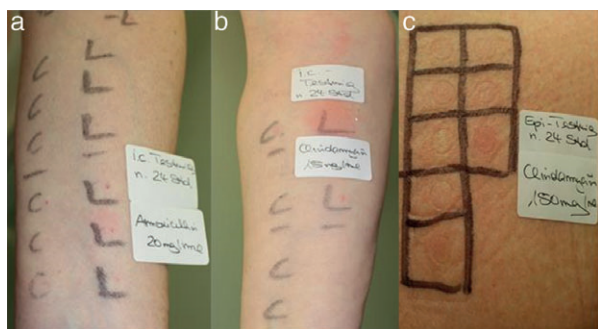


Fig. 1. Case 1. (a) A 24-h reading with positive intradermal test results with amoxicillin 20 mg/ml. (b) A 24-h reading with positive intradermal test results with clindamycin 15 mg/ml. (c) Patch test with a positive reaction to clindamycin 150 mg/ml after 24 h. No delayed cutaneous reactions to amoxicillin, penicillin-G and ampicillin were observed.

for the other tested β -lactams, or for articaine. Because of the severe symptoms, we removed the patch test from the back. A positive reaction was seen to clindamycin (150 mg/ml), with the presence of erythema after only 24 h (Fig. 1c), but there were no reactions to amoxicillin, penicillin-G, and ampicillin. The patient received oral methylprednisolone 40 mg daily for 3 days, and a topical ointment containing polidocanol, which led to remission of the symptoms within a few days. The patient was given the diagnosis of delayed-type hypersensitivity to clindamycin and amoxicillin, and was advised not to take any of these drugs or other β -lactams in the future. Also, cephalosporins should be avoided before a further allergologic work-up, including a challenge test, has been performed, as they may show cross-reactivity to aminopenicillins. We advised our patient to later perform an oral drug challenge in our clinic with alternative antibiotics, in order to have a safe alternative for potential future need, and also to clarify potential cross-reactivity to cephalosporins.

Case 2

The total serum IgE level was 29.0 kU/l (Phadia Immuno-CAP), and the levels of IgE specific for amoxicillin, ampicillin, penicilloyl G and penicilloyl V were <0.02 kU/l. Prick and intradermal tests showed no immediate reactions to the above-mentioned agents, so a patch test with clindamycin, penicillin-G-Na, amoxicillin and ampicillin in the above-mentioned concentrations was performed. Approximately 24 h later, the patient presented with severely pruritic generalized maculopapular exanthema. She reported that the symptoms began the previous night, with generalized pruritus followed by



Fig. 2. Case 2. (a) A 24-h reading with positive intradermal test results with clindamycin 15 mg/ml. (b) Development of facial oedema, in particular of the lids and the right cheek. (c) Maculopapular exanthema predominantly located on the upper trunk of the patient.

maculopapular exanthema initially located on the upper trunk that, within a few hours, became generalized. The reading of the prick test after 24 h was negative. In the intradermal test reading, a significant positive reaction to clindamycin 15 mg/ml with a 38 mm-diameter infiltrate was seen (Fig. 2a). No reactions were observed to all concentrations of other tested β -lactams. By the time of consultation, facial oedema (Fig. 2b) and maculopapular exanthema located on the trunk (Fig. 2c) could be seen. Therefore, we immediately removed the patch test from the back of the patient. No reactions were seen to clindamycin, amoxicillin, penicillin-G or ampicillin after 24 h. The patient received oral methylprednisolone 40 mg daily for 3 days, oral antihistamines, and a topical ointment containing polidocanol, which led to remission of the symptoms within a few days. The patient was diagnosed with delayed-type hypersensitivity to clindamycin, and was advised not to take clindamycin, penicillin or other β -lactams in the future unless a further allergologic work-up, including a challenge test, has proven tolerability.

Case 3

The basal serum tryptase level was normal, at 6.30 μ g/l (Phadia, Immuno-CAP). The total serum IgE level was 60.9 kU/l (Phadia Immuno-CAP). A prick test and a patch

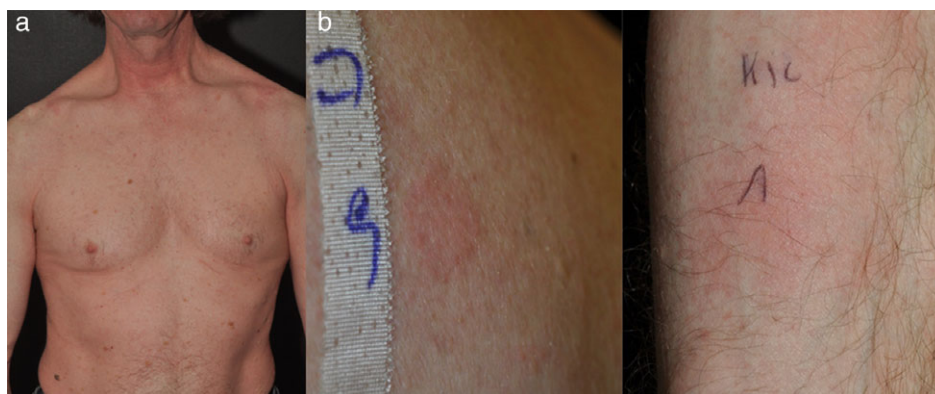


Fig. 3. Case 3. **(a)** Erythematous macular rash on the trunk with sparing of the periumbilical area 24 h after intradermal testing with clindamycin 0.15, 1.5 and 15 mg/ml. **(b)** On the left, the 72-h reading of the patch test with clindamycin 150 mg/ml showing a positive result. On the right, the 24-h reading of the intradermal test with clindamycin 0.15, 1.5 and 15 mg/ml showing a positive result.

test with clindamycin was carried out as described above, and showed no immediate reactions. The prick test gave negative results at 24 and 48 h, as did the patch test at 48 h. The intradermal test with clindamycin showed no immediate reactions to all concentrations tested. The patient attended our clinic on the following day for a 72-h reading of the patch test and a 24-h reading of the intradermal test with clindamycin. Overnight, he had developed a pruritic erythematous macular rash affecting the trunk, face, and upper extremities (Fig. 3a). There was no rash in the intertriginous areas. Both of the above-mentioned tests with clindamycin showed positive reactions with erythema and induration at the test sites (Fig. 3b). The patient refused treatment with corticosteroids, and the rash resolved within 1 week. A repeat patch test with clindamycin at a later date gave a negative result and failed to provoke a systemic reaction. Delayed-type hypersensitivity to clindamycin was diagnosed, and the patient was advised not to take this drug in the future.

Discussion

In this article, we show that skin testing with drugs, which is considered to be a rather safe diagnostic approach, if performed in accordance with the published guidelines (9, 12, 18), carries some risk of adverse local and systemic reactions that should not be underestimated.

Skin, intradermal and patch tests with drugs can all cause local irritation that may often be taken as a false-positive reaction and thus affect the diagnostic outcome. Prick testing is considered to be the safest method of skin testing, and should always be performed prior to intradermal testing. Although the intradermal test is more sensitive than the prick test, it is more likely

to induce systemic reactions (19). Systemic reactions caused by patch tests are extremely rare (20). Among skin tests with drugs, it seems that those with β -lactams are more likely to cause systemic adverse reactions, even though this happens in only 0.1–2% of all tested patients (21, 22). The clinical manifestation of these reactions varies from generalized cutaneous reactions to anaphylactic shock (9, 21, 22).

Morales-Cabeza et al. (23) reported an intense local reaction over the test area in a patient who underwent intradermal testing with clindamycin. Syrigou et al. described generalized urticarial exanthema after intradermal testing with β -lactams (24). All of our patients developed generalized maculopapular exanthema during delayed positive intradermal and patch tests: with amoxicillin and clindamycin in the first case, and with clindamycin in the second and third cases. To the best of our knowledge, our cases are the first reports of a generalized reaction with maculopapular exanthema related to skin testing with clindamycin. It is remarkable that the skin test concentrations applied (Table 1), which are far lower than the doses that are therapeutically given, caused systemic reactions. These systemic reactions might have been prevented by keeping a 2–4-day interval between patch testing and intradermal testing. However, this was not the case in our third patient, in whom a later repetition of the patch test gave a negative result with clindamycin, and did not result in a systemic reaction. Pereira et al. (25) found positive patch test reactions to clindamycin (10% pet.) in 9 of 30 adults with previous maculopapular exanthema, but none developed a systemic reaction on skin testing, which is evidence for the safety of patch testing. Lammintausta et al. (26) found true positive patch test reactions to clindamycin

(10% and 20% pet., and 100%) in 4 of 6 patients, without describing systemic reactions. However, in 1 case the patch test result was false-negative, as in our third case, in which repeat patch testing with clindamycin gave a negative result. The reason for a positive result in initial patch testing with clindamycin is unclear, but it is possibly related to the increased total dose applied in combination with prick and intradermal tests applied at that time. Regarding non- β -lactam antibiotics, an ENDA/EAACI Drug Allergy Interest Group position paper (12) states that recommendations on concentrations for non- β -lactam antibiotics such as clindamycin are currently not possible (12). We used non-irritating clindamycin test concentrations (up to 15 mg/ml) as described in the literature (12, 27, 28). Interestingly, Notman et al. (28) found a high number of false-negative intradermal test results with clindamycin when they used concentrations of 0.15 to 15 mg/ml (32% positive oral challenge tests in 31 patients with prior negative skin tests). Unfortunately, they did not patch test the patients. Our test procedure using a patch test on the same day as a prick test and an intradermal test was according to our national German guideline (10). Moreover, given a significantly higher number of negative intradermal test results with the same concentrations of clindamycin when patch testing was performed on the same day, we cannot state that clindamycin is not suitable for intradermal testing or that the concentration used might be too high. It is remarkable that immediate systemic reactions such as urticaria and anaphylaxis have been described mainly after skin testing with β -lactams (19). Syrigou et al. (24) reported a patient who reacted with anaphylaxis during prick testing for allergy to amoxicillin (24), and Riezzo et al. (29) reported an anaphylactic reaction with a fatal outcome after intradermal skin testing with ceftriaxone without a preceding prick test.

In a previous analysis of 998 skin tests on patients with a suspected β -lactam allergy, ~8.8% of patients showed systemic reactions during skin tests. It is remarkable that 5 of them had already reacted in the very early prick test step (30). It is widely accepted that intradermal tests carry a higher risk of adverse reactions than prick tests (9, 31), and a negative prick test result cannot rule out a possible positive reaction in the following intradermal or patch test, as happened in 2 of our patients. However, the relevance of any positive reaction should be evaluated before proceeding to the next step. We are not aware of any description of a systemic immediate reaction with regard to skin testing with clindamycin. It is essential for clinicians to make an individual risk–benefit analysis regarding the clinical reaction, the diagnostic and treatment possibilities, the risk of possible adverse reactions and the importance of the tested drug in every patient. Depending on the type of drug hypersensitivity, different diagnostic protocols have to be followed. In severe, non-immediate reactions such as AGEP, GBFD, DRESS, SJS, or TEN, consideration must be given to extending the time interval between tests, and not performing an intradermal test with the highest concentration before performing patch tests (8, 9). Positive patch test results are most common in patients with DRESS and AGEP, but are less common in patients with fixed drug eruption or SJS/TEN (8).

In conclusion, severe local or generalized reactions after skin testing, as in our patients, should be taken seriously, and an oral challenge test with the responsible agent should not be performed. In such cases, an oral drug challenge with a presumably safe alternative agent can be performed later. As reactions caused by drug allergy can occur at any time in routine diagnostic practice, it is important for all patients to be adequately informed about the risks associated with the testing. Written informed consent for the performance of skin tests or oral challenge should always be obtained (11).

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