

Fatal Anaphylaxis Due to Graded Drug Challenge: A Cautionary Tale



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In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Sompornrattanaphan et al¹ present a case report of a 35-year-old man with aspirin-exacerbated respiratory disease (AERD) who 15 years earlier reported a generalized pruritic rash soon after taking the first dose of oral amoxicillin/clavulanic acid. He underwent evaluation with penicillin skin testing (using penicillin G, ampicillin, and amoxicillin/clavulanic acid), which was negative, and tolerated oral graded challenge with amoxicillin/clavulanic acid. Over the subsequent 20 months, he tolerated 3 to 4 courses of oral amoxicillin. He then developed acute sinusitis not responsive to amoxicillin, and treatment with oral amoxicillin/clavulanic acid was initiated. Because of a concern of possible resensitization to clavulanic acid, it was decided to administer the antibiotic via oral graded challenge in a hospital setting. Shortly after the first dose (300 mg/21.45 mg), the patient developed dyspnea, chest pain, and generalized cutaneous erythema. Despite the administration of 2 doses of epinephrine, the reaction progressed to cardiovascular collapse and loss of consciousness, and cardiopulmonary resuscitation was initiated. The patient later died because of complications related to ventilator-associated pneumonia.

The findings described in this case report are highly unusual for several reasons. First, fatal anaphylaxis from oral antibiotics, in contrast to parental antibiotics, is exceedingly rare. In the largest published series of antibiotic-associated fatal anaphylaxis, 98% of 151 cases of penicillin-induced fatal reactions were caused by parenteral administration.² There are very few published case reports of fatal anaphylaxis due to oral beta-lactam antibiotics, and most are due to penicillins. Also, although selective IgE-mediated allergy to clavulanic acid (without allergy to penicillins) has been described in recent years,^{3,4} to my knowledge, fatal reactions to oral forms of this drug have not been reported. Clavulanic acid is structurally a beta-lactam, but there is no evidence of allergic cross-reactivity with other beta-lactams, and patients allergic to clavulanic acid are not at a higher risk of developing an allergy to penicillins over time.⁵

Graded drug challenge is a method of cautious, stepwise administration of increasing amounts of a drug to which a

patient is unlikely to be allergic.⁶ It is commonly used to reintroduce antibiotics and other drugs in patients reporting previous reactions to them, when clinical evaluation suggests the patient is not allergic. Hence, a patient who tolerates graded challenge has proven to not be allergic to that drug. Graded challenge most typically involves administering larger amounts of the drug in 2 to 3 steps, with the first dose being 1/10th to 1/100th of the full dose. Among 530 patients undergoing single-/2-step versus 3-step graded challenges, there was no difference in safety between the shorter and longer protocols.⁷ I am aware of only 1 (unpublished) fatal reaction as a result of antibiotic graded challenge (due to ceftriaxone), in a patient with a history of ceftriaxone allergy. It is possible to start graded challenge at a lower dose and add more incremental steps, but this raises the possibility of inadvertently converting the procedure into rapid desensitization (ie, induction of drug tolerance).⁸ If an allergic patient is unknowingly desensitized, he or she would be at a risk of experiencing an allergic reaction the next time the same or cross-reacting drug is used.

The patient in this case report previously tolerated a 3-step graded challenge with amoxicillin/clavulanic acid (160 mg/22.8 mg, 400 mg/57 mg, and 960 mg/136.8 mg). Given the short duration of the challenge and the rapid dose escalation, I do not believe he was unintentionally desensitized. When the patient underwent the next graded challenge with oral amoxicillin/clavulanic acid, he reacted to the first dose, which was 300 mg/21.45 mg. Because the typical dose of clavulanic acid is 125 mg, this dose translates to about 17% of the full dose. It is impossible to accurately speculate whether a lower starting dose would have led to a different outcome. At the time of challenge, the patient's lung examination was normal, but there is no mention of a measure of lung function, such as a peak flow or FEV₁. It is possible that his lung function was compromised because he was amidst acute sinusitis, which is known to destabilize asthma. Also, patients with AERD tend to have more difficult to control asthma.⁹ However, the authors do not comment on his previous overall asthma control, such as baseline lung function, which asthma controller medications he was taking, whether he was compliant with asthma treatments, how often he experienced asthma exacerbations in the previous year, or whether he had a history of severe asthma exacerbations requiring intensive care unit stays or intubation.

Allergic resensitization is the redevelopment of allergy after a period of tolerance. Our knowledge of antibiotic resensitization is limited to penicillins. Studies have shown that penicillin resensitization following oral penicillins, even after several courses, is very low and comparable to sensitization.¹⁰ There are fewer data on resensitization following parenteral penicillins, with some but not all studies showing a higher rate of conversion to allergy.^{11,12} The patient in this case report likely developed resensitization to clavulanic acid. He was 4 days into an amoxicillin course before reacting to the amoxicillin/clavulanic acid

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Conflicts of interest: R. Solensky has received research support from Stallergenes Greer (allergic rhinitis) and AstraZeneca (asthma); is on the Advisory Committee for ALK (allergic rhinitis); and has provided expert witness testimony on the topic of drug allergy.

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graded challenge, making an anaphylactic reaction to amoxicillin extremely unlikely. I am not aware of any previous reports of antibiotic resensitization leading to fatal anaphylaxis. Despite the described reaction likely being the result of clavulanic acid resensitization, taking into account all the cumulative data on resensitization, it would be premature to recommend repeat allergy evaluation in all patients with a history of beta-lactam allergy, after tolerance of 1 course of the antibiotic.

The fatal allergic reaction to oral amoxicillin/clavulanic acid described in the case report by Sompornrattanaphan et al is a cautionary tale, reminding all of us of the potential dangers of anaphylaxis during graded antibiotic challenges. This risk is likely highest in patients with underlying asthma, especially if the asthma is uncontrolled. In the aforementioned publication of 151 penicillin-induced fatal anaphylactic reactions, approximately half the patients had underlying asthma.² Therefore, every effort should be made to stabilize patients with asthma before proceeding to graded challenge. However, this rare occurrence should not serve to deter allergists from pursuing antibiotic allergy evaluations. This is particularly true to “delabel” patients with a history of penicillin allergy, more than 90% of whom are not allergic. There are many negative clinical consequences of carrying a misdiagnosis of penicillin allergy, such as overuse of broad-spectrum antibiotics including vancomycin and quinolones, higher rates of development of vancomycin-resistant enterococcus, *Clostridium difficile* colitis, and methicillin-resistant *Staphylococcus aureus* infections, higher costs, and longer hospital stays.¹³ Therefore, it is clear that the benefits of such evaluations far outweigh the potential risks. Graded drug challenge is analogous to graded food challenge or subcutaneous allergen immunotherapy, in that a recognized rare risk of fatal anaphylaxis should not dissuade allergists from pursuing those clinical endeavors in the appropriate patients.

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