ORIGINAL ARTICLE

Azithromycin Is More Allergenic Than Clarithromycin in Children With Suspected Hypersensitivity Reaction to Macrolides

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Abstract

Background: Macrolides are considered safe antibiotics with reduced allergenic activity. However, studies on the safety of macrolides are scarce, particularly in children.
Objective: The aim of this study was to assess the frequency of hypersensitivity reactions to clarithromycin and azithromycin in a group of children referred to our allergy unit for suspected macrolide allergy.
Methods: We retrospectively reviewed the charts of 90 children aged 1-17 years with symptoms suggestive of hypersensitivity reaction to clarithromycin or azithromycin between December 31, 2008 and December 31, 2013. The allergy workup included skin tests (ie, skin prick tests and/or intradermal tests), determination of serum specific IgE (sIgE) to clarithromycin and azithromycin, and, if necessary to reach a diagnosis, oral provocation tests.
Results: Seventy-seven children completed the allergy workup. A reaction to clarithromycin was recorded in 58 children (75.3%): 21 (36.2%) had a history of immediate reactions, and 37 (63.8%) had a history of nonimmediate reactions. A reaction to azithromycin was recorded in 19 children (24.6%): 6 (31.5%) had a history of immediate reaction, and 13 (68.42%) had a history of nonimmediate reaction. Positive results in skin tests and oral provocation tests with the suspect drug confirmed the diagnosis in 15.5% of reactions to clarithromycin (9 of 58) and in 47.3% of reactions to azithromycin (9 of 19) (*P*=.004).
Conclusion: A complete allergy workup enabled us to confirm a diagnosis of clarithromycin and azithromycin allergy in 15.5% and 47.3% of cases, respectively. Azithromycin was more allergenic than clarithromycin in children.

Key words: Azithromycin. Children. Clarithromycin. Drug hypersensitivity. Macrolides.

Resumen

Antecedentes: A los macrólidos se les considera antibióticos seguros, con una reducida capacidad alergénica. Sin embargo, los estudios sobre este tema son insuficientes, especialmente en los niños.
Objetivo: El objetivo de este estudio ha sido el evaluar la frecuencia de reacciones hipersensibilidad (HR) a claritromicina (clarithromycin) y a azitromicina (azithromycin) en un grupo de niños, estudiados en nuestra Unidad de Alergia, por sospecha de alergia a los macrólidos.
Métodos: Se han estudiado restrospectivamente, 90 niños (de 1-17 años) con síntomas sugestivos de HR a clarithromycin o azithromycin, entre el 31 de diciembre de 2008 y 31 de diciembre de 2013. En el protocolo de estudio se incluyeron la realización de pruebas cutáneas intraepidérmicas (prick, SPT) y/o pruebas intradérmicas (ID)], la determinación de IgE sérica específica (sIgE) a clarithromycin y azithromycin y, si se consideraba necesario para llegar a un diagnóstico, pruebas de provocación oral (OPT).
Resultados: Setenta y siete niños completaron el estudio. Cincuenta y ocho (75,3%) referían haber presentado reacciones a clarithromycin: 21 (36,2%) tenían antecedentes de reacciones inmediatas (IR), y 37 (63,8%) tenían antecedentes de reacciones no inmediatas (RIN). Diecinueve de los 77 niños (24,6%) habían presentado una reacción a azithromycin: 6 (31,5%) con una historia de IR y 13 (68,42%) con historia de NIR. Mediante pruebas cutáneas o por positividad en la OPT con el fármaco sospechoso, permitió confirmar el diagnóstico en 15,5% (9 de 58) de los casos de clarithromycin y en 47,3% (9 de 19) de los casos de azithromycin (p= 0,004).
Conclusión: Un estudio alergológico completo permitió realizar un correcto diagnóstico de alergia a clarithromycin y azithromycin en 15,5% y 47,3% de los casos, respectivamente. En este trabajo, en niños, la azithromycin fue más alergénica que la clarithromycin.

Palabras clave: Azitromicina. Niños. Claritromicina. Hipersensibilidad a fármacos. Macrolides.

Introduction

Macrolides are a group of related compounds that have a lactone ring (14 to 16 atoms) bonded to one or more deoxy sugar molecules [1]. They have bacteriostatic and bactericidal activity, good cell penetrance, and anti-inflammatory and immunomodulatory effects [2]. In addition, they are active against most of the bacteria that cause community-acquired pneumonia, such as gram-positive bacteria, which include penicillinase-producing staphylococci, and atypical pathogens (ie, *Mycoplasma* and *Chlamydia* species). Macrolides are generally well tolerated, and allergy to macrolides is an uncommon event (occurring in 0.4%-3% of treatments). In children, macrolides are widely used to treat community-acquired infections of the lower and upper airways [3-4].

Immediate reactions occur within the first hour after intake [5]. Nonimmediate reactions occur at any time between 1 hour and 72 hours after intake [6].

In a recent study [7], we showed that allergy to clarithromycin is not uncommon (detected in 4 of 64 [6%] children with a history of adverse reactions to clarithromycin). The frequency of adverse reactions to azithromycin has increased recently, most likely owing to the rapid increase in use over the last 10 years [8].

The aim of the present study was to assess the frequency of hypersensitivity reactions to clarithromycin and azithromycin in a group of children referred to our allergy unit for possible allergic reaction to macrolides.

Methods

We retrospectively reviewed charts from 90 patients (mean age, 8.5 years; range, 1-17 years) who were referred to the Allergy Unit of A. Meyer Children's Hospital, Florence, Italy for suspected hypersensitivity reaction to clarithromycin or azithromycin between December 31, 2008 and December 31, 2013. The allergy workup was performed according to current recommendations for antibiotic allergy [6,9].

Skin tests with clarithromycin and azithromycin were performed at the first visit. The concentrations used for skin prick tests (SPT) and intradermal tests (IDT) were 50 mg/mL and 0.5-0.05 mg/mL, respectively, in normal saline for clarithromycin and 100 mg/mL and 0.1 and 0.01 mg/mL, respectively, in normal saline for azithromycin [10].

We prepared a powder-based intravenous solution of clarithromycin and azithromycin no more than 2 hours before testing. SPT was initially performed with 1 drop of each of the aforementioned reagents on the volar surface of the forearm at increasing concentrations. The reactions were considered positive when a wheal larger than 3 mm in diameter with surrounding erythema appeared after 10 minutes.

When the SPT result was negative, IDT was performed by injecting 0.03 mL of the reagent solution into the volar surface of the forearm. Readings were obtained at 20 minutes and at 24, 48, and 72 hours after the injection. The results were considered positive if the initial wheal diameter increased by >3 mm with a flare. Positive controls for SPT and IDT were performed with histamine (at 10 and 1 mg/mL, respectively). Normal saline was used as a control for negative SPT and IDT results. Drug-specific IgE was determined using radioimmunoassay. According to the method of Baldo and Harle [11], the solid phase was obtained by coupling the drug (clarithromycin or azithromycin) to epoxy-activated sepharose 6B through a spacer arm. The results are expressed as the ratio of radioactivity in the detecting antibody bound to the solid phase to the total amount of radioactivity introduced. Values of at least 3 times the level of normal serum (taken from healthy, nonatopic individuals) were considered positive. Patients with positive SPT or IDT results were considered allergic, independently of the radioimmunoassay result.

The oral provocation test (OPT) was performed as an open challenge with the suspect drug in all patients with negative in vivo test results. At the time of the OPT, all patients were in their usual state of health, with no signs of acute or chronic infection and clear skin. Patients had to be off antihistamines for at least 7 days and off corticosteroid or immunosuppressive therapy for the previous 30 days. At the first visit, the OPT was performed by calculating the therapeutic dose (clarithromycin 7.5 mg/kg and azithromycin 10 mg/kg) divided into 3 doses (1/10, 2/10, and 7/10 administered every 30 minutes). After the last dose, the patients were kept under observation for at least 2 hours to monitor for adverse events. On the following day, the therapeutic dose was administered at once, and the patients were observed for 3 hours. In the case of cutaneous or respiratory symptoms or alterations in vital signs (heart rate, blood pressure, breathing rate), the challenge was stopped, and appropriate treatment was initiated. In patients with a history of nonimmediate reactions, the challenge was continued for 5 days at a therapeutic dose every 12 hours for clarithromycin and every 24 hours for azithromycin. Patients were provided with antihistamines and oral corticosteroids and a telephone number that they could use to contact us in case of adverse reactions. Written informed consent was obtained from all parents. Institutional review board approval was not required.

All statistical analyses were performed using SPSS version 22 (IBM Corp). Qualitative variables were compared using the chi-square test. Statistical significance was set at $P<.01$.

Results

The allergy workup was incomplete in 13 cases: 10 patients refused to undergo OPT, 3 had moved to another town.

Among the 77 children who completed the allergy workup, 58 (75.3%) had a history of hypersensitivity reaction to clarithromycin and 19 (24.6%) to azithromycin. Among the patients with a history of reaction to clarithromycin, 21 (36.2%) had an immediate reaction and 37 (63.8%) a nonimmediate reaction; in the patients with suspected reaction to azithromycin, 6 (31.5%) had an immediate reaction and 13 (68.42%) a nonimmediate reaction (Figure).

Skin manifestations were the most commonly reported symptoms (76.2%) in the 21 children with an immediate reaction to clarithromycin: 6 patients (37.5%) experienced urticaria, 5 (31.5%) urticaria-angioedema, 2 (12.5%) maculopapular rash, 1 (6.25%) eczema, and 2 (12.5%) undefined rash. Four patients (19.4%) presented gastrointestinal symptoms, and 1 patient (5%) presented respiratory symptoms (bronchospasm). The SPT with clarithromycin was positive in

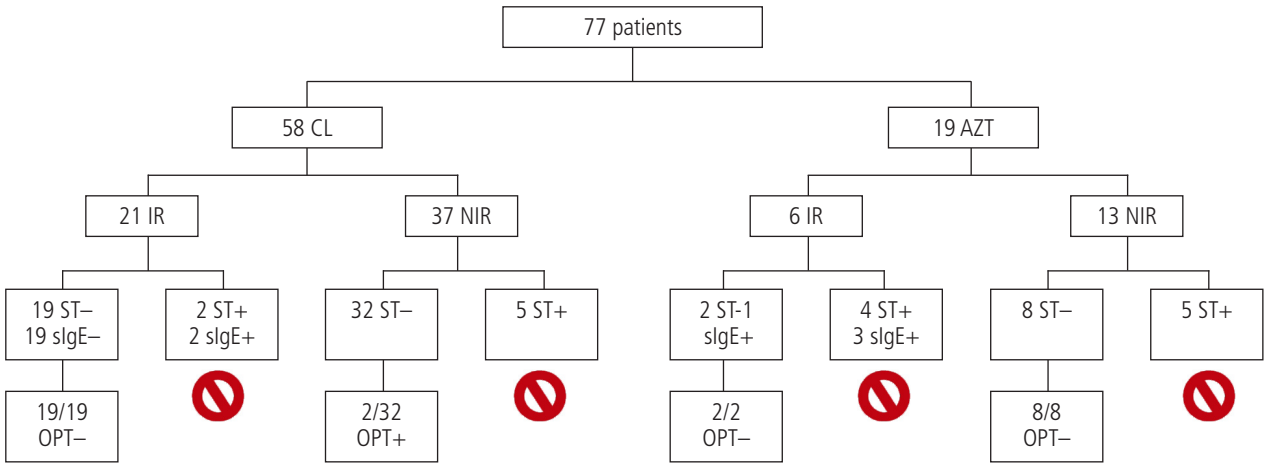

Figure. Results of the allergology workup. CL indicates clarithromycin; AZT, azithromycin; IR, immediate reaction; NIR, nonimmediate reaction; ST, skin test (skin prick test or intradermal test); OPT, oral provocation test; test stopped.

1 child. The 20 patients with a negative SPT result underwent IDT: readings at 20 minutes were positive in 1 patient. Of the 21 children with positive skin testing results, 2 (1 with a positive SPT result and 1 with a positive IDT result) were considered to be allergic. Both of these children also had positive serum specific IgE for clarithromycin. The 19 patients with negative skin test results and negative serum sIgE to clarithromycin underwent the OPT with clarithromycin, and the results were negative (Figure).

Among the 37 children with nonimmediate reactions to clarithromycin, 32 (87%) experienced cutaneous symptoms, including 17 patients (53%) with maculopapular rash, 7 (22%) with undefined rash, 5 (16%) with urticaria, 2 (6%) with urticaria-angioedema, 1 (3%) with exfoliative dermatitis, 2 (5%) with gastrointestinal symptoms, and 3 (8%) with respiratory symptoms (bronchospasm). Five of the 37 patients (13.5%) with nonimmediate reactions to clarithromycin had a positive IDT result and were diagnosed as allergic. The 32 children with a negative skin test result underwent OPT, which was positive in 2 patients (6.25%) (Figure).

Therefore, 9 of the 58 patients (15.5 %) with a history of hypersensitivity reaction were considered allergic to clarithromycin (7 patients were identified through skin testing, and 2 patients were identified through OPT).

Among the 6 patients with an immediate reaction to azithromycin, 3 had a history of mild anaphylactic reaction: of these, 2 presented urticaria-angioedema (33.3%) associated with vomiting or wheezing, and 1 had angioedema (16.6%) with wheezing and dyspnea, as described by Mori et al [12].

Four of these 6 patients had positive skin test results (1 had a positive SPT result, and 3 had positive IDT results). Four patients had sIgE to azithromycin (3 patients with a positive skin test result and 1 with a negative skin test result). The only patient with a negative skin test result and positive sIgE to azithromycin underwent OPT, which produced negative results. When the correlation between skin testing and sIgE levels was assessed in the 6 patients with an immediate reaction to azithromycin, we found that the positive predictive value (PPV) was 75% and the negative predictive value (NPV) was 50%.

Thirteen patients with a history of nonimmediate reaction to azithromycin reported the following symptoms: maculopapular rash, 7 (53.8%); urticaria, 1 (7.6%); erythema, 1 (7.6%); itching, 1 (7.6%); abdominal pain, 1 (7.6%); and asthma, 1 (7.6%). Five of the 13 patients with a nonimmediate reaction to azithromycin (38%) had a positive IDT result at the late reading and were therefore considered to have nonimmediate hypersensitivity to azithromycin. The remaining 8 patients underwent an OPT, which yielded negative results (Figure).

Therefore, 9 of the 19 (47%) patients who experienced a hypersensitivity reaction to azithromycin were considered allergic (4/6 with an immediate reaction and 5/13 with a nonimmediate reaction).

In total, 9 of 58 patients (15.5%) had a positive skin test or OPT result to clarithromycin, and 9 of 19 patients (47.3%) had a positive skin test or OPT result to azithromycin (P=.004) (Table).

Table. Skin Test or Oral Provocation Test Results in Patients With a History of Allergic Reaction to Clarithromycin and Azithromycin

		Positive ST or OPT, No.	Total No. of Patients	%
CL	P=.004	9	58	15.5
AZT		9	19	47.3
Total		18	77	26.8

Abbreviations: AZT, azithromycin; CL, clarithromycin; OPT, oral provocation test; ST, skin test.

Discussion

Allergy to macrolides is considered an uncommon event, and urticaria is the most frequent clinical manifestation [5]. Severe reactions to these compounds—including anaphylaxis in the case of erythromycin [13], clarithromycin [14], and

telithromycin [15]—are rare. A case of drug reaction with eosinophilia and systemic symptoms was reported in an 8-year-old boy with acute Epstein-Barr virus infection who took azithromycin [16]. Cases of contact dermatitis [17,18] and hypersensitivity syndrome [19] have also been described.

The consumption of macrolides, particularly those with long half-lives (azithromycin), has increased in Italy over the last few years [8]. Clarithromycin has been reported to be associated with a lower number of adverse reactions than other macrolides such as erythromycin [20], but no comparison with azithromycin has been reported.

In a previous study [7], we demonstrated clarithromycin allergy in 4 out of 64 children (6%) with previously reported adverse reactions due to clarithromycin.

The possibility of anaphylaxis to clarithromycin is very low. Specifically, the incidence of anaphylaxis to clarithromycin reported in the literature is 1 case per 1 million per year in pediatric studies [21].

In the present study, we found that 9/58 (15.5%) children with suspected clarithromycin allergy had their diagnosis confirmed by positive results in skin tests, sIgE, or OPT.

Two of the 22 children with a history of immediate reaction presented positive skin test results and were considered to have IgE-mediated hypersensitivity reaction. However, the real PPV of a positive skin test result is unknown, because OPT was not performed as recommended in these cases (6,9). The 19 patients with a history of immediate reactions and negative skin test results all had negative OPT results. Of the 32 patients with nonimmediate reactions and negative skin test results, 30 had a negative OPT result, and 2 had a positive OPT result. Therefore, the NPV of skin testing for immediate and nonimmediate reactions clarithromycin was 100% and 94%, respectively.

Azithromycin is considered a well-tolerated drug in all age groups. In one study [22], the incidence of adverse events was 12%, with most such events affecting the gastrointestinal tract. Skin eruptions have also been reported [23], as have IgE-mediated anaphylactic reactions to azithromycin [12], contact reactions [17,18], and hypersensitivity reactions [19]. We showed that hypersensitivity reaction to azithromycin can occur and that an allergy workup should be performed. Four of the 6 patients (66.6%) with immediate reactions had positive results for an immediate skin test reading, and 5 of the 13 patients (38%) with a nonimmediate reaction had positive results for a late skin test reading.

All 8 patients with negative skin test results had negative results in OPT, thus confirming the elevated NPV of a negative skin test result for both clarithromycin and azithromycin.

Ours is the first study to demonstrate that azithromycin is more allergenic than clarithromycin in children and that this difference is statistically significant (Table). We show that 9 of the 58 patients studied (15.5%) had positive skin test or OPT results to clarithromycin and that 9 of the 19 (47.3%) had positive skin test results to azithromycin.

Allergy workups for suspected macrolide hypersensitivity are not standardized, particularly those used for azithromycin. When diagnosing azithromycin allergy, we used the nonirritant concentrations suggested by the only study published to date in this area [10]. However, the fact that the 3 patients with anaphylactic reactions to azithromycin all had positive skin test results confirmed the adequacy of the concentrations used, at least in immediate reactions.

Additional studies have investigated the nonirritant IDT concentration for diagnosing clarithromycin allergy. Sanchez-Morillas et al [24] considered the intradermal concentration of 0.1 mg/mL of clarithromycin as nonirritant, although they did not provide data on the control group. Broz et al [25] used laser Doppler flowmetry and found 0.05 mg/mL to be the nonirritant intradermal skin test concentration for clarithromycin.

In the only study [7] in which the skin results correlated with the OPT results, the threshold nonirritant intradermal concentration of clarithromycin was 0.5 mg/mL, with a sensitivity of 75% and specificity of 90%. In the present study, using the same threshold concentration, we found that 7 of 58 children (12%) with reported reactions to clarithromycin had positive results to skin tests or OPT. However, because the OPT was not performed in these cases, the possibility of false-positive results should be considered.

Few studies have assessed sIgE to macrolides in suspected allergy [13,26]. In the present study, however, determination of sIgE using epoxy-activated sepharose 6B appears to be promising, particularly in cases of immediate reaction to azithromycin, where high concordance was observed with positive skin test results. When the results of skin testing to sIgE levels were correlated among patients with immediate reactions to azithromycin, we found a PPV of 75%, thus demonstrating the utility of this determination in the allergy workup for patients with immediate reactions.

In conclusion, allergy workups for cases of suspected macrolide hypersensitivity should be encouraged and based on a detailed medical history to avoid inappropriate exclusion of this important class of drugs. Moreover, the combination of skin tests, in vitro tests, and OPT to the suspect drug may lead to a greater understanding of the mechanisms underlying macrolide allergy and increase the sensitivity of the entire diagnostic workup.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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