

Allergy Diagnostic Testing in Clindamycin-Induced Skin Reactions

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Key Words

Challenge test · Exanthema · Hypersensitivity ·
Provocation test · Skin test

Abstract

Background: In clinical practice, clindamycin is increasingly used because of its good tolerability and high efficacy with excellent tissue penetration. However, with increased application of clindamycin, the frequency of side effects such as skin eruptions rises and the need for diagnostic testing to identify clindamycin allergy increases. The aim of this retrospective analysis was to demonstrate the results of skin and challenge tests in cases of clinically suspected clindamycin allergy. **Methods:** We evaluated 33 patients with a history of a skin reaction in temporal relation to treatment with clindamycin using standardized patch and prick skin testing. In the case of negative skin tests, oral challenges were performed. **Results:** Clindamycin hypersensitivity was excluded in 20 patients by negative skin tests and subsequently tolerated oral challenge tests. In 5 patients, positive skin tests strongly suggested delayed-type non-IgE-mediated allergic clindamycin hypersensitivity. In 6 skin test-negative patients (2 patients refused challenge tests), a rash was provoked by controlled challenge tests. **Conclusions:** The evaluation of patients with clindamycin-associated skin reactions should include appropriate allergologic tests establishing or ex-

cluding the diagnosis of clindamycin hypersensitivity. Combined testing, i.e. skin tests and subsequent challenge tests, appears to be necessary to definitely confirm or rule out the presence of allergic clindamycin hypersensitivity.

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Introduction

Clindamycin is a synthetic lincosamide antibiotic which inhibits bacterial protein synthesis and is approved for the treatment of anaerobic, streptococcal and staphylococcal infections. There is increased interest in the use of clindamycin because it achieves high tissue levels and appears to be effective against toxin elaborating strains of streptococci and staphylococci [1]. Its major disadvantage is its propensity to cause *Clostridium difficile*-associated diarrhea. In addition, non-IgE-mediated delayed-type hypersensitivity (DTH) to clindamycin may occur. Macular or maculo-papular exanthemata seem to account for the majority of these reactions but hypersensitivity syndrome and bullous skin reactions with internal organ involvement have also been reported [2–4].

Allergic clindamycin hypersensitivity may be suspected when (1) the symptoms and physical findings are compatible with an immune reaction; (2) there is a definite temporal relationship between administration of clinda-

mycin and the skin reaction; (3) the patient had previously received clindamycin on one or more occasions, and (4) there is no other clear cause for the skin symptoms [5]. Skin tests can be used for the evaluation of suspected clindamycin hypersensitivity, and in some cases DTH can be confirmed by positive late skin test reactions [6, 7]. In the case of negative skin tests, the most prudent way of establishing the diagnosis of clindamycin allergy is a standardized challenge test [8].

The aim of our diagnostic procedure including skin and oral challenge tests was to identify the causal drug for the skin reaction. In a retrospective analysis, we evaluated the reliability of these test methods for definite identification of clindamycin allergy.

Methods

Patients

From 2003 to 2007, all patients referred to our allergy clinic with a suggestive history of a clindamycin-induced skin reaction who had been skin tested with clindamycin were retrospectively identified. After a thorough review of patient files, all available clinical data were collected. As part of the standard practice in our allergy clinic, all subjects had been informed of any risks involved with the testing and written informed consent for an allergologic work-up (skin tests, oral challenge) had been obtained. Since determination of potential drug allergy is part of routine diagnostic practice in our clinic, further ethical approval was not required.

Skin Test

At least 6 weeks after clearance of the skin rash, prick tests on the forearm and patch tests on the upper back with clindamycin (and if necessary additionally with other suspected drugs) were performed according to international standards [9]. For patch testing, clindamycin tablets (150 mg) were ground in a mortar and suspended in 1 ml of physiological saline solution. Finn chambers with an inside diameter of 8 mm and height of 0.4 mm were filled with 1 drop of this suspension, i.e. approximately 20–30 μ l. Parenteral clindamycin preparations were used in therapeutic concentrations for prick tests, i.e. 150 mg/ml. All agents were freshly reconstituted, and physiological saline solution was used as negative control. To exclude IgE-mediated hypersensitivity, prick tests were read after 20 min. Patch tests were removed after 1 day, and late reactions were evaluated after 2, 3 and 4 days. Late reactions to prick and patch tests were documented according to the International Contact Dermatitis Research Group criteria, i.e. faint macular erythema (? = doubtful reaction), erythematous infiltration (1+ = weak positive reaction), erythematous infiltration with papules and vesicles (2+ = strong positive reaction) and bullous reaction (3+ = extreme positive reaction). In individual cases, drugs administered concomitantly with clindamycin (e.g. other antimicrobial drugs, nonsteroidal anti-inflammatory drugs) were excluded as potential triggers of the skin reaction by additional skin and challenge tests.

Table 1. Grading system for the extent of clindamycin-induced exanthema

Grade	Symptoms
1 (mild)	macular or maculo-papular eruption, <25% of body surface area
2 (moderate)	macular or maculo-papular eruption, 25–50% of body surface area
3 (severe)	macular, papular or pustular eruption, >50% of body surface area; severe, generalized erythroderma

Oral Challenge

Patients with negative skin tests were offered oral challenge tests in an outpatient setting according to an established protocol using standardized single clindamycin doses, i.e. 75, 150, 300 and 450 mg, respectively, adding up to a daily defined dose of 975 mg. The general principles of our challenge protocol were as follows [8, 10]: (1) the time interval since the hypersensitivity reaction was at least 6 weeks; (2) during the entire challenge procedure, the patient was observed and equipment for emergency treatment was available; (3) the dosage of clindamycin increased stepwise to a normal dose with intervals of 1 h between the individual doses; (4) there was strict adherence to absolute and relative contraindications for drug challenge tests, and (5) prior to challenge testing, written informed consent was obtained from each patient.

Results

Patients

A total of 33 patients was included in the analysis. The average age of the subjects (25 females and 8 males) at the time of the clindamycin-induced skin reaction was 50 years (ranging from 10 to 77 years). Twenty-eight patients had suffered most likely from macular or maculo-papular exanthema, whereas 5 patients described itchy red skin areas without resemblance to an infectious exanthema. The extent of exanthema was graded according to table 1; severe skin reactions such as acute generalized exanthematous pustulosis, Stevens-Johnson syndrome or toxic epidermal necrolysis were not observed. In table 2, clinical data including underlying infectious disease, latency of skin eruption and reaction morphology are summarized. The latency between administration of clindamycin and onset of the skin rash ranged from less than 1 day (n = 3), 1 to <2 days (n = 6), 2 to <3 days (n = 4), 3 to <6 days (n = 3), up to 6–12 days (n = 17). A definite previous exposure to clindamycin without any adverse reaction was identifiable in 10 patients.

Table 2. Clinical data of the 33 patients studied

Mean age (range), years	50 (10–77)
Males/females	8/25
Indication for clindamycin, infectious disease	
Upper respiratory tract	9
Soft tissue	13
Dental/maxillofacial	11
Latency	
<1 day	3
<2 days	6
<3 days	4
<6 days	3
6–12 days	17
Skin symptoms	
Exanthema grade 1	9
Exanthema grade 2	13
Exanthema grade 3	6
Erythema	5

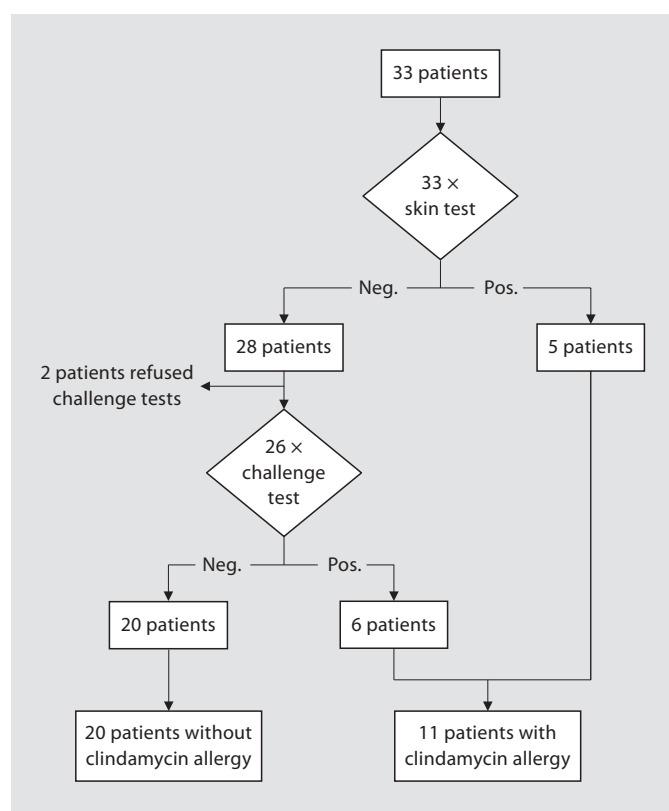
Values represent numbers of patients, except where indicated otherwise.

Table 3. Results of skin and challenge tests in 11 patients with allergic clindamycin hypersensitivity

Patient No.	Patch test on day 3	Prick test on day 3	Challenge test latency, h	Challenge test morphology
1	1+	1+	n.d.	n.a.
2	2+	1+	n.d.	n.a.
3	3+	2+	n.d.	n.a.
4	1+	–	n.d.	n.a.
5	2+	1+	n.d.	n.a.
6	–	–	12	NPFDE
7	–	–	10	exanthema grade 2
8	–	–	6	SDRIFE
9	–	–	6	exanthema grade 2
10	–	–	13	SDRIFE
11	–	–	15	exanthema grade 1

Quantification of positive late reactions of patch and prick tests was performed as described in Methods.

See table 1 for the grading system for exanthema. n.a. = Not applicable; n.d. = not done; – = negative result; SDRIFE = symmetrical drug-related intertriginous and flexural exanthema; NPFDE = nonpigmented fixed drug eruption.



Skin Test

Results of the diagnostic procedure are summarized in a flow chart (fig. 1). Prick and patch tests were performed in all subjects and the time interval between the skin reaction and allergologic work-up was less than 1 year in all cases. Prick test readings after 20 min were negative in all patients. In 28 patients, late readings of patch and prick skin tests with clindamycin were also completely negative. In 5 patients, diagnosis of DTH to clindamycin was confirmed based on positive late reactions in patch and/or prick skin tests. Results of positive skin tests are summarized in table 3.

Oral Challenge

Twenty-six subjects with negative prick and patch skin tests were challenged orally with clindamycin, while 2 patients refused challenge tests. In association with these challenge tests, 3 patients had clinically clear-cut maculo-papular exanthema as assessed by a dermatologist (ta-

Fig. 1. Steps and results of the allergologic work-up in 33 patients with a history of a skin reaction in temporal relation to clindamycin treatment. Neg. = Negative result; Pos. = positive result.

ble 3). Additionally, 2 patients suffered from a symmetrical intertriginous exanthema, whereas 1 patient showed asymmetrically distributed multiple erythematous patches without residual hyperpigmentation. Clindamycin hypersensitivity was excluded in 20 patients by performing the described allergologic work-up, i.e. negative skin tests and subsequent oral challenge tests which were tolerated uneventfully.

Discussion

The frequency of clindamycin hypersensitivity reactions has not been systematically investigated. Due to the difficulty in verifying whether symptoms occurring days after clindamycin exposure are in fact caused by clindamycin, the frequency of DTH reactions has been estimated as ranging from <1% to 10.5% [4]. However, exanthema in temporal relationship to the application of clindamycin may originate from causes other than the suspected drug, e.g. viral exanthema. Careful interpretation of anamnestic details before and after clindamycin exposure is crucial. Also, other antimicrobial or nonsteroidal anti-inflammatory drugs given concomitantly with clindamycin may trigger skin eruptions.

In our patients, the latency between initiation of clindamycin intake and development of skin symptoms provided an indication of whether sensitization had occurred under the current treatment or whether the patient had been reexposed after previous sensitization. In cases with sensitization during the current treatment, the exanthema develops at the earliest after 7–10 days, whereas reexposure after previous sensitization induces skin reactions 6 h to 3 days after initiation of clindamycin administration. Therefore, if symptoms of a DTH reaction evolve up to 14 days after onset of exposure to clindamycin, an allergologic examination including patch and prick skin tests should be performed. Retrospectively, urticaria and exanthema may not be differentiated by patients and physicians, and for this reason testing for both immediate-type (evaluation of prick tests after 20 min) and delayed-type reactions (evaluation of patch and prick tests after 2, 3 and 4 days) is reasonable.

Based on published data, the significance of clindamycin skin testing for patients with a history of clindamycin hypersensitivity is a matter of debate. Recently, Notman et al. [11] calculated a negative predictive value of merely 68% for exclusive prick and intradermal tests (without patch test) and proposed abandoning clindamycin skin testing as a diagnostic modality. However, performing

combined prick and patch tests in 33 patients with suspected DTH to clindamycin, we obtained clearly positive results in 5 patients, and experience regarding clindamycin-associated exanthema suggests that skin test positivity is an indicator of DTH [6, 11–13]. We observed that patch test reactions were stronger than prick reactions, and in 1 case only the patch test was positive. False-positive late readings of prick or patch test reactions are theoretically possible, but are unlikely due to the long experience with the test methods, reliable reading of test results including morphology and crescendo pattern and because negative skin tests with clindamycin were obtained in a subset of our patients and in 6 control subjects. To further avoid false-positive reactions, it is generally recommended that skin testing should be performed 6 weeks after clearing of the skin eruption [13, 14].

Our data and previous studies indicate that negative results of skin tests do not exclude the allergic nature of a skin reaction occurring after clindamycin application. The reasons for the relatively poor indicative value of skin testing with clindamycin are unknown. Skin tests are frequently negative in the case of fixed drug eruption or intertriginous exanthema, especially when skin tests are not performed intralesionally. Another cause for the high frequency of false-negative skin tests in patients with clindamycin allergy may be the metabolism of the parent compound. Clindamycin is extensively metabolized in the liver, probably by the cytochrome P450 isoenzyme 3A4, and some of its metabolites are active, such as N-dimethyl clindamycin and clindamycin sulfoxide [15]. Clindamycin is not capable of spontaneous covalent conjugation to carrier proteins but may require oxidative metabolism to reactive intermediates to be recognized by the immune system [7, 16, 17]. Nonstandardized skin test concentrations may also contribute to false-negative skin tests. Late readings of additional intradermal tests using nonirritating clindamycin concentrations could increase test sensitivity. However, intradermal testing with clindamycin is not routinely performed at our allergy clinic in cases with a history of a delayed-type reaction. The lymphocyte transformation test with clindamycin as a further diagnostic method is not standardized yet and should only be performed in specialized laboratories, and the results have to be interpreted very carefully [18].

Oral challenge tests are considered to be the gold standard to establish or exclude drug hypersensitivity [8]. In the case of late skin test positivity to clindamycin, oral challenges are contraindicated because patients may develop severe exanthema. However, without challenge tests it remains uncertain whether all patients with a pos-

itive skin test reaction to clindamycin will develop exanthema after reexposure. Because the negative predictive value of clindamycin skin tests appears to be low, careful controlled challenge testing with progressive increase of clindamycin may be attempted to verify or falsify negative skin test results [11]. Before performing a drug challenge test, an assessment of the risk-benefit relationship has to be undertaken, and caution and surveillance are mandatory. Challenge tests may lead to the development of skin symptoms either as early as 1–6 h or as late as 3 days after the challenge [8]. In our series, 6 patients had a positive oral challenge, of whom 2 had the reactions within 6 h and 4 between 10 and 15 h. Clinical observation of short latency between intake of the culprit drug and development of skin lesions suggests that in addition to drug-specific T cells, circulating drug-specific IgG antibodies may play a pathogenic role. If clindamycin is required by a patient with a positive oral challenge, tolerance induction may be an option [19].

Commonly, clindamycin-induced skin lesions may present as a macular or maculo-papular exanthema or as

atypical rashes without resemblance to an infectious exanthema [6, 11]. Three of our challenged patients developed more specific skin eruptions. In 2 patients, we observed intertriginous exanthema, for which the acronym SDRIFE (symmetrical drug-related intertriginous and flexural exanthema) was recently proposed, whereas 1 patient developed nonpigmented fixed drug eruption [20, 21]. In contrast to case reports describing severe bullous skin reactions, these DTH reactions to clindamycin are not life-threatening but may be accompanied by fever, pruritus and slightly elevated liver enzymes [3, 6].

In conclusion, allergic hypersensitivity may be one of the possible mechanisms of skin reactions during clindamycin therapy. In order to identify these patients, all patients with a history of skin symptoms occurring up to several days after clindamycin application should be subjected to an allergologic work-up. In a significant number of patients, skin testing alone is not sufficient to identify clindamycin allergy and on a risk-benefit assessment, oral challenge tests may be offered.

References

- Guay D: Update on clindamycin in the management of bacterial, fungal and protozoal infections. *Expert Opin Pharmacother* 2007; 8:2401–2444.
- Kapoor R, Flynn C, Heald PW, Kapoor JR: Acute generalized exanthematous pustulosis induced by clindamycin. *Arch Dermatol* 2006; 142:1080–1081.
- Paquet P, Schaaf-Lafontaine N, Pierard GE: Toxic epidermal necrolysis following clindamycin treatment. *Br J Dermatol* 1995; 132: 665–666.
- Mazur N, Greenberger PA, Regalado J: Clindamycin hypersensitivity appears to be rare. *Ann Allergy Asthma Immunol* 1999; 82:443–445.
- Executive summary of disease management of drug hypersensitivity: a practice parameter. Joint Task Force on Practice Parameters, the American Academy of Allergy, Asthma and Immunology, the American Academy of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1999; 83:665–700.
- Lammintausta K, Tokola R, Kalimo K: Cutaneous adverse reactions to clindamycin: results of skin tests and oral exposure. *Br J Dermatol* 2002; 146:643–648.
- Pichler WJ: Deciphering the immune pathomechanism of cutaneous drug reactions. *Allergy* 2002; 57:34–36.
- Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al: Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003; 58:854–863.
- Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P: General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002; 57: 45–51.
- Trcka J, Seitz CS, Bröcker EB, Gross GE, Trautmann A: Aminopenicillin-induced exanthema allows treatment with certain cephalosporins or phenoxymethyl penicillin. *J Antimicrob Chemother* 2007; 60:107–111.
- Notman MJ, Phillips EJ, Knowles SR, Weber EA, Shear NH: Clindamycin skin testing has limited diagnostic potential. *Contact Dermatitis* 2005; 53:335–338.
- Barbaud A: Drug patch testing in systemic cutaneous drug allergy. *Toxicology* 2005; 209:209–216.
- Lammintausta K, Kortekangas-Savolainen O: The usefulness of skin tests to prove drug hypersensitivity. *Br J Dermatol* 2005; 152: 968–974.
- Barbaud A, Reichert-Penetrat S, Trechot P, Jacquin-Petit MA, Ehlinger A, Noirez V, et al: The use of skin testing in the investigation of cutaneous adverse drug reactions. *Br J Dermatol* 1998; 139:49–58.
- Wynalda MA, Hutzler JM, Koets MD, Podoll T, Wienkers LC: In vitro metabolism of clindamycin in human liver and intestinal microsomes. *Drug Metab Dispos* 2003; 31: 878–887.
- Coleman JW, Blanca M: Mechanisms of drug allergy. *Immunol Today* 1998; 19:196–198.
- Evans WE, McLeod HL: Pharmacogenomics – drug disposition, drug targets, and side effects. *N Engl J Med* 2003; 348:538–549.
- Pichler WJ, Tilch J: The lymphocyte transformation test in the diagnosis of drug hypersensitivity. *Allergy* 2004; 59:809–820.
- Marcos C, Sopena B, Luna I, Gonzalez R, de la Fuente J, Martinez-Vazquez C: Clindamycin desensitization in an AIDS patient. *AIDS* 1995; 9:1201–1202.
- Häusermann P, Harr T, Bircher AJ: Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? *Contact Dermatitis* 2004; 51:297–310.
- Shiohara T, Mizukawa Y: Fixed drug eruption: a disease mediated by self-inflicted responses of intraepidermal T cells. *Eur J Dermatol* 2007; 17:201–208.