Drug & Poison Information Center—Faculty of Pharmacy—Tanta University

Drug & Poison Information Bulletin

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'Cephalosporin Allergy' Label is Misleading

Inside this issue:

Overview:

Penicillins & cephalosporins can cause a similar spectrum of allergic reactions at a similar rate. Cross-reactive allergy between them is rare, as is cross-reaction within the cephalosporins group. Patients should therefore not be labelled 'cephalosporin-allergic'.

Cross-reactive allergy may occur between cephalosporins (and penicillins) which share similar side chains. Generally, a history of penicillin allergy should not rule out the use of cephalosporins, and a history of a specific cephalosporin allergy should not rule out the use of other cephalosporins. Further investigations may be required when the index reaction was anaphylaxis, a severe cutaneous adverse reaction, or when the antibiotics in question share common side chains.

Cross-reactive side chains

Studies have revealed that the side chains of beta-lactam antibiotics are important antigenic determinants in allergy. For example, if someone reacts to the amino side chain of amoxicillin rather than the beta-lactam core structure, they are likely to have a cross-reactive allergy to ampicillin which shares a very similar side chain, but not to benzyl penicillin or other penicillins.

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Several cephalosporins are not available in a solution suitable for skin testing due to poor solubility, and the diagnostic value of extemporaneously prepared solutions has not been established.

Skin-test sensitivity to cephalosporins can decrease over time which complicates interpretation. If the skin test is positive to the index drug, then a negative skin test to a related drug might help to exclude cross-reactive allergy. However, this would need to be confirmed by oral or parenteral challenge.

Challenge Test:

Challenge testing should only be done at specialist discretion. This involves the deliberate administration of a cephalosporin, usually in graded dosage. It should be carried out under expert supervision in a center with facilities to manage acute allergic reactions.

It is the gold standard test for patients with a history of allergy to a cephalosporin. Testing with a drug putatively linked to a previous reaction (homologous challenge) is warranted when there is an indication to use the drug, if there is significant uncertainty about the history, or if the reaction occurred in the distant past. In low-risk cases (mild reactions, history suggesting index reaction intolerance rather than allergy), oral rechallenge without prior skin testing can be considered to facilitate delabelling.

Recommendations:

In general:

- A history of penicillin allergy should not rule out the use of cephalosporins.
- A history of allergy to a specific cephalosporin should not rule out the use of other cephalosporins.

Exceptions include when:

The index reaction was anaphylaxis or a severe cutaneous adverse reaction and the antibiotics in question share common side chains.

References:

- *Yuson CL, Katelaris CH, Smith WB. 'Cephalosporin allergy' label is misleading. Aust Prescr. 2018;41:37–41.*
- *Dickson SD, Salazar KC. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. Clin Rev Allergy Immunol. 2013;45:131-42.*

By: Mai Mousa, PharmD.

Antigenic determinants for cephalosporin hypersensitivity have only recently become better defined. The cephalosporin R2 side chain is usually lost after the opening of the beta-lactam ring, so is less likely to cause allergy (Fig. 1). It is thought that the R1 side chain determines the specificity of immunological reactions to cephalosporins. For this reason, cross-reactive allergy across the whole cephalosporin family is seldom if ever seen.

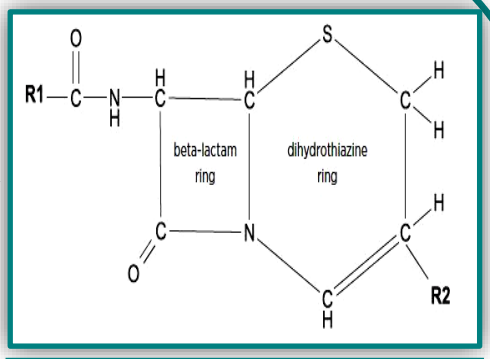


Fig. 1. General structure of cephalosporins

The R1 side chain as an antigenic determinant appears to explain the cross-reactivity that can be seen between certain beta-lactam antibiotics, as well as within the cephalosporin family. For example, amino-penicillins such as ampicillin and amoxicillin have similar R1 side chains to the amino-cephalosporins; cephalexin and cefaclor; and patients with sensitization to the amino side chain have a risk of cross-reactive allergy between amoxicillin and cephalexin but can tolerate other (non-amino) penicillins and cephalosporins without this side chain.

Predicting cross-reactivity:

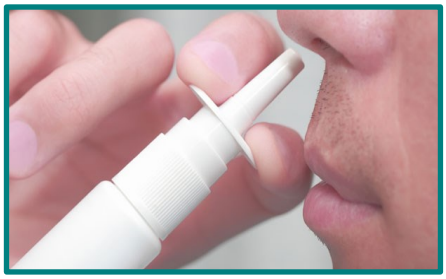
Cephalosporins currently available with similar or identical side chains can be found within the same generation or across generations. However, predicting cross-reactivity among the cephalosporins remains challenging and reactivity may be due to the entire cephalosporin molecule and not just the R1 side chain. A special case is the well-known phenomenon of cefaclor serum sickness-like reaction, occurring most commonly in childhood, which is not cross-reactive with other cephalosporins or penicillins.

Investigations:

Skin prick, intradermal (early or delayed), and patch testing are more sensitive than immunoassays. However, their negative predictive values are not established due to a lack of sufficiently powered studies.

An Investigational Nasal Glucagon for the Treatment of Severe Hypoglycemia

Findings from a randomized, non-inferiority study comparing the two glucagon formulas (nasal and intramuscularly) in 70 involving adults with type 1 diabetes were presented on October 4th, 2018 at the ***European Association for the Study of Diabetes (EASD) 2018 Annual Meeting.***



In the study, both the nasal and intramuscularly injected glucagon were 100% effective in reversing insulin-induced hypoglycemia, with no major safety issues. The study explained that the availability of a nasal formulation could help make glucagon easier to administer in stressful emergency situations compared with the injected version, which requires a multistep process of injection of syringe contents into a vial, mixing, and drawing the solution back into the syringe prior to injection.

The nasal glucagon comes as a ready to use 3 mg dry powder administered using a portable single-use device. It can be stored at room temperature. The user presses a plunger and the glucagon is expelled into the nasal cavity and passively absorbed with no inhalation required. The psychological obstacle to administer it to an unconscious person may be much lower.

Previous studies have shown the product to be effective in both adult and pediatric populations, to take less time to administer, and to successfully treat severe hypoglycemia in real-world settings. Manufacturer, *Eli Lilly* has submitted new drug applications for the product in both the United States and European Union for the treatment of severe hypoglycemia in children, adolescents, and adults with diabetes.

References:

- ***European Association for the Study of Diabetes (EASD) 2018 Annual Meeting; October 4, 2018; Berlin, Germany. Abstract 150.***
- ***Nasal Glucagon: Less Fear in Treating Hypoglycemia in Diabetes? https://www.medscape.com/viewarticle/903744#vp_2. Accesed on October 23, 2018.***

By: Bassant Maher, B.Sc

New Drugs for Prevention of Migraine

Overview:

Last September, the FDA approved both humanized monoclonal antibodies with the generic names fremanezumab-vfrm and galcanezumab-gnlm for the preventive treatment of migraine in adults. They both bind to calcitonin gene-related peptide (CGRP) ligand and block its binding to the receptor. However, the relationship between the pharmacodynamics activity and the mechanism(s) by which both drugs exert their clinical effects is unknown.

Administration:

- Fremanezumab-vfrm and galcanezumab-gnlm are administered via subcutaneous injection.
- The recommended doses of fremanezumab-vfrm are 225 mg monthly or 675 mg every 3 months (quarterly) administered as three consecutive subcutaneous injections of 225 mg each.
- Whereas the recommended doses of galcanezumab-gnlm are 240 mg as a loading dose then monthly doses of 120 mg.

Adverse Effects:

Reported adverse reactions are mainly injection site pain for fremanezumab-vfrm while for galcanezumab-gnlm are hypersensitivity.

Pregnancy & Lactation:

No adequate data are available concerning the use of these drugs in pregnancy and lactation.

References:

• Fremanezumab - FDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761089s000lbl.pdf. Accessed on October 28, 2018.

• Galcanezumab-gnlm - FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761063s000lbl.pdf. Accessed on October 28, 2018.

By: Amr Noweir, B.Sc

Chronic symptoms:

- *Constipation*
- *Abdominal cramps*
- *Polydipsia*
- *Polyuria*
- *Backache*

Findings may also include calcinosis, followed by hypertension and cardiac arrhythmias (due to a shortened refractory period).

Treatment of Toxicity:

- Place patients with vitamin D toxicity on a low-calcium diet.
- Consider oral calcium disodium edetate to increase fecal excretion of calcium.
- In cases of severe hypercalcemia, patients may require hydration, diuretics, steroids (hydrocortisone 100 mg IV q6h), calcitonin (4-8 IU/kg ,q6-12h), and/or mithramycin (25 mcg/kg qDay IV over 4-6 h for 1-4 days).
- Peritoneal or hemodialysis may be necessary if large amounts of Fluids cannot be given.

References:

- ***What is vitamin D toxicity, and should I worry about it since I take supplements? https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/expert-answers/vitamin-d-toxicity/faq-20058108. Accessed on September 26, 2018.***
- ***What are the signs and symptoms of chronic vitamin D toxicity? https://www.medscape.com/answers/819426-102386/what-are-the-signs-and-symptoms-of-chronic-vitamin-d-toxicity. Accessed on October 1,2018.***
- ***New Recommended Daily Amounts of Calcium and Vitamin D. https://medlineplus.gov/magazine/issues/winter11/articles/winter11pg12.html. Accessed on October 1,2018.***

By: Marwa EL-Sayed, PGCPD

Vitamin D Toxicity...What Should You Know About?!

Overview:

- Vitamin D toxicity, also called hypervitaminosis D, is a rare but potentially serious condition that occurs when you have excessive amounts of vitamin D in your body.

- Toxicity is usually caused by mega-doses of vitamin D supplements (not by diet or sun exposure). That's because your body regulates the amount of vitamin D produced by sun exposure, and even fortified foods don't contain large amounts of vitamin D.

- The Recommended Dietary Allowance (RDA) for most adults is 600 IU of vitamin D/ day. Taking 60,000 international units (IU) a day of vitamin D for several months has been shown to cause toxicity. These higher doses are sometimes used to treat medical problems such as vitamin D deficiency, but these are given only under the care of a doctor for a specified time frame. Blood levels should be monitored while someone is taking high doses of vitamin D.

Signs & Symptoms:

The effects of acute vitamin D toxicity are characteristic of hypercalcemia and may include the following:

- *Muscle weakness*
- *Apathy*
- *Headache*
- *Anorexia*
- *Irritability*
- *Nausea*
- *Vomiting*
- *Bone pain*

Upcoming Conferences in Egypt

- **528th International Conference on Science, Health and Medicine** (ICSHM), 11th-12th February, 2019 at Cairo , Egypt. Deadline for abstracts/proposals: 2019-01-03.
- **567th International Conference on Medical, Biological and Pharmaceutical Sciences** (ICMBPS), 11th-12th March, 2019 at Cairo, Egypt. Deadline for abstracts/proposals: 2019-02-03.
- **433rd International Conference on Pharma and Food** (ICPAF), 11th-12th April, 2019 at Cairo, Egypt. Deadline for abstracts/proposals: 2019-03-03.
- **631st International Conference on Recent Advances in Medical Science** (ICRAMS), 12th-13th May, 2019, Cairo, Egypt. Deadline for abstracts/proposals: 2019-04-04.

By: Nagwan Salama, B.Sc

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