

Letters

SUCCESSFUL CLARITHROMYCIN DESENSITIZATION IN A MULTIPLE MACROLIDE-ALLERGIC PATIENT

Macrolides are broad spectrum antibiotics commonly used in upper respiratory tract infections. Allergic reactions to macrolides include urticaria, angioedema, anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.¹ These reactions are uncommon (0.4%–3%),² and detection of macrolide-specific IgE has not been reported, to our knowledge. We describe a patient with macrolide allergy confirmed by immediate skin prick testing (SPT) who underwent successful drug desensitization with clarithromycin.

A 68-year-old woman with no history of adverse drug reactions developed urticaria and dyspnea 6 days into a course of clarithromycin, 500 mg twice daily, for probable *Mycobacterium avium intracellulare* infection. These symptoms resolved without treatment. She had tolerated a 2-week course of clarithromycin 6 months earlier. Her pulmonologist discontinued the clarithromycin treatment and administered azithromycin. Two hours after receiving an initial 250-mg “test” dose of azithromycin, the patient developed anaphylaxis with symptoms of urticaria, dyspnea, and throat tightness. These symptoms resolved with use of diphenhydramine and intravenous methylprednisolone. Because she required macrolide therapy, she was referred to our allergy clinic for further management.

Clarithromycin was prepared by suspending a pulverized 250-mg clarithromycin tablet in saline, and azithromycin was prepared by using the intravenous solution. The results of macrolides skin testing are given in Table 1. Results of SPT to clarithromycin (25 mg/mL) were negative and to azithromycin (100 mg/mL) were positive. Saline control was negative and histamine (184 mg/mL) was positive, with a 10 × 10-mm wheal with flare.

Intradermal tests with clarithromycin (1 mg/mL) and azithromycin (0.01 mg/mL) demonstrated positive reactions to clarithromycin and azithromycin. Results of intradermal tests in 8 controls were negative to azithromycin and clarithromycin using the same concentrations. A previous work³ has shown that the azithromycin concentration used (0.01 mg/mL) was nonirritating.

Based on the patient’s positive SPT results and the necessity for macrolide therapy, a clarithromycin desensitization procedure was performed (Table 2). Clarithromycin was chosen for its shorter half-life. This desensitization procedure was based on previous penicillin desensitization protocols.⁴ After providing informed consent, the patient received 1/25,000th of a clarithromycin treatment dose. Individual doses were administered at 15-minute intervals across 3.5 hours. The desensitization was performed in an outpatient clinic and was closely monitored. No adverse reactions developed, and by the end of the desensitization, the patient received a cumulative dose equivalent to her first dose of 500 mg. She began routine administration of 500 mg of clarithromycin twice daily for 3 months. She tolerated treatment without adverse effects, and her respiratory symptoms resolved.

Repeated intradermal skin testing with azithromycin 1 hour after desensitization demonstrated an equivocal reaction (Table 1). Six weeks after desensitization while taking clarithromycin, azithromycin SPT results were negative, with a decrease in wheal diameter after 15 minutes. Clarithromycin SPT results were also negative at this time.

Immediate reactions to macrolides are rarely reported, and the drug allergy has been based on clinical history alone, without confirmatory SPT. Because few confirmed IgE-mediated reactions to macrolides have been reported, clinical cross-reactivity among macrolides is unknown. This case is interesting in that results of SPTs using nonirritating concentrations of the drug were positive to clarithromycin and azithromycin. In addition, this patient’s history of reacting to azithromycin after her allergic reaction to clarithromycin is strongly suggestive of clinically relevant cross-reactivity. Finally, the reversal of her positive azithromycin SPT result to

Disclosures: Authors have nothing to disclose.

© 2010 American College of Allergy, Asthma & Immunology.

Published by Elsevier Inc. All rights reserved.

doi:10.1016/j.anai.2010.08.018

Table 1. Macrolide Skin Test Results^a

Drug	Baseline	1 h after desensitization	6 wk after desensitization
Clarithromycin ^b	Prick: negative Intradermal 0 min 4 × 6 mm 15 min 7 × 8 mm ^c	Not studied	Prick: negative Intradermal 0 min 4 × 6 mm 15 min 6 × 6 mm
Azithromycin ^d	Prick: 4 × 4 mm Intradermal 0 min 4 × 4 mm 15 min 7 × 7 mm ^c	Intradermal 0 min 5 × 6 mm 15 min 7 × 7 mm ^c	Prick: negative Intradermal 0 min 4 × 6 mm 15 min 2 × 2 mm

^a All measurements given are orthogonal wheal diameters. Positive control testing was performed before baseline skin testing using intramuscular histamine (184 mg/mL) by skin prick testing, and the patient developed a 10 × 10-mm wheal. Negative control testing used saline by the skin prick and intradermal methods and was nonreactive.

^b Clarithromycin concentrations used were 25 mg/mL for prick testing and 1 mg/mL for intradermal testing.

^c A positive skin test result.

^d Azithromycin concentrations used were 100 mg/mL for prick testing and 0.01 mg/mL for intradermal testing.

Table 2. Clarithromycin Oral Desensitization Protocol^a

Dose no.	Concentration, mg/mL	Dose	
		mL	mg
1	0.025	1.25	0.03
2	0.025	2.5	0.06
3	0.025	5	0.125
4	0.25	1	0.25
5	0.25	2	0.5
6	0.25	4	1
7	2.5	0.8	2
8	2.5	1.6	4
9	2.5	3.2	8
10	2.5	6.4	16
11	25	1.3	32
12	25	2.5	64
13	25	5	125
14	25	10	250
Cumulative dose			503

^a Serial 10-fold dilutions of a clarithromycin suspension of 125 mg/5 mL (25 mg/mL) were performed to make clarithromycin solutions at 2.5, 0.25, and 0.025 mg/mL. Each dose was administered in 15-minute intervals.

negative after desensitization to clarithromycin further supports immunologic cross-reactivity.

Drug desensitization is a procedure used to induce temporary tolerance to a drug. Although the mechanism of drug desensitization is not clear, reversal of positive to negative SPT results has been demonstrated in many patients. We describe a patient with a confirmed allergy to azithromycin who underwent successful oral desensitization to clarithromycin using a protocol based on penicillin desensitization. Holmes et al⁵ reported their experience of clarithromycin desensitization; however, the patient's allergy was based on history alone and was not verified with SPT. The present patient had a history consistent with IgE-mediated hypersensitivity to macrolides confirmed with positive SPT results. In addition, after desensitization, the positive SPT reactions to clarithromycin and azithromycin reverted to negative after 6 weeks. Although drug desensitizations are often performed in the inpatient setting, data from Castells et al⁶ demonstrated the overall safety of desensitizations performed in an outpatient setting. Because allergists' offices are equipped to treat anaphylactic reactions due to immunotherapy, outpatient drug desensitizations can be performed if appropriate.

In macrolide-allergic individuals who require macrolide therapy, drug desensitization seems to be an effective option. The frequency of clinical and immunologic cross-reactivity among macrolides as seen in this patient deserves further study.

NITHYA SWAMY, MD
SCOT A. LAURIE, MD
ERNESTO RUIZ-HUIDOBRO, MD
DAVID A. KHAN, MD

Division of Allergy and Immunology
Department of Internal Medicine
The University of Texas Southwestern Medical Center
Dallas, Texas
nithyatx@yahoo.com

1. Gruchalla RS, Pirmohamed M. Antibiotic allergy. *N Engl J Med*. 2006;354:601–609.
2. Periti P, Mazzei T, Mini E, et al. Adverse effects of macrolide antibacterials. *Drug Saf*. 1993;9:346–364.
3. Empedrad R, Darter AL, Earl HS, et al. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. *J Allergy Clin Immunol*. 2003;112:629–630.
4. Sullivan TJ, Yecies LD, Shatz GS, et al. Desensitization of patients allergic to penicillin using orally administered β -lactam antibiotics. *J Allergy Clin Immunol*. 1982;69:275–282.
5. Holmes N, Hodgkinson M. Report of oral clarithromycin desensitization. *Br J Clin Pharmacol*. 2008;66:323–324.
6. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol*. 2008;122:574–580.

SEVERE CUTANEOUS REACTION AND FEVER DUE TO ADALIMUMAB

Adalimumab is a 148-kDa, recombinant, human, high-affinity IgG1 monoclonal antibody against tumor necrosis factor α (TNF- α) that prevents cytokine binding to its receptor and lysing cells that express TNF- α on their surface.¹ The most common adverse reactions with adalimumab are injection site reactions (eg, erythema, pruritus, and pain or swelling around the site of injection), which are usually described as mild and generally do not require discontinuation of drug use.^{1–5}

A 58-year-old woman with severe psoriasis began treatment with subcutaneous adalimumab (40 mg) in April 2009. The first dose was well tolerated, and the second dose was administered 1 week later. Thirteen days after this dose the patient developed a morbilliform exanthema that affected all the skin, even the palms, soles, and scalp, with a burning sensation, malaise, headache, and fever (temperatures of 38°C–39°C). Infiltration was evident at injection sites. Physical examination revealed neither mucosal involvement nor adenopathies, and the Nikolsky sign was negative. Chest radiography results were normal, and laboratory values (eg, hemogram, erythrocyte sedimentation rate, biochemistry, urinalysis, and antinuclear, extractable nuclear antigen, and anti-DNA antibody titers) were within their respective reference ranges. Skin biopsy specimens were obtained from the involved skin of the thigh, showing exocytosis of lymphocytes, vacuolar degeneration of the basal layer, and slight necrotic keratinocytes in the epidermis spongiosis and a moderate-intense lymphocytic perivascular infiltrate in the dermis (suggesting a drug skin reaction). The patient was treated with systemic corticosteroids and antihistamines for 4 weeks. The fever disappeared within 4 days, and skin lesions evolved to superficial desquamation and faded within 1 month.

We performed cutaneous tests with adalimumab and other anti-TNF- α drugs (infliximab and etanercept) 4 months after the reaction following the same methods as in previous reports^{6,7} (Table 1). Seven days after having performed intradermal tests with adalimumab, the patient presented with a local reaction (11 × 6 cm) on the forearm around the injection areas, with erythema and pruritus lasting for 2 weeks. The skin biopsy specimen of the area with this reaction showed the same findings as a previous specimen taken

Disclosures: Authors have nothing to disclose.

© 2010 American College of Allergy, Asthma & Immunology.
Published by Elsevier Inc. All rights reserved.
doi:10.1016/j.anai.2010.09.031