

Fatal Anaphylactic Reaction to Intravenous Cephalexin

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Cephalosporin antibacterial agents are widely prescribed for common infections or are administered as first-line prophylaxis for many types of surgical procedures. They may cause allergic reactions, especially IgE-mediated ones. The incidence of reactions to cephalosporins does not seem to be less than that to penicillins,^[1] but immediate hypersensitivity reactions to cephalosporins and the nature of their allergenic determinants are neither well studied nor fully understood by many clinicians. Anaphylactic reactions to cephalosporins can occur because of IgE-mediated reactions to the β -lactam ring or side-chain structure,^[1] which may be responsible for cross-reactivity among cephalosporins.^[1,2] We report here a case of fatal anaphylaxis after intravenous cephalexin in a patient who had no history of penicillin allergy but who had been exposed to cefazolin 7 years earlier without any problems.

Case Report

A 57-year-old female with kidney stones, type 2 diabetes mellitus and a past history of urolithiasis was admitted to the hospital through the emergency room because of bilateral flank pain. A review of her previous medical records (including drugs used in a previous hospitalisation for right pyelonephritis) and current history revealed no known drug allergies. The patient had received cefazolin 1g intravenously every 6 hours for the treatment of pyelone-

phritis during a previous hospitalisation 7 years previously without any problems.

During the current admission, she was scheduled for an intravenous pyelogram and abdominal echography. However, she had mild fever on day 1 of admission before undergoing these procedures. Therefore, a dose of cefazolin 1g intravenously was given empirically to prevent infection, and no cultures were taken. One hour after the injection, the patient complained of malaise and a light tingling sensation over her palms. Her vital signs were good at that time. Blood pressure was 110/80mm Hg, body temperature was 36°C, pulse rate was 76 beats/min and respiratory rate was 20 beats/min. Physicians did not consider these to be pre-signs of anaphylaxis, but rather concluded that the patient's complaints might be adverse effects of the drug. Therefore it was decided to give cephalexin 1g intravenously instead of cefazolin as a second dose. Within approximately 15 minutes of injection, the patient began complaining of severe burning in her chest and nausea. One minute later the patient developed muscle twitching, upward-gaze palsy and urinary incontinence. No blood pressure could be detected, her heart rate was 45 beats/min, her pupils were dilated, and the patient became cyanotic. She was treated immediately with intravenous fluids, two ampoules of 1 mg/ampoule epinephrine (adrenaline) intravenously, one ampoule of 1 mg/mL atropine, 400mg of dopamine in 500mL of normal saline intravenous infusion, and two ampoules of epinephrine in 500mL normal saline infusion, and given

cardiac massage. However, her symptoms had not resolved within 1 hour and the patient unfortunately died. The physician determined that the cause of death was drug allergy.

Discussion

Development of anaphylactic shock within 30 minutes of administration of intravenous cephalexin is suggestive of an immediate IgE-mediated immunological reaction. Cephalosporin allergy is common and deaths due to anaphylaxis from cephalosporins have previously been reported,^[3] especially among patients with a history of penicillin allergy.^[4,5] Cefazolin and cephalexin are first-generation cephalosporins that are widely used in pre-operative prophylaxis or as empirical treatment for suspected infection.

The overall incidence of adverse reactions to cephalosporins ranges from 1% to 10%, with anaphylaxis estimated at 0.02%.^[5] Patients with a hypersensitivity reaction to penicillin or prior exposure to a specific cephalosporin are warned about a potential cross-reaction to cephalosporins.^[6] Our patient had reported no drug allergy but she had been treated with cefazolin 7 years earlier without any problems. Thus, no skin test or desensitisation for cephalosporin was carried out because there is no skin-testing reagent available in our country, and desensitisation to cephalosporins can be considered for patients with a previous life-threatening reaction to a cephalosporin or with a history of allergy to penicillin.^[5] Additionally, tryptase or histamine was not used to confirm anaphylaxis in this case because our infectious disease specialist did not recommend it in the guidelines to use of antibiotics. We suggest that the immediate hypersensitivity reaction could have resulted from the previous exposure 7 years earlier.

Over the past few years, Baldo and others have carried out many studies to identify the IgE-binding sites on β -lactam drugs.^[7-10] They found that antibodies that react to β -lactam drugs demonstrate a spectrum of specificities. Some are directed to a complete side chain or entire cephalosporin molecules.^[7,8] The results of Baldo et al. and others

demonstrated that at least for some β -lactam-allergic individuals, IgE antibodies might be directed to the R-group of the β -lactam drug and not to the determinants formed by the β -lactam ring.^[11] Therefore, we suggest that in our case IgE antibodies might be directed to the R-group of the β -lactam drug and not to the determinants formed by the β -lactam ring. Additionally, cephalexin may have cross-reactivity with cefazolin because of a similar R1 side chain and a different R2 side chain (figure 1). Our case may support what Baldo suggests in his review, namely that cross-reactivity may occur via R1 recognition where side-chain groups are the same or similar (e.g. ceftriaxone and cefotaxime) [figure 1] or may be caused by R2 recognition.^[9] Therefore, we may suppose that in our case the immediate hypersensitivity reaction might be explained by the fact that cephalexin and cefazolin have a similar R1 side-chain and the patient's history of exposure to intravenous cefazolin 7 years earlier, which would mean specific IgE antibodies pre-existed. Malaise and other discomfort appearing after one dose of cefazolin might have been the expression of an initial anaphylactic reaction in our case. Unfortunately, there is no skin test reagent or radioallergosorbent test available in our country that allows physicians to identify drug hypersensitivities and establish the immunological basis for drug allergies in their patients. As a result, patients are at risk for potentially life-threatening anaphylactic reactions when re-exposed to particular drugs.

Only one adverse fatal anaphylactic reaction has been attributed to the administration of oral cephalexin.^[12] Our case is the first report of an intravenous cephalexin-induced fatal anaphylactic reaction, and our aim was to alert primary-care practitioners and clinical pharmacists to the danger of widely used first-generation cephalosporins. Physicians, nurses and pharmacists should better understand the possible allergic determinants, such as the role of side chain structures in allergenicity and allergenic cross-reactivity with other β -lactams, dictating hypersensitivity to cephalosporins, and the need to look carefully for any signs of anaphylactic effects, such as malaise, tingling or numbness and

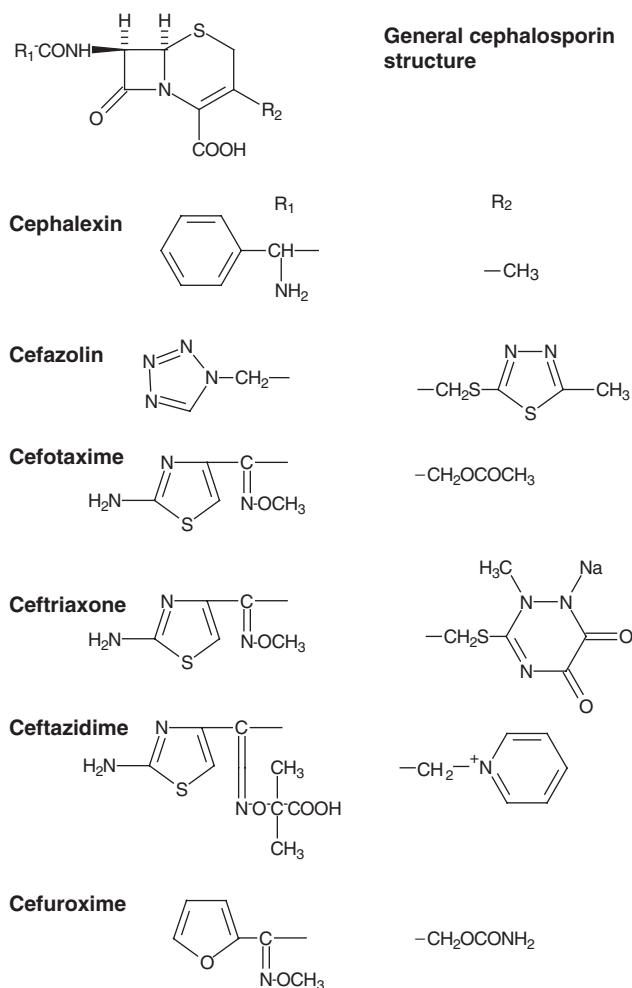


Fig. 1. Chemical structures of the cephalosporins.

any discomfort complained of by the patient after the injection, in order to prevent a recurrence of such reactions. Furthermore, review of a few studies showed that in subjects responding to an allergic reaction to different cephalosporins with a slightly different side-chain structure, such as ceftazidime and cefuroxime, cefotaxime, ceftriaxone and cefazolin (figure 1),^[13] a degree of cross-reactivity may occur between these cephalosporins. Because it is difficult to establish how the similarities and differences between these drugs impact on cross-reactivity, we concluded that in some countries in

which the *in vivo* skin test and *in vitro* immunoassay are not available, and when further characterisation of the determinants of IgE-mediated reactions associated with cephalosporins and penicillins is not possible, physicians should not use the same therapeutic class of antibacterials in patients who are suspected of having had an anaphylactic reaction.

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