Clinical Communications

Testing for clarithromycin hypersensitivity: A diagnostic challenge in childhood

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Clinical Implications

- In the case of clarithromycin hypersensitivity, the meaning of a positive intradermal test result can be doubtful, especially during childhood, and provocation tests may be used solely without a need for skin tests in patients with a history of mild mucocutaneous symptoms.

TO THE EDITOR:

Diagnostic evaluation of patients in the pediatric age group with a history of drug hypersensitivity reactions (DHRs) is strongly recommended because of the vague information frequently provided by the history alone.[1,2] Drug provocation tests (DPTs) are accepted as the criterion standard, but initial skin testing with the culprit drug before the provocation test is considered a safe, reliable, and practical approach to the appraisal of suspicious DHRs.[3] Well-defined nonirritating concentrations are currently in use during skin prick tests and intradermal tests (IDTs) for particular drugs such as betalactam antibiotics, perioperative drugs, chemotherapeutic drugs, and some of the biological agents, but there is still a lack of standardized information regarding the concentrations of nonbetalactam antibiotics including macrolides used in skin tests.[3]

Clarithromycin, belonging to the macrolides group, is one of the most frequently prescribed antibiotics in the pediatric age group after amoxicillin and amoxicillin-clavulanic acid.[4] Various types of DHRs have been reported in children during clarithromycin use, ranging in severity from frequent mild[5] to rare severe reactions.[6-8] In contrast, actual clarithromycin hypersensitivity is considered to be uncommon,[9,10] which makes the diagnostic assessment a requirement. Studies or case reports involving allergological workup for macrolides are based predominantly on adult subjects[10] and there are few data about the nonirritant IDT concentrations for clarithromycin. Because of the lack of reliable guidelines and possible differences between adults[11] and children,[5] we aimed to investigate the impact of skin testing with clarithromycin and the different concentrations used in our pediatric population.

In this study, we have analyzed the clinical features and allergy test results of the patients who were referred between August 2012 and May 2015 to Hacettepe University Department of Pediatric Allergy because of a possible clarithromycin-induced DHR. Skin and provocation tests were performed at least 4 weeks after the DHR in patients without a history of drug-related Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms syndrome, or toxic epidermal necrolysis because these are recommended.[12] Initially, the participants and the parents were informed about both the procedures of skin testing and provocation testing including their advantages and disadvantages. The ones who willed to go through an initial skin testing (they thought that this was safer) were recruited to the skin tested group, whereas the ones who did not want to be skin tested (because of its painful nature or because of time constraints) were recruited to the directly provocated group. The participants who had undergone skin testing with clarithromycin were first tested epidermally (prick test) with full-strength concentration (50 mg/mL, Klacid, Abbott, Saint Rémy Sur Avre, France) and then, if negative, they were tested intradermally with 0.02 mL of serial dilutions of the commercial solution (1:100,000, 1:10,000, and 1:1,000). The IDT dilutions were prepared with physiological saline,[3] which was also used as the negative control. An IDT result was interpreted as "positive" if the mean wheal diameter was 3 mm or larger than that of negative control 20 minutes after the injection. All patients underwent oral DPT with clarithromycin regardless of the prick test and IDT results. During DPT, the syrup form of the drug including 50 mg/mL of clarithromycin was given at a dose of 10 mg/kg orally in 4 or 5 doses at 30-minute intervals (as 1, 5, 25, 100, 500 mg in increasing divided doses) as has been recommended.[13] To elicit lower doses, the syrup in its original prescription was diluted with sterile water by nurses experienced in drug preparation and provocation. After the last dose, patients were observed for an additional 4 hours and they were instructed to call or return to the clinic in the case of a possible symptom of a reaction at home. The patients with histories of late reactions continued to take the drug in 2 equal doses (20 mg/kg/d) for 5 more days. This study was approved by the Ethics Committee of Hacettepe University, and parents provided written informed consent.

Between August 2012 and May 2015, 48 patients (50% males) with a median age (interquartile range) of 5.5 (3.7-8.4) years were referred because of a history of clarithromycin-induced DHR. Three patients could not be further tested because of high risks (Stevens-Johnson syndrome [n = 1], drug reaction with eosinophilia and systemic symptoms syndrome [n = 1], cardiac arrythmia [n = 1]). The 45 patients included for diagnostic tests had a history of mild mucosal and cutaneous symptoms such as urticaria, maculopapular exanthema, angioedema, and conjunctivitis not evolving into danger signs[12] such as bullae, blisters, or atypical target lesions. The time to appearance of the symptoms after clarithromycin intake was a median of 3 hours (interquartile range, 2-5 hours). Twenty-five patients were assessed directly via DPTs, and 20 were assessed by both skin tests and DPTs (Figure 1). The patients with or without skin tests with clarithromycin did not differ in terms of age and sex, frequency of immediate ($\leq$1 hour after the drug intake) versus nonimmediate reactions (>1 hour after the drug intake), and other clinical features (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). None of the skin tested patients had positive epidermal test results. However, IDT results were positive in 2 patients at the 1:100,000 dilution, 2 patients at the 1:10,000 dilution, and 5 patients at the 1:1,000 dilution. None of these patients with positive IDT results showed any reaction during DPTs. However, 2 patients with negative skin

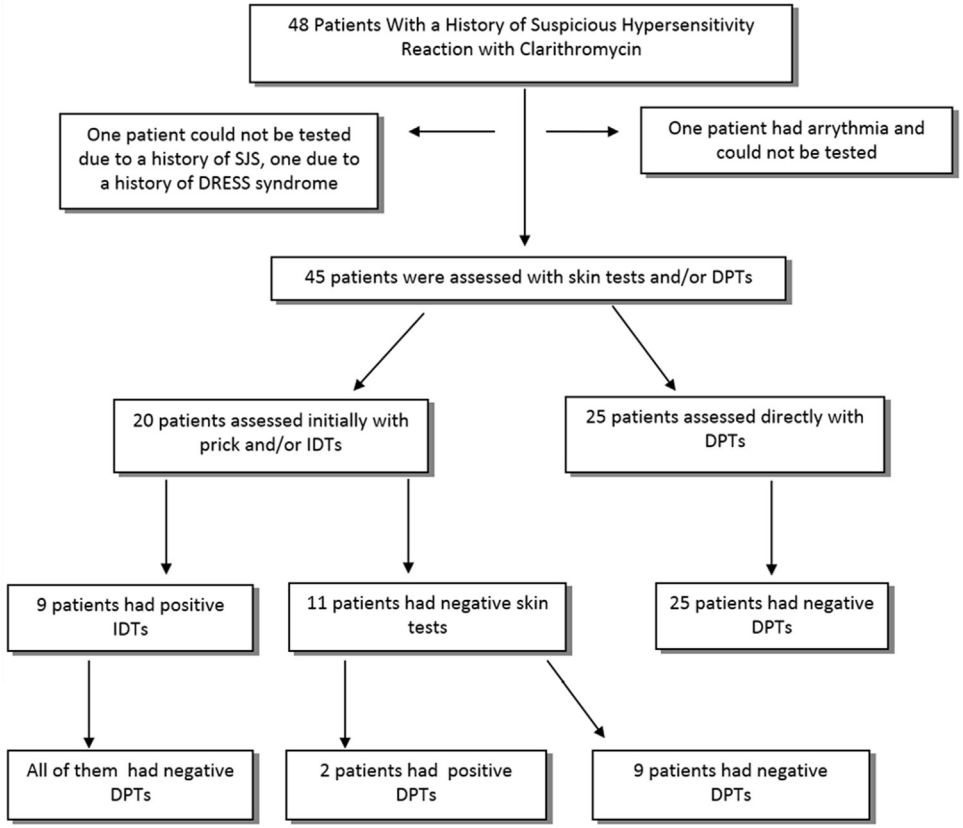

FIGURE 1. Flow chart of the study. *DRESS*, Drug reaction with eosinophilia and systemic symptoms; *SJS*, Stevens-Johnson syndrome.

test results had a reaction and had urticaria during DPT with clarithromycin (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). None of the patients evaluated solely with DPTs showed any reactions (Figure 1) during provocation.

In this study, we investigated the impact of skin testing with the culprit drug in the diagnosis of clarithromycin hypersensitivity and we found that there were 9 patients with false-positive results, even using more dilute concentrations than used in previous studies. For instance, Broz et al[11] recommended 1:1000 and 1:3000 of the original full-strength concentration (50 mg/mL) of the commercial preparation of clarithromycin as the highest nonirritant concentrations in a group of adult healthy volunteers. In addition, Mori et al[5] used 1:1000 and 1:100 dilutions of the commercial product to evaluate possible clarithromycin-induced DHRs via IDT in pediatric patients. These authors reported that 3 of 4 patients with a positive DPT result and 6 of 60 patients with a negative DPT result showed positive results during IDTs and concluded that these concentrations have a 75% sensitivity and a 90% specificity rate to predict actual clarithromycin hypersensitivity.[5] A recent study by the same group used these 2 concentrations and ended up with 7 skin test positive and 2 DPT positive patients out of 58, leading to a clarithromycin hypersensitivity rate (IDT or DPT) of 15.5%.[14] In our study, actual clarithromycin hypersensitivity was detected in 2 patients (a rate of 4.4% solely based on DPTs). These 2 patients had negative IDT results. But if we would have taken skin test results into consideration without performing further DPT to the positive ones, the observed rate would be 24.4% (11 of 45) even when more dilute concentrations were used. From a different point of view, it is also important to note that the rate of positive skin test results in our study was 9 out of 20 skin tested patients (45.5%), which is much higher than the one in the study by Barni et al[14] (7 out of 58 skin tested patients [12%]). This could be due to differences in the age range of the participants recruited, and it would be interesting to investigate the impact of age on clarithromycin-induced skin test results in further studies. Another explanation for the high skin test positive rate would be operator-related false-positive tests. However, we have 3 experienced nurses, and their positivity rate for testing with betalactams was 9 out of 205 patients (4.3%) (unpublished data, Ozge Soyer, 2015), suggesting that the much higher positivity rate for skin testing with clarithromycin (45.5 %) is not due to systematic operator error.

One could argue that perhaps the 2 patients with positive DPT results would have been diagnosed via skin test if the 1/100 concentration was also included during testing. However, before starting this study, we had realized that more concentrated solutions of clarithromycin applied intradermally to patients in the pediatric age group were more painful than other frequently administered drugs such as betalactams. We did not quantitate the degree of the pain, but because false-positive results had been previously observed with more highly concentrated solutions and in order not to cause unnecessary discomfort to the patients, we did not use the 1/100 dilution of commercial clarithromycin in this study. On the basis of these findings, we conclude that positive IDT results with clarithromycin appear to be of doubtful