
Case report

Apparent anaphylactoid reaction after treatment with a single dose of telithromycin

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Background: Telithromycin, the first ketolide antimicrobial agent available in the United States, is related to the macrolide class of antibiotics. Reports of immediate-type hypersensitivity reactions with macrolides or ketolides are rare overall.

Objective: To describe a patient with a severe, apparent mast cell-mediated reaction to telithromycin.

Methods: A 54-year-old woman with a history of hypertension was prescribed telithromycin by her primary care physician for presumed bacterial sinusitis. Shortly after ingesting the first dose of telithromycin she developed severe shortness of breath, wheezing, and angioedema. Her allergic history was significant for the development of a maculopapular rash after taking sulfonamide antibiotics, but she had received erythromycin and azithromycin in the past with no adverse effects. She was intubated with difficulty and was treated with epinephrine, diphenhydramine, and corticosteroids. The patient made a full recovery.

Results: Although not confirmed, the patient's severe symptoms were anaphylactoid and were ascribed to an immediate-type hypersensitivity reaction to telithromycin. No other causative agents, including other drugs, foods, and environmental exposures, were implicated in this case. Her history of tolerability to macrolide antibiotics is of interest considering the chemical similarities between these drugs and telithromycin.

Conclusion: To our knowledge, this is the first reported case of a severe, immediate-type hypersensitivity reaction to telithromycin. Physicians prescribing this drug should be aware of this rare but serious effect.

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INTRODUCTION

Telithromycin is the first ketolide antimicrobial agent to be approved for use in the United States.¹ This drug is structurally related to the macrolide and azolide classes of antibiotics (Fig 1) and has a similar antibacterial spectrum, adverse effects, and propensity for drug-drug interactions. Telithromycin is approved in the United States for the treatment of acute bacterial exacerbation of chronic bronchitis, acute bacterial sinusitis, and community-acquired pneumonia.² The drug has the theoretical advantage of remaining active against macrolide-resistant strains of *Streptococcus pneumoniae* and is marketed on that basis. Telithromycin is a large molecule (molecular weight, 812 Da) that might be expected to elicit type 1 reactions among susceptible individuals, although reports of such reactions to related drugs, such as erythromycin and azithromycin, are rare (especially compared with β -lactam antibiotics).³ We report a case of a severe probable mast

cell-mediated reaction after a single ingested dose of telithromycin in a patient with a history of using macrolide and azalide antibiotic agents without difficulty.

CASE REPORT

A 54-year-old woman was admitted to a large community teaching hospital's intensive care unit (ICU) after being transferred from the emergency department of an outlying community hospital. Initially, she presented to the outlying hospital with acute onset of severe shortness of breath and the inability to speak. She was found to have severe laryngeal edema and upper airway obstruction. After much difficulty, successful endotracheal intubation was completed after multiple attempts. Initial physical examination showed facial swelling consistent with angioedema and little air movement on auscultation. Her initial respiratory rate was 24/min, and her pulse oxygenation was 74%. Arterial blood gas values were obtained and initially showed pH 6.95, a P_{CO_2} of 149 mm Hg, and a P_{O_2} of 34 mm Hg. After intubation, these values improved to pH 7.4, a P_{CO_2} of 32.4 mm Hg, and a P_{O_2} of 462 mm Hg. An initial diagnosis of anaphylaxis was determined, and she received epinephrine, diphenhydramine, and methylprednisolone. During intubation she also received midazolam and rocuronium before being transferred from the outlying hospital. Her medical history was significant for type 2 diabetes mellitus (diet controlled) and hypertension.

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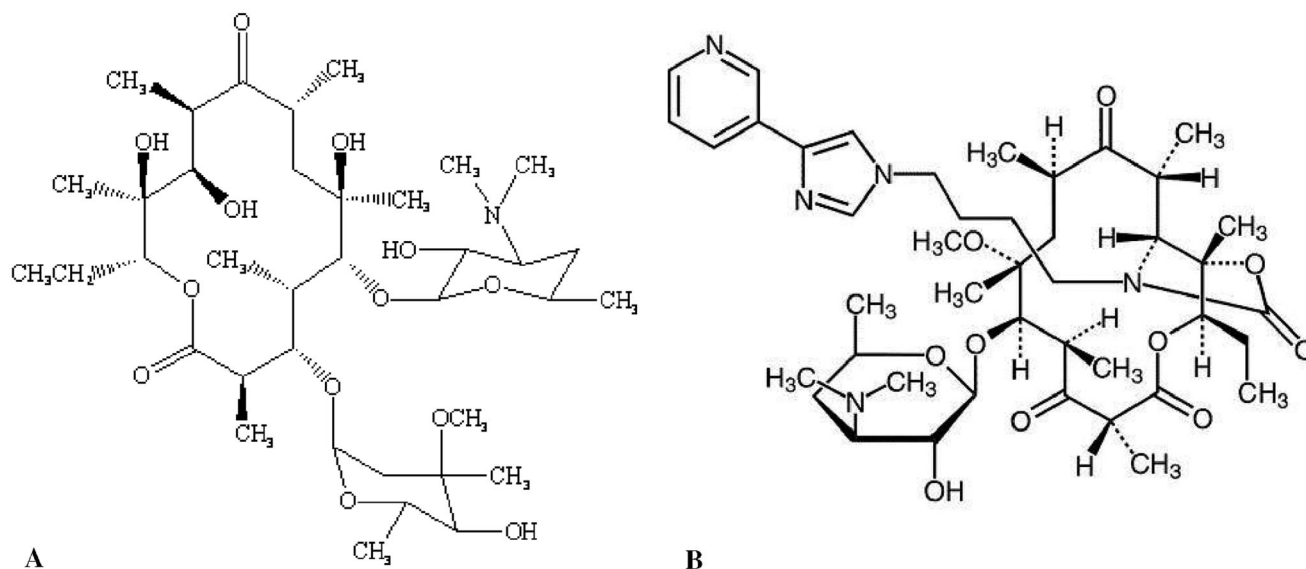


Figure 1. Chemical structure of erythromycin (A) and telithromycin (B).

There was no known history of heart disease, stroke, epilepsy, migraine headaches, asthma, or breathing problems. She had a history of allergic reactions to sulfa antibiotics; however, she had taken other antibiotics, including azithromycin and erythromycin, in the past without incident. Home medications reported by her daughter included atenolol, 50 mg/d, and hydrochlorothiazide, 25 mg/d, both of which she has been taking for at least 6 months. She previously had not been taking any angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. On arrival at the ICU at the teaching hospital, her vital signs were stable, with a heart rate of 102 min, respirations of 14/min, blood pressure of 97/66 mm Hg, and oxygen saturation of 100%. Pertinent laboratory values included sodium, 130 mEq/L; potassium, 2.6 mEq/L; and white blood cell count, 18.4×10^3 cells/mm³ (15% eosinophils). The remaining electrolyte panel values and the complete blood cell count were within their respective reference ranges. Ventilator settings were set at a synchronized intermittent mandatory ventilation rate of 14/min, a tidal volume of 600 mL, a fraction of inspired oxygen of 50%, a positive end-expiratory pressure of 5 cm H₂O, and pressure support of 10 cm H₂O. It was determined that the patient had taken 1 dose of telithromycin for the first time earlier that day. This antibiotic agent was prescribed by the patient's primary care physician for an upper respiratory tract infection. Shortly after ingestion (she was unsure of the exact time) of this first dose of telithromycin, she rapidly developed shortness of breath and airway obstruction. It was confirmed that this was the only new medication she had taken in the days preceding the event. She had done nothing out of her ordinary routine on the day of symptom onset. She had no food or drink after ingestion of the first telithromycin tablet. She had been at her home all day except for the physician

visit and a trip to the pharmacy to have the telithromycin prescription filled. She was at home when the symptoms occurred. The patient continued ventilator support until the following day in an effort to protect her airway. Intravenous corticosteroids and antihistamines were given to decrease inflammation and reverse the effects of the angioedema. She was alert and oriented. On the second day of hospitalization, a bronchoscopy-guided extubation was performed. She was given oxygen by mask and then was weaned off it to room air with no apparent residual effects from the intubation. On day 3 of hospitalization she was doing well on room air and was eating a regular diet. Consequently, she was discharged directly from the ICU in good condition. She was given a prescription for a prednisone taper and was instructed to avoid telithromycin in the future.

DISCUSSION

To our knowledge, this is the first published case of a severe, immediate-type hypersensitivity reaction to telithromycin. The reaction was life-threatening and required intubation and ICU admission. This patient had received erythromycin in the distant past and azithromycin recently with no serious adverse consequences. Allergic reactions to macrolide antibiotics seem to be rare, and only a few reports of fixed skin or urticarial eruptions have been published in the medical literature. Information concerning possible cross-reactivity between different drugs in this class is even rarer. German investigators⁴ described a patient who developed urticaria and tachycardia to roxithromycin and subsequently had positive skin prick test results to erythromycin and clarithromycin. Although this report may represent true-positive cross-reactivity, it is important to remember that allergy skin testing for this class of drugs has not been standardized, and definitive

conclusions are difficult. In fact, an earlier report of 5 patients with immediate dermatologic reactions to 1 or both of 2 macrolide antibiotics had negative skin test results to these agents.⁵

The pathogenesis of the present patient's reaction is unknown. Serum tryptase levels, which could support the diagnosis of anaphylaxis, were not obtained.⁶ Whether her symptoms were mediated by IgE as a classic type 1 reaction or from direct release of mast cell mediators (such as is occasionally seen with opioid drugs or intravenous contrast media) was not determined. No specific follow-up with an allergist/immunologist was scheduled. These specialists could perform confirmatory tests such as prick and intradermal skin testing or radioallergosorbent testing. Limitations of these tests include a lack of standardization in the former and no commercially available radioallergosorbent testing for macrolides or telithromycin in the latter. However, some cross-reactivity information could be derived from these tests. Because the important question of whether this patient should avoid all macrolides and azalides in the future as well as telithromycin remains unanswered, information from the tests mentioned previously could prove to be clinically relevant.

Telithromycin is a structural derivative of macrolide antibiotics, all of which have a basic macrolactone ring. Ketolide antibiotics differ structurally from macrolides primarily via the substitution of a 3-keto function in place of the L-cladinose moiety (the portion of the molecule primarily responsible for the antimicrobial properties of the latter class of drug).⁷ In addition, a large aromatic *N*-substituted carbamate extension differentiates telithromycin from erythromycin and clarithromycin. Still, the basic structure of ketolide antibiotics is similar to that of macrolides. Because the mechanisms responsible for hypersensitivity reactions in macrolides are largely unknown, it cannot be said whether a hapten, pro-hapten, or other molecule portion could be responsible for such effects. Thus, it is important that this patient had a history of exposure to macrolides and azithromycin with no adverse effects yet had an immediate, life-threatening reaction to telithromycin, suggesting that something in the structurally distinct portions of the molecule was responsible. Of course, an alternate explanation is a possible reaction to one of the inert substances in the tablet formulation. However, examination of the inactive ingredients demonstrates substances standard in many tablet formulations, such as hypromellose, magnesium stearate, and microcrystalline cellulose, all of which are unlikely to cause serious adverse reactions.²

Finally, a possible reason for the general lack of serious allergic reactions to these classes of antimicrobial agents is their inherent anti-inflammatory properties. Although known for more than 30 years, there has been renewed interest in the

benefits of these compounds as immunomodulators. In patients with panbronchiolitis, cystic fibrosis, and bronchiectasis, short- and long-term treatment with macrolides has been shown to decrease proinflammatory cytokines such as interleukin-1 β , interleukin-8, and tumor necrosis factor α .⁸ This leads to decreased neutrophil chemotaxis and numbers and in several studies has demonstrated clinical benefit in the diseases listed previously. Telithromycin seems to share these properties. Indeed, a recent study⁹ of patients with asthma suggested that a short course of the drug may have a modest benefit in reducing symptoms during an exacerbation.

In summary, we present a case of severe apparent anaphylactoid reaction in a patient after administration of a single dose of telithromycin. A history of tolerability to macrolide antibiotics may not ensure that a patient will not have a serious reaction to telithromycin. Clinicians should be aware of this rare but serious effect.

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