
Sensitivity and specificity of skin tests in the diagnosis of clarithromycin allergy

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Background: Clarithromycin is one of the most frequently prescribed oral macrolidic antibiotics in the pediatric population. Suspected adverse reactions to clarithromycin have been frequently described by parents of children examined in pediatric allergy units, but there is a lack of reliable methods available in detecting the presence of specific IgE antibodies.

Objective: To investigate the prevalence of a clarithromycin allergy in children seen in a pediatric allergy unit using standardized skin tests and oral provocation tests (OPTs).

Methods: Sixty-four children were referred with a history of a clarithromycin-associated adverse drug reaction. All these children underwent skin tests and OPTs. The nonirritating intradermal skin test concentration for clarithromycin was determined in a control group of 18 children who had tolerated clarithromycin in the previous month.

Results: The threshold nonirritating intradermal concentration was established at the 10:2 dilution (0.5 mg/mL). Nine of the 64 children had an immediately positive intradermal response to the 10:2 dilution and only 1 child to the 10:3 dilution (0.05 mg/mL). None had positive skin prick test results or delayed skin responses to intradermal tests. Four of 64 children (6%) with previously described adverse reactions due to clarithromycin intake had a positive OPT reaction. When we correlated the intradermal skin test results to the OPT results, intradermal test sensitivity and specificity were 75% and 90%, respectively.

Conclusion: Intradermal tests seem to be useful in allergologic workup in children with suspected clarithromycin hypersensitivity and may help reduce the need for OPTs.

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INTRODUCTION

Adverse reactions to antibacterial agents are not uncommon in children, especially reactions to β -lactam drugs because of their widespread use and antigenic properties. Allergies to macrolide antibiotics may also occur (0.4%–3.0% of treatments),¹ as this group of drugs represents an old and well-established class of antimicrobial agents, accounting for 10% to 15% of the worldwide oral antibiotic market.² In Italy, clarithromycin is the most frequently prescribed oral macrolidic antibiotic in the pediatric population.³ It belongs to the 14-membered macrolides category owing to the number of carbon atoms in the lactonic ring. In a study involving large numbers of children treated with clarithromycin, skin reaction rates were 2.8%. In other studies, cough, dyspnea, and bronchospasm immediately after clarithromycin intake⁵ and nonimmediate reactions^{6,7} were reported as well. The incidence of anaphylactic reactions provoked by clarithromycin is extremely low.⁴

In general, adverse drug reactions may be both underdiagnosed and overdiagnosed because of the lack of a specific allergologic workup. For an accurate diagnosis, a detailed

history is of paramount importance. The European Network for Drug Allergy has recently updated standardized protocols for immediate and nonimmediate skin tests to β -lactams,⁸ but reliable methods available to diagnose clarithromycin allergy are still lacking. Skin tests have sometimes been used in diagnosing clarithromycin allergy,^{7–9} but they have not been validated in terms of specificity and sensitivity.

Because in vitro tests are less sensitive in drug hypersensitivity than in the inhalant allergy,¹⁰ most authors still consider the oral provocation test (OPT) the gold standard for drug allergy diagnosis.¹¹ Suspected adverse reactions to clarithromycin were frequently described by parents of children examined in pediatric allergy units, and in many cases, an allergy evaluation was mandatory. Taking this fact into account, we decided to investigate the prevalence of clarithromycin allergy using standardized skin tests and OPTs.

METHODS

Patients

Between January 1, 2006, and June 30, 2008, 73 children were referred to our Allergy Unit of the A. Meyer Children's Hospital, Florence, Italy, because of a history of reactions to clarithromycin. The patients all reported skin reactions (19% maculopapular eruptions, 62% urticarias, and 18% angioedemas) during a 7-day treatment period. No children were reported to have anaphylactic reactions. According to their personal history, 49 children had late reactions (after 1 hour) and 20 had immediate reactions (within 1 hour) from the last antibiotic intake, most frequently after the second dose and

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Table 1. Demographic Characteristics of the 2 Study Groups

	Control group (n = 18)	Patient enrolled (n = 64)
Age, mean (range), mo	91.3 (36–179)	72.5 (12–204)
Atopy, No. (%)	NA	20 (31)
Sex, M/F, No.	9/9	33/31
Reactions, late/immediate, No.	NA	44/20

Abbreviation: NA, not applicable.

the first dose, respectively. In 4 cases, it was not possible to establish the exact timing of the reaction.

Only 64 patients were enrolled in the study because 9 refused to undergo the OPT. Evaluation of the clarithromycin allergy workup involved skin prick tests, intradermal tests, and OPTs with the culprit drug. The nonirritating intradermal skin test concentration for clarithromycin was determined in a control group of 18 children who had tolerated clarithromycin in the previous month. The demographic characteristics of the 2 groups (enrolled and control subjects) are summarized in Table 1.

Methods

Lyophilized clarithromycin, available as an injectable formulation (Veclam, 500 mg/mL; Pharmaco-Institute, Florence, Italy), was newly reconstituted to its full-strength intravenous concentration no more than 2 hours before testing. The full-strength concentration of 50 mg/mL was obtained using either saline or sterile water as a diluent. After the drug was prepared at full-strength concentration, serial 10-fold dilutions ($10^{-1} = 5$ mg/mL; $10^{-2} = 0.5$ mg/mL; and $10^{-3} = 0.05$ mg/mL) were obtained and tested to determine the highest concentration that did not elicit an irritant response. All of the reagents were initially tested at increasing concentrations on the skin of the volar forearm using the prick method, and reactions were considered positive when a wheal larger than 3 mm in diameter with surrounding erythema was present 20 minutes later. When prick test results were negative, approximately 0.02 mL of the reagent solution was injected intradermally into the forearm in duplicate. These results were considered positive when the wheal diameter, which appeared 20 minutes after the injection of 0.02 mL of the reagent solution, increased at least 3 mm and was again accompanied by erythema; results were again considered positive when an infiltrate greater than 5 mm appeared after 48 hours (late reactions).¹² Positive controls for prick and intradermal tests were obtained by testing histamine at 10 and 1 mg/mL, respectively. Normal saline was used as a negative control for prick and intradermal tests.

All the children underwent blind controlled OPTs at the hospital 1 to 6 months after the clarithromycin index reaction. When the challenge started (usually 72 hours after the skin tests), the child had to be free of any infectious or skin symptoms, and antihistamine use was not allowed in the previous 7 days and oral corticosteroid and immunosuppressive drug use the month before. The therapeutic dose was calculated based on weight (7.5 mg/kg twice daily). Increas-

ing amounts of clarithromycin or lactose were administered every 30 minutes, starting with the dose of 1:100, for a total of 4 doses (1:100, 1:10, 2:10, and 7:10) up to the cumulative therapeutic dose of 500 mg of lactose a day. The patients were single blinded and were observed for 2 hours after the last dose. After the oral challenge, they were given a prescription of oral corticosteroids and oral antihistamines to treat a possible delayed-onset reaction. This study was approved by the ethics committee of A. Meyer Children's Hospital, and written informed consent was obtained from all the parents of the individuals tested.

RESULTS

No children in the control group had a positive intradermal response to the 0.5-mg/mL dilution of clarithromycin, whereas 7 (39%) reacted to the 5-mg/mL dilution (Table 2). Of the 64 children with a reported history of clarithromycin reaction, 9 had an immediately positive intradermal response to the 0.5-mg/mL dilution and only 1 to the 0.05-mg/mL dilution. None of the 64 children had positive skin prick test results or delayed skin responses to intradermal tests (Table 2).

Two of 64 patients had immediate reactions during the OPT (urticaria 10 minutes after intake of the 2:10 dose in 1 patient and urticaria plus angioedema 20 minutes after intake of the 7:10 dose in another). The 62 patients who did not have an immediate reaction continued treatment with clarithromycin using the usual recommended doses for a total of 5 days. The OPT results were positive in 2 more patients (itchy papuloerythematous skin reactions occurred after 3 or 4 days). In the 2 patients with delayed reactions, the 5-day challenge test was repeated in a placebo-controlled, double-blind manner, and again, similar cutaneous papulous reactions were observed after 3 days of treatment with the active drug. Therefore, 4 of 64 children (6%) with previously described adverse reactions to clarithromycin had a positive OPT result. No severe

Table 2. In Vivo Diagnosis of Clarithromycin Allergy Using SPTs, ID Skin Tests, and OPTs

	Control group, No. (%) (n = 18)		Patient enrolled, No. (%) (n = 64)	
	Negative	Positive	Negative	Positive
SPT full-strength concentration (50 mg/mL)	18 (100)	0	64 (100)	0
ID (dilutions from full-strength concentration)				
5 mg/mL	11 (61)	7 (39)	Not tested	Not tested
0.5 mg/mL	18 (100)	0	55 (86)	9 (14)
0.05 mg/mL	Not tested	Not tested	63 (98)	1 (2)
OPT	18 (100)	0	60 (94)	4 (6)

Abbreviations: ID, intradermal; OPT, oral provocation test; SPT, skin prick test.

reactions were observed. Three of the 4 patients who had positive OPT results also had positive intradermal test results (sensitivity = 75%), whereas 54 of the 60 patients who had negative OPT results also had negative intradermal test results (specificity = 90%). Three of the 4 patients with positive OPT results also had immediate positive intradermal test responses at 0.5 mg/mL. Surprisingly, none of the patients had late positive intradermal test responses; only in 1 patient was a late clinical reaction associated with an immediate positive intradermal test response.

DISCUSSION

Hypersensitivity to clarithromycin can occur in children and should be accurately investigated to obtain a proper diagnosis. Currently, skin testing is apparently not a very useful procedure for diagnosing clarithromycin hypersensitivity. Few studies have investigated possible clarithromycin sensitization by performing intradermal skin tests on patients reporting a suspected clinical reaction. Moreover, the same tested dilution has been considered irritating⁹ or not⁷ in 2 different studies. In particular, Sánchez-Morillas et al⁹ considered the intradermal concentration of 0.1 mg/mL as non-irritating, but no information about the control group was provided. Empedrad et al¹³ identified the nonirritating intradermal skin test concentrations for 15 commercial parenteral antibiotics but not for clarithromycin. To this day, skin tests still need to be properly standardized for clarithromycin and for most commercially available antibiotics.

According to the present results, the 0.5-mg/mL dilution is the nonirritating threshold concentration to be used for intradermal tests with clarithromycin. When we correlated the intradermal skin test results to the OPT results, intradermal test sensitivity and specificity were 75% and 90%, respectively. It is important to point out that the sensitivity was calculated from a selected pediatric population, and the result obtained was definitely affected by the low number of truly allergic children. In fact, although the negative predictive value is high (98%), the positive predictive value is low (33%), this being due to the low allergy prevalence to clarithromycin (6%) in this population.

According to other studies on macrolide antibiotic hypersensitivity,¹¹ it was found that allergy to clarithromycin is uncommon despite its widespread use in children; only 4 of 64 children (6%) with a history of reactions during clarithromycin administration had a confirmed diagnosis of hypersensitivity after a systematic allergologic investigation. In 1 case, a late clinical reaction was associated with an immediate positive intradermal response, suggesting that clarithromycin may act through different immunopathogenetic mechanisms at the same time. With this report, intradermal tests have, for the first time, been systematically used to establish their importance in diagnosing clarithromycin allergy.

In conclusion, intradermal skin tests seem to be useful in the allergologic workup as they have good specificity and sensitivity. A standardized diagnostic workup is recommended to reduce the need for OPTs, which still remain the gold standard for confirming a real state of clarithromycin hypersensitivity.

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