

Anaphylaxis to erythromycin

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Background: Erythromycin and its salts belong to the larger class of macrolides. Erythromycin is well tolerated. The most common side effects are gastrointestinal distress, nausea, and vomiting, which are dose related. Allergic and pseudoallergic reactions due to macrolide antibiotics are uncommon. Anaphylaxis and acute respiratory distress appear in the literature as case reports.

Methods: We report a 24-year-old man who presented 12 years ago a systemic allergic reaction to penicillin, confirmed by skin tests and detection of specific IgE (RAST). Since then he had tolerated erythromycin on several occasions. Nine months ago, his general practitioner prescribed erythromycin orally as treatment for a respiratory infection. Thirty minutes after taking the first dose, 500 mg, he developed an anaphylactic reaction. The episode subsided with treatment with high dose corticosteroids, antihistamines, and epinephrine.

Skin prick tests and intradermal tests were performed with erythromycin at different concentrations. We also measured total IgE and specific IgE to erythromycin by CAP and Phadezym RAST (Pharmacia, Uppsala, Sweden), respectively. We also performed a Prausnitz-Küstner test (PK test), and oral challenge test.

Results: Skin testing to erythromycin was not helpful because of cutaneous hyperreactiveness. No significant levels of specific IgE to erythromycin were detected. The oral challenge and the Prausnitz-Küstner test were positive.

Conclusions: The positive history and oral challenge test suggested an anaphylactic reaction to erythromycin. The positive Prausnitz-Küstner test demonstrated the presence of specific IgE to erythromycin.

Ann Allergy Asthma Immunol 1996;77:456–8.

INTRODUCTION

Erythromycin and its salts belong to the larger class of macrolides, characterized by a large lactone ring with no N and one or more amino-sugar and sugar substituents. The action of erythromycin against susceptible organisms is usually bacteriostatic.

Erythromycin is well tolerated. The most common side effects are gastrointestinal distress, nausea, and vomiting, which are dose related and may occur in 5% to 30% of patients.¹

Allergic and pseudoallergic reactions to erythromycin appear to be relatively uncommon. They probably become clinically manifest in 0.5% to 2.3% of treated patients, and consist mainly in maculopapular rashes, pruri-

tus, urticaria and angioedema, but anaphylaxis and acute respiratory distress appear in the literature only as case reports and are quite infrequent.^{2,3}

Patients allergic to penicillin are at markedly increased risk of severe reactions to other haptenating drugs like erythromycin.⁴ Allergy to erythromycin is significantly more common also in patients with lupus erythematosus.⁵

We report a patient allergic to beta-lactam antimicrobials who had anaphylaxis after administration of erythromycin.

Immunologic studies were performed to confirm a Type I hypersensitivity reaction.

CASE REPORT

A 24 year-old-man with a personal history of rhinitis and asthma to house dust mites and animal danders had presented 12 years ago with systemic allergic reaction to penicillin that was confirmed by skin tests and detection

of specific IgE (RAST). Since then he had tolerated erythromycin on several occasions. In May, 1994, his general practitioner prescribed erythromycin orally as treatment for a respiratory infection. Approximately 30 minutes after taking the first dose (500 mg) of the drug, he developed a widespread pruriginous urticaria, severe facial angioedema, dysphagia, dysphonia, and progressive upper respiratory difficulty as well as vomiting, nausea, and abdominal pain. These symptoms resolved three hours after appropriate treatment with antihistamines, corticosteroids, and epinephrine.

MATERIALS AND METHODS

Skin Tests

Skin prick tests were performed with erythromycin lactobionate at different concentrations: 5 and 50 mg/mL in phosphate buffered saline (PBS). All the skin test solutions were prepared and used immediately. Histamine hydrochloride at 10 mg/mL and PBS were used as positive and negative controls, respectively. Reactions were read at intervals of 15 minutes by measuring the two perpendicular diameters of the wheal, and a wheal 3 mm larger than the negative control was considered positive.

When skin prick tests were negative, intradermal skin tests were carried out at 0.05 mg/mL of erythromycin lactobionate. No other salts were used.

Ten subjects, five atopic and five nonatopic, with no history of adverse drug reactions were used as controls.

IgE

Total IgE was measured by CAP according to the manufacturer's instructions (Pharmacia, Uppsala, Sweden).

Specific IgE was determined by Phadezym RAST (enzymimmunoassay developed by Pharmacia Diagnostics, Sweden), using available com-

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Received for publication November 15, 1995.

Accepted for publication in revised form June 13, 1996.

Table 1. Results of the Skin and PK Tests

Erythromycin Concentrations, mg/mL	Skin Prick Tests Wheal/Flare, mm	Intradermal Tests Wheal/Flare, mm	PK Test	
			Unheated Serum Wheal/Flare, mm	Heated Serum Wheal/Flare, mm
0.05	ND	5/6	5/6	0/0
5	4/4	ND	ND	ND
50	5/6	ND	ND	ND
Saline	4/4	5/6	0/0	0/0
Histamine	6/6	9/10	6/7	7/7

ND: not done.

PK test: Prausnitz-Küstner test.

mercial nitrocellulose paper discs coupled with erythromycin lactobionate-human serum albumin conjugate, supplied by Bioallergy (Rome, Italy) according to the manufacturer's instructions. The control consisted of a pool of sera from five normal subjects.

Prausnitz-Küstner Test

A passive cutaneous test (PK test) was performed on the patient's mother, by injecting 0.1 mL of the patient's serum on the back. Twenty-four hours later, we performed intradermal tests with erythromycin lactobionate solution in the same concentration as that for intradermal skin tests (0.05 mg/mL). Also we performed a control test, injecting 0.1 mL of the patient's serum heated at 56 °C for four hours (in order to destroy reagins). Previously HIV, hepatitis, and other viral infections (HTLV I, HTLV II) had been excluded by serologic tests.

Challenge Test

Single-blind, placebo-controlled, oral challenges were performed by administering progressively increasing doses of erythromycin ethylsuccinate, starting with initial doses of 75 mg and 125 mg at a 1-hour interval to be continued until an adverse reaction was observed or a therapeutic dose achieved (500 mg).

A handwritten consent was obtained from the patient prior to undertaking the challenges. He was located in our challenge room and carefully monitored. Full emergency cover was provided.

RESULTS

Prick and intradermal skin tests with erythromycin were not helpful because of cutaneous hyperreactiveness. The Prausnitz-Küstner test was positive (Table 1). The controls did not react to any of these tests.

Total IgE was less than 100 IU/mL. No significant levels of specific IgE to erythromycin were detected in our patient.

The reactions observed by oral challenge consisted of generalized urticaria, facial angioedema, dysphonia, dyspnea, and progressive upper respiratory difficulty as well as abdominal pain and vomiting, 30 minutes after the cumulative dose of 200 mg. During the reaction his blood pressure was 80/50 mm Hg, pulse rate was 120 beats per minute, and the respiratory rate was increased. Immediate treatment with antihistamines, corticosteroids, and epinephrine was provided. The reaction resolved over the next few hours.

DISCUSSION

Systemic allergic reactions to erythromycin are exceptional. There are some cases of urticaria and angioedema described in the literature and the mechanism of the reactions could not be demonstrated. There is also described in the literature one case of an anaphylactic reaction due to hypersensitivity to erythromycin, but the mechanism could not be demonstrated.⁶

We report a patient who experienced anaphylaxis following oral administra-

tion of erythromycin. Clinical findings and results of oral challenge suggest an anaphylactic reaction to erythromycin, and the Prausnitz-Küstner test confirmed that the underlying mechanism was a Type I hypersensitivity reaction, although significant levels of specific IgE to erythromycin were not detected. These drugs are, however, probably incomplete antigens due to their low molecular weights and such are incapable of eliciting specific IgE or IgG antibody responses. They would need to combine with autologous host proteins to become immunogenic.

There are no cases in the literature of specific IgE detected to erythromycin, perhaps because we don't know the antigenic determinants; and it is difficult to couple these molecules to nitrocellulose paper discs because of the low molecular weight of this drug.⁷

The cross-reactivity among macrolides is not clear, and there have been few studies of it in patients allergic to erythromycin.^{7,8} The patient was not challenged with other macrolides because of the severe reaction he experienced after a low dose of erythromycin. We therefore could not demonstrate cross-reactivity.

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