

Clindamycin skin testing has limited diagnostic potential

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We examined the role of clindamycin prick and intradermal skin testing in a tertiary care clinic population. Experience with diagnostic modalities such as prick and intradermal testing has been limited with clindamycin. A retrospective chart review was conducted for patients with immunologic reactions temporally associated with clindamycin who were referred to the Drug Safety Clinic (Toronto, Ontario). A total of 31 patients were identified who had undergone prick and intradermal skin testing. All 31 negative immediate prick and intradermal tests were followed by a 150 mg oral dose of clindamycin. 10/31 (32%) subjects had significant reactions to the oral clindamycin provocation. 2 patients reported delayed reactions at the clindamycin intradermal test sites. Our experience suggests that prick and intradermal skin testing is not adequate in identifying patients with previous allergic reactions associated with clindamycin. Oral provocation tests can be used in patients with histories of clindamycin adverse reactions; however, it should be offered on a risk-benefit basis.

Key words: antibiotics/ adverse effects; clindamycin/ adverse effects; drug eruptions/ aetiology; false negative reactions; hypersensitivity (immediate/ delayed); intradermal tests; prick testing; skin tests.

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Clindamycin is a synthetic antibiotic that inhibits bacterial protein synthesis and is used primarily in the treatment of gram-positive and anaerobic infections. Adverse events associated with clindamycin include diarrhoea and pseudomembranous colitis (1). In addition, delayed cutaneous reactions associated with clindamycin are fairly common, ranging from <1% to 10.5% (2). Severe skin syndromes and drug-induced hypersensitivity reactions with fever and internal organ involvement have also been reported (3, 4).

Prick and intradermal skin tests are used primarily to assess a patient's potential for an immunoglobulin E (IgE)-mediated reaction. These tests have been validated for IgE-mediated reactions associated with penicillin, but little information exists for other drugs, including clindamycin (5, 6). Intradermal tests with delayed readings have also been used in the assessment of delayed cutaneous eruptions (7). The role of skin tests was described in 6 patients with a history suggestive of clindamycin delayed hypersensitivity reactions (8). None of the patients tested positive on prick testing; 4 patients had positive

patch tests and 1 had false-positive patch test. Given the small sample size in this report and because only three subjects received an oral challenge, the predictive values for these tests cannot be calculated.

We describe our experience with clindamycin prick and intradermal testing in a tertiary care clinic population with patients who presented with suspected allergic reactions to clindamycin.

Materials and Methods

Subjects

A total of 31 subjects with histories suggestive of an immunologically mediated reaction associated with clindamycin and who were prick and intradermal skin tested to clindamycin were retrospectively identified. All subjects who were negative on prick and intradermal skin testing had been challenged with an oral dose of clindamycin. As part of the standard practice at the Drug Safety Clinic, all subjects are required to sign an informed consent form for the skin tests and the

oral challenge and are informed of any risks involved with the testing.

Skin tests

Prick testing was performed with concentrations of intravenous clindamycin (clindamycin phosphate, Pharmacia Upjohn, Uppsala, Sweden) varying from 0.15 mg/ml to 15 mg/ml. Histamine (1 mg/ml) was used as a positive control and saline as a negative control. Intradermal testing was subsequently performed in patients who were negative on prick testing. Intradermal injections were carried out using normal saline as the control and intravenous clindamycin in concentrations varying from 0.15 mg/ml to 15 mg/ml.

The results of the prick and intradermal skin testing were interpreted at 30 min, with positive reactions defined by a wheal 3 mm greater than the saline control for the prick testing and an increase in the wheal greater than 5 mm for the intradermal testing (9). All patients were asked to check the skin test sites for 48–72 hr following testing and report any reaction (e.g. oedema and erythema).

Oral provocation tests

Following baseline vital signs and peak flow assessment, oral provocation tests were carried out on patients who had negative prick and intradermal skin test results. Subjects were given a 150 mg tablet of clindamycin. After 3 hr of observation, a physician examined the subjects, and repeat vital signs and peak flow assessments were performed. Patients were discharged with instructions to call the clinic in the event of a delayed reaction.

Data analysis

Statistical comparisons were performed using a Fisher's exact test. The sensitivity, specificity, positive and negative predictive values were calculated according to the equations in Saarinen et al. (10).

Results

Patient demographics

A total of 31 subjects were included in the study. The mean age of the subjects was 53.6 years (range 15–79) years. 77% of the population were females. Demographic characteristics of the patients and their reaction histories are summarized in Table 1.

Prick testing and intradermal skin testing and oral provocation results

The prick and intradermal skin tests were performed on all subjects; all results were negative. Sensitivity of the prick and intradermal skin testing was determined to be 0%, specificity 100%, positive predictive value 0% and negative predictive value 68%.

All 31 negative prick and intradermal skin tests were followed by a 150 mg oral dose of clindamycin. 10/31 (32%) subjects had clinically significant reactions associated with the oral challenge, as witnessed by a physician (Table 1). 6/10 (60%) patients positive on oral challenge had previous histories of an accelerated reaction. Two patients had a delayed reaction (e.g. erythema, oedema and pruritus) at the site of the skin tests. One of these patients experienced a positive oral provocation test. Statistical comparisons were performed, and no significant correlations were found between age, sex, original reaction history, interval between the adverse drug reaction and testing and testing results.

Discussion

Delayed cutaneous reactions have been commonly associated with clindamycin, where true IgE-mediated reactions are uncommon. Intradermal skin and prick testings have been successfully applied in the assessment of IgE-mediated immunological reactions for drugs such as penicillin, where major and minor determinants have been identified (5, 6). Skin testing has also been recognized as a tool for diagnosing delayed hypersensitivity by the occurrence of delayed reactions at the skin test site, particularly with ampicillin (9, 11).

There are several reports in the literature documenting immediate prick and intradermal testing with clindamycin; none of these reports describe positive results (2, 4, 8, 12, 13). This is similar to our experience, in which 31 patients with a history of an allergic reaction to clindamycin were skin tested with this agent; none of the prick or intradermal skin tests was positive. 14/31 patients had a history that may have been IgE-mediated; yet none of these patients were positive on skin testing either. There are no reports describing delayed prick or intradermal tests with clindamycin, but there are reports of delayed rashes after oral challenge (8). 2 of our patients developed a delayed reaction at the intradermal skin test site, and 1 of these patients was positive after the oral challenge. Patch testing performed with clindamycin has yielded mixed results and may be more useful

Table 1. Patient characteristics: reaction histories and oral challenge results in skin test negative patients

Patient profile – Age (sex)	Reaction history (immediate, accelerated or delayed)	Original reaction (time to onset)	Oral challenge result/reaction*	Time to onset of reaction
57 (female)	Delayed	Urticaria (7 days)	Negative/NA	NA
59 (female)	Delayed	Rash (10 days)	Negative/NA	NA
53 (female)	Delayed	Pruritic rash (5 days)	Negative/NA	NA
32 (female)	Delayed	Breathing difficulties (5 days)	Negative/NA	NA
44 (female)	Accelerated	Urticaria (1 day)	Negative/NA	NA
37 (female)	Delayed	Rash (10 days)	Negative/NA	NA
53 (female)	Accelerated	Maculopapular rash (1 day)	Negative/NA	NA
72 (female)	Delayed	Pruritic rash (21 days)	Negative/NA	NA
47 (female)†	Delayed	Pruritic rash (7 days)	Negative/NA	NA
71 (female)	Delayed	Rash (5 days)	Negative/NA	NA
73 (female)	Accelerated	Pruritus (2 days)	Negative/NA	NA
39 (male)	Delayed	Maculopapular rash (7 days)	Negative/NA	NA
40 (female)	Accelerated	Rash (3 days)	Negative/NA	NA
44 (male)	Accelerated	Breathing difficulties (3 days)	Negative/NA	NA
55 (female)	Accelerated	Rash (18 hr)	Negative/NA	NA
79 (male)	Not documented	Erythema (NA)	Negative/NA	NA
51 (female)	Not documented	Rash (NA)	Negative/NA	NA
66 (female)	Accelerated	Nausea, urticaria (2 hr)	Negative/NA	NA
72 (female)	Accelerated	Pruritic rash (3 days)	Negative/NA	NA
44 (male)	Delayed	Urticaria (4 days)	Negative/NA	NA
68 (female)	Not documented	Facial oedema (NA)	Negative/NA	NA
29 (female)	Accelerated	Pruritic rash (5 hr)	Positive/urticaria with facial pruritus	1 day
47 (female)	Delayed	Maculopapular rash (9 days)	Positive/pruritus and oedema‡	2 hr
15 (male)	Accelerated	Pruritic rash (3 days)	Positive/pruritic rash	5 hr
77 (female)	Accelerated	Pruritic rash (2 hr)	Positive/pruritic rash	4 hr
76 (female)	Accelerated	Pruritus, Erythema (2 days)	Positive/pruritus, erythema	5 hr
57 (female)†	Delayed	Pruritus	Positive/maculopapular rash	2 days
37 (male)	Accelerated	Pruritic rash, facial oedema (1 day)	Positive/pruritic rash	5 hr
68 (male)	Not documented	Rash (NA)	Positive/pruritic rash	6 hr
65 (female)	Delayed	Rash (10 days)	Positive/pruritic erythema	5 hr
36 (female)	Accelerated	Pruritic rash (3 days)	Positive/pruritic rash	6 hr

Immediate reaction denotes reactions that manifested within an hour, accelerated reactions denote reactions that occurred within 72 hr of the first dose of clindamycin and delayed reactions are those that occurred after 72 hr from the first dose of clindamycin.

*All patients tested were skin test negative.

†Patients developed delayed reaction at the skin test site.

‡The patient underwent a double-blind, placebo-controlled oral challenge trial and was found to have a positive reaction with clindamycin.

NA = not applicable.

for certain types of drug eruptions with a specific pathophysiologic basis such as acute generalized exanthematous pustulosis, delayed cutaneous hypersensitivity reactions and fixed drug eruptions (8, 14). At the time of the study, patch tests were not performed at the Drug Safety Clinic.

Oral challenges, also known as drug provocation tests, are considered to be the 'gold standard' to establish or exclude the diagnosis of hypersensitivity (15). In our series of 31 patients, 10 patients had a positive oral challenge, with reproduction of original symptoms. 8/10 patients had reactions within 6 hr of the oral challenge, and 2 patients had reactions between 24 and 48 hr. Our standard procedure is to observe patients for 3 hr after administration of the single-dose oral challenge. However, patients are cautioned that a

delayed reaction could occur up to 2 days after their oral challenge. In those patients with a negative oral challenge, other diagnosis, including other putative medications, or missing cofactors (e.g. viral infection, co-medication and physical exercise), need to be considered as alternatives for the patient's original symptoms (15).

Despite negative immediate skin tests, 10 of the 31 patients (32%) reacted to the oral dose of clindamycin, giving a negative predictive value of 68%, which is unacceptably low for diagnostic tests. In comparison, penicillin, the gold standard for prick and intradermal skin testing, has a negative predictive value of 98.8% (16). From the literature, our testing results and the very low predictive values (negative and positive), clindamycin skin testing appears to be a poor diagnostic tool to identify patients with potential

immunologic reactions, including IgE-mediated reactions, associated with clindamycin. The reasons for the poor predictive value of skin testing for clindamycin are unknown. It is known that 13% of a clindamycin dose is excreted as active drug in the urine and faeces, and the remainder is excreted as inactive metabolites, such as *N*-dimethylclindamycin and clindamycin sulfoxide. However, the degradation products of clindamycin are still not well characterized, and adverse reactions to clindamycin may be caused by an unknown reactive metabolite or by a combination of drug, host and viral factors (17).

There are several limitations to our study. In retrospective studies, such as this one, there is an inherent weakness due to the referral bias occurring from the selection of patients on the basis of clinical history. This is recognized, but the value of retrospective studies should not be underestimated. At the time of the study, we did not use patch testing as a diagnostic tool in patients with a history of a delayed reaction to clindamycin. However, patch tests may be helpful in determining the cause of a cutaneous adverse drug reaction (7).

In conclusion, the role of clindamycin prick and intradermal skin testing for patients with a history of an immunologic reaction to clindamycin is limited on the basis of our results of skin testing and oral challenges in 31 patients. This has changed our practice, and we no longer offer clindamycin skin testing as a diagnostic modality to patients with histories of an allergic reaction associated with clindamycin. Clindamycin oral challenge is used judiciously and selectively in patients with appropriate histories, where the benefit is thought to outweigh the morbidity of inducing a potentially clinically significant reaction. Patients with observed positive oral challenges to clindamycin should be clearly advised to avoid rechallenge with this drug in the future. Patch testing is also offered to patients with appropriate clinical histories (e.g. acute generalized exanthematous pustulosis and fixed drug eruption). It is also advised that patients sensitive to clindamycin avoid lincomycin, a structurally related lincosamide that is now infrequently used. If clindamycin is required by a patient with a positive oral challenge, desensitization, which has been documented, may be an option (11).

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