

Linezolid Desensitization for a Patient with Multiple Medication Hypersensitivity Reactions

Autumn D Bagwell, Joanna L Stollings, Katie D White, Olajumoke O Fadugba, Jane J Choi

Linezolid is an oxazolidinone approved for the treatment of complicated and uncomplicated skin and soft tissue infections caused by gram-positive bacteria, including many antibiotic-resistant bacteria such as methicillin resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*.¹ Immediate hypersensitivity-type reactions to linezolid have been reported, with symptoms including hives, skin flushing, and angioedema.²⁻⁴ In 1 study, rash and pruritus were reported in 1.7% of 828 patients who received linezolid as well as in 1 case each of bullous skin lesions and throat swelling. However, it is unclear whether these reactions are mediated by drug-specific IgE, as there are currently no standardized skin testing reagents or in vitro assays available for assessment of linezolid-specific hypersensitivity.⁵ There have also been case reports of linezolid-associated reactions such as interstitial nephritis and drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), which are consistent with immune-mediated mechanisms but are not classified as immediate-type hypersensitivity reactions.⁶ There are no data on potential cross-reactivity of linezolid with other antibiotics.⁷

OBJECTIVE: To describe a case in which a linezolid desensitization protocol was successfully used for a polymicrobial surgical wound infection in a patient with multiple drug hypersensitivity reactions.

CASE SUMMARY: A 24-year-old woman with vocal cord dysfunction requiring tracheostomy was admitted for a surgical wound infection following a tracheostomy fistula closure procedure. The patient reported multiple antibiotic allergies including penicillins (rash), sulfonamides (rash), vancomycin (anaphylaxis), azithromycin (rash), cephalosporins (anaphylaxis), levofloxacin (unspecified), clindamycin (unspecified), and carbapenems (unspecified). Gram stain of the purulent wound drainage demonstrated mixed gram-negative and gram-positive flora, and bacterial cultures were overgrown with *Proteus mirabilis*, which precluded identification of other pathogens. Following failed test doses of linezolid, tigecycline, and daptomycin, all of which resulted in hypersensitivity reactions, a 16-step linezolid desensitization protocol was developed and successfully implemented without adverse reactions. The patient completed a 2-week course of antibiotic therapy that included linezolid upon finishing the desensitization protocol.

DISCUSSION: Linezolid is useful in treating complicated and uncomplicated skin and soft tissue infections caused by gram-positive bacteria. With precautions, including premedication, a monitored nursing unit, and immediate availability of an emergency anaphylaxis kit, drug desensitization allows patients the ability to safely use medications to which they may have an immediate hypersensitivity reaction. Minimal data exist on linezolid desensitization protocols.

CONCLUSIONS: Linezolid desensitization can be a viable option in patients requiring antimicrobial therapy for complicated gram-positive skin infections.

Ann Pharmacother 2013;47:xxxx.

Published Online, 28 May 2013, theannals.com, doi: 10.1345/aph.1S033

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In cases of documented or strongly suspected immediate hypersensitivity to a specific antibiotic, provocation testing and desensitization protocols can be used to enable treatment with agents that would not otherwise be tolerated. Drug desensitization allows for prevention or reduction of a hypersensitivity reaction to a medication through a series of graded doses to the allergen in a controlled and monitored setting.^{8,9} Although successful desensitization protocols for several antibiotics have been described, there is currently limited guidance in the literature for desensiti-

zation to linezolid.^{2,4} We describe the case of a patient with linezolid hypersensitivity who underwent a successful intravenous linezolid desensitization protocol.

Case Report

A 24-year-old woman with a seizure disorder, hypertension, type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, and vocal cord dysfunction requiring tracheostomy was admitted for closure of a tracheocutaneous fistula. Eight days after the surgery, she was admitted to the otolaryngology service for a surgical wound infection. Gram stain of purulent drainage from the wound demonstrated mixed gram-negative and gram-positive bacteria. Cultures ultimately grew *Proteus mirabilis*, which overtook the bacterial cultures, precluding identification of other pathogens. Given evidence of polymicrobial infection on Gram stain, broad antibacterial coverage was recommended.

The patient had multiple antibiotic allergies. She did not recall the exact nature or dates of reactions to several medications, but her allergy history was documented in her records by past providers as follows: penicillins (rash), sulfonamides (rash), vancomycin (anaphylaxis), azithromycin (rash), cephalosporins (anaphylaxis), levofloxacin (unspecified), clindamycin (unspecified), and carbapenems (unspecified). She recalled that several years prior, vancomycin had caused hives, swelling of the face and tongue, difficulty breathing, and a change in heart rate. She also had a history of diffuse hives and facial angioedema with aspirin and morphine.

She had previously tolerated aztreonam and thus this agent was started for gram-negative coverage. However, appropriate gram-positive coverage was more problematic given her multiple allergies. She had experienced hypersensitivity reactions to tigecycline and daptomycin while in the hospital. Tigecycline was initiated for gram-positive coverage since there was no record of previous reaction to this agent. About 10 minutes into the infusion, the patient developed pruritus, urticarial lesions on her neck and shoulders, swelling of tattoos on her back, and shortness of breath. These symptoms resolved approximately 30 minutes after diphenhydramine administration. Two days later, daptomycin treatment was attempted. Approximately 20 minutes into the infusion she developed pruritus (without cutaneous lesions), shortness of breath, and chest tightness. The infusion was promptly discontinued. Diphenhydramine was administered and she had rapid resolution of the symptoms. While tigecycline, daptomycin, and vancomycin desensitization were considered for gram-positive coverage, linezolid was chosen as the most appropriate agent given the patient’s severe prior reaction to vancomycin and for ease of dosing in the outpatient setting, as linezolid is available in an oral formulation. She had re-

ceived linezolid at an outside facility 5 years ago, without known adverse reactions. However, given her previous antibiotic allergies, she was initially given a full dose of linezolid 600 mg intravenously, with close monitoring for hypersensitivity reaction and with an anaphylaxis kit at bedside.

Approximately 15 minutes after initiation of linezolid infusion, the patient developed a diffuse macular erythematous rash, pruritus, raised tattoos on her arms and back, and chest pressure with associated shortness of breath. There was no angioedema or wheezing on examination, and her vital signs remained normal. Serum tryptase levels showed minimal change, from 3.0 µg/L at baseline to 3.5 µg/L (reference range 0.4-10.9 µg/L) approximately 1.5 hours after the reaction. Allergy specialists confirmed that this reaction was consistent with a probable immediate hypersensitivity reaction. Members of the Division of Allergy & Immunology, the Division of Infectious Diseases, and the Department of Pharmacy worked together to design a linezolid desensitization protocol (Tables 1 and 2).

Prior to the start of desensitization, several precautions were taken. The patient’s baseline peak expiratory flow rate was normal. She was premedicated with diphenhydramine 25 mg and famotidine 20 mg orally prior to the first dose of linezolid. An anaphylaxis kit containing albuterol, hydrocortisone, diphenhydramine, and epinephrine was also at the bedside. The desensitization protocol was designed and prepared as 3 separate dilutions in solution bags with concentrations of 600 mg/300 mL, 20 mg/100 mL, and 2 mg/100 mL. The premixed bag of linezolid 600 mg/300 mL of 5% dextrose (D5W) was used as solution bag 3. Ten milliliters from solution bag 3 were added to 90 mL of D5W to result in a concentration of 20 mg/100 mL for solution bag 2. Ten milliliters from solution bag 2 were added to 90 mL of D5W to result in a concentration of 2 mg/100 mL for solution bag 1. Fourteen sequential calculated doses were infused, using a medication infusion pump for 5 minutes except for the final 2 doses, which were infused over 15 minutes. A flush bag of normal saline was infused simultaneously given the small volume of some of the doses. The nurse monitored and documented vital signs and oxy-

Table 1. Linezolid Concentrations Used to Create Desensitization Protocol

Bag	Linezolid Concentration (mg/mL)	Drug (mg)	D5W (mL)	Amount Infused (mL)	Amount Wasted (mL)
1	0.02	2	100	5.00	95.00
2	0.20	20	100	11.25	88.75
3	2.00	600	300	298.90	1.10
D5W = 5% dextrose in water.					

gen saturation prior to the first dose and prior to each dose escalation. Additionally, a 10-minute monitoring period for signs and symptoms of allergic reaction followed each dose. The nurse assessed breath sounds prior to the first dose, prior to each dose escalation, and upon reports of respiratory symptoms including dyspnea or chest tightness. The protocol instructed the nurse to contact the provider and hold subsequent doses until further orders if any signs or symptoms of severe allergic reaction occurred. Potential actions by the provider at that time, including treating with an antihistamine and repeating the previous dose or stopping the protocol, would depend on the severity and type of reaction. Epinephrine 0.3 mg was available to be given intramuscularly every 5 minutes as needed for signs or symptoms of severe allergic reaction. The patient was monitored for 30 minutes following the final dose of linezolid. She experienced no breakthrough symptoms during the linezolid desensitization. Oral linezolid 600 mg every 12 hours was initiated and the patient was transferred to the otolaryngology service for continued care and preparation for discharge. Following completion of the desensitization protocol, the patient completed a 2-week course of aztreonam and linezolid without adverse effects.

Discussion

Drug desensitization is a strategy that induces temporary tolerance to a drug, thus allowing patients with a documented or strongly suspected immediate-type drug hypersensitivity reaction to safely use medications that they would otherwise not tolerate. This type of reaction is pri-

marily IgE-dependent.⁸⁻¹⁰ Most protocols begin with administration of a 1:100,000 to 1:100 of the fraction of the therapeutic dose, with gradual increases in concentration over a short period (several hours to days) until a full therapeutic concentration is reached.^{8,9,11} The mechanism by which clinical tolerance is induced during drug desensitization is complex and not fully understood. Fundamentally, it involves achieving antigen-specific basophil and mast cell desensitization. One mechanism for mast cell desensitization may involve low-level, subthreshold antigen stimulation by hapten-carrier conjugates.¹²⁻¹⁴

Drug desensitization protocols are best used under the following conditions: (1) the drug is irreplaceable, (2) the drug is more effective than alternatives, (3) the reaction to the drug is consistent with immediate-type hypersensitivity with mast cell-mediated mechanism, or (4) the reaction to the drug has been proven to be manageable with provocation testing and desensitization (ie, aspirin).^{8,9,15,16} Reactions not amenable to desensitization include maculopapular rashes, fixed drug eruptions, bullous eruptions such as Stevens-Johnson Syndrome/toxic epidermal necrolysis, DRESS, and interstitial nephritis.^{9,17,18}

An important clinical concept is that desensitization is an active and reversible process dependent on the continuous presence of the drug. Unlike immunotherapy to allergens, such as inhalant allergens, drug desensitization induces only short-term tolerance. Since drug desensitization does not provide long-term tolerance to medications and because drug sensitization is thought to return within 24-48 hours of withdrawal of the drug, patients must be desensitized each time use of that drug therapy is required.¹⁵

Table 2. Linezolid Desensitization Protocol^a

Step	Bag	Time	Rate (mL/h)	Infusion Duration (min)	Monitoring Duration (min)	Volume Infused (mL)	Dose (mg)	Cumulative Dose (mg)
1	1	0:00	18.0	5	10	1.50	0.03	0.03
2	1	0:15	42.0	5	10	3.50	0.07	0.10
3	2	0:30	9.0	5	10	0.75	0.15	0.25
4	2	0:45	18.0	5	10	1.50	0.30	0.55
5	2	1:00	36.0	5	10	3.00	0.60	1.15
6	2	1:15	72.0	5	10	6.00	1.20	2.35
7	3	1:30	13.8	5	10	1.20	2.30	4.65
8	3	1:45	28.2	5	10	2.30	4.70	9.35
9	3	2:00	56.4	5	10	4.70	9.40	18.75
10	3	2:15	112.5	5	10	9.40	18.75	37.50
11	3	2:30	225.0	5	10	18.80	37.50	75.00
12	3	2:45	450.0	5	10	37.50	75.00	150.00
13	3	3:00	300.0	15	10	75.00	150.00	300.00
14	3	3:25	600.0	15	30	150.00	300.00	600.00
TOTAL TIME		4:10						

^aIf the patient tolerates desensitization, begin intravenous or oral linezolid 600 mg every 12 hours.

The half-life of the drug must be considered. For example, the half-life of linezolid is 4-5 hours in adults. One would expect the drug to be completely removed from the body in 5 half-lives (20-25 hours) assuming normal liver function.⁶ However, if the drug is given as a daily regimen or at regular intervals, concentrations are maintained at a level adequate to render mast cells hyporesponsive and, thus, redensitization is not necessary. This strategy is common in aspirin desensitization protocols for patients with cardiovascular disease.⁸ Desensitization is also drug dose-dependent in that a substantial dose increase may result in breakthrough allergic symptoms.¹²⁻¹⁴

In the case of our patient, multiple drug allergies made treatment of her polymicrobial wound infection challenging. Additionally, the reaction to linezolid was consistent with immediate-type hypersensitivity with mast cell-mediated mechanism despite serum tryptase levels only showing minimal change from baseline approximately 1.5 hours after the reaction. β -Tryptase is a protease released from mast cell granules upon mast cell activation, which occurs during anaphylactic reactions. Serum concentrations peak at 1-1.5 hours after onset of anaphylaxis, but can persist for up to 5-6 hours. An elevated serum tryptase level can help support the diagnosis of anaphylaxis in the right clinical setting, but a normal level does not exclude the diagnosis. Studies have found that tryptase is more likely to be elevated with more severe anaphylactic reactions and less frequently elevated when anaphylaxis is related to food compared with a drug.^{19,20}

Given our patient's multiple drug allergies and immediate-type hypersensitivity with mast cell-mediated mechanism, we pursued a strategy of linezolid desensitization to facilitate the use of this drug for gram-positive bacterial coverage. Our review of the literature yielded only 2 case reports describing linezolid desensitization. The first showed successful desensitization to linezolid through oral administration of the intravenous formulation of the drug in an adult with multidrug-resistant *Enterococcus faecium* bacteremia.² The patient received 14 sequential dilutions of linezolid without experiencing any breakthrough symptoms. As the intravenous bioavailability of linezolid is 100%, it was hypothesized that an intravenous desensitization strategy would also be successful. The second case report showed successful intravenous desensitization in a 5-year-old boy; the patient tolerated a continuous infusion of increasing doses of linezolid, up to a maintenance dose, and continued on this for 1 week prior to switching to oral therapy.⁴ An important and unique aspect of our case was the use of a medication infusion pump to increase the accuracy and safety of linezolid administration. Because desensitization usually requires a 12- to 20-step standard protocol, proper administration of the medication at a precise dose can be arduous.¹⁷ As opposed to using 14 single-dose

syringes or compounded solutions, using a medication pump and formulating only 3 solution bags allowed for easy dose adjustment and precise dosage delivery, decreasing the chance of error in linezolid administration. This method of linezolid desensitization was successful, and as a result, our patient was able to complete appropriate antibiotic therapy despite numerous antibiotic allergies.

In this report, we have described the successful implementation of a desensitization protocol, using intravenous linezolid for the treatment of a polymicrobial soft tissue infection. While limitations to such strategies exist, the growing problem of antimicrobial resistance necessitates the use of multiple antibiotic agents, thus making desensitization an imperative component of pharmacotherapy in patients with a history of hypersensitivity reactions.

Autumn D Bagwell, PharmD Student, McWhorter School of Pharmacy, Samford University, Birmingham, AL

Joanna L Stollings PharmD BCPS, Clinical Pharmacy Specialist, Department of Pharmaceutical Services, Medical Intensive Care Unit, Vanderbilt University Medical Center, Nashville, TN

Katie D White MD, Clinical Fellow, Division of Infectious Diseases, Vanderbilt University Medical Center

Olajumoke O Fadugba MD, Clinical Fellow, Department of Allergy and Immunology, Vanderbilt University Medical Center

Jane J Choi MD, Assistant Professor of Medicine, Division of Allergy and Immunology, Vanderbilt University Medical Center

Correspondence: Dr. Stollings, joanna.stollings@vanderbilt.edu

Reprints/Online Access: www.theannals.com/cgi/reprint/aph.1S033

Conflict of interest: Authors reported none

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