

Allergic myocardial infarction (Kounis syndrome) after cefuroxime with side-chain cross-reactivity

Magdalena Absmaier, MD, Tilo Biedermann, MD, and
Knut Brockow, MD



Clinical Implications

- We report a case of allergic myocardial infarction (Kounis syndrome) caused by cefuroxime, highlighting the importance of allergological testing. By taking side-chain cross-reactivity into account, even in such severe cases tolerance to betalactams can be identified.

TO THE EDITOR:

Anaphylaxis is an acute generalized or systemic hypersensitivity reaction and may be fatal. It can affect skin, the pulmonary system, the gastrointestinal tract as well as the cardiovascular system.¹ After the skin, the cardiovascular system seems to be the second most affected organ during anaphylaxis, with involvement in about 72%, causing a range of symptoms from dizziness to cardiac arrest.² Different mechanisms may lead to cardiac arrest during anaphylaxis.

Generalized vasodilation and increased vascular permeability lead to a decrease in circulating blood volume of up to one-third, causing coronary hypoperfusion and myocardial damage due to lack of oxygen, which may result in cardiac arrest.¹

On the other hand, coronary arterial vasospasm was suggested by Kounis and Zavras³ to be a direct result of anaphylactic reactions leading directly to myocardial hypoperfusion, hypooxygenation, and damage. Mast cells are present in the heart tissue, which after activation can release various mediators (eg, histamine) shown to promote coronary artery spasm in experimental and clinical studies.⁴ Several possible elicitors of Kounis syndrome have been described. We would like to report a patient suffering from Kounis syndrome after intravenous administration of cefuroxime and his allergological management.

A 60-year-old patient with benign prostate hyperplasia, arterial hypertension, chronic obstructive pulmonary disease, and nicotine abuse was electively admitted to hospital to carry out a transurethral resection of the prostate. The patient had no history of drug or food allergy and no atopic predisposition. Before surgery, the patient received cefuroxime intravenously. About 2 minutes after the infusion was started, the patient perceived a bitter taste and a burning feeling in his whole body. Minutes later he reacted with a flush and dyspnea and he developed severe chest pain radiating to the left side. The patient was treated with 250 mg of prednisolone and 8 mg dimetindene intravenously as well as 500 mg of aspirin and 5,000 IE of heparin due to the chest pain. Subsequent hypotension with a minimum systolic value of 80 mm Hg was treated with akrinor (20:1 combination of cafedrine:theodrenaline; β -receptor and partial α_1 -receptor agonist used in Germany to treat severe hypotension). When conducting an electrocardiogram, ST elevations indicated a myocardial infarction of the inferior wall and the high-sensitivity

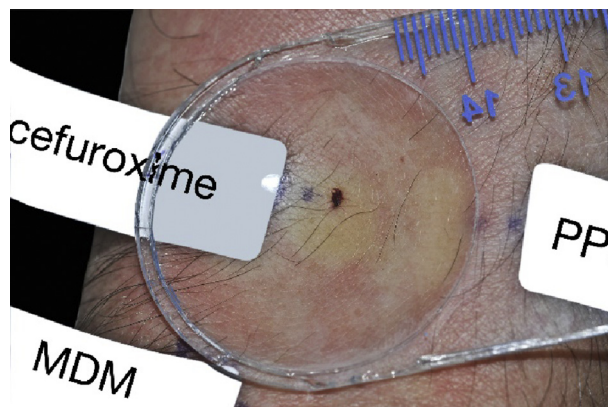


FIGURE 1. Positive reaction to cefuroxime in intradermal test. A clearly positive intradermal test result to cefuroxime is shown with a wheal diameter of 6 mm, whereas the outline of the flare is more difficult to appreciate in skin made anemic by the use of diascopy. *MDM*, Sodium benzylpenicilloate; *PPL*, benzylpenicilloyl-octa-L-lysine.

troponin T value was slightly elevated (0.132 ng/mL). Emergency cardiac catheterization showed a medial stenosis of the right coronary artery (75% degree) as well as an overall pronounced tendency toward vasospasm of the coronary vessels. The stenosis was treated by percutaneous coronary intervention/stenting.

Three months later the patient was referred to our department. He had previously received cefuroxime orally 3 times between 2008 and 2013 without any allergic reaction. Skin prick tests of cefuroxime and other antibiotics (amoxicillin, doxycycline, erythromycin, roxithromycin, clindamycin, ciprofloxacin, trimethoprim, sulfamethoxazole, penicillin V, cefixime, cefotaxime, ceftriaxone, benzylpenicilloyl-octa-L-lysine, and sodium benzylpenicilloate) as well as specific IgE antibodies against penicilloyl V, penicilloyl G, amoxicillin, and ampicillin remained negative (for skin test concentrations, see Table E1 in this article's Online Repository at www.jaci-inpractice.org); basal serum tryptase level was normal (7.95 μ g/L). Intradermal tests of benzylpenicilloyl-octa-L-lysine, sodium benzylpenicilloate, and amoxicillin/clavulanic acid showed no reactions, whereas intradermal testing with cefuroxime (see Figure 1), ceftriaxone, and cefotaxime was positive after 20 minutes (wheal and flare diameter 6 mm/7 mm, 4 mm/5 mm, and 6 mm/7 mm, respectively). By a drug provocation test, penicillin V and cefixime were shown to be tolerated. According to the findings above, the patient was diagnosed as having a severe anaphylactic event with Kounis syndrome secondary to intravenous cefuroxime administration.

Several factors support the diagnosis of Kounis syndrome in our patient: (a) the short time interval between the administration of the cefuroxime infusion and the development of anaphylaxis symptoms (involvement of skin, respiratory system, and cardiovascular system); (b) the sensitization against cefuroxime as demonstrated by the intradermal test results; and (c) vasospasms of the coronary vessels discovered by cardiac catheterization.

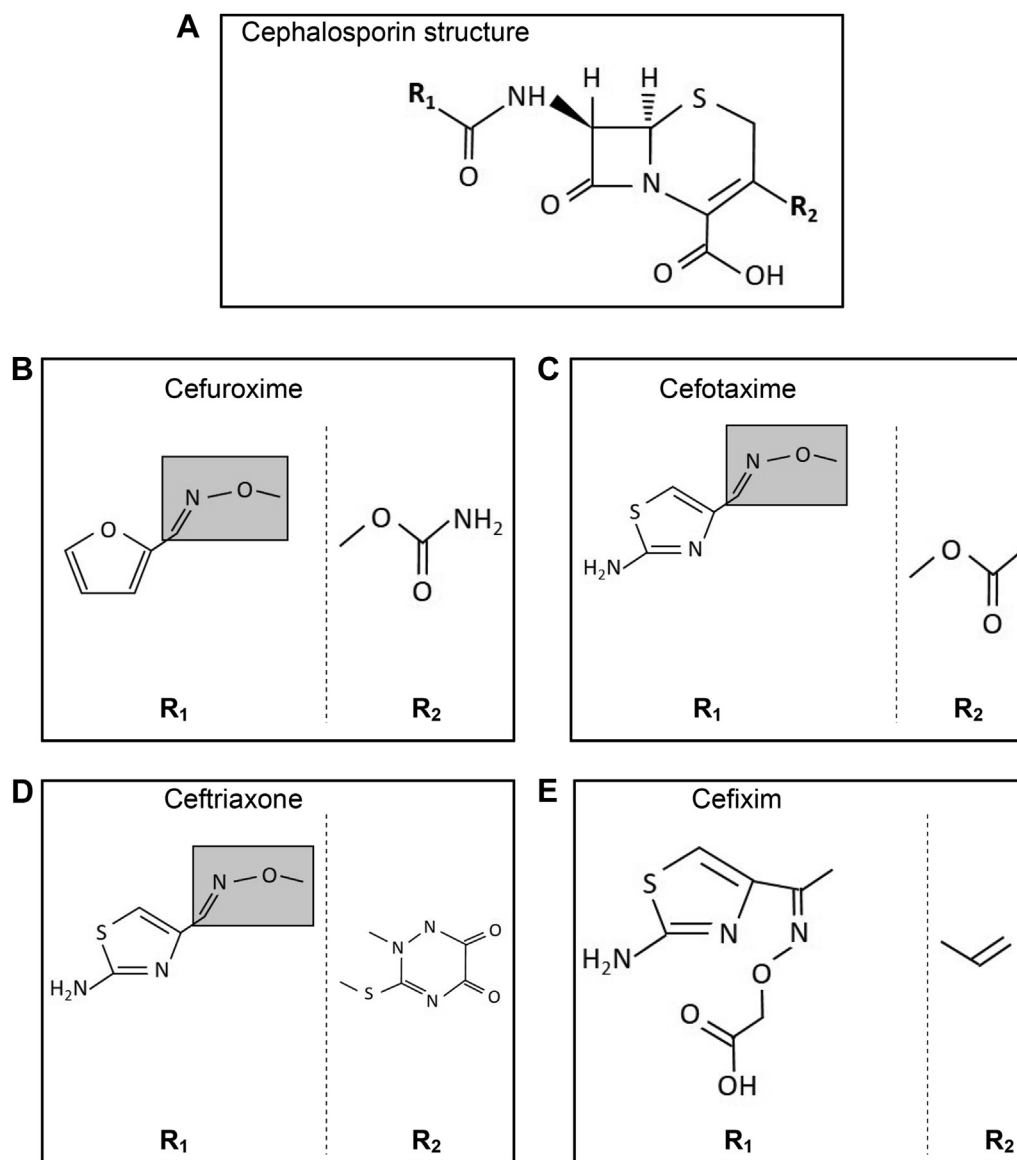


FIGURE 2. General structure of cephalosporins and side-chain similarity between cefuroxime and other cephalosporins. **A**, The general structure of cephalosporins, which can be distinguished by the variable side chains R1 and R2. **B-E**, Side chains R1 and R2 of cefuroxime, cefotaxime, ceftriaxone, and cefixim, respectively. Note that unlike cefixim, the cephalosporins cefuroxime, cefotaxime, and ceftriaxone carry a methoxyimino group in the R1 side chain that can cause cross-reactivity.

To our knowledge, only 5 case reports regarding Kounis syndrome due to cefuroxime have been published so far.⁵ Although the term Kounis syndrome is already widely used in cardiology/internal medicine, it is still not commonly used in allergology. It is undisputable that myocardial ischemia can be involved in anaphylactic reactions and that mast cells play an important role in the formation of atherosclerotic plaques.⁶ However, it remains unclear whether myocardial ischemia is a direct effect of mast cell mediators released during activation or whether it is rather caused by the hemodynamic stress that follows an anaphylactic reaction. To resolve this question, further studies are necessary.

Betalactams are important for the treatment of bacterial infections but also belong to the most frequent drugs causing

allergic reactions, and potential cross-reactivity between different betalactams is a common concern.

Cephalosporins consist of a 4-membered beta-lactam ring that is attached to a 6-membered sulfur-containing dihydrothiazine ring. Two side chains (R1 and R2) distinguish the different cephalosporins. All these structures can potentially be immunogenic.

However, it was shown that a class hypersensitivity is unlikely to be the reason for cross-reactivity to cefuroxime because the side chains most often carry the relevant epitopes.^{7,8} Cefuroxime belongs to the second generation of cephalosporins and carries a methoxyimino group in the R1 side chain. This group can also be found in the cephalosporins cefotaxime and ceftriaxone (see Figure 2), which both showed positive reactions in the intradermal skin test of our patient. Earlier studies already indicated

the importance of the R1 side chain of cephalosporins for cross-reactivity⁹ and showed cross-reactions between cefuroxime and cefotaxime as well as ceftriaxone.¹⁰

Because of near-fatal anaphylaxis and sensitization against cefotaxime and ceftriaxone, drug provocation tests of the culprit drug cefuroxime or the potentially cross-reactive substances cefotaxime and ceftriaxone were not performed. Instead, we tested antibiotics that could be applied safely as a substitute. Cefixime and penicillin V do not contain a methoxyimino group and were tolerated in titrated challenges.

Thus, in our case, the methoxyimino group in the R1 side chain mediated the cross-reactivity and all betalactams that carry this group such as cefuroxime, cefotaxime, ceftriaxone, cefepime, and cefepodoxime proxetil have to be strictly avoided. Currently available penicillins do not contain a similar structure and can be safely administered. Furthermore, an allergic reaction to non-methoxyimino group carrying cephalosporins appears highly unlikely and could be tested by titrated challenges, if needed. Our case report emphasizes the importance of allergological testing especially after severe life-threatening anaphylaxis with myocardial infarction (Kounis syndrome) as it helps to identify other betalactam antibiotics that are tolerated by the patient.

Department of Dermatology and Allergy Biederstein, Technical University of Munich, Munich, Germany

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication December 21, 2017; revised January 23, 2018; accepted for publication January 24, 2018.

Available online February 8, 2018.

Corresponding author: Knut Brockow, MD, Department of Dermatology and Allergy Biederstein, Technical University of Munich, Biedersteiner Straße 29, 80802 Munich, Germany. E-mail: knut.brockow@tum.de.

2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaip.2018.01.033>

REFERENCES

1. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
2. Worm M, Edenharter G, Rueff F, Scherer K, Pfohler C, Mahler V, et al. Symptom profile and risk factors of anaphylaxis in Central Europe. *Allergy* 2012;67:691-8.
3. Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract* 1991;45:121-8.
4. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7-14.
5. Mitsis A, Christodoulou E, Georgiou P. Coronary spasm secondary to cefuroxime injection, complicated with cardiogenic shock—a manifestation of Kounis syndrome: case report and literature review [published online ahead of print March 27, 2017]. *Eur Heart J Acute Cardiovasc Care*. <https://doi.org/10.1177/2048872617701885>.
6. Lieberman P, Simons FE. Anaphylaxis and cardiovascular disease: therapeutic dilemmas. *Clin Exp Allergy* 2015;45:1288-95.
7. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol* 2015;136:685-691.e3.
8. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259-73.
9. Antunez C, Blanca-Lopez N, Torres MJ, Mayorga C, Perez-Inestrosa E, Montanez MI, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol* 2006;117:404-10.
10. Romano A, Mayorga C, Torres MJ, Artesani MC, Suau R, Sanchez F, et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. *J Allergy Clin Immunol* 2000;106:1177-83.

TABLE E1. Skin test concentrations used in the patient

Drug	Skin prick test	Intradermal test
Amoxicillin	20 mg/mL	20 mg/mL
Cefuroxime	2 mg/mL	2 mg/mL
Doxycycline	Prick to prick	ND
Erythromycin	Prick to prick	ND
Roxithromycin	Prick to prick	ND
Clindamycin	Prick to prick	ND
Ciprofloxacin	Prick to prick	ND
Trimethoprim	Prick to prick	ND
Sulfamethoxazole	Prick to prick	ND
Benzylpenicillin	10.000 UI	10.000 UI
Cefixime	Prick to prick	ND
Cefotaxime	2 mg/mL	2 mg/mL
Ceftriaxone	2 mg/mL	2 mg/mL
Benzylpenicilloyl-octa-L-lysine	8.6×10^{-5} mol/L	8.6×10^{-5} mol/L
Sodium benzylpenilloate	1.5×10^{-3} mol/L	1.5×10^{-3} mol/L

ND, Not done.

For nonbetalactam antibiotics and cefixime, where only an oral preparation is available, a tablet was crushed to powder, placed on the forearm, and 0.1 mL of 0.9% saline was added to use a supersaturated solution ("Prick-to-Prick"). For all other betalactam antibiotics, intravenous parenteral preparations were used in nonirritating concentrations recommended by a recent position paper^{E1} on skin test concentrations for systemically applied drugs.

REFERENCE

- E1. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; 68:702-12.