



Letter

Delayed clavulanic acid–induced anaphylaxis in a patient undergoing bariatric surgery

Selective allergy to clavulanic acid is rare, although amoxicillin–clavulanic acid is used frequently.^{1,2} With the increasing prevalence of obesity worldwide, the number of bariatric operations has significantly increased in the past decade. Despite the lack of prospective data from well-controlled randomized trials, evidence from case reports and case series have revealed that absorption, first-pass metabolism, volume of distribution, and half-life of drugs may all be altered after bariatric surgery in a drug-dependent manner.^{3,4} Occurrence of delayed anaphylaxis after oral drug challenge has not been reported after bariatric operations. In this article, we report, for the first time to our knowledge, a delayed anaphylaxis that occurred 4 hours after drug provocation using clavulanic acid in a patient undergoing sleeve gastrectomy (SG).

A 25-year-old man who had undergone SG 1 year earlier presented to the emergency department (ED) with dizziness and deterioration of level of consciousness occurring a few hours after ingestion of amoxicillin–clavulanic acid, 500/125-mg tablet taken for acute pharyngitis. In the ED, he was drowsy, pale, and sweaty. He had a pulse rate of 140/min, blood pressure of 70/30 mm Hg, temperature of 37.8°C, and respiratory rate of 36/min. Physical examination revealed a congested throat. His arterial blood gas on room air revealed pH 7.18, Pco₂ of 43.5 mm Hg, Po₂ of 40.6 mm Hg, and bicarbonate level of 16 mEq/L. The patient was intubated, resuscitated with intravenous (IV) fluids, given IV noradrenaline, and admitted to the intensive care unit. Then IV meropenem was prescribed for the possibility of septic shock. He made a good recovery and was discharged home on the seventh day with a diagnosis of septic shock; however, the results of septic workup were negative. One week later, 2 to 3 hours after receiving one tablet of amoxicillin–clavulanic acid, 500/125 mg, and ibuprofen, 400 mg, for sore throat, he developed severe breathlessness and dizziness and was brought to the ED hypotensive, treated as anaphylaxis with repeated IM epinephrine administration, and discharged home 2 days later. He had no rash or angioedema observed during both presentations. Two months later, he attended the allergy unit. Allergy skin prick and intradermal test results were negative for benzylpenicilloyl-polylysine, minor determinant mixture, and amoxicillin, all provided by Diater (Madrid, Spain). Oral challenge with amoxicillin, 500 mg, was tolerated. Skin prick and intradermal tests using amoxicillin–clavulanic acid, 1,000/200-mg solution (SmithKline Beecham Plc, Worthing, United Kingdom) at dilutions of 1:100, 1:10, and 1:1, were negative. Oral challenge with amoxicillin–clavulanic acid, 500/125 mg, was performed with extreme precautions, including electrocardiographic monitoring, 2 IV catheters in place, ready availability of emergency medications, and facilities for tracheal intubation. He was discharged home after

3 hours without any reaction; however, 4 hours after the amoxicillin–clavulanic acid challenge, he presented with dizziness and breathlessness and collapsed in the ED. He was treated for anaphylaxis and received 3 intramuscular doses of 0.5 mg of epinephrine, kept 24 hours under observation, discharged home with a medical alert, and instructed to avoid clavulanic acid–containing medications. The patient tolerated nonsteroidal anti-inflammatory drugs afterward.

Amoxicillin–clavulanic acid is a widely used antibiotic composed of amoxicillin and a potent β -lactamase inhibitor (clavulanic acid).² Type 1 hypersensitivity reactions to amoxicillin–clavulanic acid could occur because of a β -lactam ring, the R-group side chain of amoxicillin, or the clavulanic acid molecule. Amoxicillin is the penicillin most frequently involved in sensitization, with the side chain playing a relevant role.⁵ Anaphylaxis typically develops within minutes after exposure to the offending drug but may occasionally occur as late as 1 hour after exposure.⁶ Sanchez-Morillas and Pérez-Ezquerro¹ described 9 patients with selective adverse reactions to clavulanic acid. Only 1 patient had anaphylaxis, which occurred within 45 minute of exposure.

Fernandez-Rivas et al² reported 2 cases of anaphylaxis, which occurred 40 and 10 minutes after the intake of the first capsule of amoxicillin–clavulanic acid, respectively. In both patients, the results of skin tests with penicillin and amoxicillin were negative but positive with clavulanic acid.

Bariatric operations may affect drug absorption and its bioavailability through different ways. The smaller volume of the stomach results in reduced gastric mixing that may prevent adequate tablet disintegration. The reduction of gastric acid production (higher pH) may decrease the absorption of some medications. Delayed gastric emptying is another postulated mechanism.⁷ Fallatah et al⁸ found that gastric emptying after SG is variable according to the point of starting SG from the pylorus. At 4 cm it is associated with delayed gastric emptying, and at 7 cm it is associated with accelerated emptying for solids.

Our patient presented with 2 episodes of delayed anaphylaxis after ingestion of amoxicillin–clavulanic acid. In the first event, the diagnosis of anaphylaxis was missed because of the presence of fever, absence of rash, and lack of information given to the ED physician about ingestion of amoxicillin–clavulanic acid. In the second presentation, the patient sought care in the ED 2 to 3 hours after taking amoxicillin–clavulanic acid, was treated for anaphylaxis, tested negative for penicillin, amoxicillin, and amoxicillin–clavulanic acid, and tolerated oral challenge with amoxicillin. Oral challenge with amoxicillin–clavulanic acid revealed no reaction after 2 hours; however, anaphylaxis occurred 4 hours after challenge. The precise challenge procedure may vary a lot from one allergy team to another, and the need to standardize its practice has not been met so far⁹;

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however, observation of the patient for 2 hours after oral challenge with a full dose of a drug is adequate and acceptable by many allergy specialists. Occurrence of delayed anaphylaxis in our patient raised the question of whether bariatric surgery has a role in the delayed occurrence of anaphylaxis. This question needs to be answered, and more studies are needed to address this issue, especially with the new era of increasing different bariatric operations.

Delayed anaphylaxis after ingestion of clavulanic acid is unusual; however, no literature report of delayed clavulanic acid–induced anaphylaxis similar to our case is available. We think our case report delivers the following messages:

1. Physicians and allergy specialists caring for patients undergoing bariatric surgery should be aware of the delayed anaphylactic reactions from drugs, specifically the antibiotics.
2. The mechanism of anaphylaxis in these patients may or may not be different, but the absorption of drugs seems to be the issue and requires more studies.
3. We encourage physicians to report anaphylactic and other allergic reactions in patients undergoing bariatric operations to have further idea about these reactions.

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